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**POSTER ABSTRACTS**

**P1.001 Lis1 progenitor mechanisms contribute to cortical malformations**

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Human cortical malformations are associated with progenitor proliferation and neuronal migration abnormalities. Progenitor cells include apical radial glia, intermediate progenitors and basal (or outer) radial glia (bRGs or oRGs). bRGs are few in number in lissencephalic species (e.g. the mouse) but abundant in gyrencephalic brains. The *LIS1* gene coding for a dynein regulator, is mutated in human lissencephaly and microcephaly, and was shown to be important during cell division and neuron migration. The goal of this work is to investigate the role of *Lis1* in bRG-like cells after their enrichment in the mouse embryonic brain. This was achieved by *in utero* electroporation of a hominoid specific gene *TBC1D3* (coding for a RAB-GAP protein) at embryonic day (E) 14.5. As described previously, *TBC1D3* overexpression generates numerous basally localized Pax6<sup>+</sup> cells resembling bRGs. We assessed these cells in *Lis1* mutant conditions by co-electroporation of *TBC1D3* and a Cre vector in *Lis1* floxed embryonic brains in the presence of a Cre-dependent GFP reporter line. Assessing GFP<sup>+</sup> and Pax6<sup>+</sup> cells in the absence of *TBC1D3*, showed a greater number of these cells in basal regions of both in heterozygous and homozygous *Lis1* mutant animals. This phenotype is further amplified upon *TBC1D3* overexpression. The number, morphology and function of these *Lis1* mutant bRG-like cells is now being assessed. Similar experiments are also being performed using *Emx1-Cre* mice, in order to assess bRG-like cells after earlier (E9.5) *Lis1* inactivation. Performing these detailed analyses will shed light on *Lis1*'s role in the generation and function of bRGs.

**P1.002 Local control of protein synthesis for cortical inhibitory wiring**

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Alterations in the cortical balance between excitation and inhibition, and defective maturation and connectivity of interneurons in particular, have been observed in several neurodevelopmental disorders such as schizophrenia and autism. Interestingly, despite diverse genetic architectures, these disorders have overlapping behavioral cognitive symptoms, which suggests shared pathophysiological mechanisms. Here we find that in the mouse cerebral cortex, ErbB4 and Tsc2, two proteins respectively associated with schizophrenia and autism, interact at the synapse at the time of synaptogenesis. We show that interneuron-specific ErbB4 regulates mTOR signaling at the synapse through modulation of Tsc2 activity and that both proteins are required for proper wiring of cortical inhibitory interneurons. Taken together, our findings suggest that these two previously disparate pathways might underlie some of the shared pathophysiological mechanisms observed in cognitive disorders.

**P1.003 Organization and role of actin at the presynapse**

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Super-resolution microscopy has recently revealed unique actin structures along axons, such as submembrane periodic rings or intra-axonal hot spots and trails. By contrast, the organization of actin within presynaptic boutons is still poorly defined and its functions still controversial. We hypothesized that the debated role of presynaptic actin stems from the presence of different actin structures with distinct and possibly opposing roles in presynaptic function. Our project is thus to define these structures and determine their functions at the presynapse.

Visualizing presynaptic actin is difficult by gold-standard phalloidin staining, due to the high concentration of postsynaptic actin. We used a validated strategy to induce isolated presynapses along the axons of cultured hippocampal neurons with polylysine-coated beads. Induced presynapses contain all presynaptic components tested: the active-zone scaffold protein bassoon, the structural protein synapsin, as well as synaptic-vesicle proteins vamp2 and synaptophysin. Importantly, actin is concentrated in 70% of the induced presynapses, and these actin-enriched presynapses contain 25% more presynaptic component than non-enriched ones. Treatment with drugs that impair filamentous actin structures decrease the concentration of presynaptic proteins to the level of presynapses non-enriched in actin. Conversely, treatments that favor actin polymerization increase presynaptic protein concentration at presynapses and along the axon. Altogether, these data indicate that around 25% of presynaptic protein accumulation is dependent on actin enrichment at the presynapse.

To understand how actin participates in regulating the presynaptic architecture, we then used multi-color super-resolution STORM and DNA-PAINT to visualize the arrangement of actin and presynaptic components at the nanoscale. The submembrane actin rings stop at the presynapse and are replaced by bundles and clusters of actin surrounding presynaptic vesicles. Presynaptic proteins are organized in clusters, with bassoon and vamp2 colocalizing in the active zone, synapsin being more widespread. We then assessed how actin perturbations affect this nanoscale organization, providing a structural basis for the role of actin at presynapses.

**P1.004 Unique properties of early-born GABAergic cells in the developing and adult hippocampus**

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The remarkable diversity of cortical GABAergic neurons is rooted, at least in part, in their embryonic origins. Adding to the spatial control of interneuron specification is a temporal schedule that has significant impact on their fate. In the CA3 region of the hippocampus, GABAergic cells born the earliest (ebGABA) form a sparse subpopulation acting as 'hubs' during development and surviving until adulthood. However, their properties and function in adulthood remain elusive. To fill this gap, we used a multidisciplinary approach involving ex vivo and in vivo calcium imaging, electrophysiology, optogenetics and anatomical analyses to examine ebGABA in the CA1 region of the hippocampus. During the early postnatal period, ebGABA coordinate spontaneous population bursts, thus operating as hubs. In adulthood, ebGABA develop into long-range projecting cells characterized by low intrinsic and in vivo activity, but their firing is remarkably concentrated during network bursts. Additionally, adult ebGABA show a distinct input connectivity profile as they receive weak local (but not long-range) inhibition and they are recruited only by specific excitatory pathways. Overall, these data demonstrate that an early birth date determines unique functional properties of GABAergic cells in both developing and adult cortical networks.

- P1.005 Time course of α-actinin-2 expression within the dentate gyrus during epileptogenesis in the rat pilocarpine model of mesial temporal lobe epilepsy suggests its role in dendritic spines plasticity of hippocampal granule cells**
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α-actinin-2 (α-actn-2) is an actin filament cross-linker, enriched within dendritic spines. In vitro studies suggested that it plays a role in spinogenesis and morphogenesis. In order to test this hypothesis *in vivo*, we investigate its expression level within the dentate gyrus (DG) during the different stages that characterized development of chronic limbic seizures (epileptogenesis) induced by pilocarpine in rat. Indeed, in this model, plasticity of DG glutamatergic granule cells (GCs) including spine loss, spinogenesis and morphogenesis as well as neo-synaptogenesis associated with aberrant sprouting of granule cell axons, and its time course during epileptogenesis have been well characterized. This reorganization begins after the initial period of status epilepticus (SE) following pilocarpine administration, continues during the latent period, and reaches a plateau at the chronic stage. We investigated hippocampal α-actn-2 expression levels during the latent period at 1-2 weeks post SE and at 12 weeks at the chronic stage by using western blot, immunohistochemistry, and *in situ* hybridization. Immunohistochemical analyses showed that α-actn-2 immunoreactivity was significantly decreased in the hilus at 1-2 weeks after pilocarpine treatment, likely due to the degeneration of hilar neurons that occur after SE. Significantly decreased α-actn-2 immunolabeling was also observed in the inner molecular layer (IML) at 1-2 weeks after pilocarpine treatment, when granule cell spinogenesis as well as morphogenesis occur. Such results suggest that newly formed spines contain low level of α-actn-2 despite the increased expression of actn-2 mRNA in the GCs observed 1-2 weeks post SE. This low level persisted at the chronic stage when newly formed synapses have become established and functional. Interestingly, this decrease of α-actn-2 protein is correlated with the relapse of drebrin, an other actin binding protein, from latent period to chronic stage, known to cause dissociation of α-actn protein from actin filaments. Altogether, our results indicate that decreased α-actn-2 is not critical for structural integrity and stabilization of dendritic spines of hippocampal granule cells at chronic stage but consistent with its role in spinogenesis and morphogenesis.

P1.006

**Heavytail stories: GABAergic topologies during development**

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GABAergic activity critically contributes to cortical development. Between birth and the onset of active sensory experience, GABAergic neurons form transient interconnected circuits that are preferential recipients of thalamic inputs. Despite their importance for the emergence of sensory experience, the dynamics of GABAergic circuits during that neonatal period remain unknown. Here, we study the emergence of coordinated activity in GABAergic cells of the mouse barrel cortex without any *a priori* focus on a specific subtype. Using *in vivo* calcium imaging, we uncover a transient structure in GABAergic population dynamics that disappears in a sensory-dependent process. Its building blocks are anatomically-clustered GABAergic assemblies composed by somata and putative perisomatic terminals, recurrently activated in a stereotyped manner. These progressively widen their territories until forming a broad GABAergic network. Such transient patterning of GABAergic activity constitutes a hidden functional scaffold that links the cortex to the external world prior to active exploration.

**P1.007 Selective axonal distribution of the Kv1 channel complex in pre-myelinated GABAergic neurons**

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In myelinated fibers, voltage-gated sodium channels ( $\text{Na}_v1$ ) are concentrated at the nodal gap to ensure the saltatory propagation of action potentials, while voltage-gated potassium channels ( $\text{K}_v1$ ) are segregated at the juxtaparanodes under the compact myelin wrap and may stabilize axonal conduction. In inhibitory neurons, the  $\text{Na}_v1$  channels are trapped by the ankyrinG scaffold at the axon initial segment (AIS). Interestingly, it has been recently reported that pre-myelinated hippocampal GABAergic neurons display high density of  $\text{Na}_v1$  channels in clusters (pre-nodes) along the axon, which accelerate conduction velocity in pre-myelinated cells.

In this study, we show that specific subtypes of hippocampal GABAergic neurons, namely the somatostatin (SST)<sup>+</sup> and parvalbumin (PV)<sup>+</sup> cells, present a selective high expression of  $\text{K}_v1$  channels at the AIS and all along the unmyelinated axon. They are also highly enriched in molecules belonging to the juxtaparanodal  $\text{K}_v1$  complex, including the cell adhesion molecules (CAMs) TAG-1 and Caspr2, as well as the scaffolding protein 4.1B. Furthermore, we found that both  $\text{K}_v1$  and TAG-1 are enriched at the AIS, whereas Caspr2 and 4.1B are distributed more distally.

In myelinated axons the juxtaparanodal clustering of  $\text{K}_v1$  channels requires their association with TAG-1, Caspr2 and 4.1B. Here, taking advantage of knock-out mice for 4.1B or TAG-1, we observed that 4.1B is required for the proper positioning of Caspr2 and TAG-1 along the distal axon, and that TAG-1 deficiency induces alteration in the axonal distribution of Caspr2. However, the localization of  $\text{K}_v1$  channels and clustering of ankyrinG/ $\text{Na}_v1$  were not modified. Intriguingly, we discovered that TAG-1 expression *in vivo* is constrained to specific CA1 hippocampal layers, being selective to the SST<sup>+</sup> cells in the stratum oriens and the PV<sup>+</sup> neurons in the pyramidal layer, and this may be related to a pre-myelinated phenotype.

In conclusion, by investigating the hierarchy between channels, CAMs and scaffolding proteins, we sought to clarify the early steps of channel compartmentalization, which may be crucial to stabilize nerve transmission during the transition from a continuous to a saltatory conduction in network development.

P1.008

**Regulation of AMPAR intracellular transport through its interaction with 4.1N**

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The efficiency of excitatory synaptic transmission is determined by the number of AMPA receptors (AMPAR) localized at the post-synaptic plasma membrane. We are studying the role of post-Golgi intracellular transport of newly-synthetized AMPAR in the establishment of synaptic AMPAR.

The cytoplasmic C-terminal domain of GluA1 binds 4.1N through an interaction dependent on two serine phosphorylations.

Using our new molecular tool together with video microscopy, we have studied the role of GluA1 and 4.1N interaction in the regulation of AMPAR transport. We have determined how synaptic plasticity regulates this interaction and thus GluA1 intracellular transport.

**P1.009 Transient receptor potential cation channel subfamily M member 5 (TRPM5) activation is required for thermosensitive plateau potentials in lumbar motoneurons contributing to postural control**

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The majority of neonatal spinal motoneurons display thermosensitive plateau potentials which emerge at temperatures > 27-28°C. These bistable behaviors are, to a large extent, determined by the interplay between four currents:  $I_K$ , L-type  $I_{Ca}$ ,  $I_{NaP}$ , and  $I_{CaN}$ ; but the identity of the channels underlying this “4-count waltz” and their function are still uncertain. We previously showed that thermosensitivity relies on  $I_{CaN}$  mainly carried by  $Na^+$ . By means of genetic and pharmacological approaches in neonatal rats and mice, we here investigated which “thermoTRP” channel(s) mediates  $I_{CaN}$  in lumbar motoneurons. The genetic deletion or pharmacological blockade of TRPV1-3 and TRPM4 channels did not alter the slow afterdepolarisation (sADP) responsible for the plateau potential evoked by a brief excitation. Instead, sADP is enhanced or decreased by the respective pharmacological activation or blockade of TRPM5 channels. Likewise, the pharmacological blockade of TRPM5 channels reversibly prevents plateau potentials. Consistent with these results, the genetic ablation of TRPM5 channels significantly decreased the sADP amplitude and reduced bistability by 50%. We next investigated the intracellular mechanisms modulating the TRPM5 channels function. We found sADP is enhanced or decreased by the respective pharmacological activation or blockade of ryanodine receptors but not altered by PKC inhibitor. All together, these data show a significant contribution of TRPM5 channels in generating sADP to promote plateau potentials by a process involving a calcium-induced calcium release. Because plateau potentials are thought to be important in postural functions, TRPM5 channels may have a behavioural role in modulating the postural control. Although no alteration of locomotion regularity index is observed in locomotor test, we showed a significant increase of the base of support highlighting a role of TRPM5 channels in postural control.

**P1.010 Elucidating the function of Huntingtin in the postnatal maturation of brain activity**  
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Huntington disease (HD) is an inherited neurodegenerative disorder caused by an abnormal expansion of a CAG repeat in the huntingtin (HTT) gene. The neuropathology of HD is characterized by the dysfunction and death of striatal medium spiny neurons and cortical pyramidal neurons. Onset occurs in mid-adulthood and symptoms include motor, cognitive and psychiatric disturbances. Despite its late onset, there is strong evidence suggesting a developmental component in HD pathogenesis. For instance, the developmental expression of mutant HTT or the reduction in HTT levels during development is sufficient to induce HD-like motor alterations and neurodegeneration. In this context, we showed that HTT depletion in cortical neurons affects radial migration leading to defects of cortical lamination that are maintained in young adults and are accompanied by a contraction of neuronal dendritic tree. It has been proposed that cortical neuronal migration and dendritic tree maturation are processes that strongly depend on neuronal activity during early life. Following these ideas, we propose that a developmental HTT depletion could lead to alterations in neuronal activity during early stages and this could be related to impairments in neuronal migration and morphology. To study this possibility, we selectively depleted HTT from layer II/III neurons by in utero electroporation and we performed ex-vivo whole cell recordings at different postnatal stages (P0-10). We found a decreased synaptic activity in HTT depleted neurons, starting as early as P1. This decrease was seen as a reduction in the frequency and amplitude of the spontaneous synaptic currents. Also, we found an increase in intrinsic excitability (seen as a higher action potential frequency with current injection) starting from P7, possibly as a compensatory mechanism for the decreased synaptic activity. This increase in firing frequency is related to a more depolarized resting membrane potential and to a reduction in the voltage-dependent potassium currents that underlie action potential generation. In conclusion, our data suggest that HTT dysfunction results in early deficits in neural circuit physiology having important implications in the context of identifying novel targets and new temporal windows for treatment.

**P1.011 Proteomic study of Huntington's disease growth cone: identification of new players in axonal growth**

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Huntington's disease (HD) is a neurodegenerative disorder caused by an abnormal polyglutamine tract expansion in the huntingtin (HTT) protein. The symptoms appear during mid-adulthood but several evidence suggest a developmental contribution to HD. MRI studies in presymptomatic patients revealed early alterations in white matter tract with a marked defect in the corpus callosum. This structural tract is mainly formed by axons projecting from layer II/III neurons. Taking advantage from in utero electroporation technic that allows us to target specifically this population of neurons, we measured the axons in HD mice during development and we observed a decrease in axonal length *in vitro* and *in vivo*. The axonal growth is driven by a highly motile structure, the growth cone that is crucial for the establishment of the neuronal network during the development of nervous system. Performing an extensive proteomic analysis of growth cones isolated from the P0 brains, we identified 34 proteins that were significantly modulated in HD. In this study we identified new players of axonal growth that could provide new understanding of molecular mechanisms of axonal growth in health and HD.

**P1.012 Role of Huntingtin in axonal growth of cortical neurons**

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Huntingtin (HTT) is the protein mutated in the devastating neurodegenerative disorder Huntington's disease (HD). The symptoms of HD only emerge during mid-adulthood but evidence suggest a developmental contribution to HD. Indeed, both the wild type and mutated forms of HTT are expressed during development and HTT inactivation in mice results in embryonic lethality. Our team previously showed that HTT is involved in early steps of corticogenesis, controlling divisions of cortical progenitors and that HTT is necessary for the correct migration and polarization of newborn neurons. **My project consists in investigating the role of HTT in axonal growth**, a later stage of cortical development/maturation. I analyze *in vitro* the axonal length upon HTT depletion and find a shortening of axons, highlighting the role of HTT in axon outgrowth. I use cellular biology approaches to characterize the localization of HTT in growth cones, highly dynamic and organized structures on which relies axonal growth. I find that HTT localized with both microtubules and F-actin cytoskeletons whose regulation is crucial for a proper pathfinding and outgrowth of axons. I propose to investigate cytoskeletons organization and regulation upon HTT depletion using biochemical approaches.

**P1.013 The source of enkephalin release in the hippocampal area CA2**

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The hippocampus plays an important role in learning and memory formation. Hippocampal area CA2 output is necessary for social recognition memory. While this region has been under-studied, it has been shown that both interneurons and pyramidal cells in this region have distinct neuronal morphology and biophysical properties. With this, there is a unique delta-opioid receptor (DOR) mediated long-term depression of inhibitory transmission (iTLD) in area CA2 that has been shown to regulate excitation in this region. While it has been shown that this plasticity may be consequential for social recognition memory, the hippocampal source of enkephalin, the endogenous ligand for DORs, is not known. We make use of a knock-in transgenic mouse line that expresses cre-recombinase in the promoter elements of the preproenkephalin locus (PENK-cre mice). We selectively label and record from PENK+ interneurons, characterizing neuronal morphology and physiological properties. We found that PENK+ neurons have small somas and are located predominantly in *stratum pyramidale* and their basal dendrites branch narrowly into *stratum oriens*, whilst their apical dendrites extend and bifurcate into *stratum radiatum* only. These neurons fire action potentials in a range of 10-50 Hz and spike in a manner consistent with regular-spiking interneurons. Upon examining synaptic inputs of these interneurons, we show that they receive a strong drive from Schaffer collateral inputs that are sufficient to evoke action potential firing. These interneurons do not form synapses directly onto CA2 pyramidal cells but appear to target other interneurons. Immunohistochemical characterization of these PENK+ interneurons reveals a co-localization for the interneuron marker calretinin. Other interneuron markers such as parvalbumin, VIP, CCK and somatostatin did not co-localize with PENK+. We further show no co-localization for CamKII suggesting that these PENK+ neurons are indeed interneurons located in the *stratum pyramidale*. To further understand the mechanism and role of these PENK+ interneurons we will silence them using DREADDs to examine its role in DOR-mediated iTLD and further investigate whether PENK+ are involved in social recognition memory by completing behavioral studies involving a 3-chamber test.

P1.014

#### Linking embryonic origin and pyramidal cell diversity in hippocampal CA1

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The hippocampus is associated to several functions including navigation, memory, and emotional processing. It is still unclear how this structure computes relevant information to support this diverse functional repertoire. Several recent studies suggest that separate subsets of principal cells (PC) that route information to specific pathways, would provide a circuit basis for the diversity of hippocampal function.

This division of labor at the cellular level is in line with the finding that in the **CA1 area**, the main output region of the hippocampus, PCs are not a homogeneous cell population like previously thought. In fact, experimental evidence demonstrated **PC heterogeneity** encompassing dendritic morphology, electrophysiological properties, connectivity profiles, gene expression and participation in oscillatory activity. These features correlate with the cell body location along the radial axis of the stratum pyramidale (SP). This adds up to the notion that PCs **segregate functionally** according to their radial position, forming a *deep* and a *superficial* sublayer with distinct characteristics.

From embryonic day 11 (E11) to E17, differentiating PN migrate via an “inside first-outside last” scheme and position themselves in progressively more superficial positions. However other migratory schemes superpose to the radial one, so that the correspondence between cell birthdate and location is not as clear-cut. Here we asked whether embryonic birthdate, rather than soma location, is a better predictor of CA1 PC identity, and ultimately function.

To this aim, we use an *inducible genetic fate mapping* approach to label PCs according to the temporal origin (E12, E14, E16) and study the morphological and electrophysiological properties *in vitro* in the adult CA1. We show that the **embryonic birthdate contributes to defining intrinsic electrophysiological and morphological properties**. Likely, a predetermined genetic program acts in synergy with other extrinsic (positional) factors in determining cell identity. This study is the first characterization of CA1 pyramidal cells in the adult hippocampus as a function of the temporal embryonic origin and provides evidence that the embryonic origin of a neuron has an impact on its properties, and possibly its function.

**P1.015 Identification of new protein partners of the serotonin 5-HT<sub>6</sub>receptor involved in its neurodevelopmental functions**

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**Aims:** The serotonin 5-HT<sub>6</sub>receptor (5-HT<sub>6</sub>R) has emerged as a particularly promising target to alleviate cognitive symptoms of neurodevelopmental diseases. Indeed, its expression is highly localised in brain regions involved in cognition, and its blockade improves cognitive performance in numerous models of cognitive impairments in rodents. Recently, we have shown that 5-HT<sub>6</sub>R finely controls key steps of neurodevelopment, but the signaling pathways underlying its effects still need to be better characterized.

**Methods and results:** We addressed this issue by using a proteomic approach, aimed at identifying new signaling pathways associated with the receptor. We then studied the functional effects of the interaction between 5HT<sub>6</sub>R and its newly found partners both in a neuroblastoma cell line and in cultured neurons. We have demonstrated that 5-HT<sub>6</sub>R plays crucial roles in the correct migration and positioning of neurons and in neuronal differentiation and neurite growth through its interaction with Cyclin-dependent Kinase (Cdk) 5. Among the new protein partners of the receptor, we also identified the G protein regulated inducer of neurite outgrowth 1 (GPRIN1), a Cdk5 substrate known to promote neurite outgrowth. We established that co-expressing GPRIN1 and the receptor enhances receptor constitutive cAMP production and promotes neurite growth and branching in a PKA dependent manner. This occurs only after the 5-HT<sub>6</sub>R-Cdk5 complex is dissociated.

**Conclusion:** Our data suggest that 5-HT<sub>6</sub>R-operated neuronal differentiation depends on a complex sequence of events involving sequential and strongly interrelated associations of the receptor with different interacting proteins.

**P1.016 Control of neural stem cell specification in the postnatal forebrain by antagonist function of Vax1 and Pax6**

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Neural stem cells (NSCs) in the postnatal mouse ventricular/subventricular zone (V/SVZ), that generate different types of interneurons for the olfactory bulb, are highly heterogeneous. Depending on their location along the ventro-dorsal axis of the lateral ventricles, they preferentially give rise to distinct neuronal subclasses with defined positions, connectivity or neurotransmitter phenotypes. Understanding the molecular mechanisms that determine the generation of the distinct neuron populations at the NSC level will be essential for directing the differentiation of NSCs into defined neuronal cell populations in therapeutic contexts.

We found that the homeodomain transcription factor (TF) Vax1 is expressed in the lateral V-SVZ stem cell compartment in a ventro-dorsal gradient, suggesting a role in stem cell patterning and determination of neuronal phenotype. We used postnatal *in vivo* electroporation to miss-express Vax1 in the dorsal NSC aspects of the V-SVZ.

Overexpressing Vax1 in dorsal or dorso-lateral NSCs led to a decrease in the dopaminergic interneuron population in the olfactory bulb. This phenotype is accompanied by a reduction of the pro-dopaminergic TF Pax6 in the stem cell compartment, suggesting that dopaminergic fate repression by Vax1 occurs through repression of Pax6. Moreover, conditional inactivation of Vax1 in NSCs along the lateral SVZ led to a reduced number of Calbindin+ neurons, showing that Vax1 is necessary for the production of this sub-set of OB neurons.

This shows that antagonistic interactions between Vax1 and Pax6 control neuronal phenotype along the dorso-ventral axis of the forebrain stem cell compartment. If these interactions are direct or implicate intermediate regulators like, for example, miR-7a is currently under investigation.

P1.017

**Role of synaptic plasticity in AMPA receptor intracellular trafficking**

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Abundance of AMPA receptors (AMPARs) at the synapse is essential for the establishment and maintenance of synaptic function. Their synaptic localization is dependent on a highly dynamic exocytosis, endocytosis and plasma membrane mobility events. Our hypothesis is that synaptic localization of AMPARs is also regulated by their intracellular trafficking at basal state and during LTP. However, AMPARs post-ER trafficking toward the plasma membrane still remains poorly understood because of the lack of appropriate biological and imaging tools. Using a new biochemical tool combined with photonic live imaging, we controlled and followed the dynamic secretion of tagged GluA1 containing receptors in cultured rat hippocampal neurons and characterize AMPAR intracellular transport. These analyzes are performed in basal condition, during induction of LTP and 20-50 min after LTP. Finally we have studied the impact of GluA1 phosphorylation on its transport by expressing phospho-mimetic mutants known to be phosphorylated during synaptic plasticity.

P1.018

**Emergence of cell assemblies in the developing hippocampus**

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The classic view of hippocampal function is that of a structure providing a cognitive map of space, involved in navigation, learning, and episodic memory. However, within the last decade, the understanding of hippocampal function started to move away from this classical vision and a more computational and less representational version of its role started to emerge. In that framework, the hippocampus is best described as a “sequence generator”, i.e. a circuit with the ability to produce sequences of transient neuronal activation segmenting a multisensory context onto a continuous variable space. These sequences arise from the interaction between external sensory inputs and internally-generated self-organized activity. We have been exploring the internal self-organization of activity in the adult mouse CA1 hippocampus and uncovered the building-blocks of this internal scaffold, in the form of functionally orthogonal assemblies. During rest, these assemblies reactivate discrete temporal segments of neuronal sequences observed during run. These stable internal modules may therefore represent the default building blocks of hippocampal organization that can be combined to encode or retrieve spatio-temporal information. It is therefore essential to determine when and how these modules emerge in the course of development. To do so, we perform *in vivo* two-photon calcium imaging in the hippocampus of un-anesthetized pups from early postnatal stages to adulthood. We use a custom designed algorithm to infer neuronal activity from calcium transients recorded in hundreds of neurons. As animals age, we observe a desynchronization of network dynamics. Additionally, preliminary results revealed the emergence of cell assemblies around the end of the first postnatal week.

**P1.019 Role of omega-3 derivatives in synaptic plasticity**

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Worldwide, depression affects about 350 million people per year and represents the first leading cause of disability. Antidepressant drugs do exist, but their efficacy remain weak in 2/3 of patients. Therefore, there is an urgent need for alternative strategies, and dietary approaches have been the focus of recent attention. The role of n-3 polyunsaturated fatty acids (PUFAs) in the pathophysiology of mood disorders have been investigated. However, the mechanisms underlying the potential protective effects of n-3 PUFAs in depression are poorly understood, limiting their use in patients. Therefore, there is a need in conducting preclinical studies in order to understand how n-3 PUFAs can exert beneficial effects on depressive symptoms. The general purpose of our research is to examine the role of n-3 PUFAs in the prevention of depressive symptoms, in mice models. First, we examined how diets enriched in n-3 PUFAs could affect emotional behaviour in a mouse model of depression, together with synaptic activity measurements. Since n-3 PUFAs-rich diets contain DHA (docosahexaenoic acid), we are also focusing on the role of a DHA derivative in synaptic plasticity, as well as other endocannabinoids. Our preliminary results using whole cell patch-clamp electrophysiology in mice suggest that depression-induced loss of endocannabinoid plasticity could be prevented by n-3 PUFAs enriched diets, an effect that may arise from the *in vivo* conversion of DHA, thus restoring synaptic plasticity through a shift towards other neuroplasticity mechanisms. Such a shift in synaptic plasticity is triggered through the orphan receptor GPR55 and calcium-dependant mechanisms. This project will therefore provide a further understanding of the link between n-3 PUFAs, depressive behaviour and synaptic functions.

**P1.020 Development of nanoscopic correlative imaging (X-ray/photonic) to study the role of metals in the neuronal cytoskeleton**

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Metals ions, such as copper and zinc, play crucial functions in the neuromodulation at the synaptic level (Perrin et al., Tian et al., 2018). Despite this, the distribution of these elements at the synapse is largely unknown due to analytical limitations in spatial resolution and sensitivity.

The nano Synchrotron X-ray Fluorescence imaging (nano-SXRF) is an analytical technique that allows to determine the intracellular concentration of the entire metal pool and to image their localization with high resolution and sensitivity. Nano-SXRF offers also the advantage to be a multi-elemental technique without need of any labeling and with a spatial resolution as low as 25 nm (beamline ID16A, European Synchrotron Radiation Facility, Grenoble).

In this framework, we developed a methodology to correlate the distribution of trace metals and proteins combining nano-SXRF and super resolution photonic microscopy to acquire a better understanding of metals role in the mechanisms of synaptic plasticity. Previous studies suggested the interaction between zinc and tubulin (Craddock et al, 2012). We used primary hippocampal neurons from rats fluorescently labeled for tubulin and actin and imaged by STimulated Emission Depletion (STED) microscopy with a resolution of 50 nm and then analyzed with nano X-ray microscopy techniques. We found that zinc is abundant in the synapse and is also present along the dendrites where the distribution of zinc is correlated with the microtubule filaments.

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Perrin L, Roudeau S, Carmona A, Domart F, Petersen JD, Bohic S, Yang Y, Cloetens P, Ortega R. Zinc and Copper Effects on Stability of Tubulin and Actin Networks in Dendrites and Spines of Hippocampal Neurons. *ACS Chem Neurosci*. 2017 Jul 19;8(7):1490-1499.

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**P1.021 3D analysis of neural network remodeling in pancreatic cancer**

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Cancers are biological systems in which tumor cells interact with a complex microenvironment. This tumor microenvironment (TME) plays a fundamental role in cancer growth and progression and in the response to treatments. In recent years, a new component of TME has been identified: axonal projections of neurons from the peripheral nervous system (PNS). The presence of neural fibers in tumors is now well established but their origin and functional impact on disease progression remain poorly understood.

The TME of pancreatic ductal adenocarcinoma (PDAC) has unique characteristics that partly explain failure of treatment response to current therapies. Here, we study the contribution of PNS projections to this TME. For this purpose, we developed new methods for quantitative analysis of neural networks in the entire mouse pancreas. These approaches combine whole-organ clearing and 3D imaging by light sheet fluorescent microscopy (LSFM). An image analysis workflow has been set-up to calculate parameters describing neural network structures and interactions with the main cellular components of the tumor microenvironment.

We observed an increased density and branching of sympathetic and parasympathetic nerve fibers in pre-malignant lesions of the pancreas of transgenic mouse models of PDAC. These fibers also infiltrated invasive tumors. Moreover, whereas in healthy tissues sympathetic and parasympathetic axons were mainly associated with blood vessels, tumor-infiltrating axons make less contact with blood vessels. Principal component analysis on innervation indicators revealed distinct patterns of innervation that differentiate healthy and symptomatic tissues.

Thus, analysis of the 3D structure of the projections could represent a predictive and prognostic value for the progression of pancreatic tumors.

P1.022

**Roles of Nav1.6 channels into the operation of the spinal locomotor network**

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The spinal circuitry for locomotion is composed of interneurons forming the central pattern generators (CPG) and motoneurons (MNs) that convey CPG outputs to muscles. The CPGs fulfill two main tasks: to generate (1) a rhythm and (2) appropriate sequences of muscle recruitment. The rhythm-generating network are sets of excitatory interneurons with the intrinsic ability to oscillate in bursts at a frequency range similar to locomotor rhythms (Brocard et al., 2010). Our research for the biophysical basis of rhythmogenesis identified the persistent Na<sup>+</sup> current ( $I_{NaP}$ ) contributing to rhythmic bursting (Brocard et al., 2015). Beyond its rhythmogenic role, we showed that  $I_{NaP}$  plays a major role in the recruitment of MNs by mediating a repetitive spiking activity triggered by a brief excitation (Bouhadfane et al., 2013). This bistable firing called “plateau” produces a long-lasting discharge suitable to generate a steady contraction of muscles. Despite numerous studies of  $I_{NaP}$  within the spinal locomotor network, its molecular correlate among the nine Nav isoforms remains unknown. The Nav1.6 and Nav1.1 are the two major sodium channel isoforms within the CNS capable of generating an  $I_{NaP}$ . In the present study, we tested Nav1.6 as the main source of the  $I_{NaP}$  in the spinal locomotor network. Compared to wild-type animals, Nav1.6-null mice moved slowly and had gait impairments associated with a weak weight-bearing of hindlimbs. These motor deficits are related with a loss of plateau potentials in lumbar motoneurons which displayed a small  $I_{NaP}$  characterized by a positive shift in its activation threshold. By contrast, biophysical properties of  $I_{NaP}$  in CPG interneurons from Nav1.6-null mice did not change and kept the ability to generate autorhythmic bursting activity. In wildtype mice, the pharmacological blockade of Nav1.6 with the toxin 4,9-anhydro-tetrodotoxin reproduced a motoneuronal plateau potentials abolition without affecting CPG interneurons in the ability to burst. In sum, Nav1.6 channels appear critical in generating  $I_{NaP}$ -mediated bistable properties in MNs but not in locomotor-related interneurons.

**P1.023 Complement C4 overexpression in the mouse prefrontal Cortex recapitulates schizophrenia-associated endophenotypes**

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Recent Genome-Wide Association Studies identified multiple genetic regions associated with schizophrenia. Several of these regions map onto the major histocompatibility complex locus, further substantiating the long-suspected association between the immune system and schizophrenia. In particular, high expression variants of the Complement C4 gene confer disease susceptibility. Furthermore, C4 knock-out mice display deficits in synaptic pruning, a process by which supernumerary synapses are eliminated in the developing brain and which is exacerbated in the brain of patients. However, the link between elevated C4 expression and neural endophenotypes of schizophrenia remains largely unknown. We used in utero electroporation in mice at embryonic stage E14.5 to selectively overexpress C4 in layer III pyramidal cells of the prefrontal cortex and studied the electrophysiological properties of electroporated neurons. While the passive and active intrinsic properties of the recorded neurons were similar in C4-overexpressing (C4-OE) and control neurons, the frequency, but not amplitude, of miniature excitatory postsynaptic currents was decreased in C4-OE neurons. In addition, *in vivo* two-photon imaging showed decreased density of dendritic spines in C4-OE pyramidal cells, which is consistent with an excess of synaptic pruning during cortical development. The AMPA/NMDA ratio was increased in C4-OE neurons, suggesting a selective decrease in NMDA receptor-mediated transmission. We also observed deficits in intrinsic excitability and synaptic activity of parvalbumin interneurons located near C4-OE pyramidal neurons. We studied the activation status of microglia using 3D morphological reconstructions. The volume of the soma was increased in C4-overexpressing mice, indicating microglial activation. Finally, to study the long-term consequences of C4 cortical overexpression, we performed behavioral tests which revealed increased anxiety but no change in locomotor activity in C4-OE mice. Our results show that targeted cortical overexpression of C4 recapitulates schizophrenia-associated cortical deficits. This new mouse model will allow to assess causal relationships between immunogenetics and schizophrenia-associated endophenotypes.

**P1.024 Beyond the looking glass in the Congenital Mirror Movement paradigm: a single pathway for RAD51, NTN1 and DCC in the development of the nervous system?**

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Congenital mirror movements (CMM) disorder is a neurodevelopmental disease characterized by involuntary movements of one hand during voluntary movements of the opposite hand. In CMM patients, midline crossing of the cortico-spinal tract (CST) at the decussation is impaired. Three main culprit genes have been identified in CMM: *DCC*, *RAD51* and *NTN1*. The *NTN1* and *DCC* genes encode the netrin-1 axonal guidance cue and its receptor *DCC*. The role of the *RAD51* protein has been largely investigated in homologous recombination during DNA repair and meiotic division. The implication of *RAD51* in the decussation of the CST is totally unexpected, and further investigations are needed to understand the physiopathology of *RAD51* mutations in CMM.

Glendining and colleagues[1] recently suggest that *RAD51* may be a negative regulator of the netrin-1 pathway *in vitro*, through the *Unc5b/c* receptors. Based on evidence collected in human and mouse, we consider and discuss the possibility of a single pathway involving *RAD51*, *NTN1* and *DCC* in the development of the nervous system.

1. Glendining KA, Markie D, Gardner RJM, Franz EA, Robertson SP, Jasoni CL. A novel role for the DNA repair gene Rad51 in Netrin-1 signalling. *Sci Rep.* 2017;7.  
doi:10.1038/srep39823.

**P1.025 Neuroprotective effect of maternal polyphenol supplementation during hypoxia-ischemia of the newborn**

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**Introduction:** Neonatal cerebral hypoxia-ischemia (HI) brain injury is a significant cause of mortality and disability with an incidence estimated at 4 per 1000 live births. A neuroprotective effect of the plan polyphenol resveratrol (RSV), has been recently reported. Piceatannol (PIC), the catecholic variant of RSV offering higher bioavailability, could exert a better neuroprotection against HI. The objective of this study was to assess the effect of these polyphenols in an HI newborn rat model as well as to determine the best supplementation window for the dams.

**Methods:** Seven-day-old post-natal (P7) rats pups distributed in five experimental groups:

- Sham (no supplementation, no HI),
- Control (HI insult, CTR),
- Treated with RSV during the last week of gestation + the first week of breastfeeding (RSV-preHI) + HI,
- Treated with PIC during the last week of gestation + the first week of breastfeeding (PIC-preHI) + HI,
- Treated with RSV during one week breastfeeding after HI (RSV-postHI).

To follow the lesion size, *in vivo* MRI images of pups brains were acquired at different times post-insult. Behavioral tests (early reflexes, modified neurological severity score, novel object recognition) were also performed in order to compare damaged structures evidenced by MRI and their functionalities.

**Results and discussion:** Significant differences among the groups were observed. When dams had been supplemented with polyphenols, the lesion size was significantly reduced in pups, in which were obtained better results in both memory tests and motor evaluation vs to control group. Long-term neuroprotective effects were provided by maternal RSV supplementation (before or after HI). PIC seemed more effective than RSV most likely because of its better bioavailability.

**P1.026 Spatio-temporal pattern of serotonin 5-HT<sub>6</sub> receptors expression during neurodevelopment: potential role in wiring neuronal networks**

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**Introduction:** The serotonin 6 receptors (5-HT<sub>6</sub>Rs) are Gs-coupled receptors that hold special promise as targets for the treatment of cognitive deficits associated with neurodevelopmental and psychiatric disorders. However, the mechanisms underlying their impact upon neurodevelopment and cognition remain partially characterized. A major limitation is the absence of specific antibodies allowing precise assessment of cellular localization of 5-HT<sub>6</sub>Rs in the brain.

**Methods:** We used a genetically modified « knock-in » (KI) mouse strain expressing 5-HT<sub>6</sub>Rs fused C-terminally to a green fluorescent protein. Here, we systematically explored 5-HT<sub>6</sub>Rs expression pattern in several brain regions at different developmental stages including embryonic (E14-17), perinatal (P1), infant (P10), adolescent (P30) and adult (P60) stages by immunohistochemistry combined with confocal microscopy.

**Results:** We show that 5-HT<sub>6</sub>Rs are expressed as early as E15, in a wide variety of areas related to higher cognitive functions including the striatum, the nucleus accumbens, the hippocampus and the cortex. In all structures examined, 5-HT<sub>6</sub>Rs are mostly expressed in projection neurons and, to a lesser extent, in interneurons. In embryonic, P30 and P60 mice, 5-HT<sub>6</sub>Rs are detected in the primary cilium (PC), a non-motile cellular structure extending from the soma of almost every cell type, where they are co-localized with the ciliary protein Arl13b. Intriguingly, 5-HT<sub>6</sub>Rs are also detected in the somato-dendritic compartment of cortical and striatal neurons specifically at the perinatal stage, between P1 and P10.

**Conclusions:** Using a new KI mouse model, we characterized the spatio-temporal pattern of expression of 5-HT<sub>6</sub>Rs in the mouse brain. We confirm 5-HT<sub>6</sub>Rs expression in regions linked to higher cognitive functions as soon as early developmental stages. Whereas 5-HT<sub>6</sub>Rs localization is restricted to the PC at embryonic and adult stages, they are also expressed in the somato-dendritic compartment at the neonatal stage, suggesting a peculiar role in wiring neuronal networks at this critical period of neural development.

**P1.027 Early pathological signs of hypoexcitability are specific to delayed-onset firing motoneurons in superoxyde dismutase 1 (SOD1) postnatal mice**

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ALS is a complex neurodegenerative disease affecting most spinal and brainstem motoneurons (MN), and pyramidal cells in the motor cortex. Unfortunately there is still no curative therapy. The transgenic SOD1 mice reproduce clinical symptoms of ALS with time course depending on the strains. Since lumbar MN in juvenile SOD1 mice already exhibit abnormal electrical properties several months before clinical symptoms appear (Bories et al 2007 ; Pambo-Pambo et al 2009), we aim to determine whether these abnormalities affect a specific group of MN during this early period. Here we used three different strains of SOD1 mice (G85R, G93A low and G93A high expressor lines) and their WT littermates and C57 Bl6/J mice. Recently we classified lumbar MN into different groups according to their discharge firing pattern (transient, sustained, delayed onset firing). The delayed onset firing group exhibited the highest rheobase and conductance in the WT mice (Durand et al 2015). Here we demonstrate an overbranching of lumbar SOD1 MN in both sustained and delayed onset firing groups in the low expressors strains. As expected we found an hypoexcitability as measured by the slope of the F/I curve, and a higher spike threshold, in the delayed onset firing group. These MN probably compensate with a lower rheobase and a more depolarized membrane potential (signs of hyperexcitability). The sustained firing groups in WT and SOD1 G93A low do not present any differences in these properties. On the other hand, a higher gain was measured in lumbar motoneurons from the SOD1 G93A high expressor strain in comparison with their WT littermates, suggesting different time course of pathological signs or compensatory mechanisms. Our results also suggest that synaptic activity involving NMDA receptors in the spinal cord may switch the delayed onset firing pattern to the sustained one at a precise postnatal period. In conclusion the delayed onset firing MN is affected very early in SOD1 mice independantly of dendritic overbranching. This may induce early neuromuscular changes when polyinnervation is still present.

Bories et al. (2007) Europ J Neurosci, 25,451-459. Pambo-Pambo et al (2009) J Neurophysiol 102,3627. Durand et al (2015) Front Cell Neurosci 9, 349

P1.028

**Functional impact of *TCF12* mutation in oligodendrogiomas**

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Oligodendrogiomas are one of the most malignant primary brain tumors in adults. These tumors exhibit morphological features of oligodendrocytes and are presumed to emerge from cells with characteristics of neural progenitors or oligodendrocyte precursors (OPCs). Although their molecular profile is rather well-defined, the mechanisms underlying their development and progression still remain elusive. Besides other alterations frequently found in oligodendrogiomas, recent work identified recurrent heterozygous mutations in the gene of *TCF12* (7.5% of cases of anaplastic oligodendrogiomas), which were associated with a more aggressive tumor phenotype. *TCF12* encodes a bHLH domain transcription factor that can bind to DNA and mediate transcription by forming homo- or heterodimers via this domain. It was shown that mutations affecting the bHLH domain compromised the transcriptional activity of the protein. An accumulating body of research has demonstrated aberrant *TCF12* expression in various human cancers and indicated a dual functional role either as an oncogene or as a tumor suppressor. This project aspires to shed light to the functional impact of *TCF12* mutation on oligodendrogloma cells of origin and to dissect its role in gliomagenesis. First, we studied *Tcf12* expression in the mouse brain, focusing the oligodendrocyte lineage at several distinct developmental stages and observed that its expression seemed to peak concomitantly with oligodendrocyte differentiation. To investigate the consequences of *Tcf12* mutation on oligodendrogloma cells of origin, we utilized a mouse line in which the region coding for the bHLH domain of *Tcf12* is flanked by loxP sites, therefore enabling conditional inactivation of *Tcf12* upon Cre recombination and recapitulating some of the commonly found mutations in patients' tumors. Our first results from both in vitro and in vivo approaches, indicated that *Tcf12* inactivation related with impaired proliferation phenotypes in neural progenitors and OPCs. Further analyses will address how *Tcf12* mutation affects the interplay with known partners and epigenetic regulators, as well as what is its effect within the frame of a glioma model, which is already in use.

**P1.029 Chronic stress suppresses hippocampal neurogenesis via the CDK5-Huntingtin pathway**

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Chronic exposure to stress is a major risk factor for neuropsychiatric disease, and studies consistently show a correlation between elevated plasma corticosterone (CORT), reduced levels of brain-derived neurotrophic factor (BDNF), and inhibition of hippocampal neurogenesis. Precisely how BDNF levels and neurogenesis are diminished by elevated CORT, however, has been difficult to decipher. Here we approach this question with a combination of microfluidic chamber cultures and *in vivo* studies. In a cortico-hippocampal network reconstituted on a chip, we show that the glucocorticoid receptor agonist dexamethasone (DXM) reduces BDNF vesicular transport in cortical axons. DXM mediates its effect through the phosphorylation of huntingtin (HTT) at serines 1181 and 1201 (S1181/1201) by the cyclin-dependent kinase 5 (CDK5). CORT induces phosphorylation of HTT at S1181/1201 *in vivo*, and blocking S1181/1201 phosphorylation constitutively in mice prevents both chronic CORT-induced anxiety/depression-like behavior and stress-induced suppression of neurogenesis in the animals. Genetically arresting neurogenesis, however, abolishes the protective effects of unphosphorylatable HTT in mice. Stress thus suppresses hippocampal neurogenesis and promotes anxiety/depression-like behavior in mice by regulating BDNF transport in the cortico-hippocampal network via this CDK5-HTT pathway.

**P1.030 Fast 3D acquisition of neuronal activity in visual cortex across multiple layers in awake mice**

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2-photon microscopy allows recordings structural and functional information deep in scattering biological tissues with cellular resolution. However, standard light steering techniques are slow, providing frame rates of a few tens of Hz, and are limited to a plane of interest. We recently developed a new type of 2-photon microscope able to sample neuronal activity from 3D cortical networks in head-fixed animals at kilohertz rate. The microscope operates in a non-imaging mode, where individual laser pulses are spatially modulated with tilt and defocus to random-address individual cell bodies within a 400x400x400  $\mu\text{m}^3$  volume. Single pulse modulation is achieved by a large aperture, two-axis acousto-optic light modulator (AOD-SLM) synchronised to a 40 kHz regenerative laser amplifier. Individual pulses are further modulated in phase and amplitude to pattern the beam into a square array of up to 25 focal spots targeting the bodies of individual cells, interleaved with a pattern of 10 spots targeting the neuropil. This spatial patterning helped

- (1) to raise the single pulse photon yield;
  - (2) to dampen the occurrence of artefacts induced by locomotion and
  - (3) to suppress contamination of somatic signal by surrounding neuropil activity.
- We validated the microscope by recording GCaMP6f signals from neurons in layer 2/3 and 5A in primary visual cortex while the animal was free to move on a treadmill. In agreement with published data we find a significantly higher level of spontaneous activity of layer 5 cells, including a higher incidence of large amplitude burst discharge, while equal fractions of layer 2/3 and layer 5 cells were sensitive to the orientation of a moving contrast grating presented as a visual stimulus. At the same time, the columnar positions of iso-directionally tuned neurons revealed no discernable spatial organisation. However, the layered organization of the evoked activity clearly appeared in the neuron pairwise correlations, in particular through significant differences in the time delays of evoked spikes between layer2/3 neurons versus layer2/3 to layer 5 neurons.

**P1.031 Dopamine and glutamate receptor heteromers: modulation and roles in cocaine-evoked adaptations**

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Drugs of abuse hijack the natural reward by increasing DA in the mesolimbic system, especially in the striatum, where it shapes the efficacy of Glu synapses and contributes to long-lasting behavioral alterations. This integration of DA and Glu inputs is achieved by striatal projection neurons (SPN), which form two mainly segregated populations: the “direct pathway” (dSPN), expressing DA D1 receptors (D1R) that promotes reward, and the “indirect pathway” (iSPN) that express DA D2 receptors (D2R) that inhibits reinforcement. We identified heteromers formed by the D1R with Glu NMDA (NMDAR) receptors as molecular bridges by which DA facilitate Glu-dependent synaptic transmission and in dSPN. Conversely, others found that the D2R/NMDAR interaction mediates the inhibitory effect of DA on NMDAR-signaling in iSPN. However, the modulation and function of these heteromers in responses to cocaine are yet unknown.

By using Proximity Ligation Assay, we found that cocaine-induced locomotor sensitization was associated with the formation D1R/NMDAR heteromers in the Nucleus Accumbens (NAcc) and the Dorsal Striatum, while D2R/GluN2B heteromerization was restricted to the NAcc. We also detected DAR/NMDAR complexes from human-post mortem caudate-putamen samples and describe their modulation in subjects with a history of dependence to psychostimulants. To identify the roles of DAR/NMDAR in the different phases of cocaine-mediated molecular, morphological and behavioral responses *in vivo*, we designed a viral-based approach to disrupt DAR/NMDAR heteromers in a time-controlled manner owing to a doxycycline-dependent promoter. We found that the disruption of the D1R/NMDAR interaction in the NAc blocks cocaine-induced ERK activation and abrogates the development, but not the maintenance, of psychomotor sensitization, whereas the blockade of D2R/NMDAR interaction only interferes with the maintenance of psychomotor sensitization. By contrast, blockade of D1R/NMDAR or D2R/NMDAR heteromers prevents cocaine-induced conditioned place preference. This work identifies DAR/NMDAR heteromers as molecular targets with a therapeutic potential not only in addiction but also for the numerous psychiatric disorders associated with an imbalance of DA and Glu transmission.

**P1.032 A possible link between KCNQ2- and STXBP1-related encephalopathies: STXBP1 reduces the inhibitory impact of syntaxin-1A on M current**

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Syntaxin-1A (Syn-1A) is a target plasma membrane SNARE protein that associates with SNAP25, synaptobrevin and with syntaxin binding protein 1 (STXBP1, a.k.a. Munc18.1) to form a complex that is instrumental for transmitter release. Syn-1A also interacts with several ion channels and affects their properties. Notably, Syn-1A modulates the activity of Kv7 channels that mediates the voltage-gated potassium M current, which plays a major role in the control of neuronal excitability. In many cortical neurons, these channels are composed by the homomeric assembly of Kv7.2 subunit and by the heteromeric assembly of Kv7.2 and Kv7.3 subunits. Syn-1A binds on the C-terminal domain of Kv7.2 and Kv7.3 subunits and decreases channel open probability. *De novo* mutations in the KCNQ2 gene, which encodes for the Kv7.2 subunit, have been identified in early onset epileptic encephalopathies (EOEEs). Functional analysis of mutant channels suggests that these diseases are caused mainly by a reduction of M current. Along with KCNQ2, *de novo* mutations in the STXBP1 gene have been also been described in EOEE. The striking similarities in STXBP1 and KCNQ2-related disorders led us to investigate a possible biologic link between these conditions. We hypothesized that STXBP1 may reduce Syn-1A interaction with Kv7 channels, while mutant STXBP1-related encephalopathies may not. We tested this hypothesis in CHO cells using both electrophysiologic and biochemical approaches. We showed that Syn-1A decreased M currents mediated by Kv7.2 or Kv7.2/Kv7.3 channels. STXBP1 had no direct effects on M current but dampened the inhibition produced by Syn-1A by abrogating Syn-1A binding to Kv7 channels. The mutation p.W28\*, but not p.P480L of STXBP1 failed to rescue M current from Syn-1A inhibition. Biochemical analysis showed that unlike the mutation p.W28\*, the mutation p.P480L did not affect STXBP1 expression and reduced the interaction of Syn-1A with Kv7 channels. These data indicate that there is a functional link between STXBP1 and Kv7 channels via Syn-1A, which may be important for regulating M-channel activity and neuronal excitability. They suggest also that a defect in Kv7 channel activity could be one of the consequences of some STXBP1 mutations associated with EOEEs

**P1.033 Oxidative stress-induced disulfide dimerization of neuronal calcium sensor proteins**

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Neuronal calcium sensor (NCS) proteins are expressed in CNS and retinal neurons, where they are involved in regulation of cell growth, function and survival in response to intracellular calcium signals. Here, we report that NCSs are redox-sensitive proteins and their structure and function are affected by the oxidation. The majority of NCSs are capable of disulfide dimerization *in vitro* in the presence of physiological concentrations of an oxidant. Notably, the susceptibility to dimerization varies among these proteins, depending on the presence of calcium and magnesium. Furthermore, NCSs are capable of binding zinc, and their oxidation is enhanced in the presence of  $Zn^{2+}$ . Disulfide dimerization of NCS proteins requires their tertiary structure, which allows increased surface accessibility of redox-sensitive cysteine residues. Using macromolecular docking simulations and site-directed mutagenesis, it was found that dimer of each NCS is stabilized by a disulfide bond involving a distinct pair of cysteines and is characterized by unique overall structure, intermolecular interface and energetics. The dimerization alters NCS stability and functional properties, such as interaction with cellular membranes and recognition of binding partners, like scaffolding protein caveolin-1 and G-protein-coupled receptor kinases. Using animal and cellular models of oxidative stress, dimerization of certain NCS proteins was demonstrated to occur under physiological conditions. We propose that an increase in zinc concentration, characteristic of advanced oxidative stress, will result in NCS dimerization and, subsequently, aberrant function and aggregation, which could trigger neuronal apoptosis and neurodegeneration.

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**P1.034 Influence of the fungal anorexigenic toxin DON on the ER stress status in hypothalamus and liver**

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Deoxynivalenol (DON) is one of the most abundant mycotoxins found on contaminated cereals. DON, known as a ribotoxin, causes acute and chronic diseases in humans and animals with symptoms including anorexia, weight gain reduction and altered nutrition efficiency. DON alters feeding behavior by modifying satiation via interference with central neuronal structures (hypothalamus and brainstem). ER stress disturbances affect numerous cellular processes, hence participating in several pathological conditions including metabolism disorders such as obesity and type-2 diabetes. Here, we sought to determine whether ER stress response could underlie DON-induced anorexia. First, we examined ER stress within the hypothalamus in response to *per os* DON administration in mice. Unexpectedly, the mycotoxin caused no change in the ER stress status of this central structure. We undertook therefore to examine DON effect on liver because of its crucial role in body metabolism. We observed hepatic steatosis development and dysregulation of lipid metabolism following DON administration. At the molecular level, we found that DON:

- 1) triggered an ER stress response associated with hepatic dysfunction;
  - 2) altered neither the thiol-disulfide status nor the overall protein redox state as shown by examining the cell thiol-disulfide balance (total thiol content);
  - 3) promoted fatty liver with lipid droplet accumulation;
  - 4) inhibited expression of various genes involved in lipogenesis and cholesterolgenesis, suggesting that lipid accumulation did not result from local abnormal lipid synthesis.
- Altogether, our results suggest that DON causes a nonalcoholic fatty liver disease (NAFLD) characterized by hepatic fatty acid infiltration. Understanding the contribution of the unfolded protein response and the mechanisms that disrupt ER homeostasis in NAFLD in the broader context of chronic, metabolic diseases have become topics of intense investigation. Moreover, it is of note that we observed increased plasmatic free fatty acid- and triglyceride- levels following DON administration, raising the question whether DON is able to modulate adipose tissue metabolism and whether this increased circulating lipids level acts at the brain level to modulate feeding behavior.

P1.035

**Role of GABAergic synapses of oligodendrocyte progenitors in regulating axonal myelination and function of cortical parvalbumin interneurons**

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Oligodendrocyte precursor cells (OPCs) represent the only non-neuronal cells receiving *bona fide* synapses from neurons in the brain. In the somatosensory cortex, OPCs receive a transient and major synaptic input from GABAergic interneurons during the second postnatal week. After this period, both the expression of the synaptic  $\gamma 2$  subunit of GABA<sub>A</sub> receptors ( $\gamma 2$ -GABAARs) and GABAergic synapses are downregulated in these progenitors. However, despite several studies, the function of neuron-OPC synapses remains poorly understood. Challenging the main hypothesis in the field, we recently found that the inactivation of interneuron-OPC synapses does not affect oligodendroglia development or the general myelination pattern in the neocortex (Balia, Benamer, Angulo, 2017, *Glia*).

In the present study, we hypothesize that GABAergic neuron-OPC synapses play a major role in the construction of inhibitory circuits, by affecting specifically the myelination and function of PV interneurons. Two major reasons motivated this new hypothesis: 1) PV interneurons are highly connected to OPCs and 2) PV interneurons represent the only GABAergic interneuron subtype that is myelinated in cerebral cortex. To test our hypothesis, we performed immunohistochemical analysis, confocal 3D axon reconstructions and patch-clamp recordings in Control and transgenic mice where the  $\gamma 2$  subunit was deleted in OPCs ( $\gamma 2^{ff}$  mice). We found that the inactivation of  $\gamma 2$ -GABAAR-mediated synapses of OPCs modifies the distribution of myelin on the axon proximal part of cortical PV interneurons. Myelination begins significantly farther from the soma, leaving uncovered part of the axon initial segment (AIS) in  $\gamma 2^{ff}$  mice compared to Controls. In line with changes in the AIS, we also observed that fast-spiking PV interneurons from  $\gamma 2^{ff}$  mice have a decreased firing frequency. Finally, our data revealed that the functional inactivation of PV interneuron-OPC synapses induces an increase in the neuronal excitation-inhibition ratio by impairing unitary PV interneuron-glutamatergic cell connectivity. We concluded that, during cortical development, the inactivation of  $\gamma 2$ -mediated OPC synapses have profound consequences in the myelination of PV interneurons, affecting specific features of cortical inhibitory circuits.

**P1.036 Molecular and functional characterization of LIMK2-1, a hominidae-specific isoform of LIMK2 associated with intellectual disability**

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LIMK1 and LIMK2 are Ser/Thr kinases that play key roles in actin dynamics. They act through phosphorylation and inactivation of cofilin, an actin depolymerizing factor. Many studies have shown a role of LIM kinases in neurodevelopment, synaptic plasticity and neuronal death.

Different isoforms of LIMK2 are described in databanks : LIMK2a, LIMK2b and LIMK2-1. LIMK2a and LIMK2b are the most characterized. A few pieces of evidence suggest that LIMK2 isoforms might not have overlapping functions. Compared to the other LIMK2 isoforms, LIMK2-1 contains a supplementary C-terminal phosphatase 1 inhibitory domain (PP1i). We found out that this isoform was hominidae -specific and showed that it was expressed in human fetal brain and faintly in adult brain.

LIMK2-1 coding sequence was sequenced in 173 patients with sporadic non-syndromic intellectual disability (ID), and we observed an association of a rare missense variant in the PP1i domain (rs1511191437, p.S668P) with ID. Our results also suggest an implication of LIMK2-1 in neurite outgrowth and neurons arborization which appears to be affected by the p.S668P variation. Therefore our results suggest that LIMK2-1 plays a role in the developing brain, and that a rare variation of this isoform is a susceptibility factor in ID. Our molecular studies of LIMK2-1 allowed us to show that it does not phosphorylate cofilin, the canonical substrate of LIMKs, although it has kinase activity and promotes actin stress fiber formation. We showed that PP1i domain interacts with protein phosphatase 1 (PP1) and partially inhibits its phosphatase activity towards cofilin. Our data suggest that LIMK2-1 regulates actin cytoskeleton dynamics by preventing PP1-mediated cofilin dephosphorylation, rather than by directly phosphorylating cofilin as its two counterparts, LIMK2a and LIMK2b. This specificity may allow for tight regulation of the phospho-cofilin pool.

**P1.038 Neurobeachin and the kinesin KIF21B are critical for endocytic recycling of NMDA receptors and regulate social behavior**

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Autism spectrum disorders (ASDs) are associated with mutations affecting synaptic components, including GluN2B-NMDA receptors (NMDARs) and neurobeachin (NBEA). NBEA participates in biosynthetic pathways to regulate synapse receptor targeting, synaptic function, cognition, and social behavior. However, the role of NBEA-mediated transport in specific trafficking routes is unclear. Here, we highlight an additional function for NBEA in the local delivery and surface re-insertion of synaptic receptors in mouse neurons. NBEA dynamically interacts with Rab4-positive recycling endosomes, transiently enters spines in an activity-dependent manner, and regulates GluN2B-NMDAR recycling. Furthermore, we show that the microtubule growth inhibitor kinesin KIF21B constrains NBEA dynamics and is present in the NBEA-recycling endosome-NMDAR complex. Notably, *Kif21b* knockout decreases NMDAR surface expression and alters social behavior in mice, consistent with reported social deficits in *Nbea* mutants. The influence of NBEA-KIF21B interactions on GluN2B-NMDAR local recycling may be relevant to mechanisms underlying ASD etiology.

**P1.039 The dendritic  $\text{Ca}^{2+}$  and  $\text{K}^+$  currents associated with the climbing fibre synaptic potential in the cerebellar Purkinje neuron**

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In cerebellar Purkinje neuron (PN) dendrites, the climbing fibre (CF) input depolarises the membrane potential ( $V_m$ ) activating voltage-gated  $\text{Ca}^{2+}$  channels (VGCCs), voltage-gated  $\text{K}^+$  channels (VGKCs) and  $\text{Ca}^{2+}$  activated SK and BK  $\text{K}^+$  channels. The resulting  $V_m$  and  $\text{Ca}^{2+}$  transients play a fundamental role in dendritic integration and synaptic plasticity of parallel fibre synaptic potentials. We present a detailed investigation of the kinetics of dendritic  $\text{Ca}^{2+}$  and  $\text{K}^+$  channels activated by CF inputs, based on cutting-edge optical voltage and  $\text{Ca}^{2+}$  measurements and on a single-compartment NEURON model matching experimental data. We initially measured  $V_m$  and  $\text{Ca}^{2+}$  signals associated with CF inputs at different initial  $V_m$  and we studied the changes in the  $\text{Ca}^{2+}$  transients produced by the inhibition of individual channels. After that, we constructed a model that incorporates six ion channels to match experiments and extract the physiological kinetics of individual channels in parallel. We discovered that two different sets of channels are activated at different conditions. When the dendrite is hyperpolarised, the CF input mainly activates T-type VGCCs, SK channels and A-type VGKCs that limit the depolarisation below  $\sim 0$  mV. In contrast, when the dendrite is statically depolarised, T-type VGCCs and A-type VGKCs are inactivated and the CF input activates only P/Q-type VGCCs, high-voltage activated VGKCs and BK channels, producing  $\text{Ca}^{2+}$  spikes. Thus, potentially physiological regulation of A-type VGKCs, controlling the activation of the second set of channels, would play a pivotal role in signal integration at PN dendrites.

**P1.040 Vesicular treadmilling in axons defines how synapses adapt to high neuronal demand**

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Neurotransmission requires efficient axonal transport to deliver secretory cargoes and synaptic components in response to neuronal activity. In the standard model, synaptic materials are transported by vesicles that travel anterogradely from soma to synapses. However, a model with a continuous flow of anterograde vesicles fails to explain how synapses can efficiently and rapidly respond to variable phases of neuronal activity. This model would result in alternated phases of traffic jam and depletion, thus impairing the efficient and rapid delivery of materials to active synapses.

Here, using microfluidic devices and high-resolution videomicroscopy of photoconvertible cargoes, we identified a dynamic pool of axonal vesicles that circle back and forth along the axon shaft with surprisingly high regularity and homogeneity. These vesicles show extreme processivity (*i.e.* they do not randomly switch directions during transport) but specifically reverse direction when reaching axon extremities (antero-to-retro switch at the distal tip; retro-to-antero switch at the proximal segment). This directional switch is actin-dependent since the vast majority of reversals take place in actin-rich domains of axon extremities and is abolished when actin dynamics is inhibited. Moreover, using microfluidic devices connected to microelectrodes, we further found that neuronal activity regulates the dynamics of vesicular treadmilling by progressively capturing circulating vesicles at active synapses. This regulation therefore allows the rapid refill of active synapses to sustain the release capacity of the neuron during high demand.

Based on these findings, we propose a new model for axonal transport that we dubbed *vesicular treadmilling*, where secretory vesicles constantly circulate back and forth along axons until their selective capture at active synapses. This dynamic, bidirectional transport determines the release capacity of synapses in response to neuronal activity and defines how synapses adapt to high neuronal demand.

**P1.041 Role of the WNK-SPAK-OSR1 signaling pathway in neuronal chloride homeostasis and in epilepsy**

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The GABAergic and glycinergic neurotransmissions are the main inhibitory signaling pathways in the mature central nervous system (CNS). Their efficacy and polarity depends on the chloride intracellular concentration ( $[Cl]_i$ ). Two transporters are essential actors in  $[Cl]_i$  tuning: the K+-Cl- cotransporter KCC2 and the Na+-K+-Cl- cotransporter NKCC1, which are respectively responsible for the main neuronal efflux and influx of chloride ions in neurons. The developmental upregulation of KCC2 expression is responsible for the early postnatal shift in the depolarizing/excitatory versus hyperpolarizing/inhibitory polarity of GABAergic and glycinergic transmission in the CNS.

In several pathological contexts including epilepsy, an increase in  $[Cl]_i$  in hippocampal pyramidal neurons was observed coincidently with a depolarizing response to GABA. KCC2 expression is down-regulated after status epilepticus, conversely to NKCC1 which expression is increased. Moreover, down-regulation of NKCC1 activity was shown to reduce the severity of epilepsy. Thus regulating KCC2 and NKCC1 may constitute a realistic strategy in the treatment of epilepsy and other diseases in which inhibition is impaired.

The WNK-SPAK-OSR1 pathway phosphorylates KCC2 and NKCC1. This in turn inhibits KCC2 activity while increasing NKCC1 activity, resulting in homeostatic regulation of  $[Cl]_i$  under physiological conditions. Therefore, regulation of the WNK-SPAK-OSR1 pathway appears as a powerful mechanism to adjust neuronal Cl- homeostasis. In neurons KCC2 was shown to be regulated by both glutamatergic and inhibitory neurotransmissions, the latter through the WNK-SPAK-OSR1 signaling activation. However little is known about NKCC1 regulation by neuronal activity. My work aims at understanding the respective impact of KCC2 and NKCC1 regulation by the WNK-SPAK-OSR1 signaling pathway on  $[Cl]_i$  in normal conditions and in the epilepsy context. I combine *in vitro* approaches to study NKCC1 membrane dynamics and stability, as well as *in vivo* techniques to determine the impact of WNK-SPAK-OSR1 inhibition on ictogenesis.

**P1.042 Gene expression profiling and pathway analysis in brain-derived microvascular endothelial cells treated with TWEAK and TNF cytokines**

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**Background:** The TNF ligand family member TWEAK has pro-inflammatory effect in animal model of multiple sclerosis. We have previously shown *in an in vitro* model of the blood-brain barrier that both TWEAK and TNF exposure induce an inflammatory profile on human cerebral microvascular endothelial cells (HCMECs) by promoting secretion of cytokines (CCL-2, IL-8, IL-6) and modulating activation of metalloprotease such as MMP-9. The mechanisms through which TWEAK acts in endothelial cells have not been fully defined. In the present study, *in vitro* activity of TWEAK and TNF exposure on HCMECs was characterized through microarray gene expression profiling.

**Methods:** For stimulation assays, HCMECs were incubated with recombinant human TWEAK or recombinant human TNF for 3 h, 12 h or 24 h. We used whole human genome oligo microarrays (40,000 genes, Agilent Technologies) to compare TNF and TWEAK induced gene expression profiles in HCMECs cultures. Data were analyzed using Agilent Feature Extraction Software (Agilent Technologies). Pathway enrichment analyses was performed using Ingenuity Pathway Analysis (IPA) software.

**Results:** Gene expression profile analyses showed the activation of different signaling pathways in HCMECs treated with TWEAK or TNF. At 3 hour, 8% and 22 % of genes were specifically deregulated by TWEAK and TNF respectively, and 16% of genes were deregulated by both cytokines. At 12h, 13% and 21 % of genes were specifically deregulated by TWEAK and TNF respectively, and 27% of genes were deregulated by both cytokines. Finally, at 24h, 23% and 24 % of genes were specifically deregulated by TWEAK and TNF respectively, and 46% of genes were deregulated by both cytokines. Most significant altered canonical pathways were identified in both TWEAK or TNF-treated cells : actin cytoskeleton (lowest p-value), VEGF, RhoA, Integrin and IL-8 signaling. Interestingly, Leukocytes extravasation, Ephrin receptor was significantly up-regulated in TWEAK-treated cells and Death Receptor and Sirtuin signaling pathways were mostly up-regulated in TNF-treated cells.

**Conclusion:** Taken together, these data suggest that overall similar but also specific pathways are transcriptionally activated in a cytokine-dependent manner in HCMECs treated by TWEAK or TNF.

**P1.043 Role of Pyk2 in the nucleus accumbens D1 neurons in acute locomotor effects of cocaine**

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Proline-rich tyrosine kinase 2 (Pyk2) is a calcium-dependent, non-receptor protein-tyrosine kinase of the focal adhesion kinase (FAK) family. Pyk2 is enriched in forebrain neurons and may be associated with several pathologies including Huntington and Alzheimer diseases. Chronic exposure to cocaine increases Pyk2 levels in rat frontal cortex and monkey nucleus accumbens.

Yet, the role of Pyk2 in the striatum is largely unknown. We explored several striatal-associated behaviors including locomotor activity and rotarod training, acute and sensitized responses to cocaine and conditioned place preference (CPP) in Pyk2 knockout mice ( $\text{Pyk2}^{-/-}$ ), Pyk2-depleted mice in D1R-( $\text{Drd1Cre/Pyk2}^{fl/fl}$ ) or D2R-( $\text{A2ACre/Pyk2}^{fl/fl}$ ) expressing neurons, and in  $\text{Pyk2}^{fl/fl}$  mice injected with a Cre-expressing adeno-associated virus (AAV) in the dorsal or the ventral part of the striatum.

We found that Pyk2 phosphorylation is increased in the striatum of mice injected with cocaine. Acute locomotor response to cocaine was decreased in  $\text{Pyk2}^{-/-}$ , and in mice with a conditioned deletion of Pyk2 in D1 neurons or in the nucleus accumbens. Basal locomotor activity, motor coordination, cocaine sensitization and CPP were not altered. Mice lacking Pyk2 in D2 neurons or dorsal striatum displayed a normal phenotype. These results suggest a critical role of Pyk2 in the acute response to cocaine and that this role is compartmentalized to dopamine D1 receptor-expressing neurons in the ventral striatum.

**P1.044 Impact of membrane composition in polyunsaturated fatty acids on dopamine D2 receptor affinity and signaling**

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Alterations in the activity of the dopamine D2 receptor (D2R) has been implicated in the etiology of several psychiatric disorders such as schizophrenia, depression or bipolar disorders. D2R is a main target of most antipsychotics. The causes for such a central role of D2R in the etiology of psychiatric symptoms is largely unclear. A substantial body of evidence has suggested an alteration of brain lipids and in particular an implication of a deficiency in long-chain n-3 polyunsaturated fatty acids (PUFA) in the pathophysiology of these psychiatric disorders. We obtained recent *in vivo* data suggesting that membrane PUFA content affects the functionality and signaling properties of D2R. We hypothesized that membrane PUFAs play the role of allosteric modulators at D2R. Our project aims at unraveling the impact of membrane PUFAs on D2R pharmacological properties and conformation through biochemical and biophysical approaches in both PUFA enriched cells and membrane model systems of controlled lipid composition. To this aim, we have investigated the impact of membrane PUFAs on receptor/ligand affinity using fluorescence anisotropy and Plasmon Waveguide Resonance (PWR) and on the recruitment of signaling effectors at D2R by BRET approach. Overall the data indicate that membrane PUFA composition impacts on both agonist and antagonist affinity for D2R. Regarding the signaling cascades, data indicate an absence of influence of membrane PUFAs on cAMP production but an impact on β-Arrestin recruitment. The results could have a significant impact in the development of novel therapeutic strategies for psychiatric disorders in which D2R plays a key role.

**P1.045 KCC2 enhancers: targeting neuronal chloride transport in temporal lobe epilepsy**  
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In neurons, the cation chloride cotransporters KCC2 and NKCC1 maintain transmembrane chloride gradients and thereby regulate signaling by the chloride-permeant GABA<sub>A</sub> receptors. Many neurological and psychiatric disorders including epilepsy, neuropathic pain, schizophrenia and some forms of autism-spectrum disorders are associated with reduced KCC2 expression. This in turn may affect the efficacy or even the polarity of GABAergic transmission and so contribute to the emergence of pathological activities that underlie these disorders. Restoring neuronal chloride homeostasis therefore represents a promising therapeutic strategy. This may be achieved either by using NKCC1 antagonists or, on the contrary, by enhancing KCC2 function, for example by promoting its membrane stability. Various compounds derived from library screening were recently identified as potential KCC2 enhancers, both in cell lines and animal models of pathologies associated with KCC2 extinction. However, their mode of action in neurons remains unknown or controversial and their effect on epileptiform activities is poorly documented.

We have studied and compared the effect of three of these compounds - including CLP-257 and closantel - on primary cultures of hippocampal neurons and then tested their effect on the emergence of epileptiform activities in human epileptic tissue. We show these compounds do not act to increase the total expression or membrane stability of KCC2, as was expected, but instead promote its clustering and dephosphorylation at specific threonine residues in its carboxy-terminal domain. This effect is associated with enhanced function of the transporter, as detected in electrophysiological recordings. In addition, our preliminary data suggest that CLP-257 reduces the occurrence of interictal activities recorded *in vitro* in hippocampal tissue resected from temporal lobe epilepsy patients. In summary, our work demonstrates that several compounds can be used to potentiate the function of KCC2 in cortical neurons. CLP-257 or its orally active and more bioavailable prodrug CLP-290 may be of particular therapeutic interest and seems to prevent some pathological activities in human epileptic tissue.

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**P1.046 Effect chitinase 3-like protein 1 on oligodendrocyte precursor cells proliferation and differentiation *in vitro***

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**Background:** Multiple sclerosis (MS) is an autoimmune and neurodegenerative pathology characterised by demyelinated plaques in the CNS. Remyelination is an active repair process involving oligodendrocyte precursor cells (OPCs) proliferation and differentiation. It is positively correlated with slower progression of MS and a prolonged survival of MS patients. With time, tissue remodelling becomes less and less effective, leading to a glial scar and to neurodegeneration. Previously, we identified an increased Chitinase 3-like protein1 (CHI3L1) expression in cerebrospinal fluid (CSF) as a prognostic biomarker of MS. CHI3L1 is ubiquitous and involved in extracellular matrix remodelling. We observed an important expression of CHI3L1 by astrocytes in demyelinated plaques. However, the role of CHI3L1 in demyelination and remyelination is largely unknown. Here, we aim to analyse the influence of CHI3L1 on proliferation and differentiation of OPCs.

**Methods:** We exposed cortical primary cultures enriched in OPCs from P2 rat pups to human recombinant CHI3L1. We monitored OPCs differentiation at 6 and 14 days using OPCs maturation markers (NG2, O4). We explored CHI3L1 effect on OPCs proliferation by EDU labelling.

**Results:** CHI3L1 effect was maximal for 100 ng/mL. Proportion of GFAP positive cells (astrocytes) was less than 20%. Using NG2 and O4 labelling, we observed different proportions of positive OPCs in CHI3L1 and control conditions (70% and 60% respectively). Proportion of O4+ cells was similar in both conditions at 6 and 14 days while NG2+ cells were more numerous in CHI3L1 exposed OPCs at 6 days. There were no significant differences at 14 days. OPCs morphology was more packed and less ramified in CHI3L1 condition compared to control at 6 days.

**Discussion:** Here, we show CHI3L1 has an impact on OPCs differentiation *in vitro*. The effect seems transient, either accelerating differentiation or reducing proliferation. Next step will be to identify the CHI3L1 pathway(s) involved in OPCs at cell surface (receptor) and intracellularly. Moreover, we will investigate if cell shape modification by CHI3L1 influences OPCs migration, essential for efficient remyelination *in vivo*.

**P1.047 Direct and non-invasive probing of the polarity of perisomatic GABAergic transmission in the adult mouse hippocampus *in vivo***

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Numerous *in vitro* studies have reported high intracellular chloride levels, depolarizing and potentially excitatory actions of GABA in various pathological conditions such as epilepsy, autism spectrum disorders, or schizophrenia. It has therefore been recently proposed that drugs restoring low  $[Cl^-]_i$  may provide novel therapies for a wide range of brain disorders. However, the relevance of this hypothesis *in vivo* remains largely speculative because of the technical difficulty to evaluate the polarity of GABAergic transmission *in vivo*.

Combining non-invasive extracellular detection of unitary perisomatic inhibitory postsynaptic field-potentials (fIPSPs) with silicon probe recording of the firing activity of multiple individual neurons, we were able to probe the polarity of GABAergic transmission at the population and individual cell level in the hippocampal circuit *in vivo*. We now provide direct evidence for depolarizing actions of perisomatic GABAergic transmission and time-locked excitation of CA3 pyramidal neurons in acute and chronic mouse models of epilepsy. This approach will also prove useful to investigate alterations in the interplay between excitation and time-locked perisomatic inhibition in pathological conditions such as neurodegenerative and neurodevelopmental disorders.

**P1.048 Helping analgesia by targeting the serotonin 5-HT<sub>7</sub> receptor**

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The serotonin 5-HT<sub>7</sub>R receptor (5-HT<sub>7</sub>R) is the most recently cloned member of serotonin receptors family which comprises at least 15 subtypes. The 5-HT<sub>7</sub>R belongs to the superfamily of the G proteins coupled receptors (GPCRs). In the last decade, 5-HT<sub>7</sub> receptor has become a promising target for the treatment of neuropsychiatric disorders, sleep and circadian rhythm disorders and of neuropathic pain. Antagonists of the 5-HT<sub>7</sub>R showed beneficial effects for the treatment of cognitive disorders or mental retardations. On the other hand, 5-HT<sub>7</sub>R agonists showed potential therapeutic interest for the treatment of pain, however, they are less specific compared to antagonists and their bioavailability is insufficient. Considering the role of 5-HT<sub>7</sub>R in these various disorders, development of new 5-HT<sub>7</sub>R ligands may offer interesting therapeutic issue.

In this study, we characterized the pharmacological profile of new 5-HT<sub>7</sub>R ligands derived from pharmacomodulation studies. For that purpose, we studied their capacity to activate specific signaling pathways in vitro and defined their agonist, inverse agonist or antagonist activity by measurement of cAMP levels using BRET or TR-FRET methods in HEK cells stably expressing the 5-HT<sub>7</sub>R. We also investigated their ability to activate others 5-HT<sub>7</sub>R signaling pathways (ERK activation, calcium mobilization, recruitment of G proteins and Barrestins). Our results demonstrate that some molecules can engage different transducer-effector systems compared to classical agonists.

Considering the 5-HT<sub>7</sub> receptor implication in pain, we also investigated the anti-nociceptive properties of our compound in three different pain behavioral tests. We showed that systemic or local administrations of our 5-HT<sub>7</sub> ligand, decreased pain behavior in mouse. This anti-nociceptive effect is fully blocked by administration of SB269-970, a specific 5-HT<sub>7</sub> antagonist. Therefore, the in vivo results revealed that our new 5-HT<sub>7</sub> ligand clearly decreases the hyperalgesia and pain sensation in response to thermal, mechanical and inflammatory stimulation.

**P1.049 Identification of the underlying pathogenic pathways in a mouse model in Hereditary Spastic Paraplegia SPG11 through transcriptional study**

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Hereditary spastic paraplegias are rare inherited neurological diseases characterized by a large heterogeneity in both clinical and genetic aspects. Mutations in SPG11 account for the most common form of autosomal recessive cases. Patients present mainly with spasticity associated with neuropathy and mental impairment. This gene encodes the protein spatacsin, with still unknown function.

Nevertheless, spatacsin is known to be involved in lysosomal recycling, and interacts with the AP-5 complex involved in membrane sorting.

The Spg11 knockout mouse recapitulates the full range of symptoms associated with SPG11 mutations observed in patients. To understand the molecular changes in the brain of those mice (KO versus WT), we sampled mRNA from cortex, cerebellum and hippocampus at 3 different ages (6 weeks, 4 and 8 months) corresponding respectively to the onset of symptoms, the occurrence of the full clinical features and the onset of neurodegeneration. RNAseq was performed using the NextSeq500 sequencer.

As expected, SPG11 mRNA levels were decreased. Then, we also found a dozen of deregulated genes involved in the lysosomal pathway, according to the role of spatacsin in this cellular function.

Although spatacsin interacts with AP-5 complex members, we found none of them deregulated at the mRNA level, which does not exclude a post-translational regulation of those partners.

More interestingly, we found that the most deregulated genes were involved in lipid metabolism, supporting recent studies in SPG11 in which lipidic accumulations have been observed.

Further analyses are ongoing to identify new interesting targets and decipher the mechanisms involved in this pathology.

**P1.050 The role of monocarboxylate transporter-1 on cognitive deficits development during non-alcoholic fatty liver disease**

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Non-alcoholic fatty liver disease (NAFLD) is a major complication of obesity. Certain observations regarding NAFLD induced neuropsychiatric and neurochemical alterations have been reported but mechanisms are unknown. In this context, monocarboxylate transporter-1 (MCT1) haploinsufficient mice, which resist high fat diet (HFD) induced hepatic steatosis represent an interesting model. Using a mouse model of NAFLD (HFD+high fructose/high glucose in water [HF/HG]) we investigated the development of cognitive deficits and state of cerebral oxygenation and cerebrovascular reactivity.

Behavioural tests (open field/novel object recognition/forced swimming test [FST]) were performed in mice fed control diet (NC; WT+NC, MCT1<sup>+-</sup>+NC) or HFD HF/HG (WT+HFD HF/HG, MCT1<sup>+-</sup>+HFD HF/HG) for 16 weeks. Baseline  $PO_2$  (in somatosensory cortex) and in response to systemic hypercapnia (10%  $CO_2$ ) was monitored under anaesthesia by a fluorescence method. Microelectrode biosensors were used for measurements of lactate release by cortical slices. EchoMRI was performed to assess lean/fat mass.

Increased fat mass (not lean mass) was observed in WT and MCT1<sup>+-</sup> mice (50% less) on HFD HF/HG compared to NC controls. Liver mass was only significantly higher in WT+HFD HF/HG mice compared to NC controls. Behavioural tests did not reveal any significant differences between groups except for FST, which indicated a depression-related behaviour in the WT+HFD HF/HG group compared to their controls. This was not observed with MCT1<sup>+-</sup>+HFD HF/HG mice. WT+HFD HF/HG mice had a lower cerebral  $PO_2$  baseline and  $PO_2$  response induced by systemic hypercapnia compared to NC controls (although significance was not reached), while the MCT1<sup>+-</sup> groups remained unchanged. Tonic lactate release was unaltered between all groups although the MCT1<sup>+-</sup>+HFD HF/HG group indicated a trend of decreased lactate tone.

Our results suggest that NAFLD is associated with a depression-related behaviour and a trend of decreased cerebral  $PO_2$  baseline and cerebrovascular reactivity. MCT1 haploinsufficient mice were resistant to the reported phenotypes, suggesting a link between liver metabolism and neuropathophysiological alterations in NAFLD.

**P1.051 Pre-clinical evaluation of checkpoint inhibitor immunotherapy in GBM implementing ultrasound Mediated blood-brain barrier opening (UMBO)**

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Outcomes for glioblastoma, the most aggressive primary cancer of the brain, remain dismal. Despite surgical resection and adjuvant chemoradiation, the median overall survival remains poor, below 24 months after initial diagnosis. Because of the dismal prognosis, attention has shifted to alternative adjuvant treatment modalities.

The blood brain barrier (BBB) in the setting of brain tumors is a major limitation for the penetration of these large therapeutic agents within the brain and the tumor for therapeutic activity. Ultrasound-induced BBB opening (UMBO) has been shown to increase the penetration of multiple chemotherapeutic agents within the brain among animals. However, anti-tumor effects of larger therapeutic agents has been poorly investigated.

Inhibition of immune checkpoints, including cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and its ligand PD-L1, has demonstrated exciting remissions across solid malignancies however, the effect of ICI in glioblastoma is still under investigations.

We therefore are going to evaluate the antitumor efficacy of murine antibodies targeting a immune checkpoint proteins, including CTLA-4, PD-1 and PD-L1 when administered as single-agent therapy and in combination with UMBO against an orthotopic, immunocompetent murine glioblastoma models. Mice will be treated with ultrasound twice a week over the course of a month. Tumor growth and survival will be measured and compared to control mice receiving either the immunotherapy alone or UMBO.

In this poster, I will be presenting the main results obtained to determine the blood brain barrier opening in healthy immune competent mice to validate the efficacy and the reliability of the method in our setup.

**P1.052 Preliminary study of the prevalence of the G2019S mutation in the Leucine-Rich Repeat Kinase-2 gene in patients with parkinson's disease in the South-West of Morocco**

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Parkinson's disease (PD) is a chronic age-dependent neurodegenerative disorder. The prevalence of the disease is estimated to 1% in individuals over 60 years old, increasing to 4% in individuals over 85 years. The etiology of PD is still not fully understood. However, it is strongly suggested that this pathology is caused by the combination of the genetic predisposition and the exposition to some recognized risk factors in the environment. Recent studies have identified more than 32 loci that were potentially associated with the progression of the PD; among them, a specific mutation in the position G2019S of the *Leucine-rich repeat kinase-2* gene (LRRK-2).

The aim of our study is to investigate the prevalence of the G2019S mutation of the LRRK-2 gene in patients diagnosed with the PD. The patients were recruited in private and public neurology clinics in Agadir. All the patients participating in this study gave their written consent, according to the recommendation of the Ethics Committees of Faculty of Medicine and Pharmacy of Marrakech.

The genomic DNA was extracted from peripheral blood mononuclear cells, isolated from fresh blood samples of both patients and healthy controls. The DNA was amplified by PCR using specific primers, then the presence of G2019S polymorphism was investigated by RLFP.

Our results showed a high frequency of the G2019S polymorphism in patients with PD compared to the healthy controls. This result strongly suggests an association between the presence of the G2019S mutation and the development of the PD in patients from the south-west of Morocco. Further investigations and statistical analysis, in a larger cohort of patients and healthy controls, are under way to confirm this finding.

**Keywords:** Parkinson's disease; *Leucine-Rich Repeat Kinase-2*; G2019S mutation; Polymorphism; south-west Morocco.

**P1.053 Epigenetic control of brain wiring: role of axonal miRNAs in fetal alcohol spectrum disorders**

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Prenatal exposure to environmental factors, such as maternal nutrition, drug use or air pollutants, influences fetal brain development resulting in neurological diseases. Converging data suggest that environmental factors act through epigenetic mechanisms, including the deregulation of microRNAs. Recently, subsets of microRNAs specifically located in the axon have been identified and are thought to regulate brain wiring. Our research aims to determine whether axonal microRNAs are involved in the pathological rewiring of brain circuits induced by *in utero* exposure to environmental agents. To answer this question, we have developed a new mouse model of Fetal Alcohol Spectrum Disorders (FASD), in which embryos are exposed to moderate doses of alcohol during the stage when the major axon tracts develop. Mapping the connectivity of the entire brain using 3D imaging of cleared brains has revealed that prenatal exposure to alcohol causes axonal guidance anomalies that affect different tracts such as the corpus callosum and striatonigral projections. A screening of microRNAs deregulated by prenatal alcohol exposure allowed us to identify candidate microRNAs present *in vivo* in growing callosal axons. We are currently testing how the deregulation of these candidates could be responsible for alcohol-induced abnormalities, via functional knockdown approaches by *in utero* electroporation of microRNA-sponges. The results of this study will provide new insights into the mechanisms by which epigenetic changes may be responsible for the cognitive and behavioural abnormalities associated with FASD.

**P1.054 Role of *Tshz3* in the development and function of corticostriatal connections and its involvement in ADS-like behavior**

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*Tshz3*, which encodes for a Zinc-finger transcription factor, has been recently identified as a novel effector in neocortex development. *Tshz3-null* (*Tshz3<sup>lacZ/lacZ</sup>*) mice show defects in layer-specific markers of cortical projection neurons (CPNs), whose human orthologues are strongly associated with Autism Spectrum Disorder (ASD). Moreover, *Tshz3<sup>lacZ/+</sup>* mice heterozygous for *Tshz3* exhibit ASD-like behavioral deficits (as impairment in social communication and repetitive behaviors) and functional changes at CPNs synapses which are established after birth. While the development of the glutamatergic CPNs has been extensively studied, little is known about the link between ASD and defects in CPNs synapses formation and/or function at postnatal stages. Interestingly, preliminary data suggest that ADS-related behavioral abnormalities involve defects in distinct component of the corticostriatal circuits. Indeed, embryonic conditional removal of *Tshz3* from CPNs or striatal cholinergic interneurons leads respectively in deficit in social interactions or repetitive behavior suggesting that these both neural populations contribute to the repertoire of ASD-related behavioral abnormalities linked to *Tshz3* deficiency. Moreover, removing *Tshz3* from glutamatergic CPNs after the birth results in synapse change at the corticostriatal circuitry and in ASD-like behavior as reported in *Tshz3<sup>lacZ/+</sup>* mice, whether: impairment in social communication and repetitive behaviors. These results reveal a dual role of *Tshz3*, in development and maturation of the brain circuits implicated in ASD from embryonic to postnatal stages, involving different neural populations. Investigating the reversibility of *Tshz3*-associated dysfunctions in *Tshz3* heterozygous mice by restoring the postnatal expression of *Tshz3* in specific neural populations and identifying TSHZ3 direct target genes that are required for proper formation and function of brain circuits will uncover the postnatal function of *Tshz3* in corticostriatal circuit formation and maturation related with ASD dysfunctions. To address this, we use a combination of genetics, behavioral tests, imaging, single cell RNA-sequencing and ChIP sequencing experiments

**P1.055 Human induced pluripotent stem cell-based Alzheimer's disease modeling reveals APOE4 as a modulator of inflammation**

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Neuroinflammatory changes such as astrocytosis are among the first pathological marks within the brains of Alzheimer's disease (AD) patients, even before the onset of the formation of A $\beta$  deposits. However, whether neuroinflammation can act as a driver event in AD pathogeny remains an unanswered question.

In this study we identified APOE4, the most relevant genetic risk factor in AD, as a modulator on inflammation in human induced pluripotent stem cells and brain derivatives, especially astrocytes. Our observations pinpoint APOE4 as a genetic polymorphism that affects inflammation in a cell-specific manner, able to trigger a pro-inflammatory state in basal condition or to exacerbate inflammation in response to stimuli. Leveraging on CRISPR-Cas9 genome editing strategies, we shed light on APOE4-specific signatures in the activation of signaling molecules involved in inflammatory processes, comparatively to those cells carrying an APOE3 genotype.

Our results indicate that the action of APOE4 on inflammation is independent of the AD status of the patients/donors.

This supports that APOE4-driven inflammation may be one of the triggering events of AD pathogeny in those patients carrying the APOE4 genetic risk factor. Consequently, targeting APOE4-mediated inflammation could emerge as a new preventive strategy in patients at risk for developing late onset AD.

P1.056

**Sucrose bingeing alters reward processing: role of mu opioid receptors**

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Binge eating disorder (BED) is defined by excessive food intake within a short period of time, that is not driven by any metabolic need. These episodes of compulsive eating are usually directed towards highly palatable food, high in fat and sugar. We argue that hedonic effects of these foods can override homeostatic control of food intake, thereby increasing the risk of developing metabolic and psychiatric disorders. Furthermore, there is growing evidence for similarities between BED and substance use disorders (SUD) at the symptomatic and the neurological levels.

To investigate the behavioral and molecular consequences of binge eating, we established a mouse model of BED using daytime limited access to sucrose solution in food restricted mice over 14 days. Animals with sucrose and food restriction exhibited bingeing behavior, defined as increased intake of sucrose during the first hour of access. Given that BED patients, like individuals with SUD, show alterations in opioid system function, we examined the role of the mu opioid receptor (MOP) in binge eating by examining sucrose intake during limited access sessions in MOP knock-out mice. These animals showed the same pattern of sucrose intake, characterized by escalation across the training, although the overall effect was reduced compared to the wild type mice. These results help to elucidate the underlying biological mechanisms involved in BED.

**P1.057 Molecular mechanisms underlying altered epigenetic regulation in Huntington's disease: role of SRF**

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Huntington disease (HD) is a progressive neurodegenerative disease, caused by an expanded CAG trinucleotide repeat in the *HTT* gene, which leads to the production of mutated HTT protein with toxic polyglutamine expansion. In HD, the striatum is primarily affected, resulting in motor, cognitive and psychiatric symptoms. Transcriptional dysregulation in HD is a key pathological mechanism. However, the underlying mechanism remains elusive. Using ChIPseq and RNAseq, we showed that genes regulating neuronal identity and function are selectively down-regulated in HD mouse striatum, which correlated with decreased H3K27 acetylation and reduced enhancer transcription (eRNAs) of associated enhancers. Regions showing reduced eRNAs were also enriched in binding motif for transcription factor SRF. SRF is a key factor regulating neuronal activity as well as learning and memory, suggesting SRF might contribute to cognitive deficits in HD through altered regulation of neuronal enhancers. Our RNAseq data show that *Srf* transcription is early decreased in the striatum of HD mice, including R6/1 transgenic mice and Q140 knockin mice. Moreover, we show that induction of *Srf* mRNA during striatum-dependent learning and memory task is impaired in the striatum of HD mice, correlating with impaired learning and memory. Western-blotting analyses further show that SRF protein level is impaired in HD mouse striatum, both in basal condition and during memory formation. The immediate early gene *Egr1*, a known target of SRF is also decreased at transcriptional and protein levels in the striatum of HD mice. To identify SRF target genes in the striatum, we have started to perform SRF ChIPseq experiments. SRF target genes include known targets such as *Fos*, *Egr1* and *Actb*. Furthermore, our RNAseq data show that SRF target genes are globally down-regulated in the striatum of R6/1 mice, particularly when mice are subject to cognitive task. Together, these data show that SRF regulation is early impaired in HD striatum, supporting a role in cognitive deficits.

P1.058

**Gene therapy for spinocerebellar ataxia 7: restoring cholesterol metabolism**

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Brain cholesterol is almost exclusively synthesized in situ and defects in this metabolism may contribute to neurodegenerative disease such as Parkinson's, Alzheimer's (AD) and Huntington's (HD). Previous data in rodent and human patients have demonstrated the impairment in AD and HD of key proteins involved in brain cholesterol metabolism. Like HD, 6 neurodegenerative Spinocerebellar Ataxias (SCAs) diseases are caused by the expansion of a translated CAG repeat leading to abnormally long polyglutamine (polyQ) tracts in the respective proteins. SCA7 is one of those SCAs. It is characterized by cerebellar ataxia with retinal degeneration and pigmentary macular dystrophy, and caused by a pathological repeat of 34 to 460 polyQ in the ATXN7 protein. Currently there is no curative treatment for SCA7. The aim of our work is to evaluate the role of brain cholesterol metabolism dysfunction in SCA7 disease and demonstrate if gene therapy targeting key proteins of brain cholesterol metabolism can correct this disease in the ATXN7 140Q knock-in mouse model.

**P1.059 The pro-amyloidogenic effects of membrane-type-matrix metalloproteinase involve MMP-2 and BACE-1 activities, and the modulation of APP trafficking**

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**Objectives:** We previously demonstrated that membrane-type 1 matrix metalloproteinase (MT1-MMP) was upregulated in the hippocampus of the 5xFAD transgenic mouse model of Alzheimer's disease (AD), and that the proteinase increased the levels of beta amyloid peptide (Abeta) and its APP C-terminal fragment C99 in a heterologous cell system. We know want to gain insight into how MT1 affects APP metabolism and Abeta production.

**Methods:** We used HEK293 cells stably expressing the APP Swedish mutation (HEKswe), and transient transfections using plasmids encoding active and inactive MT1-MMP and TIMPs. The proteolytic activity of BACE-1, gamma-secretase and MMPs was modulated with their respective inhibitors C3, DAPT and RxP03.

**Results:** We demonstrate here that MT1-MMP interacts with APP and promotes amyloidogenesis in a proteolytic-dependent manner in HEKswe. MT1-MMP-mediated processing of APP releases a soluble APP fragment (sAPP95), which requires the activation of endogenous MMP-2, but is independent of BACE-1 or alpha-secretase activities. In contrast, MT1-MMP-mediated increase of Abeta levels involves BACE-1 activity and is inhibited by TIMP-2, a natural inhibitor of both MT1-MMP and MMP-2. Interestingly, near abolishment of basal Abeta production upon BACE-1 inhibition can be rescued by MT1-MMP, suggesting that the latter can mimic beta-secretase-like activity. Moreover, MT1-MMP promotes APP/Abeta localization to endosomes, where Abeta production mainly occurs.

**Conclusions:** Our data unveil new mechanistic insights to support the pro-amyloidogenic role of MT1-MMP based on APP processing and trafficking, and reinforces the idea that this proteinase may become a new potential therapeutic target in AD.

**Keywords:** Beta amyloid peptide, amyloid precursor protein, Alzheimer's disease, secretase, endosome.

**P1.060 Conditional inactivation of the translation initiation factor *eif2b5* gene in oligodendrocytes induced a delayed acute neurological distress**

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Mutations in the ubiquitous eukaryotic translation initiation factor 2B (*eIF2B*), which is involved in regulating global protein synthesis particularly in stress conditions induced a recessive form of vacuolating leucodystrophy named childhood ataxia with central nervous system hypomyelination (CACH) or vanishing white matter disorder (VWM). The specific involvement of the white matter could result from the unique regulation of *eIF2B* and/or the increased stress vulnerability of specific brain cell types. Abnormalities of glial cells such as proliferation of immature oligodendrocytes contrasting with paucity of astrocytes were seen. In order to investigate the role of *eif2b* in different brain cell populations, we developed an inducible knock out (cKO) mouse model for *eif2b* using CreERT2 system. The gene conditional deletion was specifically induced in oligodendrocytes and their precursor cells by the insertion of CreERT2 system under Plp1 promoter in *eif2b5<sup>flox/flox</sup>* mouse model. In these mice, the temporal induction is obtained with 5 days injection of tamoxifen in 2-month-old female mice. An acute neurological deterioration with progressive lower limb paralysis leading to death in 1 week is observed at 8 weeks (W8) post induction (PI) of depletion. Behavioral analysis showed motor coordination and locomotor activity deficiencies in addition to loss of muscular strength only at W8 PI. Immunohistochemical analysis at W8 PI of brains showed a significant decrease in mature oligodendrocytes' number with myelin loss in corpus callosum area (for myelin) in contrast with an increase in NG2 expression in Dentate Gyrus area and significant increase in GFAP and Nestin expression levels. Significant increase in microglia number in addition to significant decrease in neurons' number were also observed. These results show that inhibition of *eif2b* expression in radial glial cells or oligodendrocyte cell lineage in the adult female mouse brain leads to a delayed acute neurological distress as observed in CACH/VWM patients. RNAseq data from oligodendrocytes isolated from 10 days (D10) and W8 PI brains are being analyzed in order to better understand the pathways and mechanisms.

**P1.061 Early events in cytomegalovirus infection of the developing rat brain: a pathophysiological role for viral chemokine r129?**

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Congenital cytomegalovirus (CMV) infections of the fetal brain represent one leading cause of human neurodevelopmental disorders (0.5% of all live births in Western Europe).

Despite their severity and high prevalence, the pathophysiological mechanisms remain elusive and no effective preventive or curative therapies are available. Insights into the early events following CMV infection of the developing brain are particularly needed. In the recent years, studies in rodent models have suggested the involvement of neuroimmune alterations. In a rat model of CMV infection of the developing brain *in utero*, we recently detected prominent infection of brain immune cells and early neuroimmune defects at the cellular (alteration of microglia, infiltration by peripheral cells) and molecular (overexpression of chemokines) levels (ref.1). Severe postnatal phenotypes reminiscent of the human disease (e.g. epileptic seizures, altered sensorimotor development) were observed in the first postnatal weeks. At the cellular level, we already showed that fetal microglia might play pivotal role in the pathophysiology (ref.2). At the molecular level, we now intend to investigate the possible pathophysiological role of the r129 chemokine, which is encoded by the rat CMV (RCMV) genome and that showed early RNA expression in RCMV-infected rat fetal brains. Co-infection experiments of the rat developing brain *in utero* with wild-type (wt) RCMV and with RCMV encoding a dominant-negative r129 isoform dramatically rescued the severe postnatal phenotypes caused by wt RCMV alone. Starting from these promising data, more experiments are now needed in order to decipher the pathophysiological role of r129 during CMV infection of the developing brain, notably with respect to the postnatal emergence of neurological and other severe outcomes.

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**P1.062 Role of the BLA-ACC pathway in major depressive disorder**

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Major Depressive Disorder (MDD) is a chronic and debilitating disease with poor treatment outcomes. Although significant achievements have been yielded in the field, there is still a need for identifying mechanisms underlying major depressive disorders. Compelling evidence from animal models and human studies suggest a crucial role of the anterior cingulate cortex (ACC) and the anterior part of the basolateral amygdaloid nucleus (BLA) in the development of MDD. Indeed, lesion or inhibition using deep brain stimulation of the ACC in mice and human respectively alleviate depressive symptoms. Regarding the BLA, imaging and anatomical studies revealed alterations in volume and cell numbers in MDD. In addition, our track tracing analyses showed that there is a strong reciprocal connection between the ACC and the BLA. To elucidate the role of the connection between the BLA and the ACC in depression, we studied the impact of the manipulation of this pathway using optogenetic approach in mice. Our results suggest that chronic activation of the BLA-ACC pathway is sufficient to induce depressive but not anxiety-like behaviors in naive animals and blocking this pathway alleviates the chronic pain induced depressive-like behavior. Moreover, the activation of the BLA-ACC pathway alters the functional connectivity of several networks, evaluated by using resting state fMRI. Altogether, these results highlight the importance of the BLA-ACC pathway in depression.

**P1.063 Facilitating glutamate mGlu4 receptor activity relieves autistic-like deficits in *Fmr1* knockout mice**

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Metabotropic glutamate receptor 4 (mGlu4) is a member of the metabotropic glutamate receptor family (mGluRs), consisting in 8 G-protein-coupled receptors (GPCRs) activated by glutamate. mGluRs modulate many physiological functions of the brain and, as such, have received considerable attention as therapeutic targets for CNS disorders. Among mGluRs, mGlu4 receptor is an emerging target for the treatment of Parkinson's disease, neuropathic pain, anxiety, obsessive-compulsive disorder, depression, psychosis and, more recently, autism. We indeed have shown that mice lacking the mu opioid receptor (*Oprm1<sup>-/-</sup>*), a murine model of autism, display decreased levels of *Grm4* transcripts (coding for mGlu4) in the striatum. Remarkably, chronic facilitation of mGlu4 signaling using a positive allosteric modulator (PAM) of mGlu4, VU01550141, completely relieves autistic-like symptoms in these animals (Becker et al. 2014). Here we aimed at testing whether this treatment would also demonstrate beneficial effects in the *Fmr1* knockout mouse model of Fragile X syndrome. First, we detected in these animals, similarly as in *Oprm1* mutants, a down-regulation of *Grm4* expression in the striatum. Then we evidenced that acute and chronic VU0155041 administration in *Fmr1* null mice alleviated partially (acute) or completely (chronic) autistic-like symptoms, notably deficient sociability. Interestingly, mGlu4 PAM treatment demonstrated more promising therapeutic effects than chronic administration of a negative allosteric modulator of mGlu5 receptors, GRN-529. Finally, we tested the effects of two more mGlu4 compounds in *Fmr1* knockout mice, the mGlu4 PAM ADX88178 and the orthosteric mGlu4/mGlu7 agonist LSP4-2022, to assess whether different pharmacological profiles of mGlu4 compounds may differentially influence *Fmr1* knockout phenotype. Together, our results further demonstrate the therapeutic potential of mGlu4 receptors as a target to treat autism or other pathologies affecting sociability.

**P1.064 Major depression: metabolomic signature of treatment response and of remission**  
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According to the World Health Organization, major depression (MD) has already become the second most prevalent cause of illness-induced disability, which makes this disorder one of the main contributors of the Global Burden of Disease. It is generally treated with chronic antidepressants (ADs), which consist of drugs increasing monoaminergic neurotransmission such as selective serotonin reuptake inhibitors (SSRIs). However, nearly 65% of the patients do not respond to this first-line therapy, and it is established that 30-50% of patients are resistant to AD compounds, which means they do not show remission after treatment with several ADs: this condition is conventionally referred to as treatment resistant depression (TRD). Currently, no pre-treatment biomarkers enable to predict TRD. Further on, mechanisms underlying remission are totally unknown. Using a mouse model of depression, the unpredictable mild stress, our objectives were: a) to describe a metabolomic signature predicting resistance to pharmacotherapy, b) to describe the metabolomic signature of remission after pharmacotherapy. Analyses were done both in the blood and in brain regions such as hippocampus, amygdala, habenula, nucleus accumbens, anterior cingulate cortex and prelimbic cortex. Result show that in the blood, several pre-treatment metabolites predicted non response to treatment, including Galactidol, lumichrome, oleic acid, glyceric acid, L-Homoserine, L-Pipecolic acid. In the blood, there was no overlap with the markers of remission which included L-carnitine, adenosine monophosphate, theophylline, homovanillic acid. In the brain, the two groups were distinct mainly concerning metabolites of the purine, the taurine and the hypotaurine. Further on, 54% of the molecules were region specific and only two metabolites were different in all the 4 brain regions: adenosine monophosphate and xanthine. In conclusion, the metabolomic analysis provided a comprehensive view of the pathways involved and show that the mechanisms involved in treatment response are different from the ones underlying remission.

P1.065

**Repeated inhalation of aerosols containing titanium dioxide nanoparticles reveals potential neurotoxicity in mouse**

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Nanoscaled titanium dioxide ( $TiO_2$ ) is one of the most used engineered nanomaterials in the building industry. The global aim of our project is to determine whether chronic exposure to sanding dusts containing  $TiO_2$  nanoparticles (NPs) has a neurotoxic effect. Our hypothesis is that nanomaterials inhalation may be accompanied by NPs translocation to the brain that could have an impact on the brain function.

Airborne particles released during abrasion of paints additived with  $TiO_2$  NPs were used for *in vivo* studies to evaluate realistically their potential neurotoxicity in mice, after repeated inhalation, that mimics painters' exposure. Emited aerosol was coupled to an exposure chamber containing groups of 36 C57Bl6 mice for 1h30/day, 5 days/week, during 8 weeks. Mice were either exposed to  $TiO_2$  NPs only or to (lab or marketed) paints with or without  $TiO_2$  NPs. The neurologic effects were investigated using motor performance parameters (coordination and balance), measured on a rotarod, once a week, for 8 weeks, at 20 rotations per minute (rpm) or using an accelerating program from 4 to 40 rpm. A linear mixed model was fitted in each exposed group and explained the trend of the average time spent on the rotarod during the 8 weeks. A subgroup of mice (N=6) was also imaged with multi-parametric MRI (7T), at baseline and after 2, 4 and 8 weeks, notably to evaluate the impact of exposure on longitudinal changes in diffusion tensor imaging metrics. Brains collected at week 1, 2, 3, 4 and 8 in order to study the time dependent effect on glial (GFAP) and microglial (Iba1) expression using immunohistochemistry were blindly scored. At 8 weeks, the amount of titanium (Ti) in the brain (N=6) was also measured using ICP-MS.

The results indicated that exposure to emitted aerosols from  $TiO_2$  nano-additived paint, could possibly impact the brain: locomotor abilities in mice chronically exposed are impaired; the first results of ongoing histopathological studies indicate an overall increase in microglial activation at week 4 and 8, in coherence with a trend towards an axial diffusivity increase at week 4 in trigeminal nerves, olfactory bulbs and cerebellum, which remained steady at week 8. In line with this, Ti content is also significantly higher in the brains of this group.

**P1.066 Short-term memory deficits and CA3 hippocampal damage in a murine model of lupus**

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**Background:** In some autoimmune diseases, the central nervous system can be affected as a result of systemic inflammation. Along with inducing aberrant brain-resident immune cell activation, systemic inflammation may lead to a leakage of the blood-brain barrier, and production of antibodies cross-reacting with brain antigens. This is exemplified in systemic lupus erythematosus (SLE) whose neuropsychiatric form (NPSLE) is extensively studied in the lupus-prone murine model MRL/lpr mice. The aim of our study was to characterize the behavioral outcomes of MRL/lpr mice, to link them to cerebral and autoimmune abnormalities, and to evaluate the effects of the therapeutic phosphopeptide P140 developed in our team.

**Methods:** Y- and T-maze alternation were used to assess short-term memory in MRL/lpr and MRL+/+ mice treated or not with P140. Brains were collected and used for flow cytometry to evaluate cellular infiltration and histology to visualize integrity.

**Results:** Compared to MRL+/+ littermates, MRL/lpr mice display higher proteinuria ( $P \leq 0.05$ ) whose development is slowed down by P140 treatment ( $P \leq 0.05$ ), reduced brain weight ( $P \leq 0.01$ ), and cerebral infiltrates by immune cells ( $P \leq 0.001$ ). They are significantly impaired in the Y-maze and the T-maze ( $P \leq 0.05$  and  $P \leq 0.01$ , respectively). The latter deficit is totally compensated by P140 administration ( $P \leq 0.001$ ). Congruently, Nissl staining showed neuronal loss in the CA3 hippocampal region of diseased MRL/lpr mice.

**Conclusion:** In addition to confirming that MRL/lpr mice are affected at the periphery, as evidenced by higher proteinuria levels, and centrally, as attested by reduced brain weight, our present data highlight that MRL/lpr mice suffer from short-term memory defect, likely reflecting hippocampal damage, and which may be mediated by infiltration of peripheral immune cells. Furthermore, the peptide P140 is a promising drug as it compensates such short-term memory deficit. We suggest that SLE specially impacts memory due to peripheral activation, an issue that should be addressed when diagnosing and treating cognitively-impaired SLE patients. Collectively, these data demonstrate that P140 exerts beneficial cognitive effect and arouse hope for patients suffering from NPSLE for whom there is nowadays no specific treatment.

**P1.067 Links between Parkinson's disease, dopaminergic agonist treatment and cognitive flexibility**

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Dopaminergic agonists used to alleviate motor symptoms of Parkinson's disease can produce non-motor complications (pathological gambling, hypersexuality, compulsive eating) called impulse control disorders (ICD). Whereas the underlying pathophysiology of ICD remains elusive, several studies suggest that patients with ICD show an altered executive profile.

This work aims at determining the effects of dopaminergic neurodegeneration and subsequent treatment with pramipexole (D2/D3 dopaminergic agonist) on cognitive flexibility and at identifying neuronal networks involved.

Cognitive flexibility is assessed in rats at baseline using an attentional set-shifting task in which animals have to switch between a visual and an egocentric rule. Rats in the first and fourth quartiles are respectively classified as flexible or inflexible, whereas the remaining are classified as intermediate. Dopaminergic lesion is performed with bilateral viral-mediated alpha-synuclein overexpression (AAV-SYN) in the *substantia nigra pars compacta* (SNC). Control group is injected bilaterally in the SNC with AAV-GFP. At baseline, akinesia, locomotor activity and anxiety are respectively estimated with stepping test, open-field and elevated plus maze tests. Behavioral tests are realised at 4 and 9 weeks after surgery and during pramipexole therapy. Brain collection is carried out immediately after the last flexibility test session, and immunohistochemistry against immediate early genes (IEG) is used to map brain regions potentially involved in the attentional set-shifting task and in differences between lesioned and control rats. Number of tyrosine hydroxylase positive cells and alpha-synuclein expression are evaluated in the SNC.

Preliminary results show a deficit in the stepping test in the lesioned group, 4 weeks after surgery, confirming ongoing dopaminergic neurodegeneration. We posit a decreased cognitive flexibility after surgery further exacerbated by pramipexole treatment. We also expect to demonstrate specific patterns of IEG activation in fronto-striatal loops.

**P1.068 Characterization of glioblastoma stem cells: identification of factors involved in their transcriptome regulation**

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Glioblastoma (GBM) is the most common and aggressive primary adult brain tumor. GBM dismal prognosis can be explained by the presence of treatment resistant cells responsible for tumor relapse known as glioblastoma stem cells (GSC). Characterized by an important cellular plasticity, they are able to adapt to hostile environments. Thus, despite aggressive multimodal treatments, GBM curative therapies have provided only a modest benefit; it is therefore necessary to better characterize these cells in order to develop new GSC targeted therapies. The role of post-transcriptional mechanisms of gene expression regulation in the maintenance of cancer stem cells has been demonstrated in different tumors. However, few RNA-binding proteins (RBPs), key regulators of these events, have been identified in GSC. The identification of RBPs critical for self-renewal and increased survival properties of GSC is under current investigation. The aim of our study is to deepen our knowledge of the underlying molecular mechanisms of GBM development or recurrence. GSC molecular heterogeneity was taken into account by carrying out a comparative study of the transcriptome of 5 glioblastoma stem cell cultures from different patients. This analysis also included in vitro differentiated cells originating from GSC as well as human neural stem cells. Using a transcriptome sequencing approach, our work has led to the identification of a family of post-transcriptional regulators enriched in GSC, nELAVL proteins. Co-expression of nELAVL proteins with OLIG2 or SOX2 was observed thus confirming their association with stemness. Among nELAVL members, ELAVL4 represents the most differentially expressed upon GSC differentiation. Knock-down and gain-of-function tools targeting ELAVL4 are being developed to further assess its roles in GSC maintenance.

**P1.069 The mGlu7 receptor provides protective effects against epileptogenesis and epileptic seizures**

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Finding new targets to control or reduce seizure activity is essential to improve the management of epileptic patients. We hypothesized that exogenous activation of the pre-synaptic and inhibitory metabotropic glutamate receptor type 7 (mGlu7) reduces spontaneous seizures.

We tested a recently developed mGlu7/4 agonist with unprecedented potency on mGlu7 receptors, LSP2-9166. Using genetically modified mice, video-EEG (electroencephalography), qPCR and immunohistochemistry, we studied the contribution of mGlu7 in two paradigms of epileptogenesis. In a model of chemically induced epileptogenesis (pentylenetetrazole systemic injection), LSP2-9166 induces an anti-epileptogenic effect rarely observed in preclinical studies. In particular, we found a bidirectional modulation of seizure progression by mGlu4 and mGlu7 receptors, the latter preventing chemical kindling. In the intra-hippocampal injection of kainic acid mouse model, that mimics the human mesial temporal lobe epilepsy, we found that twice-daily treatment of IHKA mice with LSP2-9166 during the first 15 days post-induction reduced seizure frequency and hippocampal sclerosis. LSP2-9166 also acts as an anti-epileptic drug on established seizures in both models tested. No chronic behavioural side effects were observed.

The two complementary models we tested show that targeting mGlu7 has an impact on epileptic seizure burden and neuronal damage. Specific modulation of the mGlu7 receptor could represent a novel therapeutic approach to reduce pathological network remodeling.

**P1.070 Targeting Kruppel-like factor 9 in excitatory forebrain neurons protects against chronic stress-induced impairments in dendritic spines and fear responses**

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Stress exposure is associated with the pathogenesis of psychiatric disorders including post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). Here, we show in rodents that chronic stress exposure rapidly and transiently elevates hippocampal expression of *Kruppel-like factor 9* (*Klf9*). Inducible genetic silencing of *Klf9* expression in excitatory forebrain neurons in adulthood prior to, but not after onset of stressor, prevented chronic restraint stress (CRS)-induced potentiation of contextual fear acquisition in female mice and chronic corticosterone (CORT) exposure-induced fear generalization in male mice. *Klf9* silencing prevented chronic CORT and CRS induced enlargement of dendritic spines in the ventral hippocampus of male and female mice, respectively. *KLF9* mRNA density was increased in the anterior dentate gyrus of women, but not men, with more severe recent stressful life events and increased mortality. Thus, *Klf9* functions as a stress responsive transcription factor that mediates circuit- and behavioral resilience in a sex-specific manner.

- P1.071 Variable selection using machine-learning to identify new signatures of patient-derived aggregated  $\alpha$ -synuclein-induced neurodegeneration in non-human primates**
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Intracellular  $\alpha$ -synuclein ( $\alpha$ -syn)-rich protein aggregates termed Lewy bodies and neuronal death are commonly found in the brains of Parkinson's disease (PD) patients. Clinical, neuropathological and experimental evidence strongly suggests that  $\alpha$ -syn plays a role not only as a trigger of pathology but also as a mediator of disease progression, through its pathological spreading. These properties of  $\alpha$ -syn have been described in rodents and non-human primates, but still remain controversial. Building up on this recent literature, we here used an unbiased machine learning-based approach to unravel unique signatures of degeneration induced by distinct  $\alpha$ -syn pathogenic structures derived from PD patients in non-human primates. Our results show that a small amount of certain  $\alpha$ -syn aggregates are as toxic as larger amyloid fibrils present in the LB and pinpoint the long anticipated, yet unproved, primate-specific susceptibility to  $\alpha$ -syn toxicity thus reinforcing the need of preclinical research in this species. Furthermore, our results provide evidence supporting the true multifactorial nature of PD as multiple causes can induce similar outcome regarding dopaminergic degeneration.

**P1.072 Ex-vivo electrophysiological analysis of a mouse model carrying a KCNQ2 variant associated with early epileptic encephalopathy**

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Early Onset Epileptic Encephalopathies (EOEE) represent a group of rare and intractable devastating epileptic syndromes of infancy that are characterized by epileptic activity beginning during the three first month of life and accompanied by rapid deterioration of brain function. There is a genetic basis for EOEE. Notably *de novo* mutations of KCNQ2 encoding the Kv7.2 subunit of the potassium Kv7/M channel have been identified in EOEE and are even the major cause of the Othahara syndrome (OS) but the underlying pathophysiological mechanism remains poorly known. Thanks to collaboration with the Marseille Medical Genetics center (INSERM UMR-S1251) we currently study a mouse model carrying a heterozygous p.T274M KCNQ2 mutation previously identified in patients with EOEE. This mutation reduces M current in heterologous cells by 60% in a configuration mimicking the patient situation. Here, we wondered if in mice, the heterozygous p.T274M mutation affected the intrinsic properties of cortical neurons. We performed ex-vivo whole-cell patch-clamp recordings of pyramidal cells located in the layer II/III and V of the somato-motor cortex of wild type and mutant mouse from postnatal day (PND) 7 to PND35. We observed that the mutation leads to a hyperexcitability of pyramidal cells already at PND 7 in the layer II/III and one week later in the layer V. However the increase in neuronal firing in cells of both layers was transient and observed only during the 3 first weeks of life but not latter. In other series of experiments we analyzed the effect of XE-991, a Kv7 channel blocker, in pyramidal cells of wild type mice during same period of development. We found that the blocker affected the neuronal excitability in same manner than did by the mutation but the blocker still increased neuronal excitability of pyramidal cells of both layers after 3 weeks. Together these data suggest that the heterozygous mutation have functional consequences on intrinsic properties of pyramidal neurons already during the neonatal period and that compensatory mechanisms develop with time to restore normal cellular activity. This is particularly interesting knowing that in many OS patients there is a progressive remission of the epilepsy and normalization of the electrographic activity.

P1.073

**Deciphering preventive action of vitamin A on Alzheimer's disease pathology**

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**Introduction:** Vitamin A (VA) is necessary to maintain memory processes in the adult brain, *via* its active metabolite, retinoic acid (RA). VA metabolism is decreased during aging, leading to a lower availability of RA in the brain, but also in the early stages of Alzheimer's Disease (AD). Thus, we hypothesize that an age-associated deficit of VA contributes to the development of AD, and that maintaining optimal availability of RA in the brain during aging could prevent the onset of AD. We evaluated whether a VA supplementation can prevent memory deficits and curb amyloidogenesis and tau neuropathology in two complementary mouse models of AD: the 3xTg-AD mouse and the intra-cerebro-ventricular (ICV)-injected A $\beta$ <sub>25-35</sub> mouse.

**Methods:** VA-enriched diet (20 IU/g) (control diet: 5 IU/g) was administered to both models. From 8-month-old (before frank neuropathology and behavior deficits, starting at 12-month-old) to 14-month-old in 3xTg-AD mice; and from 5 to 14-week-old in A $\beta$ <sub>25-35</sub>-injected mice (the injection occurs at 8 weeks of age). We evaluated hippocampal-dependent-memory, metabolic status, and neuropathology after dietary treatment.

**Results:** VA supplementation preserved short-term memory in both 3xTg-AD and A $\beta$ <sub>25-35</sub>-injected mice in the Y-maze. In both cases, locomotion and anxiety-like behavior was similar between groups. This protective effect of VA is not attributable to an action on metabolic status evaluated in glucose and insulin tolerance test, neither on body weight gain of both models.

**Conclusion:** Overall, VA had a robust effect in avoiding spatial memory deficits in two different AD models. Analysis of neuropathology is currently ongoing to better understand how this micronutrient triggers such memory protection in each case. These preclinical data suggest dietary VA could be a nutraceutical tool in the prevention of AD.

**P1.074 Neuro-microglial communication contributes to the detrimental role of adenosine A<sub>2A</sub> receptors in Alzheimer's disease**

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Neuronal accumulation of hyperphosphorylated and aggregated Tau proteins is correlated with cognitive decline in Alzheimer's disease but mechanisms underlying Tau-induced memory deficits remain unclear. Previous epidemiological and experimental studies pointed out that chronic caffeine consumption reduces AD risk and associated cognitive deficits. These protective effects were ascribed to the blockade of adenosine A<sub>2A</sub> receptors (A<sub>2ARs</sub>), found upregulated in hippocampal neurons of patients with AD. Interestingly, we found an association of such neuronal dysregulation of A<sub>2ARs</sub> and Tau pathology in patients with fronto-temporal dementia with tau mutation. To which extent A<sub>2AR</sub> upsurge is instrumental towards the development of Tau pathology and associated cognitive deficits remains however unknown. To address this question, we have developed a conditional mouse model (Tet-Off) allowing A<sub>2AR</sub> overexpression in CAMKII-positive neurons. This model was crossed with THY-Tau22 mice, who develop a progressive hippocampal Tau pathology associated with cognitive decline. In the different groups of animals, we evaluated Tau pathological changes (phosphorylation, aggregation) and functional impairments (learning and memory) at 5-6 months of age, when pathology is expressed but not maximal in the THY-Tau22 model. We found that neuronal A<sub>2AR</sub> overexpression favors spatial memory impairments of Tau transgenic mice. This detrimental effect was associated with a limited increased of hippocampal Tau pathology. Interestingly, following RNA sequencing, we uncovered that neuronal A<sub>2AR</sub> overexpression in Tau mice led to a significant altered hippocampal gene expression profile mostly ascribed to microglial cell function, underlying a functional link between neuronal A<sub>2A</sub> dysregulation and microglia in a Tau pathology context. Among others, we could observe the upregulation of C1q that was associated with atrophy of CA1 and dentate gyrus. Altogether, these data suggest that neuronal A<sub>2AR</sub> dysregulation seen in the brain of patients with AD and fronto-temporal dementia contributes to the development of Tau-induced cognitive impairments by modulating the interplay between neurons and glial cells.

**P1.075 Mimicking schizophrenia symptoms in mice by combining factors: genetic, early environmental stress and late pharmacological conditioning**

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Schizophrenia is a disabling psychiatric disease found in approximately 1% of the population, with an unknown but multifactorial etiology. Currently, patients are treated with antipsychotic drugs, which are only symptomatic and not curative. Unfortunately, these treatments do not cover the entirety of symptoms and are inefficient in 30 % of patients. Moreover, cognitive symptoms can even be worsened by antipsychotics. There is, therefore, a crucial need to find treatments that are more efficient.

In this context, we are developing a mouse model of schizophrenia based on three factors (3-hit), which take into account the multifactorial nature of the pathology. The present study aims at dissecting the respective effects of three factors, and their combination. The factors are: *i.* a partial genetic deletion of *MAP6* gene (heterozygous mice), *ii.* an early-life stress triggered by maternal separation of 9-day old pups for 24 hours, and *iii.* a chronic administration of MK801 (0.05mg/kg, i.p., 5 days) in early adulthood.

Cognitive functions were assessed, and particularly, working memory (spontaneous alternation), long term memory (object recognition), sociability and social recognition (two steps of approach avoidance test), anxiety-like behaviour and locomotor activity (open field). Then, density of parvalbumin-positive neurons in prefrontal cortex and hippocampus were measured *via* immunochemistry.

Behavioural study showed that each factor, taken separately (1-hit), induced some behavioural deficits: *MAP6* deletion impairs working memory; maternal separation impairs social recognition, and MK801 induces deficits in social and object recognition. The 3-hit group showed alterations of working memory and social recognition together with an increased distance in open field.

Behavioural results reveal that the 3-hit schizophrenia model displays cognitive dysfunctions mimicking those observed in schizophrenia. Therefore it gathers a relevant face validity, which, combined with a powerful construct validity gives new insight for further research of treatments for cognitive functions. Ongoing immunochemistry study will give possible mechanisms involved.

**P1.076 Regulation of dopamine and endocannabinoid transcripts in reward and homeostatic brain regions following diet-induced obesity in rats: a cluster analysis approach**

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Increased availability of high-calorie palatable food in most Western countries has led to overconsumption, suggesting that this behavior is driven by pleasure, rather than metabolic need. This has led to a dramatic rise in eating disorders, obesity, and associated pathologies (diabetes, cardiac diseases, cancers...). Brain activation and behavioral adaptations linked to palatable food overconsumption overlap closely with those induced by drugs of abuse, giving rise to the debated concept of «food addiction». The mesocorticolimbic dopamine system plays a central role in the switch from controlled to compulsive intake of both drug and palatable food. Dopamine and endocannabinoid systems contribute to both feeding and reward and have both been involved in obesity. In our study, we used a RT-qPCR approach to investigate the effects of a 6 weeks high fat high sugar diet (fCHFHS) on gene expression of key components of dopamine, endocannabinoid and homeostatic systems in mesocorticolimbic (PFC, NAc, VTA) and hypothalamic (LH, Arc) rat brain regions. Km cluster analysis allowed us to examine separate groups of animals based on their individual sensitivity to obesity and palatable food intake. We also measured dopamine and endocannabinoids levels in the PFC and NAc using mass spectrometry.

Our results show that the fCHFHS diet induced hyperphagia and obesity in rats. Cluster analysis revealed that the propensity to develop obesity and excessive palatable food intake can be differently associated with dopamine and endocannabinoid systems gene expression in reward and homeostatic brain regions. Moreover, transcriptional data are consistent with observations of hypodopaminergic in obese subjects and point to cannabinoid receptors as GPCR targets involved in neuroplasticity mechanisms associated with both maladaptive responding for palatable food and obesity.

**P1.077 Complement-C3-dependent alterations of the dentate gyrus are involved in memory deficit at the early stage of experimental multiple sclerosis**

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Memory impairment is an early and disabling manifestation of multiple sclerosis whose anatomical and biological substrates are still poorly understood. In experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, we previously identified that early memory impairment was associated with selective alterations of granular neurons from the dentate gyrus secondary to particular vulnerability of those neurons to microglial activation while it was not the case in the CA1 subfield. In particular, daily infusions of minocycline, a potent microglial inhibitor, specifically within the dentate gyrus were sufficient to prevent memory impairment in EAE-mice while infusions of minocycline within CA1 were not.

In the present work, we investigated the molecular pathways that could be involved in this deleterious interaction between microglia and neurons in the dentate gyrus. We first screened several genes involved in the phagocytic interaction pathways between microglia and neurons by using rtqPCR on laser micro-dissected CA1 and dentate gyrus from EAE and control mice. We showed that the complement pathway was the only one to show upregulation of several components in EAE-mice. Especially, the central component C3 mRNA was about 10 times higher in the dentate gyrus of EAE mice compared to control mice but not in the CA1 subfield. We confirmed this increase by quantifying C3 protein with Elisa test. Furthermore, blockage of C3 complement component by pharmacological approach using rosmarinic acid or by genetic approach using C3KO mice decreased phagocytic activity of microglia, prevented dendritic loss from granular neurons of the dentate gyrus, and in turn prevented memory impairment in EAE-mice.

We concluded that the complement component pathway and especially C3 is involved in the interaction between neuron and microglia in the dentate gyrus of EAE-mice and has a key role in the occurrence of memory deficits in the early stages of multiple sclerosis.

**P1.078 Ganglioside accumulation in a model of slowly progressive Amyotrophic Lateral Sclerosis**

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Motor neuron diseases regroup a variety of neurological disorders with overlapping phenotypes. Among these diseases, Amyotrophic Lateral Sclerosis (ALS) is the most frequent and is characterized by spasticity, muscle wasting and the loss of both upper and lower motor neurons. Hereditary Spastic Paraplegias (HSP) constitute the second most frequent group of motor neuron diseases characterized by progressive spasticity, muscle weakness and axonal degeneration of the upper motor neurons.

The clinical overlap between these pathologies is supported by the mutations found in the *ALS5/SPG11* gene, which are the main causes of autosomal recessive HSP and are also responsible for slowly progressive autosomal recessive ALS with juvenile onset.

We generated and characterized an *Als5/Spg11* knockout mouse model that recapitulated most of the clinical hallmarks observed in patients. All the knockout mice showed progressive gait impairment, coordination problems and motor dysfunction that started early and worsened with time. They also exhibited muscle strength loss, developed lower limb spasticity and walked with stiff legs. These behavioral deficits were associated with progressive brain atrophy with loss of neurons in the primary motor cortex as well as global spinal cord atrophy with loss of the large surface motor neurons and accumulation of dystrophic axons in the corticospinal tract.

Interestingly, examination of the motor neuron alterations showed that the degeneration was preceded by an accumulation of lipid material in lysosomal structures. Lipidomic approaches combined with immunostaining revealed these lipids were simple gangliosides (GM3, GM2, GD3 and GD2). We assumed the Spatacsin, the protein encoded by *ALS5/SPG11* gene, plays a role in clearance of gangliosides from lysosomes. In addition, we showed recently that neurons of knockout mice were more sensitive to glutamate toxicity compared to neurons from controls and this could be corrected by reducing simple ganglioside levels. Furthermore, we improved the motor phenotype of a *zals5/zspg11* knockdown zebrafish model by preventing the synthesis of gangliosides with a Miglustat treatment. Altogether, these data suggest that targeting ganglioside synthesis could be a therapeutic option in *ALS5/SPG11* pathology.

**P1.080 Stable analogue of diadenosine-polyphosphates, AppCH<sub>2</sub>ppA, suppresses epilepsy by enhancing adenosine signaling in neocortex**

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Epilepsy is a multifactorial disorder associated with neuronal hyper-excitability affecting more than 1% of human population. It has long been known that adenosine can reduce seizure generation in animal models of epilepsies. However, in addition to various side effects, the instability of adenosine has precluded its use as an anticonvulsant treatment. Here we report that a non-hydrolysable analogue of diadenosine-polyphosphates, AppCH<sub>2</sub>ppA, effectively suppresses spontaneous epileptiform activity *in vivo* and *in vitro* in a mouse model of Tuberous Sclerosis Complex (*Tsc1<sup>+/−</sup>*), in post-surgery cortical samples from TSC human patients as well as in a more general *in vitro* pharmacological model of epilepsy. These effects are mediated by enhancement of adenosine signaling in the cortex by local neuronal adenosine release. The released adenosine induces adenosine A1 receptor-dependent activation of potassium channels thereby reducing neuronal excitability, temporal summation and hyper-synchronicity thus leading to a disruption of the excitation loop necessary to generate epileptic waves. AppCH<sub>2</sub>ppA does not cause any disturbances of the main vital autonomous functions in *Tsc1<sup>+/−</sup>* mice *in vivo*. Therefore, we propose this compound as a potent new candidate for adenosine related strategy to suppress intractable epilepsies.

**P1.081 Hippocampal rhythmic activity modifications associated to epileptogenesis and ictogenesis in a mouse model (*Scn1a*<sup>R1648/+</sup>) of genetic epilepsy**

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Mice carrying the human R1648H mutation of the Nav1.1 voltage gated sodium channel (*SCN1A* gene) reproduce the patients' phenotype characterized by sensitivity to hyperthermia-induced seizures and a phenotypic spectrum ranging from asymptomatic to severe epileptic encephalopathy with cognitive impairment. A recent study from our team demonstrated that the interaction between seizures and the genetic mutation can be a key factor for the development of severe phenotypes (Salgueiro-Pereira et al. 2019 *Neurobiol. Disease* 125:31). However, how seizures precisely impact the phenotype of this mouse model still remains to be understood. Here, we propose that the pattern of brain activity is a fundamental variable to explore within this complex dynamic.

Thus, we asked: 1) whether the interaction between seizures and the genetic mutation could determine a rearrangement of the network dynamic responsible of the development of the severe phenotype; 2) whether the study of brain activity could also elucidate mechanisms of seizure generation, revealing a brain state that characterizes the onset of seizures (i.e. the preictal period).

To this aim, we chronically recorded hippocampal local field potentials (LFP) of *Scn1a*<sup>R1648/+</sup> mice before, during and after the induction of seizures by hyperthermia, in resting conditions as well as during the exploration of a novel object. Preliminary results suggest that:

- 1) Induction of seizures and the consequent epileptogenesis cause modifications of hippocampus' rhythmic activity, suggesting it as a possible mechanism of cognitive impairment associated to epileptogenesis.
- 2) Brain activity modifications could be an early signature of seizures' onset, offering the possibility of preictal period detection and seizure prediction.

This study could help to unveil mechanisms of cognitive impairment associated to *SCN1A* epileptic encephalopathy. Moreover, it could open new therapeutic approaches through seizure prediction and prevention.

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**P1.082 Effect of anti-VEGF treatment on the innate immune response in a mouse model of multiple sclerosis**

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Multiple sclerosis is an inflammatory disease, characterized by infiltration of immune cells into the central nervous system leading to myelin and axonal damages. Although this disease was previously thought to be led by adaptive immune cells, e.g. T cells, recent findings lead us to focus on innate immune cells, such as monocytes, neutrophils and microglial cells.

We used Thy1-CFP/LysM-EGFP/CD11c-EYFP triple transgenic mice induced for EAE. In these mice Thy1-CFP is expressed by axons, LysM-EGFP by peripheral innate immune cells, CD11c-EYFP by activated microglial cells and both LysM-EGFP and CD11c-EYFP by monocyte-derived dendritic cells. These markers allowed us to precisely study the spatial and temporal recruitment of these cells in the spinal cord of EAE mice, in relation with axonal loss and clinical signs.

First on day 10 after induction, EGFP neutrophils and monocytes invade the meninges, then (day 13) they enter into the spinal cord parenchyma through the meninges, rather than by extravasation. Axonal losses occur in the white matter concomitantly with immune cell infiltration. Once in the parenchyma, monocytes mature into EGFP/EYFP monocyte-derived dendritic cells whose density is maximal on day 17 when the axonal degradation and clinical signs stabilize. Meanwhile, microglia is progressively activated in the entire spinal cord and subsequently recruited to plaques.

As a direct effect of VEGF on immune cell has been demonstrated in other diseases, we examined the effects of VEGF blockade (with bevacizumab) on the innate immune response in triple fluorescent EAE mice. In animals treated with bevacizumab from disease onset, we found no significant difference in the numbers of fluorescent cells recruited to the spinal cord, compared to controls. We are now focussing on the phenotypes of these cells after treatment.

P1.083

**Brain insulin sensitivity and peripheral metabolic changes in Tau transgenic mice**

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Accumulation of hyper-phosphorylated and aggregated Tau protein is a neuropathological hallmark of Alzheimer's Disease (AD) and Tauopathies. AD patient brain's exhibit insulin resistance. Whereas, under normal physiological conditions insulin signaling in the brain mediates plasticity and memory formation, it can also regulate peripheral energy homeostasis. Brain insulin resistance in AD may thus lead to both cognitive and metabolic changes in patients. Contribution of Tau pathology in the development of this brain insulin resistance has been overlooked. Our recent data (Marciniak et al., 2017) demonstrated that one of the physiological function of Tau is to sustain brain insulin signaling. We postulated that under pathological conditions, hyper-phosphorylated/aggregated Tau likely lose this function, favoring the development of brain insulin resistance. To address the potential link between Tau pathology and brain insulin resistance, we have here evaluated the brain response to insulin in a transgenic mouse model of AD-like Tau pathology (THY-Tau22). This murine model overexpresses mutated human Tau under the control of a neuronal promoter and progressively develops hippocampal Tau pathology and cognitive deficits. Using electrophysiological and biochemical evaluations, we observed that at a time when Tau pathology and cognitive deficits were overt and obvious, the hippocampus of THY-Tau22 mice exhibited enhanced response to insulin. In addition, we demonstrated that the ability of i.c.v. insulin to promote body weight loss was enhanced in THY-Tau22 mice. In line with this, THY-Tau22 mice exhibited a lower body weight gain, hypoinsulinemia and hypoinsulinemia and finally a metabolic resistance to High Fat Diet. Collectively, these data indicate that the development of Tau pathology in THY-Tau22 mice does not associate with brain insulin resistance but rather enhanced brain response to the hormone. These data open the debate on the relationship between Tau pathology and brain insulin resistance but also point a possible bias regarding the use of transgenic mouse models that overexpress Tau.

**P1.084 A new conditional mouse model allowing the adult truncation of FUS-PY NLS domain to study ALS-FTD**

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FUS (Fused in Sarcoma) is a RNA-binding protein involved in multiple steps of RNA metabolism. FUS is shifted from a mostly nuclear localisation in control conditions to cytoplasmic inclusions in a significant subset of patients with amyotrophic lateral sclerosis (ALS) or fronto-temporal dementia (FTD). To mimic FUS cytoplasmic mislocalization found in ALS-patient, we previously characterized a mouse model in which we completely removed the so called PY-NLS domain responsive of FUS nuclear import. Homozygous mice died at birth and showed motor neuron loss, while heterozygous mice develop mild, late onset motor neuron degeneration. Here, we report the characterization of a novel knock-in mouse model, called *Fus (loxPΔNLS)*, allowing the conditional truncation of the exon 15 of the *Fus* gene, leading to loss of the PY-NLS. We crossed *Fus (loxPΔNLS)* mice with Thy1Cre ERT2 YFP mice (SLICK-H mice) in order to trigger adult onset truncation of FUS in long projection neurons. Consistently, 2 weeks after tamoxifen induction, robust recombination was observed in the cortex and hippocampus at the DNA, RNA and protein level. Western blotting using antibodies recognizing N-terminal epitopes on FUS protein showed maintained or increased levels of FUS, while western blotting using PY-NLS targeting antibodies indicated strong loss of these epitopes. Two months after induction of recombination, mice either homozygous or heterozygous for the floxed allele did not show altered performance in motor capabilities (grip/inverted grid tests), nor on cognitive tests (marbles burying/nest building test). Using nuclear fractionation followed by western blotting, we observed that wild type mice showed a prominently nuclear localization of FUS signal mostly in the nucleus. Contrastingly, mice heterozygous for the *Fus (loxPΔNLS)* allele displayed a partial mislocalization of FUS in the cytoplasm that was further enhanced in homozygous mice. Surprisingly, a substantial proportion of the FUS protein remained nuclear despite lack of NLS. In all, we generated and provide here a preliminary characterization of a novel mouse model allowing the adult onset cell specific truncation of FUS. Further molecular, histological and behavioural characterization of these mice will be presented at the meeting.

P1.085

**Re-expression of the neurodevelopmental protein filamin A in glioblastoma: major impact on tumor proliferation and invasiveness**

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Filamin A (FlnA) is a platform protein of actin anchorage widely expressed during the development. The key role of FlnA in many cancers was recently suggested. Our team previously demonstrated that the vasoactive peptide urotensin II (UII) and its GPCR UT are systematically expressed in human glioblastoma (GBM), activates chemotactic invasion and tumor angiogenesis. A two-hybrid screening of human cDNA isolated FlnA as a protein partner of the C terminus tail of UT, suggesting a potential involvement of FlnA in UT signaling pathways in GBM.

Immunohistochemistry of patient's glioma excision (Rouen Hospital) revealed re-expression of FlnA in high grade gliomas, showing the highest level in IDH non-mutated gliomas. In high grade gliomas, FlnA and UT were strongly co-expressed more specifically in perinecrotic areas. Analysis from The Cancer Genome Atlas database confirmed high level of FlnA mRNA expression in GBM, correlated with a bad prognosis and a lower survival rate for glioma patients. *In vitro* UII induced chemotactic migration of the U87 GBM cell line via formation of dynamic focal adhesion points. This effect was inhibited by down-regulation of FlnA expression, or by competition with the UT C-terminal tail transiently expressed in GBM cells, suggesting a physical interaction of FlnA with UT mediating migration. When FlnA expression is genetically knock-out by the CRISPR/Cas9 strategy (U87-KOF), GBM chemotactic migration was significantly decreased compared with U87, accompanied by complete loss of lamellipodium extension, stress actin fibers, focal adhesions and decreases of cell cytoplasmic area in the absence of FlnA. *In vivo*, brain striatal injections of U87 and U87-KOF cells in Nude mice showed that a median survival of 45 days for U87-mice and 56 days for U87-KOF mice suggesting a better prognosis ( $p < 0.01$ ) GBM cells did not express FlnA. Immunohistochemical analysis of xenografted mouse brains (15 days post-injection) revealed a circumscribed non invasive tumor morphology for U87-KOF with reduced expression of MMP9, compared with the invasive and extended shape of U87 based tumors.

FlnA likely plays a key role in the invasive properties of high grade gliomas, relaying chemokine receptor activity, responsible for high tumor recurrence.

P1.086

### Pathogenicity of TDP-43 fragments in Amyotrophic Lateral Sclerosis

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Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by a progressive and irreversible loss of cortical and spinal motor neurons. The formation of protein aggregates in these motor neurons is involved in the pathogenesis of ALS.

Transactivation response (TAR) DNA-binding protein (TDP-43) is identified as a major protein in these aggregates. This nuclear protein is delocalized in the cytoplasm in motor neurons in ALS, where it forms insoluble, ubiquitinated and hyperphosphorylated aggregates.

Post-mortem studies in ALS also identified several truncated forms of TDP-43. Fragment generation appears to be involved in aggregate formation and might increase cytotoxicity. The biochemical properties and the functional roles of these TDP-43 fragments on neurodegeneration remain poorly understood. First we listed the 7 cleavage sites responsible for the truncated forms of TDP-43 identified in post-mortem brains of ALS patients. Interestingly we identified in an ALS patient a new mutation in one of these sites position, p.N291, which is cleaved by an Asparaginyl Endopeptidase (AEP). The cleavage of TDP-43 at each of the 7 sites resulting in two fragments (N-and C-terminal regions), we cloned the 14 TDP-43 fragments into plasmids. The consequence of their expression on protein aggregation, neurite length and cell viability are studied in motor neuronal cell lines (NSC-34) and in primary cultures of motor neurons. In order to study the pathogenicity of these truncated forms of TDP-43 in relation with aggregation, we searched for intrabodies (ScFv) able to bind TDP-43 protein and to prevent protein aggregation. This phage display protocol was done in partnership with the IRCM.

The aim of this study is to provide a better understanding of the role of TDP-43 fragments in the pathophysiology of ALS, and to open new therapeutic perspectives. This research program is part of an ARD2020 program funded by the Centre Val-de-Loire Region and supported by the Labex MabImprove.

**P1.087 The role of dopamine in nociceptive transmission in a rat model of Parkinson's disease**

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Pain experienced by patients affected by Parkinson disease (PD) is one of the most debilitating symptoms, diminishing significantly their quality of life. It is estimated that approximately 91% of PD patients suffer from chronic pain, but only 23% of them are diagnosed. This demonstrates that pain is under-recognized and consequently not well treated, as its underlying mechanisms in the context of PD remains unclear. Dopamine has long time been established as the leading neurotransmitter responsible for the manifestation of motor symptoms in PD. This neurotransmitter has also been shown to play a role in pain sensitivity. The present study aimed to investigate the involvement of dopamine in nociception in the 6-hydroxydopamine rat model of PD, by studying the consequences of selective lesions of dopamine descending pathways, projecting to the dorsal horn of the spinal cord, on mechanical and thermal nociceptive sensitivity. Using several pain behavioural tests, including Vonfrey and Plantar tests, we showed that dopamine depletion by 6-OHDA induced hypersensitivity to mechanical and thermal stimuli. The 6-OHDA-lesioned animals showed a significant decrease in paw withdrawal threshold and latency for the left contralateral hind paw compared to the ipsilateral side. These abnormal behaviours were paralleled by increased neuronal responses and hyper excitability of wide dynamic range neurons of lamina V of the dorsal horn of spinal cord in response to electrical stimulations of the sciatic nerve in the 6-OHDA lesioned rats compared to sham animals. Animals with dopamine depletion showed an increase in the c-fibre action potentials in response to electrical stimulation of the sciatic nerve. Application of dopaminergic agents reverse the effect of dopamine depletion on the paw withdrawal threshold and latency of animals and re-established the c-fibre mediated response in 6-OHDA animals. These results provide the first demonstration of an alteration of nociceptive integration in the spinal dorsal horn neurons in 6-OHDA rats that can reflect changes in pain behaviour.

P1.088

### Therapeutic potential of the Bornavirus X protein and X-derived peptide in amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a fatal and non-curable neurodegenerative disease of upper and lower motoneurons for which the etiology remains poorly understood.<sup>[1]</sup> However, among the pathophysiological hallmarks observed both in patients and in animal models, axonal mitochondrial dysfunctions appear to be one of the earliest events, and thus might be causative for the progressive loss of motor neurons (Le Masson et al, 2014). Interestingly, in SOD1<sup>G93A</sup> mouse model of ALS recent results have evidenced a defective energy production in motoneurons that occurs from an uncoupling between mitochondrial respiration and ADP phosphorylation(Szelechowski et al, 2018). This energy shortage could be fatal for motor neurons that have a high metabolic demand. Therefore restoring the mitochondrial function could be a therapeutic area of interest in the development of new therapy against SLA.

For this reason , we are interested in Bornavirus (or BDV for Borna disease virus) that is a highly neurotropic and non-cytolytic RNA virus that persists in neurons of infected animals. BDV expresses a small 10 kDa protein, the X protein that is specifically addresses in mitochondria of infected cells where it blocks the cell apoptosis. It was recently demonstrated that ectopic expression of BDV X protein could protect neurons from the earliest stages of degeneration in a toxic Parkinson model through the preservation of mitochondrial function (Szelechowski et al, 2014). Therefore we tested the administration of X protein of BDV in a SOD<sup>G93A</sup>micemodel of ALS. We used intramuscular injections of Canine Adenovirus type 2 (CAV2) expressing wild type or mutated (non protective) X proteins and/or intranasal deliveries of therapeutic X-derived peptide (PX3) or control scramble peptide (Psc). In animals treated with both strategies, we have observed with rotarod test that the disease onset was delayed and the motor function was preserved during 20 days. Electromyographic recordings of hindlimb muscle were realized and show a preservation of motor units. Moreover, motoneurons survival determined by SMI32 and ChAT immunostaining was increased in lumbar spinal cord. Therefore, this study clearly shows the therapeutic neuroprotective effect of BDV X protein in SOD model of ALS.

**P1.089 Novel high throughput tools for detecting age associated epigenetic changes in liquid biopsies**

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Aging-associated epigenetic changes such as global DNA hypomethylation, loss of histones, and alterations in specific histone marks, have been described in humans and other organisms, and likely contribute to aging-associated cellular dysfunction. Liquid biopsies show promise for biomarker identification and treatment evaluation as clinical researchers use cfDNA to assess risk, disease progression, and treatment strategies prospectively. Here, we highlight Active Motif's high-throughput approaches to detect epigenetic alterations in human serum samples from healthy young and old individuals. Studies have shown that methylation levels of Long Interspersed Nucleotide Element 1 (LINE-1) repeats serve as reliable proxy for assessing global DNA methylation. We demonstrate that aging-associated decreases in DNA methylation in LINE-1 repeats can be quantified in cfDNA using an ELISA-based assay to assess global DNA methylation. Differentially methylated regions are confirmed with MeDIP-Seq in a subset of samples. We also determined the levels of intact nucleosomes circulating in serum using a novel ELISA-based approach.

Next, we plan to use a histone H3 bead-based multiplex ELISA to screen relevant histone marks, to inform downstream ChIP-seq analyses. Together we aim to show that these tools can be used to aid in discovery and detection of biomarkers and screening patient samples using clinically relevant biopsies, as well as inform mechanistic studies.

**P1.090 Pyramidal neuron growth and increased hippocampal volume during labor and birth in autism**

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We report that the apical dendrites of CA3 hippocampal pyramidal neurons are increased during labor and birth in the valproate model of autism but not in control animals. Using the iDISCO clearing method, we show that hippocampal, especially CA3 region, and neocortical volumes are increased and that the cerebral volume distribution shifts from normal to lognormal in valproate-treated animals. Maternal administration during labor and birth of the NKCC1 chloride transporter antagonist bumetanide, which reduces  $[Cl^-]_i$  levels and attenuates the severity of autism, abolished the neocortical and hippocampal volume changes and reduced the whole-brain volume in valproate-treated animals. These results suggest that the abolition of the oxytocin-mediated excitatory-to-inhibitory shift of GABA actions during labor and birth contributes to the pathogenesis of autism spectrum disorders by stimulating growth during a vulnerable period.

P1.091

**Ethosuximide modulation of GIRK channels ameliorates the aberrant neuronal activity underlying GNB1 syndrome: a precision medicine approach**

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*De novo* mutations in *GNB1*, encoding the G $\beta$ 1 subunit of G proteins which mediate G protein-coupled receptor signaling, cause a neurodevelopmental disorder with global developmental delay, ambulatory and speech deficits, and epilepsy. In an effort to elucidate the specific neuronal functions of *GNB1* affected by the mutations and help guide treatment options, we generated the first mouse model of *GNB1* Syndrome by introducing a reported pathogenic mutation, K78R, using CRISPR/Cas9. *Gnb1*<sup>K78R+/-</sup> mice recapitulate many aspects of the disorder, including developmental delay, motor and cognitive deficits, and very frequent (>70/hr) spike-wave discharges (SWD) during wakefulness, an incidence not previously observed in other mouse models of epilepsy. Mutant cortical neurons from cultured networks display aberrant bursting activity as monitored by multielectrode arrays (MEA). Strikingly, the antiepileptic drug ethosuximide (ETX) restores normal neural network behavior, and prevents SWD *in vivo*. In contrast, valproic acid (VPA) prevents SWD but does not restore normal network behavior *in vitro*. This suggests that ETX has mechanistic specificity for the effects of aberrant *Gnb1* signaling. Consistent with this, we show that the K78R mutation acts as a gain-of-function of G protein-coupled potassium (GIRK) channel activation and that ETX potently inhibits GIRK channels. This work suggests that altered *Gnb1* signaling causes disease in part through effects on GIRK channels, and illustrates the utility of cultured neuronal networks in compound screening.

**P1.092 Effect of NF $\kappa$ B inhibitors on reconsolidation of memories associated with cocaine self-administration**

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Persistent and intrusive memories play a key role in maintaining certain psychiatric disorders, such as posttraumatic stress disorder or substance abuse (Evans and Cahill, 2016). Memory for drug-paired cues plays a critical role in sustaining addiction as these are potent triggers for relapse. Modulation of these memories may alter the propensity to relapse suggesting that reconsolidation of drug-cue associations may be a potential target to reduce addictive behaviors. Experimental data in animals confirm that retrieved memories become transiently labile for a few hours post-retrieval. Altering a drug-cue memory reduces drug-seeking behavior in a later reinstatement test. Previous work from our lab showed that chronic cocaine intake alters DNA methylation in the rat prefrontal cortex; pathway analysis clustered some of the target genes around the nuclear factor  $\kappa$  B (NF $\kappa$ B) system. Although implicated primarily in inflammation, this transcription factor also plays important roles in learning and memory. Specifically, NF $\kappa$ B is involved in consolidation and reconsolidation of memories in different conditioning paradigms (e.g., conditioned fear, place preference). Our study assessed the effect of NF $\kappa$ B pharmacological inhibition on reconsolidation of cocaine-associated memories using an intravenous self-administration (ivSA) paradigm. Briefly, male rats were allowed to self-administer cocaine over 12 daily sessions (1h 45 min) under an FR1 schedule of reinforcement; a light stimulus (conditioned stimulus, CS) was turned on during each infusion. After instrumental extinction (18 sessions) with no CS presentation, rats underwent one reactivation session in which the CS was presented (4 X 40s separated by 30s) with no access to cocaine or the operant response. They were immediately injected with NF $\kappa$ B inhibitor. CS-induced reinstatement was assessed 24h later. Our preliminary results show that parthenolide, an NF $\kappa$ B inhibitor, affects the reconsolidation process, leading to alterations in CS-induced cocaine seeking. Identifying neural mechanisms involved in reconsolidation of drug memories could be beneficial for the development of therapeutic strategies to treat addictive disorders.

**P1.093 Glypican4 as a target for innovative cell based replacement therapy in Parkinson's disease**

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Human induced pluripotent stem cells (hiPSCs) are considered a major breakthrough for biomedical science. One of their most promising applications is Parkinson's Disease (PD) therapy in which the aim is to restore the dopamine (DA) deficit through transplantation of hiPSCs-derived ventral midbrain (vm) DA neurons. However, hiPSCs clinical application still requires overcoming two major issues: their intrinsic ability to generate tumors after transplantation and their low differentiation efficiency. In embryos, the signalling proteins Shh, Wnt and Fgf8 establish the development of vmDA neurons and prevents the development of other neural cell types. These findings have led to an extensive research of the right medium formulation that would trigger *in vitro* the highest yield of vmDA progenitors. The alternative solution we are exploring is the possibility to increase hiPSCs acquisition of DA neuron fate at the expense of self-renewal and tumorigenesis. This is based on our discovery that downregulation of morphogen regulator Glypican4 (GPC4) in hiPSCs enables:

- 1)** maintenance of self-renewal/pluripotency in stemness conditions,
- 2)** efficient lineage entry in differentiation conditions,
- 3)** loss of tumorigenicity in flank xenografts.

hiPSCs with downregulated GPC4 levels undergo a more efficient commitment towards vmDA fate at the expense of self-renewal and serotonergic identity and they generate a larger amount of DA neurons. We performed transplantation experiment in rat brains to determine whether GPC4 downregulation permits to engraft cells at neural committed state instead of more differentiated state. Ongoing analyses of dissected brains at two-month post-transplantation show that grafts of Gpc4-mutant cells are enriched into Foxa2+/Lmx1a+, markers of vm precursors. We anticipate that GPC4 downregulation is a promising strategy for improving hiPSCs-based PD therapy. The involvement of GPC4 in regulating key signals for vmDA neuron differentiation will be discussed.

**P1.094 Recovery of BDNF/TrkB signaling by P42 peptide in Huntington's disease: from BDNF transport to TrkB reception**

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Huntington's disease (HD) is a rare genetic neurodegenerative disorder. Curative treatments are still actively sought. HD is induced by a mutation in the *HTT* gene resulting from abnormal expansion of polyQ domain in the Huntingtin protein (mHtt). The mechanisms and consequences of this mutation are now well described and indicated effects on the BDNF signaling, where BDNF and its receptor TrkB are reduced, and transport of BDNF along the axons affected. We have identified a 23aa peptide (P42), derived from Htt, capable of rescuing pathological phenotypes of HD, such as aggregation, axonal transport defects and impaired neuronal viability.

In order to understand P42 mechanisms of action and to optimize its therapeutic potential, we analyzed whether P42 is acting on BDNF/TrkB signaling pathway. We first measured BDNF and TrkB, levels of expression in HD condition and found that P42 is mainly increasing the protein level of TrkB in the striatum, whereas it had smaller effect on the expression level of BDNF in the cortex. We also used a P42 treatment of R6/2 HD mice, and analyzed the pathologic phenotypes in R6/2 mice that are related to the BDNF/TrkB pathway: From motor coordination and memory to synaptic plasticity, therefore confirming the action of P42 on this pathway. Interestingly, using a novel innovative tool, the Hamlet test, we observed that there might be a synergic effect of P42 with enriched environment, known to increase BDNF transcription. These results could be explained by a differential effect on the BDNF pathway. Finally, we observed the role of P42 on vesicular transport, using *Drosophila* model, and performed live imaging studies, in different transgenic conditions: with or without mHtt or P42. These experiments indicate that P42 is able to rescue the effect of mHtt on the transport of DNT1, the BDNF *Drosophila* homolog. All together, these observations confirmed the therapeutic potential of P42 in HD and brought new information on its mechanisms of action.

P1.095

### Genetic architecture of bipolar disorder in multiplex families

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Bipolar disorder (BD) is a severe psychiatric disorder with a complex pattern of inheritance. Genome wide association studies have revealed an additive polygenic contribution of common polymorphisms to the liability of BD. However, according to recent studies the common polymorphism-based risk pattern would explain only 25% of the overall genetic variance in the heritability of BD. Family studies with a high density of illness have a particular relevance to identify rare high penetrant variants, which might explain this missing heritability.

To estimate the contribution of common and rare variants in BD, we combined both whole exome sequencing and genotyping arrays in 8 multiplex families with BD (39 subjects, of whom 22 were affected). We compared the common polymorphism-based polygenic score in families with a population of 445 patients with BD and 1,636 controls. Though we showed a higher polygenic score in families with BD than in general population, no difference was observed between affected and unaffected individuals in these families. In addition, we looked for rare variations in constraint genes shared in affected individuals in multiplex families with BD. We showed these genes encode proteins that interact in a network and that were significantly enriched in neuronal and developmental biological pathways, as well as in the regulation of gene expression. For these genes, we compared the rare mutation frequency in a cohort of 241 patients with BD and the 21,071 individuals from the non-Finnish and non-psychiatric European cohort of the ExAC consortium. Four genes showed a higher mutation rate in patients with BD than in the ExAC population after correction for multiple testing, including three involved in epigenetic regulations. Moreover, we characterized a specific clinical profile for individuals carrying mutation in these genes. Altogether, our results suggest that common and rare genetic variants both contribute to the familial aggregation of BD and suggest a neuro-developmental impairment for this disease.

**P1.096 Effects of deep brain stimulation on speech clinical assessment and acoustic features in Isolated Generalized Dystonia**

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Isolated Generalized Dystonia (IGD) is characterized by intermittent and sustained muscle contractions generating involuntary movements or abnormal postures; a so-called hyperkinetic dysarthria is often present. Internal pallidum deep brain stimulation (IP-DBS) is a neurosurgical procedure often used for treatment of dystonia. This study aimed at evaluating the effects of IP-DBS associated with other subcortical targets (thalamus [Th-DBS] or subthalamic nucleus [STN-DBS]) on the speech clinical assessment and acoustic features in patients with IGD.

We recorded speech of 11 patients with IGD pre- and post-surgery: all patients benefited from IP-DBS; 6 patients underwent an additional electrode implantation in the STN and the remaining 5 patients, in the thalamus. The neurological assessment was performed using the Burke-Fahn-Marsden Dystonia Rating Scale (BFM-DRS), which allowed for the subjective scoring of speech and swallowing, neck, trunk and global motricity. The patients performed three speech production tasks: maximum phonation time (MPT), sustained vowel /a/ and oral diadochokinesis. These two latter tasks allowed for the calculation of the shimmer (cycle-to-cycle loudness variation) and articulatory rate (syllables/sec), respectively. Speech outcomes (improvement or worsening) following DBS were estimated from percentages of change ([pre - post] / pre \* 100%).

For the patients implanted both in the IP and the STN, our preliminary exploration of data showed an improvement of the majority of speech parameters and in all stimulation conditions, except a degradation of the speech/swallowing sub-score (IP-DBS, IP-STN-DBS, STN-DBS), the shimmer (IP-DBS) and the MPT (STN-DBS). Concerning the patients implanted both in the IP and the thalamus, preliminary results revealed a global improvement in all stimulation conditions, except a degradation of the trunk sub-score (Th-DBS), the shimmer (IP-DBS), the MPT (IP-Th-DBS, Th-DBS) and the articulatory rate (Th-DBS).

Ours preliminary findings suggest that the effects of STN and thalamus DBS are not efficient for the respiratory control. Thus, this study represents a unique opportunity for research and clinical management on speech in IGD.

**P1.097 Dissecting the dynamics of DNA damage repair as a vital component to neuronal development and maintenance in Huntington's disease**  
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There is accumulating evidence for the importance of stress response pathways and cellular compensation systems in modulating HD pathogenesis. Previous studies have highlighted a link between alteration of DNA damage repair and HD pathogenesis (Enokido et al., 2010; Maiuri et al., 2016). Stress resistance and cellular compensation mechanisms such as DNA repair are highly regulated and dynamic systems, calling for a temporal analysis of their efficiency in the course of HD pathogenesis. To this end, we study DNA damage and DNA Damage Response (DDR) in human stem cell models of HD pathogenesis, combining markers of DNA damage levels and reporters of DDR pathway activities in response to Single Strand Breaks (SSB) and Double Strand Breaks (DSB). Our results suggest that the dynamics of DDR may be altered in the earliest phases of the HD process, during neuronal differentiation. We will discuss how understanding the temporal features of DDR alterations in human cells may shed light on HD mechanisms while fostering target prioritization.

**P1.098 Inhibition of Tau aggregation by targeting its nucleation core with a camelid heavy-chain-only antibody**

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Tau proteins aggregate into filaments in brain cells in Alzheimer's disease and related disorders referred as tauopathies. Although the mechanisms leading to these pathological Tau species is not clearly understood, different molecular features have been identified as involved in the aggregation process, including the identification of the peptides motif PHF6\* (275-VQIINK-280) and PHF6 (306-VQIVYK-311) that compose the nuclei of Tau aggregation.

In this study, we used camelid heavy-chain-only antibodies (or VHVs) targeting Tau as immuno-modulators of its aggregation. A synthetic phage-display library of VHVs was screened against Tau. The epitopes recognized by the selected VHVs were defined using Nuclear Magnetic Resonance spectroscopy (NMR). The affinity parameters of each Tau-VHH interaction were determined by Surface Plasmon Resonance (SPR). These two experiments allowed the selection of a VHH targeting the PHF6 motif of the microtubule-binding domain, composing the core of Tau fibrils, with a KD in the nanomolar range. This lead VHH was optimized using yeast two-hybrid to improve its biochemical properties, resulting in VHH Z70. VHH Z70 was more efficient than the lead and fully inhibited in vitro Tau aggregation in heparin-induced assays. Finally, expression of VHH Z70 in a cellular model of Tau seeding decreased the fluorescence-reported aggregation. The therapeutic effect of VHH Z70 is now evaluated in the THY-Tau30 mouse model of tauopathy by using a lentiviral vector approach.

Hopefully, VHH Z70, by targeting Tau aggregation, could provide a new tool to explore strategies of gene therapy and immunotherapy in tauopathies.

P1.099

**Development of a Tau seeding mice model in the P301S-PS19 transgenic mouse**

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**Background:** Neuropathological hallmarks of Alzheimer's disease include intracellular neurofibrillary, tau-containing tangles, extracellular β-amyloid-containing plaques and a likely interrelated impairment of synaptic structure and function. Since many clinical trials aimed at clearing neurotoxic species of β-amyloid have failed to demonstrate efficacy, tau-based treatments have become a point of increasing focus, including the development of tau-aggregation inhibitors. In order to characterize such agents and *in vivo* validate novel tauopathy-targeting hypotheses, well-established rodent models are essential. Accordingly, we developed *in vivo* disease-relevant models of tau aggregation by using tau seeds derived from transgenic mouse tissue.

**Methods:** Pathological tau was extracted from 9 months old Tau-P301S mice (PS19 line) and used as seeds to promote aggregation in young Tau-P301S mice. Different experimental conditions have been evaluated (number of injections, different brain areas, 1 and 3 months post-injection time) to promote tau pathology formation. Tau aggregates were biochemically measured by an homogenous time-resolved fluorescence (HTRF) assay. Histologically, specific tau stainings were done performed by immunochemistry (AT8 and MC1 markers) to evaluate the onset of tau pathology.

**Results:** Tau seeds derived from TauP301S-PS19 mice were able to induce progressive tau aggregate formation at the site of infusion after 3 months post-injection. A significant increase of tau aggregate amount was observed on HTRF assay. Moreover, intense MC1 and AT8 stainings were also detected after 3 months post-injection.

**Conclusions:** We have developed an inducible *in vivo* model of tau aggregation using tau seeds derived from TauP301S-PS19 transgenic mice. Complementary studies are currently underway to optimize our experimental conditions in order to minimize potential variability due to seed competencies or intracerebral injections. Finally, the development of such an induced-tauopathy model in TauP301S-PS19 mice will be useful to assess *in vivo* efficacy of small molecules inhibitors of tau aggregate formation.

**P1.100 Cocaine-induced epigenetic modifications of the endocannabinoid system in brain reward regions**

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Drug addiction is a complex pathology inducing long-term neuroplasticity. Understanding the neurochemical mechanisms underlying the reinforcing effects of drugs of abuse is critical to reduce the burden of drug addiction in society. The endogenous cannabinoid system (ECS) is strongly involved in the modulation of drug reward. The ECS comprises endocannabinoids (ECB), enzymes for their synthesis and degradation, and two well characterized receptors, CB1 and CB2, both coupled to Gi/Go proteins. Blocking CB1 decreases cocaine-seeking while CB2 activation reduces cocaine intake. However, the underlying mechanisms of this modulation remain poorly understood. In this study, we investigated whether chronic cocaine treatment induces long-term adaptations including transcriptional modifications and their potential associated epigenetic processes. We first examined gene expression following either passive- (intraperitoneal injections (IP), 20mg/kg, 10 days) or voluntary-cocaine (intravenous self-administration (SA), 0.33mg/kg, FR1, 10 days) in reward related rat brain regions. Interestingly, despite almost no regulations induced by cocaine-IP, we found an increase of CB1 gene expression in several structures with cocaine-SA, with a marked increase in the hippocampus (Hipp). Chromatin immunoprecipitation followed by qPCR revealed, in the Hipp, that histone modifications (H3K4Me3 and H3K27Ac) were enriched by cocaine-SA at ECS genes. Using chromosome conformation capture, we will investigate whether cocaine-SA induces interaction changes at ECS gene promoter loci. With GTPYS binding and immunofluorescence, we demonstrated an enhancement of CB1 receptor activity without protein expression regulation in the Hipp of cocaine-SA animals. Finally, ECB levels measured by mass spectrometry were specifically increased in the Hipp. Our data suggest a key role for the Hipp in ECS adaptations following voluntary cocaine intake, suggesting a major role for the ECS in reward associated-memories.

**P1.101 The role of external tufted cells in olfactory processing**

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Olfaction undoubtedly plays a vital role for an animal to assess its environment. Odorant molecules attach to olfactory receptors which are expressed by olfactory sensory neurons (OSNs) situated in the olfactory epithelium within the nasal cavity. OSNs project their axons to the olfactory bulb (OB), the forebrain area that evolved to specifically decode odorant information. The first step of olfactory processing takes place in the glomeruli. Glomeruli are spherical structures where OSN axons converge in a receptor-specific manner. These axons make contact with a variety of interneurons before the olfactory input reaches the OB output neurons. Interestingly, while most OB interneurons are inhibitory, there is also one type of excitatory OB interneuron: external tufted cells (ETCs). Although ETCs have been subject of many *in vitro* studies and computational models, *in vivo* data still remains scarce and thus our understanding of their role in the OB circuit remains fragmentary.

Here, we use NeuroD6Cre/tdTomato/GCaMP6s mice that specifically mark excitatory neurons of the OB to study odor-evoked neuronal activity in anesthetized and awake mice. By acquiring a three-dimensional structural image before onset of odorant stimulation, we are able to unequivocally assign ETCs to their affiliated glomeruli and study their dynamics as cell ensembles. We found that ETCs readily respond to odors and display excited, inhibited and mixed responses. Moreover, when ETCs show excited or mixed odor-responses, they act as cell ensembles, i.e. the majority of cells are engaged in a response. Interestingly, this observation does not hold true for inhibitory responses. Furthermore, we show that odor-responses change significantly when animals were anesthetized or awake, suggesting that ETCs are likely targeted by cortical structures which are active during wakefulness. Taken together, our results represent the first *in vivo* study of excitatory ETCs and thus bridge the current gap between *in vitro* and *in vivo* data available on ETC function.

**P1.102 Specific reorganization of striatal network dynamics during habit formation**  
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Procedural memory, the memory of habits, is formed by the repetition of a given action. The neural substrates underlying this memory are the basal ganglia, long known to be critical for normal motor control, but now also recognized as influencing cognitive and motivational aspects of behavior. The striatum, the input stage of basal ganglia, relays information between the cortex and other subcortical structures, thus insuring the selection and integration of cortical information by forming functional parallel loops (associative, sensory-motor and limbic). The associative loops include the dorsomedial striatum (DMS) and mediate the first phase of procedural learning (goal-directed behavior). The sensorimotor loops include the dorsolateral striatum (DLS) and mediate habit formation. Although the anatomy of the circuits involved in procedural learning has been well described, virtually nothing is known about the dynamics of the striatal networks responsible for the engram of procedural memory.

The goal of our study was to characterize the dynamics of the striatal networks involved in the different phases of procedural learning. Using an accelerated rotarod paradigm, we formed procedural memory in animals with moderate or intensive training to form goal-directed behavior and habit, respectively. We monitored the striatal networks' activity using two-photon calcium imaging and we processed the signal to build functional maps of the networks. We first observed that in naïve animals, DMS and DLS networks have different properties. Then, after training, we observed a re-organization of the networks' activity with different patterns emerging in the two territories.

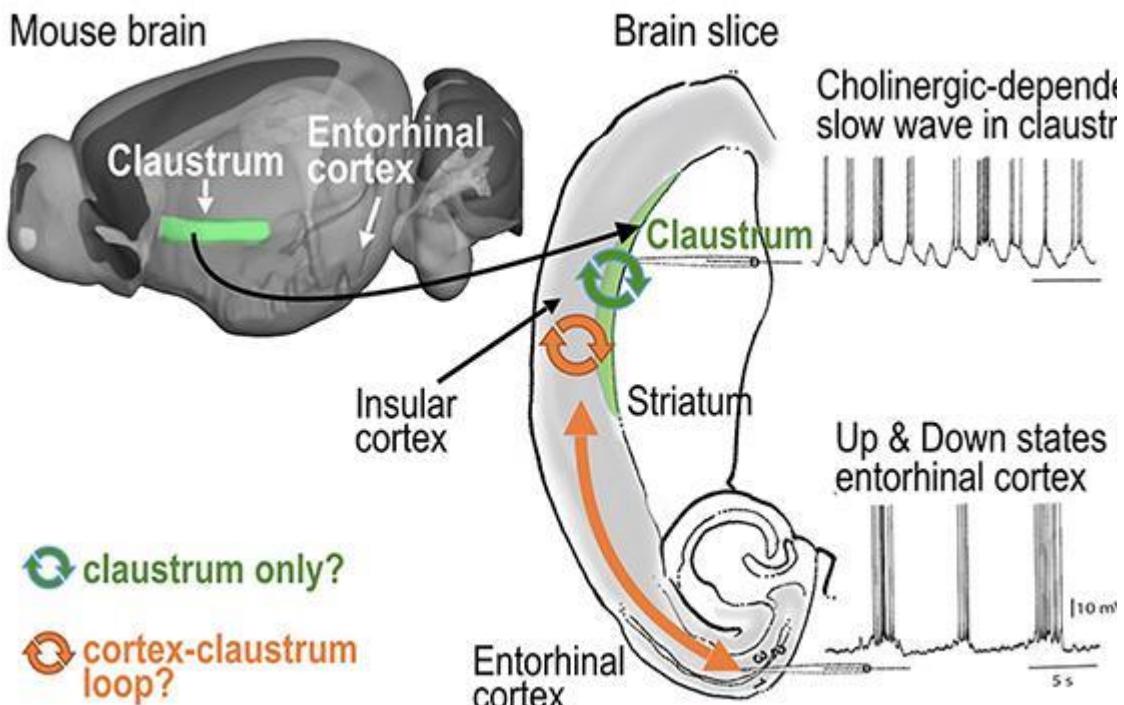
Altogether, our findings show a rapid and major territory-specific change in the striatal network dynamics during procedural learning.

**P1.10 Cholinergic-dependent slow-wave activity in the claustrum *in vitro***

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The claustrum (and the endopiriform nucleus) form a complex containing a small proportion of interneurons and a majority of far-projecting excitatory neurons that lay deep below the insular cortex. It is the most reciprocally connected structure in the brain and receives cholinergic and a variety of neuromodulatory inputs from subcortical structures (Goll et al., 2015). Its functional role remains largely unknown. It has been proposed to be a “seat of consciousness” (Crick & Koch, 2005), a hub for attention (Atlan et al., 2018), for multi-sensory binding, or for the synchronization of neocortical slow-wave activity (Narikiyo et al., bioRxiv 2018). Little is known on the claustrum circuit properties or on its cell-types: the membrane and synaptic properties, the sensitivity to neuromodulation, and spontaneous states of activities. We use techniques to preserve recurrent slow oscillations (resembling the *in vivo* up & down states) in cortical circuits in mouse brain slices. In a slice that contains parts of the claustrum and neocortex, we found that the claustrum generates two different types of activities. 1) A spontaneous and moderate spiking discharge in individual neurons generated by background synaptic activity appears randomly, can last seconds to minutes, and returns to quiescent periods reminiscent of the down states of cortical circuits. 2) Application of the cholinergic agonist carbachol induces a robust 0,5-1 Hz rhythmic recurrent network activity in about 50% of the slices. We are exploring the mechanisms of this claustrum slow-wave activity: Does it result solely from the interactions of neurons within the claustrum, and/or is it due to synaptic loops between the claustrum and neocortex, such as the adjacent insular cortex, or the entorhinal cortex that spontaneously generates Up & down states in the same slice?



[Recurrent rhythmic activity in the claustrum *in vitro*]

P1.104

**Cortical recruitment determines learning dynamics and strategy**

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Salience is a broad and widely used concept in neuroscience whose neuronal correlates, however, remain elusive. In behavioral conditioning, salience is used to explain various effects, such as stimulus overshadowing, and refers to how fast and strongly a stimulus can be associated with a conditioned event. Here, we identify sounds of equal intensity and perceptual detectability, which due to their spectro-temporal content recruit different levels of population activity in mouse auditory cortex. When using these sounds as cues in a Go/NoGo discrimination task, the degree of cortical recruitment matches the salience parameter of a reinforcement learning model used to analyze learning speed. We test an essential prediction of this model by training mice to discriminate light-sculpted optogenetic activity patterns in auditory cortex, and verify that cortical recruitment causally determines association or overshadowing of the stimulus components. This demonstrates that cortical recruitment underlies major aspects of stimulus salience during reinforcement learning.

**P1.105**

**Implication of the cortico-spinal pathway in sensory-motor control**

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A well-coordinated movement relies on a properly planned motor command. But it also requires to distinguish, among sensory inputs, those that are “expected” (because it is linked to the motor command itself) from the more “relevant” one (that might require correcting the ongoing movement). The cortex is involved in both these functions, and it has been recently hypothesized that it does so through a common pathway: the corticospinal tract (CST). The goal of this study is to unravel how the cortical filtering of sensory inputs hinges on the cortical motor command itself to produce well-coordinated voluntary motor behaviors. As serious motor afflictions can result from dysfunction of these circuits, their better characterization could unveil potential therapeutic targets.

We started by mapping the regions of the cortex that elicit muscle contractions and sensory filtering using photostimulation. Then, in the identified area, we injected a virus encoding for the trans-synaptic tracer wheat Germ agglutinin (WGA) fused to the cre-Recombinase. Together, we injected in the spinal cord a virus encoding for Cre-dependent form of ChannelRhodopsin2. This allowed us to identify CST's postsynaptic neurons in the spinal cord, to analyze their localization and nature, and to test the effect of their specific activation *in vivo*.

We first demonstrate that the same area of sensorimotor cortex evokes both muscular contraction and primary afferent depolarization (PAD), i.e. sensory filtering. We show that CST neurons located in the area in charge of top down sensory-motor control project in the spinal cord onto interneurons located in the deep dorsal horn (lamina IV to VII).

Importantly, their selective activation leads exclusively to PAD, but no muscle contraction. This result suggests that while sensory filtering through PAD and muscular contractions originates from the same region of the sensory-motor cortex, they diverge in their pathways and reach different populations of neurons in the spinal cord. PAD is controlled by the CST whereas the motor command is indirect and convey its message through subcortical structures.

**P1.106 Dynamics of privileged processing of straight-ahead visual stimuli in human cortex**  
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Processing of peripheral visual stimuli localized straight-ahead the body is privileged in primates. In macaque, this privileged processing is characterized by a higher neural sensitivity in visual area V1. In human, it is reflected by stronger BOLD responses in early visual areas and faster detections but the dynamics of this privileged processing remain unknown. To characterize when neural responses from human cortex are modulated by straight-ahead location of peripheral visual stimuli, we measured the event-related potentials (ERPs) in response to brief presentation of checkerboard wedges in 28 subjects. Those checkerboards were localized along the horizontal meridian at 10°, either leftward or rightward the point of fixation. To modify their position relatively to the body, we manipulated gaze direction which was 10° either to the left or to the right of the straight-ahead direction. Subjects were involved in a simple detection task to maintain their attention on the stimuli. We used Matlab to pre-process (band-pass filter, artifact rejection and mean referencing) the data and estimate the ERPs and their associated Global Field Power, peak amplitudes and statistical parametric maps. Straight-ahead stimuli led to stronger responses than eccentric stimuli for different peaks (P1, N1, P3) whose latencies ranged between 80 and 350ms after stimulus onset. The earliest effects were found at 80ms for a component that reflects responses from low to mid-level retinotopic areas, the contralateral P1. To determine whether the straight-ahead direction can lead to earlier effect, specifically in primary visual cortex, we performed an additional experiment ( $n = 28$ ) within which the checkerboard wedges were localized in the four visual quadrants. This paradigm is known to generate two robust components, the C1 and C2, whose cortical origins are constrained within areas V1, V2 and V3. Our analyses confirmed all the results of the first experiment and also revealed that the C2 (but not the C1) amplitude between 130 and 160ms after stimulus onset was significantly stronger for straight-ahead stimuli. Altogether, our EEG data suggest that the straight-ahead direction is associated with stronger responses from visual cortex as early as 80ms after stimulus onset.

**P1.107 Complex selectivity to sounds in inferior colliculus and in primary auditory cortex p**  
**{margin-bottom: 0.1in; line-height: 120%}**

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The auditory system, as other sensory systems, is thought to be hierarchically organized encoding increasingly complex features from peripheral to more central stages. Yet the precise transformations of auditory representations across stages of the most central auditory system are not fully characterized. To start addressing this question in a systematic manner, we extensively recorded responses in the supragranular layers of the auditory cortex (AC) and the superficial layer (0-200 µm) of the inferior colliculus (IC) using two-photon microscopy in awake mice. Each of the 148 laboratory sounds (including pure tones, AM sounds, chirps, chords, chirps of different lengths, ramps in intensity) was presented 15 times. We thereby collected a dataset of 59590 neurons (7 mice, 60 sessions) in the AC, fully sampling the horizontal extent of AC, as assessed with global tonotopic mapping. We also obtained activity from 15311 neurons in the IC (31 mice, 101 sessions).

Using model-free clustering to organize this rich dataset, we observed many sound response types, which clustered in few hundred groups of functionally identical cells. These clusters often displayed non-linearities (NL) in both AC and IC, such as non-monotonic intensity tuning and direction preference for linear intensity or frequency modulations, non-additive responses to chords, tuning for frequencies modulation speed and others. Many of these NL were described previously, but in isolation. In this study, we assess systematically their co-occurrence in the same neurons, and show that some NL are mutually exclusive, others are systematically co-occurring and others are randomly associated with each other. Thus the auditory system encodes selected combinations of non-linear sound features that could serve as building blocks for representing auditory objects (1). Moreover, and somewhat surprisingly, we found several groups of cells, in the IC and in the AC, which had identical selectivity to all the presented sounds.

P1.108

### The associative parietal cortex in rats: a multimodal motion hub?

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In a constantly moving environment, our brain builds up a stable representation of the motion of objects and oneself. Most frequently, motion information is brought to the central nervous system through several sensory channels simultaneously. Their integration into a unique percept enables the disambiguation of signals if needed and the facilitation of perception. While visual motion is processed in the well-studied area *Middle Temporal* area (MT) in primates, the processing and multisensory integration of motion signals in rodents is less well understood.

This study is aimed at characterizing the visuo-tactile integration of motion information in the rat's APC, a potential zone of multisensory convergence, located at the interface of the primary visual and somatosensory cortices.

The stimuli, intended to mimic both exo- and egocentric motions, were moving visual gratings and air-puffs deflecting all the whiskers in the anteroposterior axis. Using voltage-sensitive dye imaging we observed the convergence of visual and tactile stimuli-evoked activations onto the APC, propagating from the primary sensory cortices. The electrophysiological unit recordings of over 900 APC neurons allowed us to show that this region contains both unimodal (visual or tactile only) and bimodal neurons. Analogously to MT properties, we revealed both direction and speed selectivity in APC visual neurons. Remarkably, not only the visual but also the somatosensory neurons showed direction selectivity during whisker displacement, proving APC's ability to compute motion from several channels. To be considered as a multisensory integration area, the APC must also contain multimodal neurons that extract and combine unimodal motion features. Visual and somatosensory direction selectivity in the bimodal population (388 neurons) was also observed, meeting the requirement for potential multisensory integration of motion.

By combining the visual and tactile motion stimuli and by modulating the congruency, we revealed multisensory integrative processes. These results strongly suggest that APC, potential homolog of MT, is a multimodal hub for motion processing. Gathering and processing all sensory information about motion in a unique area could be a parsimonious way to build up a unified percept.

**P1.109 Frequency-dependent short-term synaptic plasticity of GABAergic connections onto lamina II neurons**

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Nociceptive information conveyed from the periphery by primary afferents is integrated in the dorsal horn of the spinal cord before being forwarded to brain areas. Frequency is a key parameter for coding information by primary afferents, suggesting that short-term synaptic plasticity may be involved in information processing by dorsal horn networks. Our aim is to examine the short-term synaptic plasticities engaged during repeated recruitment of inhibitory connections within lamina II.

Using spinal cord acute slices prepared from adult transgenic mice expressing Green Fluorescent Protein (GFP) under the GAD65 promoter, we performed patch-clamp recordings of unitary GABAergic synaptic currents evoked by local electrical stimulation. We assessed the frequency dependence of these short-term plasticities and we examined whether distinct plasticities were expressed by connections involving GAD+ or GAD- neurons as postsynaptic elements.

Our data indicate that GABAergic synapses onto lamina II neurons express frequency-dependent short-term synaptic plasticity. This short-term plasticity depends on the excitatory/inhibitory nature of the postsynaptic target.

**P1.110 Targeted cortical manipulation of auditory perception**

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Driving perception by direct activation of neural ensembles in cortex is a necessary step for achieving a causal understanding of the perceptual code and developing central sensory rehabilitation methods. Here, using optogenetic manipulations during an auditory discrimination task in mice, we show that auditory cortex can be short-circuited by coarser pathways for simple sound identification. Yet, when the sensory decision becomes more complex, involving temporal integration of information, auditory cortex activity is required for sound discrimination. More importantly, targeted activation of specific cortical ensembles changes perceptual decisions as predicted by our readout of the cortical code. Hence, auditory cortex representations contribute to sound discriminations by refining decisions from parallel routes.

**P1.111 Fear memory engram and its plasticity in the hypothalamic oxytocin system**  
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Oxytocin (OT) release by axonal terminals onto the central nucleus of the amygdala exerts anxiolysis. To investigate which subpopulation of OT neurons contributes to this effect, we developed a novel method: **virus-delivered Genetic Activity-induced Tagging of cell Ensembles** (vGATE). With the vGATE method we have identified and permanently tagged a small subpopulation of OT cells, which, by optogenetic stimulation, strongly attenuates contextual fear-induced freezing. Pharmacogenetic silencing of tagged OT neurons impaired context-specific fear extinction demonstrating that the tagged OT neurons are sufficient and necessary in controlling various aspects of contextual fear. Intriguingly, OT cell terminals of fear-experienced rats displayed enhanced glutamate release in the amygdala. Furthermore, rats exposed to another round of fear conditioning displayed five-fold more activated magnocellular OT neurons in a novel environment than a familiar one, possibly for a generalized fear response. Thus, our results provide first evidence that hypothalamic OT neurons represent a fear memory engram.

**P1.112 Atypical cortico-subcortical functional connectivity in developmental dyslexia and developmental coordination disorder**

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Developmental dyslexia (DD) and developmental coordination disorder (DCD) affect 2-10% of the school-age population. Children with DD often present sensorimotor abnormalities, suggesting that DD and DCD share some common ground. The main proposal is that DD and DCD are linked to problems with the procedural learning system. Neural substrates of this system are reasonably well understood, with cortico-subcortical connections playing critical roles. We studied whether impaired intrinsic cortico-cerebellar and cortico-striatal functional connectivity are hallmarks of DD and/or DCD. 136 right-handed children (8/12 years) participated in the study, including 45 DD children, 20 DCD children, 29 DD-DCD children, and 42 typically developing (TD) children. Children with DD and/or DCD met the DSM-V diagnostic criteria. Subjects were scanned over two sites (Toulouse or Marseille, France) using T1-weighted MPRAGE and EPI rs-fMRI sequences performed on 3T MRI scanners with a 32-channel head coil. The study was approved by the local ethics committees and was conducted in accordance with the Declaration of Helsinki. Processing pipeline for rs-fMRI images included pre-processing steps and seed-driven functional connectivity with aCompCor noise reduction. Cerebellar and striatal seed regions were associated to common functional systems (visual, somatomotor, dorsal/ventral attention, limbic, frontoparietal, default). Fisher-transformed first-level connectivity maps were used in univariate GLM and multiple kernel learning (MKL) classification. Univariate results showed reduced functional connectivity of the cortico-cerebellar somatomotor pathway in DCD and DD-DCD children compared to TD and DD children. A reduced functional connectivity of the cortico-striatal frontoparietal pathway was also found in children with learning disorders compared to TD children, this lower than normal connectivity being the most reduced in DCD/DD-DCD children. Combining cortico-cerebellar somatomotor and cortico-striatal frontoparietal maps, MKL distinguished between TD and DCD/DD-DCD children with good accuracy (balanced accuracy: 73.81%; p=0.001). Thus, DD and/or DCD have atypical cortico-subcortical functional connectivity, with prominent findings in the frontoparietal and somatomotor systems.

### Prenatal chronic exposure to titanium dioxide nanoparticles alters breathing in neonates

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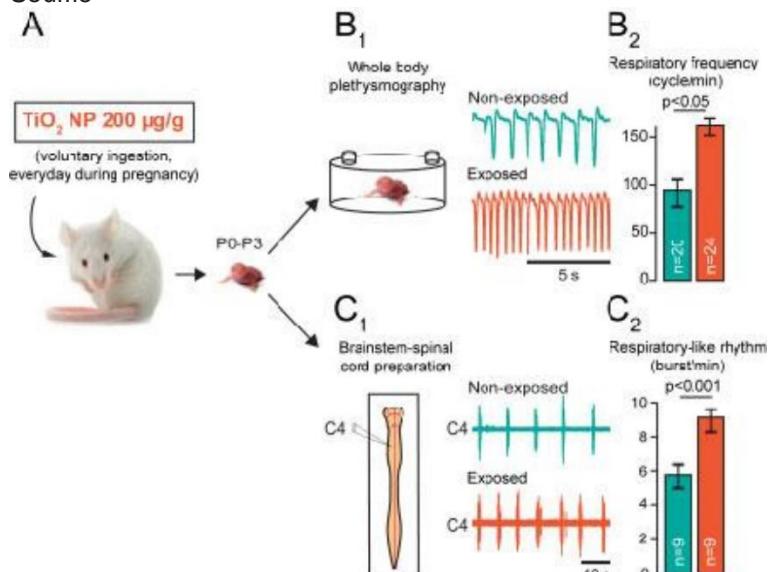
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Nanotechnologies and **nanoparticles** represent one of the greatest technological advances since the last two decades. This allows significant innovations in numerous fields as technology (such as energy or computer), food industry, cosmetic and medicine. However, materials that are generally thought to be inert may react differently when introduced in the body as nanosized particles.

**Titanium dioxide nanoparticles** ( $\text{TiO}_2$  NPs) are one of the five most used nanomaterials found in everyday consumer products (toothpaste, paint, drugs, cosmetics). It is also noteworthy that, due to their extremely small size, nanoparticles can cross different biological barriers (such as the blood-brain barrier) and can cause adverse effects on human health. Although some studies have reported neuronal damages and cognitive dysfunctions in animals chronically exposed to  $\text{TiO}_2$  NPs, knowledges of their impact on motor functions such as **respiration** remain poorly documented.

Here we show that a chronic exposure to  $\text{TiO}_2$  NPs of pregnant mice (Fig. 1A) affects respiratory activity of offspring, characterized by an abnormal elevated respiratory frequency in prenatally-exposed neonates (Fig. 1B). Similarly, experiments conducted in *ex vivo* conditions show that the respiratory-related rhythm, spontaneously generated by brainstem-spinal cord preparation of newborn mice, is significantly and abnormally higher in exposed animals than control (Fig. 1C). Therefore, our results clearly show that **prenatal exposure to  $\text{TiO}_2$  NPs may affect development and operation of respiratory centers in the neonate**.

**Financial support:** "Fond de Recherche en Santé Respiratoire" and "Fondation du Souffle"



**Figure 1. Prenatal exposure to  $\text{TiO}_2$  NPs abnormally increases respiratory frequency in neonates.** (A) Protocol of gestational exposure to  $\text{TiO}_2$  NPs. (B1) Illustration of plethysmographic chamber (left) and recordings of respiration in nonexposed (green) and exposed (orange) neonatal mice (P0-P3). (B2) Histograms showing the respiratory frequency in nonexposed (green) and exposed (orange) neonates. Bars represent mean values and vertical lines represent SEM. (C1) Schematic illustration of brainstem-spinal cord preparation from neonatal mouse (left) and recordings of cervical (C4) ventral root activity in non-exposed (green) and exposed (orange) newborn animals. (C2) Histograms showing spontaneous respiratory-like activity in non-exposed and exposed neonates. Bars represent mean values and vertical lines represent SEM.

[Colnot et al. (2019) NeuroFrance, Marseille]

**P1.114 Modulatory effects of hand position relative to visual stimulus position on neuronal activity in multiple cortical sensorimotor systems**

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During reaching behavior, eye and hand movements are tightly coordinated through the continuous processing of sensory and motor signals [1, 2]. This interaction between eye motor and hand motor systems requires widely distributed neuronal network dynamics from visual input to motor output [3, 4]. Our goal is to investigate large-scale neuronal activity in visual areas V1, V2 and DP (dorsal prelunate), posterior parietal area 7A, and motor areas M1 and PMd in response to different coordinated eye-hand behaviors. We collected eye and hand movement data from a trained female macaque, together with massively parallel electrophysiological recordings from five chronically implanted high-density microelectrode ('Utah') arrays in all above-mentioned areas. Preliminary results show that during center-out movements, the discharge frequency of neurons from all cortical areas varied significantly in relation to movement direction. Analyses at a finer temporal scale reveal to what extend visual, parietal and motor areas coordinate and update their activities during different phases of the task, from movement planning to execution. These results offer an insight into multi-area functional interactions during complex visuo-motor behavior.

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[<sup>2</sup>] Reina, G., & Schwartz, A. B. (2003). Eye hand coupling during closed-loop drawing: Evidence of shared motor planning? *Human Movement Science*, 22(2), 137-152.  
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**P1.115 Neural activity in the barrel cortex of freely behaving mice during cortical remapping**

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Sensory cortices are organized in topographic maps characterized by a precise spatial distribution of sensory inputs that are essential to perception and sensory-guided action. These maps remain highly dynamic and show plasticity in response to training, altered sensory use, and injury. The whisker map system in rodent somatosensory cortex has emerged as a canonic model system for investigating such experience-dependent map plasticity. For example, the deprivation of all but one whisker (SWE, single-whisker experience) drives the representation of spared inputs to expand over deprived barrels. Although this activity-dependent reallocation of neuronal resources is thought to reflect long-lasting changes in synaptic strength that eventually results in the selection of behaviorally-relevant sensory inputs, much less is known about the driving force for such plasticity mechanisms and how it impacts sensory-guided behavior. Here, we investigated the activity of neurons driven by sensory perception during cortical remapping (SWE). We combined tetrode recordings and intrinsic optical imaging to monitor over time the activity of neurons in deprived and spared barrels of mice performing a whisker-dependent behavioral task. The so-called gap-crossing paradigm requires the mouse to jump a gap between two suspended platforms after palpating the far side with its whiskers in order to get a reward on the other side. Our data showed that specific units increased their firing rate during the detection of the platform edge location in successful trials. After SWE, mice showed reduced behavioral performance associated with a decreased firing rate of single units in the deprived barrel during the detection of the edge location. After learning, the improvement in behavioral performance was associated to the increase in the responses of single units in the deprived barrel during the detection of the edge location. Altogether, our data suggest that, after SWE, neurons in deprived barrel cortical columns are increasingly engaged in the computation that mediates the perception of edge location.

**P1.116 Delayed syngeneic transplantation of nasal olfactory stem cells improves locomotion and axogenesis after peroneal nerve injury**

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Over the recent years, several methods have been experienced to repair injured peripheral nerves. Among investigated strategies, the use of natural or synthetic conduits was validated for clinical application. In this study, we assessed the therapeutic potential of olfactory stem cells (OSC) transplanted in vein guides, two weeks after peroneal nerve loss.

Fisher adult female rats were randomly allocated to six groups. Animals with a 2 mm peroneal nerve loss were repaired with a 1 cm long femoral vein, filled or not with OSCs, two weeks post-injury. These two groups were compared to unoperated rats (control group) and rats immediately autografted with the nerve section in an inverted position (gold standard group). Olfactory stem cells were purified from male olfactory mucosae. Three months after surgery, nerve repair was analyzed by measuring locomotor index, muscle mass, maximal relaxation rate, axon number and myelination.

Our study reveals that stem cell transplantation, when delayed two weeks after surgery, significantly increases

- i) locomotor recovery,
- ii) muscle maximal relaxation rate and
- iii) axogenesis.

In addition, it has been observed that OSCs remain in the nerve and do not migrate in other organs. These promising results open the way for a phase I/IIa clinical trial based on the autologous engraftement of OSCs in patients with a neglected nerve wound.

**P1.117 Theta-gamma coupling dynamics in the dentate gyrus across learning of goal-directed spatial navigation**

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The hippocampal formation is strongly involved in spatial representations but surprisingly few studies have highlighted hippocampal activity specific to the destination at the start of goal-directed navigation. We previously identified a potential correlate of such representation in the molecular layer of the dorsal dentate gyrus (DG) of freely-moving mice, that developed across training in a modified version of the Barnes maze task (Bott et al., 2015). Bouts of theta (4-12 Hz)-gamma (60-100 Hz) phase-amplitude coupling were observed several seconds before arrival to the target area in the DG but not in dorsal CA1 (*stratum radiatum*). This activity might mediate the temporal organisation and transfer of the representation of the planned trajectory to the goal. Hence, to better estimate when the animals choose their navigational path, we used a new task based on a reference-memory radial maze task presenting more obvious decision points (exit/entry of each arm).

Preliminary results (n=3 mice) replicate and extend the previous observations: the dentate theta-gamma coupling increased across training days before the mice committed to the correct arm, but not before entering adjacent non-rewarded arms. More specifically, the coupling between theta and 1) 60-100 Hz gamma would occur at the entry of the correct arm, and 2) 100-140 Hz gamma, from the exit of the starting arm to the arrival to the reward. However, the frequency range of the coupled gamma appears broader and less constant in the DG than in CA1, suggesting these two sub-bands might not adequately reflect the dynamics of the dentate theta-gamma coupling. For this reason, we use an unsupervised algorithmic approach to identify typical gamma bursting patterns. We find that a continuum of gamma burst types exists, contrasting with scenarios proposing only a discrete number of gamma types. However, this continuous repertoire is sampled in a temporally structured manner, giving rise to complex switching sequences of bursts. We are now investigating the theta-gamma coupling dynamics along the trajectory on a theta cycle-by-cycle basis.

**P1.118 Neural circuit dynamics underlying first-order motion energy perception in the zebrafish larva**

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Interactions with the external world rely on sensory receptors which transmit information to the brain. The analysis of this information and the generation of adequate motor behaviors depends on the ability of the brain to detect from the external scene the elements that are biologically relevant for the larva.

Moving stimuli consisting of square-wave gratings can be modulated by attenuating the power of the fundamental frequency (first Fourier component). Orger et al (2000) showed that the zebrafish larva uses dominantly first-order signals (pure sinus waves) for motion detection, and that for a stimulus whose features and principal Fourier component move in opposite directions the larva would follow the Fourier motion energy.

In my project, I am investigating how stimuli with or without the first Fourier component (square-wave signal or missing fundamental signal), capable of inducing a similar behavioral output, are represented in the zebrafish brain.

For this purpose, I used two-photon microscopy to record neuronal circuit dynamics in the optic tectum and the pretectum (the two main visual centers in teleost fish) of zebrafish larvae expressing GCaMP6f.

In the optic tectum, I found neurons that responded to the directionality of the square-wave signal, whereas the responses to the missing fundamental signal were independent of the direction of movement. In the pretectum, I observed neurons that respond to these two types of stimuli, but also neurons responsive to the perceived direction of the stimulus' movement (highly correlated with the directionality of the optokinetic behavior), independently of the type of stimulus presented (square signal, missing fundamental, etc.). In both the tectum and the pretectum, the neurons responsive to the missing fundamental signal responded also to the static signal. I am currently investigating more precisely to which characteristics of the signal those cells are reacting to.

Overall, these results might shed light on the functional interactions between the pretectum and the optic tectum leading to visual perception in the vertebrate system.

**Reference:** M. B. Orger, M. C. Smear, S. M. Anstis, and H. Baier, "Perception of Fourier and non-Fourier motion by larval zebrafish." Nat. Neurosci. 2000 Nov;3(11):1128-33.

**P1.119 Large sway enables cortical sensory facilitation during natural standing: combined behavioral, EEG and microneurographic approaches**

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During standing, activation of the foot sole receptors largely depends on the speed and amplitude of the body oscillations. We hypothesized that during natural standing, small body sways may not generate sufficient somatosensory transmission to the cortex, due to continued skin compression (i.e. depressed signal transmission). Under such circumstances, central mechanisms would trigger a large sway to gather plantar tactile information. To test this hypothesis, we compared the amplitude of the P<sub>50</sub>N<sub>90</sub> somatosensory cortical potentials evoked by electric stimulations of the foot sole during either small and large sways produced in 16 young adults that were standing still with the eyes closed. Our results showed greater P<sub>50</sub>N<sub>90</sub> SEP amplitude during large sways as compared to small sways, consistent with an increased sensory transmission in the former case. The depressed sensory transmission observed during small sways is coherent with our microneurographic recordings showing adaptation/suppression of tactile fibres discharge during continuous pressure applied to the mechanoreceptors. Our hypothesis that large sways during standing correspond to a self-generated functional behaviour to release skin compression is supported by cortical source and EMG analyses showing respectively that large sways were preceded by activation of cortical areas known to be engaged in motor planning (superior parietal cortex, supplementary motor area, and the dorsolateral prefrontal cortex) and by ankle muscle activations. The present findings provide evidence for an important sensory function of large body sways for maintaining equilibrium.

- P1.120 Interplay between intact and injured hemispheres in cortical map remodeling and functional recovery after focal ischemic stroke to the primary somatosensory cortex**  
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After ischemic injury to S1, most studies have focused on the remodeling of perilesional areas and its role in functional recovery. In contrast, consequent alterations within the contralesional cortex remain poorly understood despite its involvement in the functional recovery. Our study investigates in rats the time-course of cortical cutaneous map remodeling in the intact hemisphere following unilateral focal ischemic damage to S1. In parallel behavioral deficits are assessed in order to better understand the role of hemispheric interactions in functional restoration. Using electrophysiological mapping and behavioral tests, we explored the post-lesion changes within the cutaneous representation of the non-affected forepaw at several time points during four weeks after the cortical damage induction. We also used behavioral tests assessing tactile sensitivity and sensorimotor coordination. Cortical maps show a representational dedifferentiation inducing a degradation of the somatotopic organization starting from 1 hour and worsening until 14th post-injury day. These changes are underpinned by a dramatic enlargement of cutaneous receptive fields accompanied with an increase of neuron sensitivity to mechanical stimulation of the skin that mainly occurred over the first two weeks postlesion. Our behavioral observations show a strong impairment of tactile sensitivity and sensorimotor adjustments for the forepaw contralateral to the injured hemisphere, that gradually abated. No impairment was observed for the intact forepaw during behavioral assessments. Interestingly, a substantial, yet incomplete, restoration of somatotopic organization was found to occur over the first month. This partial restoration appeared to be temporally related to the time course of the functional recovery. These data are in line with the model of lesion-induced alterations of the interhemispheric imbalance as they are compatible with the transitory decrease of inhibition originated from the injured to the intact cortex. Our findings underscore the critical role of hemispheric interactions in maintaining a fine somatotopic organization of cutaneous maps in the intact brain and suggest a major implication of the interhemispheric balance in the functional recovery following focal stroke.

- P1.121 Spatiotemporal properties of whisker-evoked tactile responses in the mouse secondary somatosensory cortex**  
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Because of its unique cellular organization, which makes the functional units of the cortex clearly distinguishable, the representation of rodents' mystacial vibrissae within the primary somatosensory (S1) cortex has become an important model for studying the cortical processing of tactile sensory information. However, upon vibrissal stimulation, tactile information first reaches S1 but also, almost simultaneously, the secondary somatosensory cortex (S2). The rapid activation of S2 neurons is likely to rely on the direct projections it receives from the thalamus. Hence, although S2 is considered as a higher order area in comparison with S1, cortical processing of tactile information does not follow a strict serial scheme in rodents. Knowledge about the involvement of S2 in the integration of vibrissal tactile information remains limited.

Electrophysiological recordings made in S2 show generally larger receptive fields than in S1. Analysis of responses to complex multi-whisker stimuli in anesthetized rats have recently revealed that S2 neurons are likely to integrate sensory information over larger time and spatial scales compared to S1 neurons. Studies on behaving mice have suggested that a cortical representation of the tactile scene could emerge through coordinated activity between S1 and S2, which are densely interconnected in a reciprocal and topographic manner.

To further understand the role of S2 in the processing of whisker inputs it is essential to describe the spatiotemporal properties of whisker-evoked activity dynamics in this area. The topography of the whisker representation in S2 has been functionally explored in rats using surface electrodes but reported rather qualitatively in mice. Here we aim at providing a thorough description of the topography of the whiskers representation in the mouse S2 by means of functional voltage sensitive dye imaging. Quantitative analysis of the spatial properties of the early S2 responses induced by stimulating individually 24 whiskers in 7 mice revealed that they are spatially ordered and occur in a mirror symmetric map compared to S1 responses. Our results further show similar amplitude of evoked signals in S2 relative to S1, and confirm a very short delay (< 3ms) between S1 and S2 early activation.

**P1.122 Cholecalciferol (vitamin D3) reduces rat neuropathic pain by modulating opioid signaling**

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The impact of vitamin D on sensory function, including pain processing, has been receiving increasing attention. Indeed, vitamin D deficiency is associated with various chronic pain conditions, and several lines of evidence indicate that vitamin D supplementation may trigger pain relief. However, the underlying mechanisms of action remain poorly understood. We used inflammatory and non-inflammatory rat models of chronic pain to evaluate the benefits of vitamin D3 (cholecalciferol) on pain symptoms. We found that cholecalciferol supplementation improved mechanical nociceptive thresholds in monoarthritic animals and reduced mechanical hyperalgesia and cold allodynia in a model of mononeuropathy. Transcriptomic analysis of cerebrum, dorsal root ganglia and spinal cord tissues indicate that cholecalciferol supplementation induces a massive gene dysregulation which, in the cerebrum, is associated with opioid signaling (23 genes), nociception (14), and allodynia (8), and, in the dorsal root ganglia, with axonal guidance (37 genes), and nociception (17). Among the identified cerebral dysregulated nociception-, allodynia- and opioid-associated genes, 21 can be associated with vitamin D metabolism. However, it appears that their expression is modulated by intermediate regulators such as diverse protein kinases and not, as expected, by the vitamin D receptor. Overall, several genes - Oxt, Pdyn, Penk, Pomc, Pth, Tac1, Tgfb1 - encoding for peptides/hormones stand out as top candidates to explain the therapeutic benefit of vitamin D3 supplementation. Further studies are now warranted to detail the precise mechanisms of action but also the most favourable doses and time windows for pain relief.

**P1.123 Combined two-photon imaging and modeling of endogenous and evoked dynamics in the auditory cortex of awake mouse**

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The adult brain is characterized by a prominent ongoing activity even in the absence of clear sensory inputs. In auditory cortex, spontaneous activity has been shown to contain population events of random size occurring at relatively random time intervals. To investigate the spatial structure and the network machinery that drives these auditory cortex (AC) endogenous dynamics, we used chronic two-photon Ca<sup>2+</sup> imaging of large populations of neurons in superficial and deep layers in awake and anesthetized head-fixed mice (about 13000 neurons in 12 mice). Spike trains of up to 1000 neurons recorded in parallel over a 1x1 mm fields of view were estimated from calcium signal thanks to the new ML Spike algorithm.

Consistent with electrophysiological measurements, we found that, in the awake state, populations of neurons in AC have average firing rate of 0.23 Hz in superficial layers and 0.15 Hz in deep layers and display spontaneous synchronous events of about 200 ms, and frequency of 0.3 Hz, that recruit in average 10% of all neurons. Under isoflurane anesthesia, population events were even more prominent and inter-event activity was strongly diminished.

In general, not only the size but also the location of spontaneous events was highly variable. However, comparison of consecutive events demonstrated a consistent (10 out of 12 animals) non-monotonic relationship between spatial overlap of the events and inter-event intervals with a peak of spatial overlap around 3s intervals. This indicates that events interact with each other, excluding or promoting one another depending on elapsed time. Sound-evoked responses were as variable as spontaneous event but included a core of robustly responding neurons. Thus, in AC, complex stochastic population dynamics closely preceding cortical sensory response might substantially modulate auditory representations. We integrated these data and analysis to constrain network models of spiking neurons with conductance-based synapses, and show under which conditions the network can generate collective firing patterns consistent with experiments.

**P1.124 Beta oscillations in a large network during an olfactory discrimination task: what do they signal?**

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When dealing with the question of information transfer across brain regions, beta rhythm often appears as a good candidate for supporting functional coupling of neurons over long distances. In the olfactory system, beta activity is a major rhythm. Several studies converge towards the idea that beta expression goes well beyond the olfactory areas, suggesting it could represent widely coherent states.

In an attempt to get a more unified view of the conditions of beta expression in a large network, we analyzed its expression in brain areas suspected to be task-related when rats performed a two-alternative odor choice task. These areas involved sensory, limbic and sensorimotor regions.

Beta expression was analyzed during a simple discrimination, rule transfer, short- and long-term tests, and reversal tasks. We observe that beta amplitude is correlated with the level of expertise of the animals: maximal when rats reach learning criterion, it collapses when a new odor pair discrimination is introduced and increases again with performance. However, reversal test and intra-session analyses reveal that beta is not correlated with the performance but with the level of certainty the animal has towards the experimental context. Interestingly, we show that a new discrimination cannot be achieved as long as beta expression has not decreased. This is striking during reversal learning. Coherence analysis indicate that, when expressed, beta appears in a large network including olfactory areas and striatum, but neither hippocampus CA1 nor cerebellum.

Overall, our data suggest that beta rhythm signals a consolidated, unyielding and widely coherent state.

P1.125

**In vitro expansion of neural stem cells from adult mouse area postrema is stimulated by the orexigenic ghrelin agonist JMV-2894 and blocked by the anorexigenic hormone leptin**

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Area postrema (AP) is the neurohemal nucleus of the dorsal vagal complex (DVC) i.e. the brainstem integrator of autonomic reflexes. The rodent DVC was shown to harbor a neurogenic niche with adult genesis of new neurons, intrinsic neural stem cells, radial glia-like astrocytes and reactivity to *in vivo* stimuli. In the nestin-GFP mouse, the neural stem cells were anatomically localized to the AP (Bennett et al 2009). Fluorescence-Activity-Cell-Sorting (FACS) of freshly dissociated cells from AP vs subventricular zone (SVZ) of adult mouse after neurogenesis stages marking, revealed enrichment of AP cells in Lex(bright)/EGF-Receptor-negative (ie quiescent stem) cells as compared with SVZ cells. Although unknown, the physiological role of this adult neurogenic niche seems related with appetite since AP neurogenesis was enhanced *in vivo* by the anorexigenic hormone amylin (Liberini et al 2016). The major appetite-regulating hormones with central actions: orexigenic ghrelin and anorexigenic leptin, are known to modulate neural stem cells in adult SVZ and hippocampus. We now address their effects on AP neural stem cells of adult mouse, by using the neurosphere assay. Microdissected AP from adult mice were dissociated in accutase for culture at 50.000 cells/mL of DMEM/F12/Glutamax medium supplemented with B27, 40ng/mL EGF, 20ng/mL bFGF. Resulting spheres were passaged 3 subsequent times by 8-10 days after plating. Leptin or the ghrelin agonist JMV-2894 were added once at each plating. JMV-2894 had no effect on the numbers of primary spheres, but it increased the number of secondary spheres up to 20 times above control with a bell-shaped dose-response curve, which was maintained in subsequent generations. It shows that JMV-2894 stimulates self-renewal of AP neural stem cells, with a peak dose of 30nM. Leptin decreased the number of spheres with concomitant 90% increase of TUNEL-stained apoptosis as compared to controls, which was restricted to b-tubulin-positive neuron progenitors. Expression of receptors for ghrelin (GHS-R) or leptin (Ob-Rb) was detected by RT-PCR on RNA extracts of pelleted proliferating spheres. Both ghrelin and leptin thus modulate the expansion of AP neural stem cells, in opposite directions but likely via different subcellular targets.

**P1.126 Immunomodulatory functions of endogenous neural stem cells for myelin repair**

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In response to an acute corpus callosum (CC) demyelination, subventricular zone-derived neural progenitors (SVZdNP) migrate to the demyelinated CC to replace dead oligodendrocytes. This mobilization is regionalized, with preferential recruitment in the rostro-lateral CC compared to caudal-medial CC (Brousse et al., 2015; Xing et al., 2014). Interestingly, areas with high SVZdNP mobilization correspond to those less affected by cuprizone-induced demyelination. Although the majority of SVZdNP recruited in the demyelinated CC adopt oligodendrocyte identity, some stay undifferentiated and could protect the CC from demyelination and/or promote remyelination through immunomodulation. Indeed, several studies showed that transplantation of neural stem cells improve functional recovery in many pathological contexts, and do so mainly through immunomodulation (reviewed in Kokaia et al., 2012). In our demyelination model, we observed more activated microglia in areas where SVZdNP are poorly recruited (caudal-medial CC) and a more aggressive inflammatory profile. Thus we analyzed whether endogenous SVZdNP spontaneously recruited to the demyelinated CC could dialog with microglial cells to modulate their inflammatory properties and exert protective functions. Using genetic tracing we sorted SVZdNPs and microglia in demyelinated CC and single cell RNA drop sequencing we searched for ligand-receptor couples implicated in SVZdNP/microglia dialog. We identified MFGE8 secreted by SVZdNP and integrin  $\beta 3$  expressed by microglial cells as a couple implicated in cell-cell interactions to promote myelin debris phagocytosis, a prerequisite for myelin repair.

P1.127

**Role of thyroid hormone in the control of neural stem cell fate throughout life**

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In the adult mammalian brain, neural stem cells (NSCs) localized in the subventricular zone (SVZ) produce new functional neurons and oligodendrocytes throughout life. SVZ-NSCs generate neuroblasts that migrate through the rostral migratory stream (RMS) toward the olfactory bulbs (OB) where they differentiate into mature neurons, which participate to the olfaction. Furthermore, few NSCs give rise to oligodendroglial precursor cells (OPCs) that migrate toward the surrounding white matter where they differentiate into myelinating oligodendrocytes.

Thyroid hormones (TH) are involved in neurogenesis and gliogenesis during adulthood. A crucial question is to determine how TH regulates adult NSC fate toward a neuron or a glial fate. In the young adult, we recently demonstrated that TH is required for NSCs commitment toward a neuronal fate. In contrast, a low TH status is involved in the generation of new SVZ-OPCs, capable of restoring functional nerve conduction after a demyelinating insult (Remaud et al 2017). Furthermore, low TH status is known to be associated with healthy ageing (Gusselko, 2004). Thus, our hypothesis is that low TH status associated with ageing maintained oligodendrogenesis at the expense of neurogenesis.

To analyze how TH signalling regulates NSC fate during ageing, we studied the neuron/glia balance in young vs. ageing mice by immunohistochemistry. Surprisingly, the OPC density is increased with ageing, whereas neuroblast density decreased. Moreover, the short-term olfactory memory is disrupted with ageing as for long-term hypothyroid mice, suggesting that SVZ-neurogenesis is functionally impaired. Together, these results indicate that a low TH status observed during hypothyroidism or ageing alters the neurogenesis/oligodendrogenesis balance to favor SVZ-OPC generation. Further, we will examine whether neuroblast migration along the RMS and their differentiation into OB neurons are affected with ageing. Lastly, using the cuprizone mouse model, the remyelination capacity of young vs. ageing SVZ-OPCs will be investigated. Our work could have numerous applications in NSCs research for neurodegenerative diseases, by providing a better understanding of the mechanisms underlying TH in the regulation of glia-neuron cell-fate choice.

**P1.128 Metabolic dysfunctions and neuro-inflammation responses induced by hypothyroidism**

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Thyroid hormones (THs) triiodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ) are produced and released by thyroid gland. THs play a crucial role in the brain development particularly in the central nervous system. Moreover, THs are one of the most important regulators of metabolism through their actions in many organs, including brain, adipose tissues, liver and muscles, to maintain metabolic homeostasis. However, it is well known that thyroid dysfunction disrupts energy balance. Hypothyroidism, a reduction of TH levels, is characterized by low energy expenditure and a decrease of lipid and carbohydrate metabolism. Hence, it is described that hypothyroidism generates neuro-inflammation and cognitive impairment. Moreover, TH dysfunction has been recently associated to neurodegeneration diseases like Alzheimer Disease (AD) as a possible risk factor. In this context, we made the hypothesis that TH status alteration could disrupt metabolic homeostasis leading to neuro-inflammation and thus favoring the onset of neurodegeneration diseases as AD. Thus, the objective of this study was to analyze the hypothyroidism impact on metabolism and the consequence on the peripheral and central inflammation responses, potentially favoring neuro-inflammation.

To this aim, we compared wild-derived WSB/EiJ mouse strain, characterized by an obesity resistance due to its high metabolic flexibility phenotype, with C57BL/6J mice, prone to high-fat-diet (HFD) induced obesity. After hypothyroidism induction by propylthiouracil treatment for 7 weeks, we characterized the lipid metabolism of mice according to their strains and their thyroid status. Furthermore, we evaluated the peripheral and central inflammation responses by measuring circulating factors and microglia /astrocytes activation in hippocampus. According to their lower sensitivity to metabolic deregulations, WSB/EiJ mice should be protected from neuro-inflammation induced by the metabolic consequences of hypothyroidism, contrary to C57BL/6J mice. In a second set of experiments, we will explore the cognitive consequences of hypothyroidism. Our project should emphasize the importance of maintaining the metabolic and thyroid homeostasis for the avoidance of neuro-inflammation development and cognitive impairment.

**P1.129 Prenatal exposure to testosterone increases anxiety-like behaviour and cortisol levels in Ile-de-France ewe lambs**

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PCOS (Polycystic Ovary Syndrome) is the most common hormonal abnormality affecting ~7% of reproductive-age women. This syndrome can lead to infertility, metabolism disorders such as type-2 diabetes but also to anxiety disorders. Prenatal exposure to testosterone is known to be a cause of PCOS and previous studies highlighted an increased anxiety in mice and rats prenatally-exposed to testosterone. Sheep are known to be a good model for PCOS syndrome but investigations focussed mainly on reproductive and metabolism disorder, no information is available about anxiety-like behaviour. Hence, by prenatal exposure to testosterone, we obtained 22 PCOS ewe lambs that were compared to 20 control ewe lambs for their response to two anxiety test. All females, aged of eleven weeks, were let alone in a new pen for 10 min on day 1 (Open Field), we did the same on day 2 to test their habituation ability and on day 3 a construction cone was disposed in the pen before lambs enter (Novel Object).

Regarding the Open Field Test, no difference was found between Control and PCOS sheep for the occurrence of bleating or flight attempt but we observed that 10/22 PCOS lambs exhibit more flight attempt on day 2 than day 1 while it is the case of only 4/20 Control lambs. Moreover, during the Novel Object Test, latency before touching the object was 2 times more elevated in PCOS than in controls sheep. To confirm behavioural observations, we took blood samples to assay cortisol levels and we observed that PCOS females had increased levels of cortisol in comparison to control females.

All together, those results suggest that PCOS females could be more anxious than Control females as they took more time before touching an unknown object but also because they seem to have a lesser habituation capacity as stated by the dynamic of flight attempts between the day 1 and 2 in the Open Field.

**P1.130 Ablation of microglia exacerbates anorexia induced by the mycotoxin Deoxynivalenol**

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Deoxynivalenol (DON), one of the most abundant trichothecenes found on cereals, has been implicated in mycotoxicosis in both humans and farm animals. DON-induced toxicity is characterized by reduced food intake and weight gain, diminished nutritional efficiency and immunologic effects. We previously shown that exposure to DON induced an inflammatory response by increasing the expression of pro-inflammatory cytokines within both peripheral organs and brain. This central production of inflammatory cytokines was proposed to contribute to DON-induced disturbance of energy balance and anorexia.

Microglia are the primary immune cells of the central nervous system that contribute to multiple physiological and pathophysiological processes in the brain, in particular they play a central role in neuroinflammation and neuroprotection. To date, the contribution of these cells to DON-induced brain inflammation and anorexia is not defined. Here, we evaluated the kinetic of microglia activation in response to anorectic DON doses administered *per os* and we reported strong microglia activation, attested by IBA-1 reactivity, in different brain regions including structures known to regulate feeding behavior. To evaluate the possible contribution of microglia in DON-induced anorexia, we took advantage of pharmacological microglia deletion using PLX3397-containing diet. After 3 weeks, PLX3397 consumption reduced microglia population by more than 90 %. In interesting ways, PLX3397-treated mice showed a higher sensitivity to DON-induced anorexia. Indeed, anorexia was observed with dose ineffective in control mice. In agreement, c-Fos expression mapping performed after low DON dose administration revealed a strong neuronal activation in structures related to food intake in PLX3397-treated but not in control mice.

Altogether, these preliminary results suggest that microglia activation observed during DON intoxication is mainly protective. While the mechanism underlying this action remains to be characterized, this model could allow to address the broad question of microglia function during central pathogen exposure.

**P1.131 A NALCN-like conductance is critical for the excitability of mouse adrenal chromaffin cells**

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In response to stress, catecholamines (epinephrine and norepinephrine) are the first hormones to be released into the blood circulation. Catecholamine secretion is allowed by a tightly coordinated sequence of cellular and tissular and cellular mechanisms ("stimulus-secretion coupling"), in which the adrenal neuroendocrine chromaffin cells play a crucial role. Chromaffin cells are excitable cells and exhibit action potentials. In addition to the neurogenic control exerted by the splanchnic nerve, chromaffin cell excitability also relies on intrinsic electrical properties, including the resting membrane potential, defined by the palette of ion channels expressed at the plasma membrane. The recently discovered *sodium leak channel* (NALCN) contributes to set the resting membrane potential in neuronal cells. This prompted us to investigate the involvement of NALCN in mouse chromaffin cell excitability. By using double *in situ* hybridization in adrenal glands, we first unveiled a specific expression of NALCN mRNA in chromaffin cells. To address whether NALCN channel could contribute to chromaffin cell excitability, spontaneous electrical activity was next recorded in acute slices, in response to a low Na<sup>+</sup>-containing saline challenge. Reducing extracellular [Na<sup>+</sup>] from 125 to 15 mM elicits a robust membrane membrane hyperpolarization, abrogating action potentials. Neither TTX application nor intracellular Cs<sup>+</sup> impair the hyperpolarisation. Depolarizing voltage ramps show that lowering external [Na<sup>+</sup>] blocks a current in a linear manner between -130 and -50 mV. Calculated reversal potential argues for a non-selective conductance and permeability challenges unveil a P<sub>Na</sub>/P<sub>K</sub> ratio of 2.9. Collectively, these results contribute to the first evidence of a background conductance, mainly permeable to [Na<sup>+</sup>], in modulating chromaffin cell excitability in the mouse adrenal medulla. Even though our data match with attributes to the current described for NALCN, the precise contribution of NALCN channels to chromaffin cell excitability remains to be ascertained. Because of the lack of selective inhibitors for NALCN channels, it will be necessary to manipulate NALCN gene expression, in the adrenal medulla *in vivo*, to decipher the role of NALCN in chromaffin cells.

**P1.132 Role of the POMC-ventral striatal neurocircuit in the development of diet-induced obesity**

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Eating is a process essential for life. Powerful brain mechanisms have evolved to allow not only the matching of the organism's energy needs with energy intake, but also the recognition of food rich in calories so to guarantee survival under variable environmental food sources. To control food intake, neuronal circuits classically aiming at integrating information about the organism's energy status must interact with circuits underlying "liking" and "wanting" signals. We have hypothesized that such interaction involves hypothalamic pro-opiomelanocortin (POMC) neurons, which are typically recognized as the mediators of hunger/satiety in response to metabolic and hormonal changes, and medium spiny neurons (MSNs) of the nucleus accumbens (NAc) in the ventral striatum, which decode reward and motivation.

Based on a paradigm of fasting/refeeding, where mice are fasted and then allowed to access food for 2 hours on either normal chow or palatable food, we showed that animals eat more when they have access to palatable food than to normal diet. Using patch-clamp electrophysiological recordings, we showed that NAc MSNs synaptic inputs and intrinsic electrical properties are differentially changed depending on the nature of the food eaten. Additionally, we showed that direct POMC projections are present in the ventral striatum and that during electrophysiological recordings in NAc acute slices, selective optogenetic activation of POMC terminals affect MSNs' excitability. Finally, we are investigating the nature of the neuromodulation involved in the preference for palatable food by assessing the impact of intra-NAc injection of selective antagonists against opioid/melanocortin (both being produced by POMC neurons) receptors on stimulated food intake.

The findings obtained so far suggest that POMC neurons modulate the activity of NAc MSNs and that the POMC-NAc circuit may be critical for the overconsumption of palatable food.

**P1.133 Tanocyte-AMPK $\alpha$ 1/ $\alpha$ 2 ablation modulates hypothalamic hormone sensitivity**  
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AMP-activated protein kinase (AMPK) is a known regulator of cellular and whole-body energy homeostasis. In the hypothalamus, it has been described that AMPK mediates ghrelin, glucose-like peptide 1 and thyroid hormone induced changes to neuronal lipid metabolism. However, in order to reach their hypothalamic targets, peripheral hormones must first cross the blood-brain barrier (BBB) through highly specialized hypothalamic glial cells, named tanocytes. Tanocytes line the floor of the 3rd ventricle (3V) sending projections to the median eminence and have been shown to act as a physical barrier preventing the diffusion of circulating molecules extravasating from fenestrated capillaries to the rest of the brain via into the cerebrospinal fluid (CSF), where they may then freely diffuse into the hypothalamus. Taking into account the relevance of AMPK as an energy sensor and tanocytes as transporters of peripheral signals that sense body energy status, here we sought to study the role of AMPK at this hypothalamic blood-CSF barrier interface.

Injection of recombinant TAT-Cre protein in the 3V of AMPK $\alpha$ 1/ $\alpha$ 2<sup>Loxp-Loxp</sup> animals results in the ablation of this kinase within tanocytes (AMPK $\alpha$ 1/ $\alpha$ 2<sup>TanKO</sup>). AMPK removal in tanocytes results in a significant reduction in body weight due to decreased food intake, with no alteration in either energy expenditure or respiratory quotient. In addition, peripheral injection of both ghrelin and leptin induce a hypersensitivity response of the AMPK $\alpha$ 1/ $\alpha$ 2<sup>TanKO</sup> animals, increasing or decreasing food intake and body weight respectively compared to AMPK $\alpha$ 1/ $\alpha$ 2<sup>Loxp-Loxp</sup> animals. It is therefore proposed that AMPK removal from tanocytes may induce impairment in the median eminence barrier, thus indicating a deficiency in tanycytic function. To elucidate this phenotype, *in vitro* studies are currently in progress to decipher the response of cultured tanocytes to either AMPK activation or blockade and to clarify how AMPK ablation modifies the architecture of the median eminence barrier *in vivo*.

**P1.134 Brain network dynamics during spontaneous strategy shifts and incremental task optimization**

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With practice, humans may improve their performance in a task by either optimizing a known strategy or discovering a novel, potentially more fruitful strategy. How does the brain support these two fundamental abilities? In our experiment, subjects performed a simple perceptual decision-making task. They could either use and progressively optimize an instructed strategy based on stimulus position, or spontaneously devise and then use a new strategy based on stimulus color. We investigated how local and long-range BOLD coherence behave during these two types of strategy learning by applying a recently developed unsupervised fMRI analysis technique that was specifically designed to probe the presence of transient correlations. Converging evidence showed that the posterior portion of the default network, i.e. the precuneus and the angular gyrus bilaterally, has a central role in the optimization of the current strategy: these regions encoded the relevant spatial information, increased the level of local coherence and the strength of connectivity with other relevant regions in the brain (e.g. visual cortex, dorsal attention network). This increase was proportional to the task optimization achieved by subjects, as measured by the reduction of reaction times, and was transiently disrupted when subjects were forced to change strategy. By contrast, the anterior portion of the default network (i.e. medial prefrontal cortex) together with rostral portion of the fronto-parietal network showed an increase in local coherence and connectivity only in subjects that would at some point spontaneously choose the new strategy. Overall, our findings shed light on the dynamic interactions between regions related with attention and with cognitive control, underlying the balance between strategy exploration and exploitation. Results suggest that the default network, far from being "shut-down" during task performance, has a pivotal role in the background exploration and monitoring of potential alternative courses of action.

**P1.135 Hippocampal CB1 receptors control obesogenic diet-induced memory impairment**  
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Obesity is associated with adverse cognitive outcomes. Its growing prevalence during adolescence is alarming since it is a developmental period crucial for neurocognitive shaping and particularly vulnerable to the effects of obesogenic high-fat diet (HFD) on hippocampus-dependent memory. The endocannabinoid system, which participates in obesity and regulates memory processes, is altered by HFD. However, the causal involvement of this system in mediating hippocampus-dependent memory deficits remains to be addressed.

We first showed that long-term but not short-term object recognition memory (ORM) is impaired in a mouse model of adolescent HFD-induced obesity. ORM impairment was associated with increased hippocampal endocannabinoid levels (specifically anandamide) after ORM training in HFD-fed mice. Systemic pharmacological blockade of the main cannabinoid receptor (CB1R) after training or specific hippocampal CB1R deletion rescued ORM impairment in HFD-fed mice, indicating that hippocampal CB1R over-activation after training impairs ORM in HFD-fed mice. Using c-Fos as a marker of neuronal activity, we then showed higher hippocampal c-Fos activation after ORM training in HFD-fed mice. Chemogenetic inhibition of hippocampal pyramidal cells rescued ORM in HFD-fed mice suggesting that hippocampal over-activation is responsible for the memory deficits.

Moreover, systemic CB1R blockade normalized hippocampal c-Fos activation as well as aberrant *in vivo* long-term potentiation after ORM training in HFD-fed mice, indicating that the upregulated hippocampal endocannabinoid system lead to abnormal hippocampal activation.

We are currently examining which cell type carrying CB1R (astrocytes, glutamatergic or GABAergic neurons) is responsible for HFD-induced ORM impairment using CB1R-*flox/flox* mice and cell-type specific hippocampal deletion. We are also using *ex vivo* electrophysiological approaches in the hippocampus to decipher the impact of adolescent HFD at the synaptic level. Altogether these results will help to understand the mechanisms underlying HFD-induced memory deficits within hippocampal networks.

**P1.136 Proprioception changes after tool use**

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Tool-use has been widely used as a paradigm to assess the plasticity of the body schema (BS) (Cardinali et al., 2009), which is a body representation that tracks the posture of the body and is used to control actions. Prior studies have highlighted the importance of proprioception on updating BS. For example, we found that a deafferented patient showed no body schema plasticity (Cardinali et al., 2016), suggesting that proprioception plays a critical role in BS plasticity following tool-use. However, it is currently unknown whether tool-use actually affects proprioception. Here we tested whether tool-use, involving flexion/extension movements at the level of the elbow, affects the forearm proprioception. To this aim, we evaluated right and left elbow proprioception before and after tool-use and a weighted-wrist control condition (counterbalanced and ran on separate days) in 30 subjects. Elbow proprioception was measured with three position matching tasks: IRR (ipsilateral remembered right arm), IRL (ipsilateral remembered left arm) and CC (contralateral concurrent). Both tool use and weighted wrist conditions were performed with the right, dominant hand. The matching error was measured in degrees and compared across three tasks. Results showed that after the tool use session there was a decrease in the absolute error specific for the right elbow proprioception, as measured by the IRR and CC matching tasks. No change was observed for the IRL, not involved in tool-use. We also did not observe any change in proprioception following the control session. We conclude that tool use improves forearm proprioception by decreasing error values. Prior work using a touch localization task suggested arm representation becomes longer after tool use. In a second experiment (n=20), we therefore assessed the relationship between improvement in proprioception and touch localization before and after both sessions. The selective reduction of proprioceptive errors was replicated. The tactile localization task showed that after the tool use, but not the weighted wrist session, participants tended to localize touches as being farther apart from each other. To conclude, tool use not only updates the representation of the forearm length, but also improves its proprioception.

**P1.137 Are obesogenic diet-induced memory alterations during adolescence related to changes in amygdalo-hippocampal pathway?**

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Obesity epidemic is currently reaching an alarming level, with the prevalence and severity of overweight also increasing dramatically in youth and persisting even in adulthood. Obesity is associated with numerous comorbidities such as neurocognitive dysfunctions, specifically those affecting learning and memory function. This is particularly worrisome since childhood and adolescence are crucial periods for the maturation of certain brain structures, including the hippocampus (HPC) and the amygdala, necessary for shaping cognitive function for life duration. In this context, previous studies in the laboratory have shown that obesogenic high-fat diet (HFD) intake during adolescence is associated with opposite changes in the HPC- and amygdala-dependent memory systems: adolescent HFD intake impaired HPC plasticity and HPC-dependent memory and enhanced basolateral amygdala (BLA) plasticity and BLA-dependent aversive memory. As anatomical and functional connectivity between BLA and ventral HPC (vHPC) establishes during adolescence, these differential memory effects of HFD may be related to changes in reciprocal BLA-vHPC pathways. The aim of the current study is, therefore, to examine the contribution of these pathways to the memory changes observed in adolescent HFD-fed rats. Using chemogenetic-induced inhibition of projecting neurons from either the BLA or the vHPC (AAV-CaMKII-hM4Di), we first demonstrate that decreasing activity of vHPC, but not BLA, projecting neurons abolished HFD-induced impairment of long-term recognition memory whereas inhibition of BLA, but not vHPC, projecting neurons rescued HFD-induced enhancement of long-term aversive memory (conditioned odour aversion). We are currently characterising the reciprocal projections between BLA and vHPC via a neuroanatomical approach using retrograde or anterograde viruses (rAAV-tdTomato, CAV2-GFP or AAV-CamKII-mCherry) in order to specifically manipulate BLA-vHPC projections using advanced chemogenetic tools (combination of AAV vector carrying CRE-dependent DREADDs with retrograde virus carrying the CRE) to hopefully restore some memory dysfunctions. Results obtained from this study will be beneficial in the context of adolescent obesity impact on brain structures and cognitive functions.

**P1.138 Examining the effects of corticotropin-releasing factor in locus coeruleus (LC) on cortical network activity**

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The locus coeruleus (LC) is part of a stress responsive system that is involved in arousal and cognitive function. This is accomplished through extensive projections to many regions, including the prefrontal cortex (PFC). The reciprocal connection between the LC and the PFC has been shown to underlie the role of arousal on cognition. Additionally, this circuit is disrupted following chronic stress, which is thought to underlie impairment in executive function that arises during stress. Evidence suggests that stress-induced alterations of LC activity are mediated through the release of corticotropin-releasing factor (CRF) in the LC. A previous study from our lab in male animals showed that intracoerulear infusion of 20ng of CRF impacted performance in the attentional set shifting task, which engages the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC). However, it is unknown how CRF release in the LC affects network activity of neurons in the OFC and in the mPFC to influence behavior. This study examined the effects of CRF administered into the LC of male and female rats on mPFC and OFC network activity, measured as local field potentials (LFPs). In awake, behaving animals, network activity was recorded in the mPFC and OFC for 30 minutes before and after intracoerulear infusion of aCSF or 20ng of CRF in male and female adult rats through a cannula. Following this, power spectral density (PSD) was calculated. Our data show that, following infusion of 20ng CRF, there is increased activity in the high theta (7-9 Hz) frequency band in the mPFC in both sexes, and in OFC in females as compared to their respective aCSF (control) groups. This is the first analysis of the effect of LC activation with CRF on network activity in these cortical areas and the preliminary results suggest a greater impact on cortical network activity following CRF actions in the LC of females compared to males. These data are consistent with sex differences in CRF receptor internalization. In ongoing studies, we are examining additional doses of CRF in both sexes and determining if activating LC with CRF affects performance in the attentional set-shifting task in female rats, a paradigm that is dependent on cortical activity.

P1.139

### The Broca neurocorrelates of gestural communication in Baboon

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Language and its hemispheric specialization of the brain have been historically considered as unique to *Homo sapiens* evolution (Crow, 2004), the left hemisphere playing a predominant role over the right hemisphere for most language functions. Specifically Broca's area plays a critical part within this complex lateralized multimodal language network, known for motor-planning and speech production. Whether prerequisites of such language lateralization might be older than *Homo sapiens* emergence has been recently investigated by comparative brain imaging studies on our closest primate relatives (Catalupo, 2001) within the theoretical framework of a multimodal origin of language including not only verbal modality but also gestural communication (Gentilucci, 2007). Interestingly it was found that production of communicative manual gestures in baboons show not only an increased use of the right hand but also independent hand preference in comparison to non-communicative actions, indicating greater left-hemisphere dominance for communicative signaling. We have thus proposed the hypothesis that gestural communication in nonhuman primates might be related to a specific lateralized system for communication which might be homologue to human brain specialization for language (Meguerditchian, 2013).

To further explore this hypothesis, in the present study, we have investigated in 36 baboons the inter-hemispheric asymmetries of the inferior arcuate sulcus' depth in the frontal cortex. The most ventral portion of this sulcus has been described as the border of the homolog of Broca area (BA44) in monkeys. To explore the behavioral correlates of this region, we further tested whether these neuroanatomical asymmetries were associated with contralateral hand preference detected for communicative gestures in baboons in contrast to handedness for manipulative actions.

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**P1.140 Local hippocampal fast gamma rhythms precede brain-wide hyperemic patterns during spontaneous rodent REM sleep**

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**Aims:** Rapid-eye movement sleep (REMS) is a peculiar brain state, combining the behavioral components of sleep and the electrographic patterns of wake. Though classical REMS models have assumed that the brain recreates wake conditions to perform its functions, thorough data over distributed networks is still largely missing, mainly owing to the difficulty to adapt current state-of-the art techniques for sleep imaging.

**Methods:** The combination of EEG and fUS imaging, a novel neuroimaging modality based on ultrafast ultrasound imaging [Tanter & Fink 2014], provides new insights into brain dynamics thanks to global imaging of hemodynamics in conjunction with local recordings of electrographic activity.

**Results:** Here we reveal brain-wide spatiotemporal hemodynamics of single REMS episodes and demonstrate the close association between massive hyperemic events and fast gamma oscillations in rats that previously performed a track-running task. We show that vascular activity divides into tonic and phasic regimes. The phasic component of this vascular activity contained vascular surges (VS), i.e. large-amplitude spatially-extended hyperemic waves. The amplitude of these VS outmatched waking levels and were robustly preceded by sustained theta (6-10 Hz) and fast gamma oscillations (80-110 Hz), the power of fast gamma being strongly correlated to the amplitude and duration of each subsequent VS.

**Conclusions:** Our findings question the evolutionary benefit of such high energy-demanding vascular patterns, considering the ubiquitous nature of REMS along mammalian species. It also opens the way for the combined local controlled manipulation of brain rhythms and global imaging of sleep hemodynamics.

**P1.141 Specificity of different chronic stress paradigms on prefrontal cortex-dependent behavior**

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Stress is an environmental factor that modulates different mutually inclusive aspects of behavior, namely, emotions and cognition. It elicits activation of the Hypothalamic-Pituitary-Adrenal axis and ensuing release of glucocorticoids (GC), enabling the organism to produce adaptive responses. However, chronic stress exposure and abnormal GC levels often lead to persistent cognitive and mood dysregulation, facilitating the development of psychopathological disorders. Current literature suggests that stress may induce cognitive deficits through the action of GCs within the prefrontal cortex (PFC). However, although the deleterious effects of stress on the PFC and its crucial role in cognition have been repeatedly established in both humans and rodents, the underlying molecular and physiological mechanisms are still poorly understood.

In this study, we dissociate the behavioral outcomes of different kinds of chronic stress exposure in mice. We demonstrate, using several frequently used stress inducing paradigms, namely, social defeat stress, unpredictable mild stress, and early-life maternal separation, as well as, systemic treatment with corticosterone, that different kinds of chronic stressors evoke different and specific outcomes in terms of PFC-dependent behavior. We also show that the observed specific alterations in cognitive flexibility, working memory, novel object recognition and object location capabilities are accompanied by certain specific alterations at the molecular level. Finally, we study the effects of local inactivation of GR specifically in the medial PFC. This study facilitates mechanistic dissociation of stress-induced molecular and physiological pathways in the PFC.

**P1.142 The sense of proximity enhances emotional perception**

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**Background:** Physical proximity of social stimuli is an important factor in social interactions. Intriguingly, large faces, that may be perceived as closer, have not been systematically associated with enhanced emotional perception. Here, using looming emotional faces to modulate the sense of proximity, we hypothesized that it will increase perceived emotional intensity and associated physiological responses.

**Materials and methods:** 10 healthy volunteers (4 men and 6 women) were shown video clips of emotional (angry or happy) faces from The Karolinska Directed Emotional Faces database. The sense of proximity was induced with a looming silhouette, changing in size. The movement of the looming mask stopped at two positions that corresponded to two perceived distances, 0.5 or 3 meters. The video clips were then presented to the participants. We asked them first to imitate the expression displayed on the screen, and then to rate the perceived intensity of the expression on a visual analog scale. We also recorded pupillary responses and the activity of *corrugator supercilii* muscle.

**Results:** The perceived intensity of the emotion was stronger with large compared to small faces, corresponding respectively to the two perceived distances, 0.5 and 3 meters. The imitation of angry and happy expressions induced a contraction and a relaxation of the corrugator supercilii, respectively. The amplitude of those responses, for both happy and angry expressions, was also stronger with large as compared to small faces. Finally, the difference in pupillary response for angry *versus* happy faces of the same size was more pronounced for large as compared to small stimuli.

**Conclusions:** We show that emotional intensity judgements were stronger with faces perceived physically closer (0.5m) as compared to faces perceived physically farther away. This difference in rating was also accompanied by enhanced physiological responses for faces perceived closer. These results show that the physical proximity enhances emotional perception.

P1.143

**Phenotyping of a new mouse model of Alzheimer's disease**

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Over the past twenty years, our understanding of Alzheimer's disease (AD) has been widely promoted through the study of transgenic mouse models. However, there are some caveats that reduce their potential to represent the disease. The overexpression of amyloid precursor protein (APP) and its derivatives often lead to perturbations in CNS development and function. Moreover, these mouse models mainly overexpress mutated genes from familial forms of AD (FAD) whereas the large majority of the patients suffer from the sporadic form of AD. Tau mutations leading to frontal lobe dementia are often used to add tau pathology, but do not represent the sporadic nature of Tau pathology in AD patients. Finally, the presence of equivalent murine proteins in transgenic animals may also contribute to their phenotype. To address some of these issues, this work consists in characterizing a new, doubly humanized model resulting from the cross of two knock-in (KI) mouse lines for the *App<sup>NL-F</sup>* (Beyreuther/Iberian and Swedish FAD APP mutations) and for the human tau (*MAPT*) which were both produced by T Saido and T Saito (RIKEN Brain Science Institute, JAPAN) and sent to us by the RIKEN BioResource Center. Our hypothesis is that the combination of mouse promoter-controlled expression of APP with two FAD mutations and of all normal human tau isoforms in absence of equivalent murine proteins should favor the development of AD-like pathology closer to the human condition. In order to detect the earliest recognition memory deficits in the *App<sup>NL-F</sup>/MAPT* double knock-in (dKI) mouse model, we used a barrage of spontaneous object exploration tasks differentially sensitive to AD-like pathology progression. Each task relies on different types of recognition memory which in turn rely on different but overlapping structural networks. Our latest results show that at 4 months of age, *App<sup>NL-F</sup>/MAPT* dKI mice show specific deficits in the object-in-place (OIP) task. This task tests the memory for an association between an object and place in which it was previously encountered. Our next step will be to identify the structural networks involved in our OIP task and the functional alterations linked to OIP deficits in *App<sup>NL-F</sup>/MAPT* dKI mice using an ex-vivo imaging approach.

**P1.144 Cognitive rehabilitation improves balance in the elderly**

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**Introduction:** The effects of aging on postural control do not result solely from the alteration of sensory and motor functions regulating balance. Cognitive aging, including the decline in attentional control, is an important factor that has been revealed by the dual-task paradigm. In this paradigm, attentional resources should be shared to achieve correct postural and cognitive tasks. The aim of this study was to analyze the relationship between postural and cognitive functions with a new perspective: we tested the hypothesis that a specific training which targeted consciously controlled processes and their attentional control would improve postural performance in dual-task situations due to a better management of the two simultaneous tasks.

**Methods:** To this aim, subjects were trained with a personalized cognitive training program based on cognitive-cognitive dual-tasks. We evaluated the benefits of training on pre- and post-training postural and cognitive dual-tasks in a group of 8 subjects ( $77 \pm 5$  years) and compared the performance with those of a group of 9 untrained subjects ( $74 \pm 4$  years). Our pre- and post-training dual-task paradigm is based on postural (dynamic conditions) and cognitive tasks (visual-spatial memory).

**Results:** The results show an improvement in postural performance of trained subjects. On the contrary, there is no change in cognitive performance. Therefore, the improvement of postural performance could come from improved management of attentional sharing, with more effect on postural than on cognitive task.

**Conclusions:** We hypothesize that our attention training that emphasized highly controlled processes and yielded benefits for the practiced tasks promoted training transfer to postural balance functions by positively affecting sensory information processes necessary to maintain balance.

**P1.145 Dynamic adaptation of hippocampal spatial coding resolution to local 3D objects during virtual navigation**

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Flexible navigation in mammals such as rodents or humans is thought to rely on an internal cognitive map. When animals move in their surroundings, hippocampal place cells fire in specific locations (their place fields). This spatial firing is believed to provide a neuronal substrate to the cognitive map. It is still unclear if the coding resolution of this internal map of space can dynamically adapt to the sensory cues within a single environment. In this study, we took advantage of virtual reality to selectively manipulate visual information as mice commuted between the ends of a virtual linear track in presence or absence of 3D virtual objects. Once behavioral performance was stable, we recorded the activity of putative pyramidal cells in area CA1 of the hippocampus. Objects improved spatial coding resolution globally with a higher proportion of place cells, smaller place fields, increased spatial selectivity and stability. Spatial coding resolution was enhanced near objects and could be rapidly tuned by their manipulations. In the presence of objects, place cells also displayed improved theta phase precession and theta timescale spike coordination. These results suggest that local visual cues can rapidly tune the resolution of the hippocampal mapping system within and between environments. Such type of dynamical coding could optimize the cost of storing and using spatial information for efficient navigation.

**P1.146 Inhibition of B-Glucocerebrosidase activity preserves motor unit integrity in a mouse model of amyotrophic lateral sclerosis**

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Multiple lines of evidence suggest a link between sphingolipid metabolism and the physiopathology of amyotrophic lateral sclerosis [1]. Glucosylceramide, a sphingolipid, is the precursor of gangliosides. And degradation of glucosylceramide is performed by GBA1 and GBA2, two beta-glucocerebrosidases. Our previous results have shown a benefit for SOD1G86R mice after inhibition of glucosylceramide degradation [2]. Ambroxol hydrochloride is a safe and generic drug known to inhibit GBA2 activity. In SOD1G86R mice, an animal model of amyotrophic lateral sclerosis, ambroxol preserves neuromuscular junctions from denervation, delays disease onset, improves motor function and preserves motor neurons from degeneration. Taken together, our results suggest that GBA2 is a therapeutic target for ALS and that its inhibition preserves motor unit integrity in the SOD1G86R mice. In addition, our results suggest that ambroxol hydrochloride is a candidate drug for this devastating disease.

[1] Henriques et al. 2017 Frontiers in Mol neuroscience

[2] Henriques et al. 2017 Scientific reports

**P1.147 The laterodorsal tegmental nucleus: a new actor in freezing**

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Mammals are constantly challenged, both physically and psychologically, by environmental stimuli, which can persistently modify one's behaviors. These environmental stressors trigger a large panel of responses ranging from classical fight or flight responses to more complex modulations of cognitive processes. The stress response per se is adaptive and hence beneficial when promptly shut off. Studies in laboratory animals have commonly used foot shock exposure to study freezing behavior and associated fear responses. A wealth of evidence implicates the amygdala in the neuronal circuit underlying freezing or escaping behaviors. Here, we identified the laterodorsal tegmental nucleus (LDTg) as a new player in the circuit of stress-induced freezing. The LDTg is located in the brainstem and comprises intermingled cholinergic, glutamatergic and GABAergic neurons that send ascending projections to sensori-motor and associative brain regions. Using chemogenetic tools in transgenic mouse lines, we analyzed the contribution of the different LDTg cell types in response to mild foot shocks and monitored freezing behaviors as well as associated fear responses. We found that GABAergic, but not glutamatergic or cholinergic, neurons are key to modulate immediate freezing. Using ex-vivo patch recordings, we have measured the cellular changes induced by stress. Combining retrograde Cre-expressing viruses with Cre-dependent inhibitory DREADDs, we are currently dissecting the contribution of LDTg projections to these processes.

Our results establish a key role of the LDTg in freezing responses and further extend our knowledge of the neuronal circuitry behind the stress response, which could help for development of therapeutic intervention in the case of abnormal freezing behaviours.

**P1.148 Modeling decision-making under uncertainty: a direct comparison study between human and mice gambling data**

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Decision-making (DM) is an evolutionary conserved process involved in choosing one option among several alternatives and relies on cognitive and affective functions. Many neuropsychiatric disorders display maladaptive DM behaviors and animal modeling is contributing to study the underlying mechanisms. The Iowa Gambling Task (IGT) is widely used to assess human DM under uncertainty. The optimal choice strategy requires maximizing monetary gains by selecting cards from 4 decks with various cost-benefit probabilities. Animal versions have been adapted with nutritional rewards. Nevertheless, interspecies data comparisons are still scarce, which restricts the validity of the model. Our study directly compared adult physiological DM performances between healthy humans (n=40; male, right-handed) and wild type mice (n=40; male, C57BL/6JRj). Human subjects fulfilled an electronic version of the IGT and were not informed of the nature of the different options. Mice performed a maze-based adaptation of the IGT with 4 arms baited in a probabilistic way. Our data showed that DM performances in mice closely resemble those of humans, both populations making comparable long-term advantageous choices. Intraspecies variability was investigated by k-mean clustering stratification in 3 subpopulations according to choice strategies (good, intermediate, and poor DM). Interspecies comparison revealed excellent fit of the corresponding subpopulations proportions. Preliminary exploration of the choice strategies' determinants, reflecting adaptive behavior required for optimal DM, suggested some interspecies differences among DM subpopulations. To conclude, the results of our direct comparative study plead for good face validity of the rodent version of IGT as already proposed in the literature when looking at global performances. Whether the putative interspecies differences in choices strategies' determinants are relevant and should question the construct validity of the animal model has to be further evaluated. Future studies with extended behavioral characterization and pathological animal models should help disentangle processes subserving choice strategies to better understand constructs of DM in animals and humans.

**P1.149 Ventral midline thalamus lesions prevent persistence of new (learning-triggered) hippocampal spines, delayed neocortical spinogenesis, and spatial memory durability**

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The ventral midline thalamus encompasses the reuniens & rhomboid nuclei (ReRh) and contributes to hippocampo-cortical interactions supporting systems-level consolidation of memories (Cassel et al., *Prog Neurobiol* 111, 2013). It is established that recent hippocampus-dependent memories rely on hippocampal connectivity remodeling. Remote memories are, in whole or in part, underpinned by neocortical connectivity remodeling. After a fiber-sparing lesion (NMDA) of the ReRh, recent spatial memories are formed normally but fail to last longer than a few days (Lourenco et al., *J Neurosci* 32, 2012). Why such memories do not endure after the lesion is unknown. We hypothesized that a ReRh lesion (vs. a sham-operation) could interfere with hippocampal and/or neocortical connectivity remodeling. In order to test this hypothesis, male rats were subjected to a fiber-sparing ReRh lesion, trained in a water maze over 8 days (4 trials/d), and tested in a probe trial (60 s) at a post-acquisition delay of 5 or 25 days. Rats with ReRh lesions performed above chance level after 5 post-acquisition days, and at chance level after 25 days. Dendritic spines were counted on Golgi-stained sections of the dorsal hippocampus and medial prefrontal cortex (mPFC). Spatial learning resulted in a significant increase of mushroom spines in CA1 region in both Sham and ReRh rats. This modification persisted between 5 and 25 days post-acquisition in Sham rats, not in rats with ReRh lesion. Furthermore, 25 days after acquisition, the number of mushroom spines in the anterior cingulate cortex (ACC) had undergone a dramatic increase in Sham rats; ReRh lesion prevented this gain. In a second experiment, the increase of c-Fos expression in CA1 accompanying memory retrieval was not affected by the lesion, be it for recent or remote memory. However, in the ACC, the lesion had reduced the retrieval-triggered c-fos expression observed 25 days post-acquisition. These observations confirm a role for the ReRh in memory persistence, and show that a ReRh lesion disrupts two learning-triggered phenomena: persistence of remodeled hippocampal connections in CA1, and delayed spinogenesis in the mPFC. These alterations could reflect the absence of systems-level consolidation of a spatial memory after ReRh lesions.

**P1.150 Role of dopamine signalling in the central extended amygdala in the control of fear processing**

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The central extended amygdala, comprising a part of the nucleus accumbens (NAc), the central amygdala (CEA) and the lateral part of bed nucleus of the stria terminalis (BNST) serve complementary roles in the integration of fear-relevant information and orchestration of fear- and anxiety-related behaviors.

Within these circuits the dopamine (DA) inputs are thought to facilitate discriminative learning between stimuli representing safety or threat by signaling salience and motivational value. However, the identity of the neural population, in which DA acts to control threat processing, remains largely unknown. The analysis of GFP expression in *Drd1a-eGFP* and *Drd2-eGFP* mice revealed that D1R and D2R neurons were both found in the BNST, the CEA and the NAc. In these three nuclei, a high proportion of D2R neurons co-expressed the protein encoding for Wfs1 (Wolfram syndrome 1 or Wolframin), a marker previously shown to identify the central extended amygdala circuit. To determine the role of D2R signaling within this circuit, we have generated a cell-type specific conditional D2R mutant mice (cKO) by crossing Drd2-floxed mice with the Wfs1-CreERT2 mouse line expressing a tamoxifen-inducible Cre recombinase under the control of Wfs1 promoter/enhancer regions. The cKO, that show no alteration in anxiety level are tested in cued fear conditioning and extinction. The contribution of D2R autoreceptors is assessed in parallel in DAT-Cre:Drd2-floxed mice.

This work will contribute to better understand how DA signaling participate to fear processing in the central extended amygdala circuits.

**P1.151 Noradrenergic modulation of the orbitofrontal cortex mediates behavioral flexibility**  
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For an organism, knowledge of the consequences of its actions and the ability to assign a value to these consequences are both crucial processes allowing an appropriate goal-directed response. The crucial role of prefrontal regions, e.g. prelimbic cortex, for these processes has been very well described. However, the mechanism by which the organism quickly adapt its response to unexpected environmental changes remains unknown. It is possible to study this ability using instrumental learning. Typically, during an initial phase, an animal must associate voluntary actions with delivery of rewarding outcomes. Then, during a reversal phase, the animal must respond flexibly to a reversal of these associations. Using this task and chemogenetic tools allowing specific inhibition of cerebral regions, we have recently demonstrated a crucial role of the ventrolateral orbitofrontal cortex (vlOFC) for flexible response adaptation during the reversal phase (Parkes et al., 2017). In the present study, we focused on the noradrenergic input to the vlOFC, since locus coeruleus-noradrenaline (LC-NA) system has been commonly involved in flexibility-required tasks. In a first experiment, using a toxin (anti-D $\beta$ H saporin) we selectively depleted noradrenergic fibers in the vlOFC and showed a deficit of behavioral flexibility. Notably, this effect was not only specific to the reversal phase but also to vlOFC input since a similar depletion restricted to the medial portion of the PFC had no effect. Using an intersectional chemogenetic approach aiming at selectively targeting the LC input to the vlOFC, we are deciphering the time course involvement of this pathway during behavioural flexibility. In addition, current work are interested in revealing the specificity of NA action in the vlOFC compared to another neuromodulator, i.e. dopamine. Taken together, these results demonstrate a central role for noradrenergic input to the vlOFC in behavioural flexibility and reinforce the idea that the LC exerts a strong modulation of OFC functions.

**P1.152 Left inferior parietal cortex plays a key role in temporal order processing**

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Processing the temporal order of events in time is crucial for understanding the world around us. In most functional magnetic resonance imaging (fMRI) studies of temporal order processing, participants must judge which of two consecutive events appeared first. However, these tasks not only engage temporal order processing but also overt decision-making. We conducted an fMRI study of a new paradigm to identify regions involved in temporal order processing without the need for an explicit judgement. Twenty-two participants processed either the relative temporal order or, as a control task, the relative spatial position of two stimuli. In one scanning run, we asked participants to explicitly judge the temporal order of two differently coloured stimuli (which appeared first?) or their relative spatial position (which appeared on the left?). In another scanning run, participants performed our new paradigm: a choice reaction time (RT) task in which the temporal order or spatial position of a compound cue could be used to predict the shape of a subsequent target. In this paradigm, no explicit judgement is required but accurate order (or position) processing allows the target to be discriminated more quickly. First, a direct comparison of temporal to spatial trials during the judgement task replicated previous findings of right prefrontal cortex (PFC), bilateral temporoparietal junction (TPJ) and left inferior parietal cortex (IPC) for explicit temporal order judgements. Importantly, direct comparison of temporal and spatial conditions during the RT task again revealed left IPC, as well as parahippocampal gyrus and Supplementary Motor Area (SMA). Visual areas necessary for object and colour processing were preferentially activated by the temporal order condition in both runs. We conclude that task-induced activations common to the two runs, in left IPC and extrastriate visual cortex, are specific to temporal order processing while activation of other regions is related more to specific task instructions.

**P1.153 Involvement of dopaminoceptive neurons of the prefrontal cortex transmission in goal-directed actions**

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Dysfunction of cortical dopaminergic neurotransmission is a common neurobiological feature of many psychiatric conditions such as schizophrenia, major depression and addiction. A main shared symptomatic dimension of these psychiatric conditions is an impairment in executive functions that translates notably in an inability to adapt to changing environmental conditions. This maladaptive behavior can result from

- i) impairment in action selection,
- ii) insensitivity to manipulations of outcome value, and
- iii) failure in the discriminative ability between valuable and invaluable options.

The involvement of dopamine transmission, especially in the prefrontal cortex, in this behavioral alteration is at present still debated. Some preclinical work in rodents have shown that the expression of goal-directed action is independent of prefrontal dopaminergic neurotransmission, but pharmacological in vivo interventions with D1 and D2 receptors ligands suggest that the imbalance of dopamine signal in this brain region may play a role.

In this study, we assessed the role of dopamine receptor-expressing neurons of the medial prefrontal cortex in goal-directed behaviors using a specific satiety-outcome devaluation procedure. For this purpose, we employed a pharmacogenetic approach to selectively potentiate or inhibit the activity of D1 and D2 receptor-expressing neurons via viral mediated expression of designer receptors exclusively activated by designer drugs (DREADDs). Our findings show that while the activation or inhibition of D1 receptor-expressing neurons impair the performance of mice in the outcome-devaluation paradigm, suggesting the involvement of two independent mechanisms, the manipulation of D2 receptor-expressing neurons had no effect. These data highlight a differential role of subpopulations of dopaminoceptive neurons of the prefrontal cortex in goal-directed actions.

**P1.154 Looking for cortical correlates of motor imagery-based brain-computer interface learning**

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Non-invasive Brain-Computer Interfaces (BCIs) can exploit the ability of subjects to voluntary modulate their brain activity through mental imagery. Despite its clinical applications, controlling a BCI appears to be a learned skill that requires several weeks to reach relatively high-performance in control, without being sufficient for 15 to 30 % of the users. This gap has motivated a deeper understanding of mechanisms associated with motor imagery (MI) tasks.

We recorded brain signals from electroencephalography (EEG) while subjects performed a BCI task during four sessions. It consisted of modulating their brain activity to control the vertical position of a moving cursor displayed on a screen. Twenty BCI-naïve subjects (aged  $27.45 \pm 4.01$  years, 12 men), all right-handed, participated in the protocol. To study the evolution of the activations and of the functional connectivity during the training, we computed respectively the power spectra and the imaginary coherence between each pair of region of interest in the source space.

In both  $\alpha$  and  $\beta$  ranges, we found a progressive involvement of distributed sources in the cortical hemisphere contralateral to the movement corresponding to a significant power decrease ( $p < 0.025$ ). The observed decreases tended to focus more on the pre-and postcentral gyri at the end of the training. We found a progressive decrease of task-related connectivity in both  $\alpha$  and  $\beta$  ranges across sessions. Significant across-session decreases were spatially diffused involving bilaterally frontal, temporal and occipital areas in  $\alpha$  ranges, while they were more focused over the left primary motor cortex, the left central and parietal areas in the  $\beta$  ranges ( $p < 0.025$ ). Power changes in  $\alpha$  and  $\beta$  ranges significantly predicted the BCI accuracy in the subsequent session ( $p < 0.005$  in  $\alpha_2$ ). The connectivity decrease in the frontal and the temporal areas was associated with a better future performance in  $\alpha_2$ .

We elicited cortical changes associated with a dynamic brain reorganization during BCI training. They were characterized by an increase of the desynchronization rate and by a decrease of the connectivity that can be used as predictors of BCI performance. Taken together, our results offer insights into processes underlying BCI training.

**P1.155 EEG profile might be a new objective physiological marker of horses' welfare**  
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Assessing welfare of horses, which is a particularly critical point in terms of ethics, safety and performance, is still under debated. Although, clear behavioral and postural indicators have been validated, their use remains restricted to persons trained to observational techniques and the physiological parameters used so far gave contradictory results.

Furthermore, these indicators concern particularly horses' ill-being. Therefore, in order to assess clearly and simply horses' welfare we need objective markers that can be used by non-specialists.

Recently, it has been shown that a horse in a good welfare level seems to be quiet and attentive to its environment. The telemetric EEG headset developed in our lab allowed us to show that horse attentional state can alter the EEG profile (proportion of brain waves). In the light of these results we hypothesize that welfare may also alter EEG profile and that EEG profile may become a good objective physiological marker of welfare. In order to test this hypothesis, we performed EEG recordings on two populations of horses living in two different environment and presenting different welfare levels. One population was living in riding center with restricted conditions (single stalls, limited access to roughage...) and the other population was living in naturalistic conditions (stable groups, pasture with grass or hay adlibitum...). The welfare of these horses was precisely evaluated using behavioral markers. We recorded separately the EEG of the left and right hemispheres of the horses while they were quietly watching their environment. We then built the individual EEG profiles (proportion of the different brainwaves) of left and right hemisphere.

The results show a clear difference of well-being of both populations, horses living in naturalistic conditions presented a well-being state clearly better than the horses living in riding center. The EEG profiles varied as a function of the population and were correlated to horse well-being. These results show that EEG may become a new objective marker of welfare in horses.

**P1.156 Impaired hippocampal-dependent fear memories despite potentiated fear memory extinction in VGLUT3 knock out mice**

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Emotional memories rely on a complex network involving the prefrontal cortex, the hippocampus and the amygdala. This network is functionally impaired in anxiety pathologies such as post-traumatic stress disorders (PTSD). It has been shown that about thirty percents of persons exposed to high stress such as traumatic events would eventually develop PTSD. The co morbidity between previous anxiety traits, or addictive behaviors and following PTSD is well documented.

Accumulating evidence suggests aberrant glutamatergic function in mood, anxiety, and trauma-related disorders. Dysfunction in glutamate neurotransmission is increasingly considered a cardinal feature of stress-related psychiatric disorders including PTSD. Glutamate is accumulated in synaptic vesicles thanks to vesicular transporters named VGLUT. If VGLUT1 and 2 are present in canonical glutamatergic neurons, VGLUT3 has the peculiarity to be expressed in neurons originally described as non-glutamatergic. We previously showed that VGLUT-KO mice show excessive anxiety traits (Amilhon et al 2010) as well as a predisposition for addictive behaviors (Sakae et al 2015). Therefore, we wondered if the loss of VGLUT3 expression could trigger impairment of emotional memories as observed in PTSD.

By using VGLUT3-KO mice, we studied emotional memories using the Pavlovian fear-conditioning paradigm. Our study revealed dysfunction of contextual memories, with generalization to a safe context that could be due to a deficit of pattern separation in those mice.

Our data indicate that VGLUT3 network plays a key role in regulating emotional memories. Therefore, glutamate co-transmission should be seen as a key player in the processing of fear-associated memories.

**P1.157 Very slow (minutes) attentional rhythms in the prefrontal cortex**

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Oscillations in brain activity are described as a major feature supporting attentional processes. However, this rhythmic mechanism is always described at the sub-second time scale, in specific theta and alpha frequency ranges. In contrast, the description of slower oscillatory mechanisms at the minute to hour time scales are missing. Here, we apply machine learning methods to ongoing monkey population prefrontal multi-unit activity (MUA) and local field potential (LFP), to decode, in real-time, the (x,y) location of the attentional spotlight (Astrand et al., 2016). We describe that the decoded spatial attention information oscillates every 2-3min and 10-15min. In these cycles, prefrontal attentional content alternates between distinct states of rich and low information. These oscillations are both described in the LFP and MUA signals, in two monkeys, revealing robust global state rhythmicity, systematic from one session to the next. Importantly, these oscillations in the decoded attentional information content account for variations in overt behavioral performance. As a result, we demonstrate that both PFC attentional mechanisms and overt performance are rhythmic at multiple time-scales ranging from the fast alpha scale to a much lower 10-15min scale. This result participates to a new multiscale and dynamic model of attentional processes, the understanding of which is critical to develop and optimize attention interventions including attention driven cognitive brain machine interfaces.

**P1.158 Impact of dietary habits on stress-induced cognitive alterations in healthy adults**  
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Stress exposure is notorious for representing a potent modulator of cognitive function. Poor dietary habits have been hypothesized to potentiate this effect. Not only diet and stress reactivity are closely interrelated, but it is also increasingly recognized that diet affects cognitive processes. However, the direct effect of diet on stress reactivity and its relationship with cognitive function has not been systematically assessed in experimental studies. The present study, performed in the frame of the AMBROSIAC JPI project, aims at investigating the impact of diet on stress-induced cognitive alterations in a group of healthy adult subjects.

Fifty healthy adult volunteers were recruited. Participants were stratified on the basis of their nutritional habits, i.e., healthy (balanced diet) *versus* unhealthy (unbalanced diet group), according to adherence to the French nutritional recommendations, assessed by the “*Programme National Nutrition et Santé*” (PNNS) questionnaire. Visual and verbal memory, sustained attention and working memory were evaluated through performance in the tests of Paired-Associated Learning (PAL), Verbal Recognition Memory (VRM), Rapid Visual Information Processing (RVP) and Spatial Span (SSP), respectively, from the CANTAB battery. Assessments were performed before and after exposure to a psychological stressor, the Trier Social Stress Test (TSST). Stress response was evaluated by salivary cortisol, blood pressure and heart rate, measured at different time points.

The TSST produced a significant endocrine and autonomic stress response, regardless of dietary habits. Exposure to TSST was also associated with cognitive alterations in the CANTAB battery, notably in the form of impaired performance on the VRM test and improved scores on the RVP, SSP and PAL tests. These stress-induced alterations were apparent in both subjects with unbalanced and balanced diet. Interestingly, however, participants with unbalanced diet exhibited lower performance on the PAL and VRM tests post-TSST in comparison to participants with healthy dietary habits.

These results are consistent with the hypothesis that poor dietary habits negatively impact the effect of acute psychological stress on cognitive performance.

**P1.159 Different cognitive functioning between high and low creative people underlying by a different attentional network connectivity at rest**

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Creativity has been defined as the ability to produce work that is both new and appropriate for a task (Stenberg and Lubart, 1996). To better understand cognitive mechanisms underlying the creative potential of an individual, we investigated the creative performances of healthy subjects ( $n= 45$ ) with regard to their cognitive profile with a SEM-PLS analyse. Furthermore, we investigated the functional connectivity at rest with the fMRI, we were interested on the default mode network, the executive network, the salience network and the attentional network. We were able to distinguish two different cognitive profiles: one associated with subjects with high creativity and the second associated with subjects with low creativity. In low creative people creativity is negatively correlated to problem solving whereas in high creative people, creativity is negatively correlated to problem solving but positively correlated to attentional flexibility performance. These difference in creative ability is accompanied by an increase in functional connectivity at rest in the attentional network, in high creative people.

These results indicate that a high creative potential can be associated to a specific brain functioning and thus participate to highlight the mechanisms underlying creativity. In our future investigations concerning cognitive rehabilitation for traumatic brain injury, these data will be of great interest. Indeed, in this pathology where the ability to cope and be creative is essential for an optimal recovery, it will be very helpful to identify what kind of creative is the patient in order to optimise his cognitive care.

**P1.160 Social dimension of peripersonal space**

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In everyday life, humans and animals evolve in an environment composed of various objects with which they dynamically interact. The peripersonal space (PPS), defined as the region of space in close proximity to our body, constitutes a privileged area for the processing of external stimuli. The representation of this space is flexible, allowing us to adapt quickly and optimally to our environment, for example in order to grasp a cup of coffee or avoid sudden threats. However, our world is not only made of objects: navigating in a social world also requires a flexible adjustment according to the distance from our peers.

The present study aimed to understand how the social context (i.e. the presence of another individual) modulates behavioral and physiological signatures of PPS. Participants were asked to discriminate male from female faces (gender discrimination task) presented at different distances (50 cm to 300 cm) in a virtual reality environment. The faces displayed different emotional expressions (happiness, anger or neutral). We measured accuracy and response times (RTs) as well as pupillary responses and heart rate.

Our results show that participants are faster to discriminate faces when they are presented close to the body, even when farther ones appear bigger. Moreover, we found that participants' performances are influenced by the emotions displayed by the faces. Finally, these behavioral effects were accompanied by a modulation of participants' autonomic responses. Specifically, close faces induced an increase of the heart rate and a constriction of the pupil diameter. Altogether, these results suggest that the fastest processing classically found for objects in PPS extends to social stimuli. They also highlight physiological changes during the processing of social stimuli in the PPS.

**P1.161 Lateral habenular dysfunction induces emotional memory deficits**

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The lateral Habenula (LHb) is a brain structure implicated in cognitive and emotional processes such as memory, aversion and response to stress. It is suggested that one of the main roles of the LHb is to adapt one's behavior facing highly emotional situations. Interestingly, during a cognitive task in an aversive context, we have shown that the LHb, in addition to its involvement in memory formation, modulates the hypothalamo-pituitary adrenal axis, suggesting that it is at the crossroads of emotional and cognitive processes. To test the hypothesis, we addressed the role of the LHb in emotional memory and used fear conditioning as a behavioral paradigm. During conditioning, rats received six electric footshocks (unconditioned stimulus, US), each preceded by a tone (conditioned stimulus, CS) delivered 30 seconds before. We first used an immunochemistry approach (c-Fos protein) to see whether the conditioning phase engaged the LHb and integrated it within a network including the dorsal hippocampus (dHPC) and the amygdala (AMG), known for their involvement in fear conditioning. Our results show a preferential implication of the more medial part of the LHb (LHbM) during fear encoding. In addition, a factorial analysis revealed two factors: a context-related factor (mainly composed of the dHPC and the basolateral nucleus of the AMG) and a CS-related factor (mainly composed of the AMG subnuclei), while the LHbM was included in both factors. This analysis suggests that the LHbM participates in both context and CS integrations and possibly their association to the US. Then, we used a DREADD approach to selectively and temporarily inactivate the LHb during conditioning and assessed the impact of this inactivation on context and CS memories. We found that LHb inactivation reduces fear elicited by the context and exacerbated the fear response to the CS. These results indicate that the LHb is engaged in the competition between contextual and discrete cues to gain control over conditioned fear, and, suggest that the LHb is an important actor in learning about threatening environments.

P1.162

**Ambiguous learning in drosophila: from behavior to neural networks**

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Learning can be defined as behavioral changes resulting from individual experiences underlain by neural plasticity. In particular, individuals can associate several stimuli presented together by means of associative learning (e.g. a specific scenery can be associated with the presence of food) and adjust their behavior accordingly. This way, simple associations enable individuals to establish and memorize logical rules about the world, at least in theory. In natural conditions however, a same sensory stimulus can yield different (sometimes opposed) outcomes, depending on the context. How animals extract relevant associations from such complex sets of sensory cues remains unclear. Here we adapted a classic associative conditioning paradigm and showed that individual Drosophila flies are able to solve various ambiguous tasks that were assumed to be restricted to more elaborate organisms. Furthermore, using genetic tools, we showed that unlike simple discriminations, solving this kind of problem required the involvement of a pair of brain neurons both during learning acquisition and restitution. Finally, our findings demonstrate the importance of repetition and shows how a gradual tuning of stimuli's representation can lead to robust associations in an ambiguous world.

**P1.163 Glial lipoprotein receptor LSR as potential molecular link between olfactory and memory deficits, and brain cholesterol homeostasis**

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Regulation of cholesterol, an essential brain lipid, ensures proper neuronal development and function, as demonstrated by links between perturbations of cholesterol metabolism and neurodegenerative diseases, including Alzheimer disease (AD). The central nervous system (CNS) acquires cholesterol via de novo synthesis, where glial cells provide cholesterol to neurons. Both lipoproteins and lipoprotein receptors are key elements in this intercellular transport, where the latter recognize, bind and endocytose cholesterol containing lipoproteins produced by glia. CNS lipoprotein receptors are similar to those in the periphery, among which include the apoB,E lipolysis stimulated lipoprotein receptor (LSR). Complete inactivation of murine *lsr* gene is embryonic lethal, but studies on *lsr*<sup>+-</sup> mice revealed altered brain cholesterol distribution and cognitive function. LSR profiling by immunoblots of murine tissue homogenates from different CNS regions revealed region-specific expression of LSR. This was confirmed by qPCR analysis and immunocytostaining using primary cultures of mature murine neurons or glial cells isolated from different CNS regions, with strong LSR expression predominantly in glial cells. We postulate that glial LSR may play a role in feedback control of cholesterol synthesis, limiting circulating cholesterol in brain extracellular fluid, thus maintaining cholesterol homeostasis. To pursue this hypothesis, we obtained glia-specific LSR KO animals by crossing GLAST-CreER (glia specific inducible) mice with floxed LSR mice (*f/f-f/f-lsr*); adult mice were treated with tamoxifen. Behavioral phenotyping of these animals revealed a deficit in olfactory function affecting social memory as well as visual memory (despite no effect on vision), as well as changes in short (Y-maze) and long term (Barne's maze) memories, demonstrating that glial LSR is important for working, spatial and social memory related to sensorial input. Studies have reported olfactory deficits in early AD, and since aging *lsr*<sup>+-</sup> mice show increased susceptibility to amyloid stress, we propose that LSR represents a novel pathway to study the link between cholesterol trafficking, olfaction and age-related neurodegeneration.

**P1.164 The activation of sensory-motor and emotional experience during speech production**

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Speaking requires to transform an idea into articulated speech sounds through the selection of words. Picture naming is used as a proxy to investigate speech planning processes, however it is restricted to imageable concrete objects (e.g. *cat*) while we also refer to abstract concepts such as *faith* or *merit* to share ideas about science, religion or politics. According to embodied cognition, mental representations of words referring to concrete objects are driven by sensory-motor experience while emotional information plays a larger role in the semantic representations of abstract words. Here, we used inferential naming tasks to investigate naming differences between abstract and concrete words, and test whether sensory-motor and emotional information associated to word-referents are retrieved during speech production.

Two experiments were conducted, in which participants (N=38) were asked to overtly produce words in response to definitions. Using sensory-experience ratings and emotional valence, we constructed 278 written definitions to elicit the production of neutral abstract words (e.g. *clause*), abstract words with emotional associations (e.g. *ardor*), neutral concrete words (e.g. *flashlight*) and concrete words with emotional associations (e.g. *morgue*). Overall, accuracy was lower and production latencies slower for neutral abstract words. Mixed-effect regression models were performed on accuracy and production latencies. Facilitatory effects of sensory-experience ratings and emotional valence were observed on production latencies, such that words with high sensory-motor and/or emotional associations were produced faster. Electroencephalographic (EEG) data are currently used to unravel how these processing differences relate to the involvement of differential neural networks.

Our results indicate that sensory-motor and emotional information are activated during inferential speech production. Moreover, words with strong grounding in sensory-motor and/or emotional experience are better retrieved than words with relatively poor grounding, independently of whether they refer to concrete or abstract entities. We provide further evidence that the meaning of words is anchored in external and internal experience with their referents, supporting embodied semantics.

**P1.165 Altered gene expression in medial prefrontal cortex correlates with social cognition deficits derived from perinatal malnutrition in a mouse model**

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Early life adversities such as perinatal malnutrition can modulate neuronal plasticity through epigenetic mechanisms contributing to neurophysiologic and behavioral alterations. However, factors mediating these effects remain unknown.

To evaluate these factors, we used CF1 dams fed with normal protein diet (NP, casein 20%) or low protein diet (LP, casein 8%) during pregnancy and lactation, and the offspring were analyzed at P56. Through a preclinical PET analysis, we found evidence of diminished glucose metabolism in the prefrontal cortex (mPFC) of LP mice, suggesting a potential deficit in the function of this brain's region. The mPFC may be a candidate regulator in mediating social cognition in both humans and rodents. Therefore, we performed different behavioral tests in order to evaluate cognition and social memory in LP mice. We found that contextual recognition memory was impaired in LP mice. In addition, malnourished mice displayed a diminished social interaction and social memory.

Conversely, LP mice exhibited an increased dominance hierarchy. Interestingly, these behaviors were transmitted to the next generation. Using RNAseq, we evaluated the global gene expression profile in mPFC of NP and LP mice. From this analysis, Kdm6b, Ezh1 and Ezh2 and transcription factor Npas4 turned out to be interesting candidates for this study since methylation/demethylation of H3K27 and Npas4 pathway are involved in neurodevelopment and cognitive abilities. RT-qPCR analysis showed that these four genes were differentially expressed in primary cultures MEFs. Furthermore, Kdm6b and Ezh1 expression were significantly decreased in the mPFC of LP female mice at P56. Social cognition deficits in animal models have been linked to an altered balance of excitation and inhibition (E/I) within the cortex generally, and mPFC specifically. To investigate the potential contribution of E/I imbalance in the mPFC to these behaviors, we evaluate the expression of several genes involved in Gabaergic and Glutamatergic transmission. LP mice expressed higher levels of Gria1 and Vglut1 than their NP counterparts.

We propose that disturbed H3K27me3 levels during brain development caused by perinatal malnutrition could lead to altered E/I balance and subsequent deficits in the social domain.

**P1.166 Influence of cell types and local circuitry on intrinsic timescales in the midcingulate and lateral prefrontal cortex**

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Fluctuation in spiking activity is constituent of neurons across cortical areas. The timescales on which such fluctuation operates are likely to be shaped by anatomical properties and network connectivity. Prefrontal regions such as the lateral prefrontal cortex (LPFC) and especially the midcingulate cortex (MCC) exhibit the longest timescales across the primate cortical areas. Long timescales indicative of a stable activity state across time could grant integration over extensive time period, a fundamental feature of higher cognitive functions. To finely describe intrinsic timescales we computed between trials time autocorrelograms of spiking activity and true spike autocorrelograms of individual MCC and LPFC units (251 MCC units and 248 LPFC units) recorded in awake monkeys engaged in a cognitive task. Because area intrinsic timescales might reflect properties of local dynamics and excitation/inhibition balance in local networks, we hypothesized that single unit types (fast or regular spiking) could reveal differences between MCC and LPFC. We replicated findings showing that MCC units have longer timescales than LPFC on average. Moreover we found that the MCC temporal signature differ in particular by the dynamics of its regular spiking units. Additionally, local circuitry dynamics revealed particular excitation/inhibition driven by fast spiking units in the MCC. Together those findings provide clues that MCC unit cell type and their local network contribute to its notable long timescales, shaping the MCC as a core area for higher cognitive functions and reward based decision-making.

**P1.167 Control of conditioned fear memories by the cerebellum**

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The formation and retrieval of conditioned fear memories critically depend on specific areas such as the amygdala and the prefrontal cortex (PFC). Recently, some data have been suggesting an involvement of the cerebellum in emotional disorders. Therefore, using a combination of neuroanatomy, behavior, pharmacogenetic approaches, and electrophysiology, we have been studying the involvement of the cerebellum in fear conditioning, and mapping the brain circuit linking the cerebellum to the limbic system. Through stereological injections of retrograde viral tracers in PFC and amygdala, and anterograde virus in the deep cerebellar nuclei, we analyzed the possible link between these areas. We found fibers from the cerebellar fastigial nucleus and neurons projecting to amygdala and PFC in the parafascicular and mediodorsal (MD) nucleus of the thalamus. Moreover, we found fibers from fastigial nucleus projecting to the ventrolateral periaqueductal grey (vIPAG) which is known to be important for fear responses. Thus, we investigated the effects of transient silencing or excitation of neuronal activity of cerebellar projections to thalamic nuclei and vIPAG, during fear conditioning and extinction in mice. We virally expressed inhibitory or excitatory DREADDs in the fastigial nucleus, combined with the injection of retrograde CAV-Cre in the target areas, and we examined the effects during fear learning and extinction training after clozapine-N-oxide (CNO) injection. We have found a modulation on extinction learning by the fastigial-MD pathway and modulation of fear memory by fastigial-vIPAG pathway. Taken together, these results indicate that the cerebellum might be an important modulator of conditioned fear memories.

**P1.168 Pet dogs present social preference for people who synchronize their walk with theirs. Evolutionary perspectives for behavioral synchronization**

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Behavioral synchronization is broadly defined as individuals doing the same thing (activity synchrony) at the same time (temporal synchrony) in the same place (location synchrony) (Duranton & Gaunet, 2016). Pet dogs have been recently found to synchronize their walk with that of their owners (Duranton, Gaunet & Bedossa, 2017, 2018). Further, humans display increased affiliation towards people who synchronized their behaviors with theirs (Richardson et al., 2007; van Ulzen et al., 2008; Kendon, 1970; Richardson et al., 2008). Little is known about this phenomenon at interspecific level: only Capuchin monkeys display affiliation toward humans who imitate them (Paukner et al., 2009). We explored whether human synchronization with dogs could affect dogs' social preference towards humans as in Paukner et al. (2009). Dogs were confronted with two unfamiliar persons in their living room -one synchronized her walk with that of the dogs free, and the other one walked randomly. Then the two persons were presented together to the dogs, and we observed dogs' first choice. Molossoids exhibited a clear social preference for the synchronized person, unlike shepherds: significantly more molossoids (12) than shepherd dogs (6) chose the synchronized experimenter,  $\chi^2 = 1.76$ ,  $df = 1$ ,  $p = 0.0048$ , Cohen's  $d = 1.25$ , 95% CI [-0.83, -0.20]. We found no effect of condition on the amount of time the dogs spent close to the experimenter during the preference phase. We found no difference in the number of stress-associated behaviors exhibited by the molossoids and shepherds. Within each breed, there was no effect of the condition on the number of stress-associated behaviors. We conclude that pet dogs show a greater affiliation with humans who mimic their walking behavior, although genetic selection modulates this propensity. Behavioral synchronization, therefore, acts as a social glue in dogs too. It is the first time that such a human-like ability has been highlighted in domesticated canids at an interspecific level. Implications for the evolution of behavioral synchronization are that

- 1) a human-like social skill have evolved in dogs for an interspecific function and
- 2) likely by convergent evolution based on selective pressure (domestication).

**P1.169 EEG Multivariate Pattern Analysis reveals higher-order linguistic extraction of phonetic features at 3 months of age**

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Fundamental to language comprehension is the ability of the listener to systematically map continuous speech onto discrete segments: the phonetic units. Speech segments are defined by bundles of distinctive features that describe speaker's articulatory actions and their acoustic correlates (Stevens, 2002). Two main phonetic domains, *manner* and *place*, specify the general modalities of oral constriction and the active articulators. We investigated the perception of speech segments by preverbal infants. At 3 months native phonemes are not discriminated, meaning that all phonetic contrasts are processed in the same way regardless of their linguistic role. For this reason it is generally assumed that at this age speech processing is merely acoustic and not yet phonetic.

Subjects listened to natural syllables composed of six consonants for which manner and place varied orthogonally. Consonants were associated to either "i" or "o" and spoken by a female or a male voice. Further acoustic variability was inserted in the stimulation so that to disentangle acoustic from phonetic processing (each phonetic profile was presented in many spectrotemporal variants). Since phonetic feature estimation requires a very fast, fine-grained spectrotemporal analysis of the input, we aimed at imaging infant neural responses with extremely high temporal and spatial resolution. We employed a 256-channels prototype EEG recording system, featuring 140 dry electrodes disposed over temporal areas at a distance of 5mm one another. Data analysis was conducted with a multivariate approach: series of classification algorithms were trained and tested on short time slices of the neural responses (King & Dehaene, 2014). The algorithms reliably decoded the manner and the place of articulation over a time window ranging from 100 to 750 ms after syllable onset. Crucially, classifiers trained on single vocalic and harmonic contexts were able to generalize on unseen vowel and voice conditions, unrevealing an acoustically invariant phonetic code. Further, we show that the structure of phonetic representations changed over time, possibly following a specific neural trajectory. Overall, our pattern of results suggests that at 3 months infants are already processing speech in abstract, linguistic terms.

**P1.170 Parameter analysis in a computational model of the hippocampus**

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The hippocampus produces various fast and slow oscillatory rhythms over the sleep-wake cycle, such as theta-nested gamma oscillations during exploratory behaviours (at a frequency of 5-10Hz and 30-100Hz), or delta waves (1-4Hz) and sharp-wave ripple complexes (120-200Hz) during rest and slow-wave sleep.

We have previously built a computational model of the hippocampus with more than 30000 Hodgkin-Huxley neurons, with realistic topology and connectivity, able to reproduce these sleep-wake oscillatory rhythms [1]. We now propose an analysis of the influence of the parameters of our hippocampal network on the generated rhythms, including neuron types, synapses conductances, and synaptic connexion probabilities, under stereotypical inputs. The aim of this work is to better understand what controls the slow (delta-theta) and fast (gamma-ripple) components of the hippocampal oscillations. From these results, we also want to investigate the changes that may lead the hippocampus to generate pathological activity.

Our simulation results suggest that the fast oscillations frequency can easily be tuned by changing synaptic properties, but these parameters have little to no effect on the slow component of the oscillations. On the other hand the slow component of the oscillations seems to be mostly influenced by individual neuron properties, as well as by the frequency of the input stimulation.

[1] Aussel, A., Buhry, L., Tyvaert, L. and Ranta, R., A detailed anatomical and mathematical model of the hippocampal formation for the generation of sharp-wave ripples and theta-nested gamma oscillations J Comput Neurosci (2018) 45: 207.

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**P1.171 Bursting activity in STN-GPe circuit determine the presence of pathological beta oscillations**

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The STN-GPe circuit is considered to play an integral role in generating and modulating the pathological beta oscillations in the basal ganglia. However, what feature of these nuclei, i.e their firing rates or firing patterns are responsible for these pathological oscillations, is unclear. We performed spiking neural network simulations of STN-GPe circuit using a neuron model, where firing rates and firing patterns (specifically bursting) can be independently controlled and used this framework to independently study the effect of firing rates and bursting on oscillations. Firstly, we find that an increase in STN firing rates is integral for generating oscillations, but no such correlation is present with a change in GPe firing rates. In case of bursting, however, we find that the effect of GPe/STN bursting is state-dependent. For network states on the border of oscillatory and non-oscillatory regime, an increase in GPe bursting facilitates the emergence of oscillations whereas an optimal level of STN bursting is compensatory and suppresses pathological oscillations. We suggest that in healthy conditions, the network operates at the border of oscillatory and non-oscillatory state and this tandem of STN-GPe bursting could be a mechanism to generate short-lived oscillations or beta bursts, thereby assigning a functional role for bursting in healthy conditions. However, during PD, the network state shifts deeper into oscillatory regime where this tandem fails and leads to run away pathological oscillations.

**P1.172 Neural mechanisms underlying economic decisions under sequential offers**

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Economic choices involve two mental stages - values are assigned to the available options and a decision is made by comparing values. Evidence from lesion studies, functional imaging, neurophysiology and computational modeling suggests that economic decisions between goods are formed within the orbitofrontal cortex (OFC). Importantly, current notions emerged almost exclusively from studies where two offers were presented simultaneously. Yet, in many real-life decisions, offers available for choice appear or are examined sequentially. Previous work on choices under sequential offers suggested that choices in the two modalities (sequential and simultaneous offers) rely on fundamentally different mechanisms. Unfortunately, discrepancies in data analyses make it difficult to compare findings from different lines of work. To shed light on this critical issue, we recorded from the OFC of rhesus monkeys choosing between two juices offered sequentially and in variable amounts. An analysis of neuronal responses across time windows revealed the presence of different groups of neurons encoding the value of individual juices, the binary choice outcome and the chosen value. These groups of cells closely resemble those identified under simultaneous offers, suggesting that decisions in the two modalities are formed in the same neural circuit. We then examined four hypotheses on the mechanisms underlying value comparison (i.e., the decision). Our data clearly confuted the notion of a single neuronal pool. They were also inconsistent with mutual inhibition between pools of offer value cells. Interestingly, we did not find any sustained representation of the first offer value in OFC. Instead, decisions appeared to involve mechanisms of circuit inhibition whereby each offer value inhibited the population of neurons representing the opposite choice outcome. Our results reconcile seemingly divergent findings on the neural mechanisms underlying good-based decisions. They also shed light onto the role played by shifts of attention or mental focus in economic choices.

**P1.173 A spiking neural-network model of goal-directed behaviour**

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In mammals, the acquisition and consolidation of instrumental behaviour involves two processes, one is related to flexible goal-directed behaviours used to explore and find solutions to new problems and the other one is related to habits used to store and exploit inflexible but effective stimulus-response behaviours. In brain, goal-directed behaviours rely on ventral/associative basal ganglia and frontal cortex, whereas habits rely on motor basal ganglia and sensorimotor/premotor cortices. In this work, we present a spiking neural-network computational model built to study the mechanisms underlying goal-directed behaviour operating the underlie the solution of the “arbitrary visuomotor learning task” requiring human participants to explore and then exploit the correct associations between three coloured circles and five finger movements to obtain a positive feedback and avoid a negative one. The model is composed by components formed by integrate-and-fire spiking neurons: (a) an input neural layer encoding colours, feedback, and the action afferent copy; (b) a fully-connected associative network learning to represent the input patterns and the sequences with which they are observed; (c) an output layer selecting the actions to execute in the environment and also anticipating stimuli; (d) a goal layer encoding the goal to pursue, e.g. the positive feedback, and learning to bias the dynamics of the associative network to perform actions leading to the goal. The input and goal layers activate the associative network that in turn activates the output layer. The associative network uses spike-timing dependent plasticity to form winner-take-all circuits that implement a stochastic Hidden Markov Model (HMM) reproducing the experienced input-action-feedback sequences, i.e. a model of the world. The novelty of the model is that it uses the world model and the goal achievement to implement a one-step planning process leading to learn suitable connections linking the goal layer to the associative network. The model is able to reproduce the behaviour of the participants of the target experiment and represents an operational hypothesis on how goal-directed behaviour might rely on probabilistic inference processes relying on the stochasticity of spiking neurons.

**P1.174 The canonic cortical circuit connectome flexibly shapes layer-dependent multi-frequency oscillations**

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Cortical connections are organized into a multi-layered architecture, whose role in shaping neuronal responses and inter-areal routing has not yet been elucidated. Here, we analyze a rate model of a canonic local circuit with a realistic connectivity based on anatomical reconstructions. We find that this circuit generates a rich repertoire of possible dynamical states, including an oscillatory regime in which gamma- and beta-oscillations dominate in superficial and deep layers, respectively. Our simulations thus match as a "free lunch" empirical observations that different cortical layers oscillate at different dominant frequencies. Furthermore, we also reproduce in the model the repeated finding that neuronal oscillations at different frequencies are exploited for communication in different directions.

This laminar specificity of oscillations is often explained in terms of multiple inhibitory populations with different resonance frequencies. However, we show here that it could also more generally emerge as a byproduct of non-linear interactions between layers, independently from their intrinsic oscillatory properties.

Furthermore, our modelling study indicates that the empirically observed multi-frequency oscillatory patterns could not be reproduced by a random interlayer connectivity. Therefore, we prove that the adopted realistic connectome is "special". Nevertheless, we also find that it is potentially not unique, since other, very different connectomes may lead to matching dynamical behaviors. We thus predict that a multitude of alternative —yet undiscovered?— canonical circuit templates could give rise to analogous routing capabilities, possibly achieved and maintained via functional homeostasis mechanisms.

**P1.175 A non-negative measure of feature-specific information transfer**

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Quantifying the amount of information communicated between neural population is crucial to understand brain dynamics. To address this question, many tools for the analysis of time series of neural activity, such as Granger causality, Transfer Entropy, Directed Information have been proposed. However, none of these popular model-free measures can reveal what information has been exchanged. Yet, understanding what information is exchanged is key to be able to infer, from brain recordings, the nature and the mechanisms of brain computation. To provide the mathematical tools needed to address this issue, we developed a new measure, exploiting benefits of novel Partial Information Decomposition framework, that determines how much information about each specific stimulus or task feature has been transferred between two neuronal populations. We tested this methodology on simulated neural data and showed that it captures the specific information being transmitted very well, and it is also highly robust to several of the confounds that have proven to be problematic for previous methods. Moreover, the measure was significantly better in detection of the temporal evolution of the information transfer and the directionality of it than the previous measures. The new measure was also tested on source-level high-gamma activity estimated from MEG data collected from participants performing a visuomotor association task. Our measure allowed for tracing of the stimulus information flow and it confirmed the notion that dorsal fronto-parietal network is crucial for the visuomotor computations transforming visual information into motor plans. Altogether our work suggests that our new measure has potential to uncover previously hidden specific information transfer dynamics in neural communication.

**P2.001 Modulation of acute inflammation in a rodent model of vestibular pathology: cellular and functionnal approaches.**

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Inflammation is a complex process, constituting the body's response to stress, injury or infection. In the central nervous system, it systematically involves microglial cells, resident brain macrophages, and astrocytes. The deleterious consequences of chronic inflammation on brain tissue have led to the administration of anti-inflammatory corticosteroids in patients from the acute phase onwards. However, the benefits of these treatments are now questioned. This is particularly true in patients with vestibular neuritis, a sudden and isolated peripheral vestibulopathy that appears to be caused by inflammation of the vestibular nerve and characterized by various perceptual-cognitive, vegetative, oculomotor and posturo-locomotor disorders. One study model for this pathology is unilateral vestibular neurectomy (UVN) in rodents, which is both a model of post-lesional plasticity and a model of neuroinflammation.

Our objective was to study the behavioral and cellular consequences of a pharmacological modulation of inflammation expressed in the acute stage in vestibular nuclei in rats subjected to UVN. Three groups of rats were submitted to 3 different pharmacological treatments during 3 days after UVN (a vehicle; a pro-inflammatory; a anti-inflammatory). Using cellular and behavioral approaches, we quantified the impact of such treatment on vestibular syndrome, functional restoration, and the expression of plasticity mechanisms in deafferented vestibular nuclei.

Our results showed that acute pro- or anti-inflammatory treatment in UVN rats alters the expression of microglial and astrocytic cells as well as cellular proliferation in the deafferented vestibular environment. Moreover, it generates functional deficits that persist for several weeks.

Although preliminary, these data suggest a beneficial role for endogenous acute inflammation in vestibular functional recovery, and pave the way for new pharmacological strategies in patients.

**P2.002 AMPA receptor mobility is important for spatial memory consolidation through ripples modulation**

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We recently showed that surface diffusion of AMPARs at neuronal surface was essential to the expression of Long-term potentiation at the CA3 to CA1 synapses both in vitro and in vivo. Furthermore, AMPARs immobilisation within the dHPC impaired contextual fear response, if mediated before or immediately after the conditioning, but not 24 hours later, opening the possibility that AMPARM-dependent LTP expression in the dHPC could mediate the encoding and/or early consolidation of the contextual threat. To gain insights onto this question, we adapted a declarative task requiring multiple training sessions over several days, and tested the impact of AMPAR immobilisation on memory acquisition, consolidation and retrieval. Groups of mice were implanted above the dHPC with injection cannula and trained for a delayed spatial alternation (DSA) task in a Y-maze. Bilateral dHPC injections of AMPAR X-linking antibodies - or their monovalent controls - were performed at dedicated time points. Our results showed that if DSA memory formation was not impaired, animal performance severely dropped after long resting periods, suggesting that AMPARM-dependent synaptic plasticity could be important for memory consolidation. We then investigated the impact of AMPARs immobilisation on sharp waves ripples - high frequency oscillations occurring during rest, forming replays of recently acquired memories - which physiology is highly correlative to memory consolidation performance. To this aim, Local field potentials were recorded in dorsal hippocampus and medial prefrontal cortex in resting mice before/during and after task learning. Preliminary results showed that DSA learning and AMPAR immobilisation affect sharp waves ripples during slow wave sleep, suggesting that blocking AMPARS mobility affected a form of synaptic plasticity crucial for sharp waves ripples maintenance during consolidation. Further investigations are ongoing to understand the mechanisms behind the modulation of ripples through AMPARs mobility.

**P2.003 Boc acts as a Shh-dependent endocytic platform for Ptch1 internalization and Shh-mediated axon guidance**

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During development, Sonic hedgehog (Shh) attracts commissural axons towards the floor plate through a non-canonical, transcription-independent signaling pathway that requires the receptor Boc. Here, we find that Shh induces Boc internalization into early endosomes, and that endocytosis is required for Shh-mediated growth cone turning. Numb, an endocytic adaptor, binds to Boc and is required for Boc internalization, Shh-mediated growth cone turning *in vitro* and commissural axon guidance *in vivo*. Similar to Boc, Ptch1 is also internalised by Shh in a Numb-dependent manner. Using Shh mutants, we demonstrate that the binding of Shh to Ptch1 alone is not sufficient to induce Ptch1 internalization nor growth cone turning. Therefore, the binding of Shh to Boc is required for Ptch1 internalization and growth cone turning. Our data highlight the importance of endocytosis for Shh-mediated axon guidance and support a model where Boc endocytosis via Numb is required for Ptch1 internalization and Shh signaling in axon guidance. Thus, Boc acts as a Shh-dependent endocytic platform gating Ptch1 internalization and Shh signaling.

P2.005

**Physiology of hippocampal Sharp Waves Ripples *in vitro*: importance of AMPA receptor mobility and related synaptic plasticity.**

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Sharp-Waves Ripples (SPW-Rs) are neuronal network activities that occur in the hippocampal region during awakened resting periods and slow wave sleep. They are thought to support various functions, such as working memory and memory consolidation. Among their unique properties, SPW-Rs propagate within and outside the hippocampal formation, with an occurrence of about 1 Hz. During SPW-Rs, a large number of pyramidal cells and interneurons synchronize leading to high frequency ripples (200-250 Hz). Functionally, the link between SPW-Rs and hippocampal synaptic plasticity remains largely unknown, as SPW-Rs being potential LTD-like and/or LTP like inducers. We recently described that AMPAR mobility (AMPARM) at neuronal membrane is a key mechanism to allow long-term potentiation of excitatory synapses at CA3->CA1 projections. In a general effort to understand the functional importance of AMPARM, we tested the functional relationships between SPW-Rs, AMPARM and synaptic plasticity in hippocampal acute slices that exhibit spontaneously SPW-Rs. Our data demonstrate that AMPARM is crucial to allow LTP-dependent modulation of SPW-Rs in the CA3 region and explore the influence of SPW-Rs onto CA3->CA1 synaptic physiology. Our *in vitro* data shed light onto possible mechanisms by which AMPARM could affect various phases of hippocampus-dependent memory processes.

P2.006

**Formins modulate Axon Initial Segment cytoskeleton and plasticity**

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The axon initial segment (AIS) is a specialized compartment crucial for generating action potentials and maintaining neuronal polarity. An integrated structure of voltage gated ion channels, specific cytoskeleton architecture, as well as, scaffold proteins like ankyrinG and βIV-spectrin, contributes to these functions. Recent studies reveal that AIS is dynamically regulated in molecular composition, length and location in response to neuronal activity. Some mechanisms acting on AIS plasticity have been uncovered lately, which include Ca<sup>2+</sup>, calpain or calmodulin mediated modulation, as well as, post-translational modifications of cytoskeleton proteins and actin cytoskeleton associated proteins. However, it is still elusive how to perform the complex AIS structural and functional regulation.

In this study, using pharmacological methods together with RNA interference we identified Formins that function both in the AIS assembly and maintenance *in vitro* and *in vivo*. Besides, its activity inhibition or reduced expression affects AIS length and structural and functional AIS proteins. Consistently, action potential is affected, as well as, axonal polarity maintenance after blocking Formins' activity. These effects are due to the deficiency of axonal protein transportation and can be offset through modulating cytoskeleton related proteins. Taken together, our results indicate a new regulator related with AIS formation, maintenance and plasticity which provides more insight on AIS regulation mechanisms. This work was supported by research grants from Ministerio de Ciencia, Innovación and Universities to JJG (SAF2015-65315-R). Wei Zhang thanks the China Scholarship Council (CSC) (No. [2015]3022) for fellowship support.

P2.007

**Activity of Cajal-Retzius cells regulates their distribution and survival: impact on cortical wiring**

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The neocortex, which controls sensory perception, motor behavior and cognitive functions, relies on complex circuits. The superficial layer 1 is a major site for input integration as it contains incoming axonal projections, apical dendrites of pyramidal neurons and interneurons, which are essential for the excitation/inhibition (E/I) balance. Although there is increasing evidence that layer 1 plays important roles in sensory perception and the integration of top-down information, we still have a limited understanding on how it assembles. During development and early postnatal stages, layer 1 is colonized by Cajal-Retzius (CR) cells, a transient population of cortical neurons, which have been involved in the lamination and wiring of underlying cortical circuits. CR cells are amongst the earliest generated cortical neurons and are eliminated by the second postnatal week, potentially via an activity-dependent process. Recent work from our laboratory revealed that the density of CR cells modulates the cellular composition and neuritic outgrowth in layer 1, thereby regulating the E/I balance in upper layers (de Frutos et al., 2016). However, how electrical activity in CR cells impacts on their distribution and on layer 1 circuit formation remains to be investigated. Using CR cell-specific inactivation of NMDA receptors and overexpression of the hyperpolarizing inward rectifier Kir2.1, we found that neuronal activity in CR cells constitutes a major regulator of their density: first by acting at embryonic stages on their migration in an NMDA receptor-dependent manner; second, by modulating the postnatal survival of these cells in the neocortex. These two distinct activity-dependent phases impact onto the formation of cortical circuits. Overall, by using new state-of-the-art genetic and imaging approaches, our studies highlight how a transient neuronal population is regulated by activity and modulates the wiring of an essential but understudied layer of the neocortex.

**P2.008 KIF2A conditional mutant knock-in mouse: a flexible model to study cortical malformations**

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Development of the human cerebral cortex is based on three major, highly regulated processes: progenitor's proliferation, followed by migration of post-mitotic neurons to reach the cortical plate and finally their differentiation. Alteration of one of these processes can lead to malformations of cortical development (MCD), often associated with intellectual disability and pharmaco-resistant epilepsy. Our team has previously identified mutations in *KIF2A* gene in patients with MCD diagnosed by MRI sequences with posterior pachygryria and microcephaly (Poirier et al., 2013). More recently, we carried on *in-utero* electroporation studies and showed that *KIF2A* mutations' overexpression leads to proliferation and migration deregulation (Broix et al., 2017).

In order to better understand the *in vivo* implications of *KIF2A* mutations in the pathophysiology of MCD, we have designed and engineered, in collaboration with the Institut Clinique de la Souris (ICS), a conditional knock-in mouse model expressing the heterozygous human mutation p.His321Asp at physiological level. This model enables us to control the expression of the mutation in time and space and to evaluate independently the effect on different developmental processes.

We first validated by qPCR and sequencing the proper functioning and expression of the conditional knock-in allele. Then, immunofluorescence analysis on *KIF2A* knock-in brain slices showed a re-localization of *KIF2A* protein similar to that observed in patient fibroblasts (Poirier et al., 2013). Neuro-morphological study on adult mice revealed severe heterotopia in hippocampus and enlarged lateral ventricles. Moreover, adult mutant mice show behavioural deficits and susceptibility to epilepsy. Further developmental investigations on different embryonic stages showed that *KIF2A* mutation affects neuronal positioning and radial glia integrity.

Altogether, these results show that the important need of cKI could now be addressed and provide a reliable and relevant modelization of a *KIF2A* heterozygous point mutation in order to investigate its effects on brain developmental processes.

**P2.009**

**Optogenetic manipulation of the dendritic spine cytoskeleton**

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In glutamatergic synapses of the adult mammalian brain, the sizes of synaptic structures are tightly correlated with each other and with the efficacy of transmission. Recent work has shown that the volume of dendritic spines and the area of their associated postsynaptic density (PSD) are actively readjusted to each other following plasticity-related spine expansion. The mechanisms allowing homeostatic regulation of the spine/ PSD ratio are poorly understood. One possibility is that actin assembly within spines may couple PSD protein recruitment to spine volume changes. Here we use optogenetic stimulation of actin polymerization in single spines to investigate this question. Results of this approach will be described.

**P2.010**

**Role of sympathetic nervous system in pancreatic cancer development**

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Clinical data have shown that the presence of axonal fibers in human tumors often correlates with aggressive disease and short survival, suggesting an active role of tumor axonogenesis in cancer progression. Large amount of data has led to the notion that cancers depend on axonal nerves to progress. It remains less clear whether and how the peripheral nervous system modulates tumor development. The various components of the peripheral nervous system may perform different and sometimes antagonistic activities on tumor growth and progression, and these activities may vary depending of the type of cancer. From these data, it seems possible that inhibiting infiltration of specific fiber types could have a clinical value in the treatment of cancers. We explored how nerve fibers exert their tumor-modulatory role in an *in vivo* murine model of pancreatic ductal adenocarcinoma (PDAC) by focusing on the sympathetic nervous system (SNS). We performed chemical and surgical pancreatic sympathectomy in KIC<sup>PDX1</sup> mice. Contrary to findings in other cancer types, we found that ablation of sympathetic fibers led to more aggressive pancreatic cancer, increased metastatic spreading and decreased overall survival of tumor-bearing mice. Increased tumor growth was confirmed by bioluminescence imaging in an orthotopic syngenic model of pancreatic cancer that underwent chemical sympathectomy prior to grafting. These data support the hypothesis that sympathetic axons have a protective effect against pancreatic cancer. A potential mechanism by which the SNS could modulate pancreatic cancer tumorigenesis is through the modulation of the immune system to generate a local immune response against cancer. Indeed, sympathetic fibers regulate the inflammatory state of macrophages and alternatively activated macrophages (CD163<sup>+</sup>) correlate with metastasis and shorter survival in PDAC. Our data showed that sympathectomy increases CD163<sup>+</sup> macrophages in pre-cancer lesions, suggesting that the SNS regulates macrophage populations to mediate pancreatic tumorigenesis.

**P2.011 Transmembrane protein 240 (TMEM240), mutated in spinocerebellar SCA21, is involved in cerebellar afferent connections to Purkinje cells**

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Missense mutations and a stop mutation in transmembrane protein 240 (*TMEM240*) have been reported as the causative mutations of spinocerebellar ataxia 21 (SCA21). The aim of the present study was to explore the expression of *TMEM240* in mouse brain at the tissue, cellular and subcellular levels. Immunofluorescence labeling highlighted *TMEM240* protein expression in different areas of the brain with higher values in hindbrain and cerebellum. Focusing on cerebellum, *TMEM240* is detected in the white matter and in the cerebellar cortex, mostly in Uvula and Nodulus lobules. In the cerebellar cortex, the protein is localized in all three layers, in different cerebellar neurons, and especially in Purkinje cells. *TMEM240* is involved in climbing, mossy and parallel fiber afferents projecting to Purkinje cells as evidenced by co-immunostaining with VGLUT1 and VGLUT2. Next, we investigated synaptic expression of *TMEM240* by co-immunostaining with Synaptophysin. This synaptic expression was validated by electron microscopy localizing *TMEM240* at the postsynaptic side of synapses around the Purkinje cell soma. Finally, similar expression was observed in human cerebellum. Our study suggests that *TMEM240* might have a crucial role in cerebellar network, especially in synaptic inputs converging to Purkinje cells. The present data provide new characterization of *TMEM240* expression in normal mice brain, leading to future ways to explore the physiopathological mechanisms underlying SCA21.

**P2.012 Spike timing dependent plasticity rules in physiological calcium**

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Spike-timing-dependent plasticity (STDP) is a form of synaptic modification that is controlled by the relative timing between pre- and post-synaptic activity and depends on intracellular  $\text{Ca}^{2+}$  signaling. Yet, most if not all *in vitro* STDP studies used non-physiological external  $\text{Ca}^{2+}$  concentrations ranging between 2 and 3 mM, whereas the physiological  $\text{Ca}^{2+}$  concentration ranges between 1.3 and 1.8 mM in the young rat hippocampus. CA1 pyramidal neurons were recorded in whole-cell patch-clamp in acute slices of young rat hippocampus and STDP was examined at the Schaffer to CA1 pyramidal cell-synapse in physiological extracellular  $\text{Ca}^{2+}$  concentration. At the CA3-CA1 hippocampal synapse under different extracellular  $\text{Ca}^{2+}$  concentrations, we found that the sign, shape and magnitude of plasticity strongly depend on  $\text{Ca}^{2+}$ . A pre-post protocol that results in robust LTP in high  $\text{Ca}^{2+}$ , produced only LTD or no plasticity in the physiological  $\text{Ca}^{2+}$  range. LTP could be restored by either increasing the number of post-synaptic spikes, increasing the pairing frequency or adding neuromodulators during the STDP protocol. A calcium-based plasticity model in which depression and potentiation depend on postsynaptic  $\text{Ca}^{2+}$  transients was found to fit quantitatively all the data, provided. NMDA receptor-mediated non-linearities and short-term facilitation were implemented. In conclusion, STDP rule is profoundly altered in physiological  $\text{Ca}^{2+}$  but specific activity regimes restore a classical STDP profile.

**P2.013 A new population of PKD2L1positive neurons in the ventromedial medullospinal region in link with the ependymal stem cell niche**

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The central canal (CC) along the spinal cord and medulla represents a unique region, also known as stem cell niche, where regenerative processes have been reported following lesions. It is delimited by a monolayer of ependymal cells and contains a heterogenous cell population as well as stem cells. Interestingly, a specific population of neurons in contact with the CSF is also observed in the sub-ependymal layer: the cerebrospinal fluid-contacting neurons (CSF-cNs). These CSF-cNs exhibit a morphology conserved in all vertebrate and selectively express the PKD2L1 channel, a member of the TRP family. PKD2L1 was suggested to contribute to the sensory function of CSF-cNs, because of its ability to detect and integrate CSF changes in pH and osmolarity as well as spinal cord torsion. Although there are reports in lower vertebrates indicating a role as neuromodulator of the motor networks, the function of CSF-cNs remains largely elusive in Mammals. Here using an immunohistological and electrophysiological approach, we describe PKD2L1 immunoreactive neurons that are present in the ventromedial part of the mouse spinal cord and medulla up to 600 micron away from the CC and even in the ventral white matter. These cells generate the characteristic PKD2L1 unitary current activity and are neurons since they are capable of generating action potentials. Distal PKD2L1+ neurons exhibit long neurites, some of which contacting the CC, and they often form cell chains toward the CC. They are morphologically and phenotypically similar to CSF-cNs around the CC. Thus, they are mainly GABAergic, characterized by an incomplete maturity state, as indicated by poor NeuN immunoreactivity and by the expression of markers of juvenile neurons as Dcx and Nkx6.1. Both pericanal PKD2L1+ CSF-cNs are found in close proximity to ependymal cells/fibers within an astrocyte enriched zone. The unique features of PKD2L1+ CSF-cNs raise numerous questions regarding their function and whether they may take part to reparatory and plasticity processes associated with the ependymal stem cell niche and lesion. One of the future challenge will be to further characterise the properties of distal CSF-cNs and determine their origin and their link with radial ependymal cells.

**P2.014 Effects of SCI on the synaptic transmission onto Axon Initial Segment of lumbar spinal motoneurons**

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**Background:** Spasticity is a motor disorder that affects 70% of people with spinal cord injury (SCI). Therapies of spasticity are ineffective without serious side effects. One of the mechanism underlying spasticity is an hyperexcitability of motoneurons (MNs) resulting from an imbalance between inhibition and excitation. Our team highlighted key factors involved in each of the 2 mechanisms

- 1) after a SCI a disinhibition results from a down-regulation of the expression of the co-transporter KCC2 in the membrane of MNs (Boulenguez et al., 2016)
- 2) the calcium dependant protease calpaïn is responsible for the cleavage of Sodium Nav 1.6 channels which results in an increase of plateau potential and spasms (Brocard et al., 2016).

**Aim:** Given that the Axon Initial Segment (AIS), critical region of initiation of the axon action potential of the neuron, is enriched in Nav 1.6 channels, the aim of this study was to study the effects of SCI on the inhibitory and excitatory innervation of the AIS of lumbar MNs.

**Methods:** *Animals* : Wistar adult rats with T8T9 spinal cord transection.

*Immunohistochemistry* : We studied presynaptic and post synaptic inhibition by use of GAD65 and VGAT antibodies. We combined these labelings with the immunodetection of Ia afferent VGLUT1 excitatory innervation. Finally, we were also interested in neuromodulatory afferent systems and studied the expression of cholinergic terminals on the AIS. Analysis of morphometric parameters and quantification of innervation of lumbar MNs was made with Laser scanning confocal microscopy.

**Results:** Using ankyrinG as a marker of the AIS, there was no difference of morphometric parameters between transected and control rats. We observed an increase of post synaptic inhibition on AIS, which is congruent with previous results on soma (Khalki et al 2018). However, the presynaptic inhibition on Ia afferents, as well as the density of these VGLUT1 afferents were unchanged. The density of C boutons was decreased in transected rats compared to controls. Understanding the pathophysiology of spasticity after SCI is an important issue to find new therapeutic targets. Concerning the afferent networks to MNs, the present results indicate that the inhibitory and excitatory innervations seem relatively preserved after SCI.

**P2.015 Early origins of adult disorders after postnatal sensorimotor restriction**

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Sensorimotor experience appears crucial in shaping motor control and body representation in the central nervous system during development. Postnatal movement restriction provides limited and atypical patterns of sensory inputs that leads to muscle and movement disorders, and maladaptive plasticity in the sensorimotor circuitry in adult rats. This sensorimotor restriction (SMR) from birth induces a functional disorganization of the somatosensory and motor cortices and lumbar spinal cord, as well as hyperexcitability in adulthood. We also found hyperreflexia and signs of spasticity in adult SMR rats (Delcour et al., 2018ab). Our main question is: what are the early mechanisms at the origin of the emergence of adult neurodevelopmental disorders? In the present study we investigate the early impact of SMR on the functional properties of the lumbar network during the first postnatal week. Using electrophysiological recordings in the *in vitro* whole spine, we showed that SMR pups exhibit lumbar hyperreflexia (i.e., reduced rate-dependent depression) combined with hyperexcitability and abnormal reverberation of the signal in the lumbar network, compared to control pups. These alterations could be explained by imbalance between excitation and inhibition (E/I) with loss of inhibition and/or increase of excitability in the lumbar network, including motoneurons. We used patch-clamp recordings in lumbar motoneurons to assess passive and plateau properties, and expression of NKCC1/KCC2 to assess the E/I imbalance. Briefly, it seems that only a few days of SMR are enough to induce drastic functional disorganization of the lumbar network and hyperexcitability. Our results suggest that the emergence of neurodevelopmental disorders without brain damage may result from early atypical sensorimotor experience.

P2.016

**A novel vector system for direct readout of neural stem cell transgenesis**

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In developmental neuroscience, transfection of neural stem/progenitor cells with genome-integrative vectors is increasingly used as an alternative to the generation of transgenic animals. However, current genome-integrative vectors present important limitations:

retroviral vectors traditionally used in cell lineage studies are cumbersome to produce and limited in cargo capacity. Naked DNA vectors such as transposons are easier to implement, but enable expression from non-integrated episomes in addition to that of integrated transgenes. This causes a transient burst of expression that prevents reliable identification of transgenic cells and can cause transgene leakiness and toxicity.

We bypass this issue with a novel expression strategy termed “*iOn*” (integration-coupled On expression), enabling to activate DNA transgenes introduced by standard transfection procedures as they integrate in the host genome, while episomal transgenes remain silent. Toxic and non-physiological effects due to high episomal expression are thus avoided. Marker expression solely reflects activity of integrated transgenes, enabling straightforward identification and analysis of integration events directly after transfection both in vitro and in vivo.

We demonstrate applications of the *iOn* strategy for stable additive somatic transgenesis in neural progenitors of the cortex, retina and spinal cord of mice and chicken embryos, where we use it for fate mapping, clonal analysis, Cre-lox intersectional recombination and functional genetic mosaic manipulations. We also show that *iOn* vectors provide an efficient mean to stably transfect and rapidly isolate clones of stem/pluripotent cells in vitro. These results establish *iOn* as a highly efficient and versatile strategy for “direct transgenesis” in any model accessible to transfection.

P2.017

**Muscarinic control of motoneuronal activity : differential response of F and S motoneurons and presynaptic control of synaptic transmission to Renshaw cells**  
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Motoneurons (MNs) are contacted by a specific set of cholinergic synapses: the C-boutons that originate from a subpopulation of cholinergic V<sub>0</sub> interneurons<sup>1</sup>. The postsynaptic receptors associated with the C-boutons are muscarinic m2 receptors that co-localize with Kv2.1 K<sup>+</sup> channels<sup>2-4</sup>. This suggests that m2 muscarinic receptors control the excitability of spinal MNs. Indeed, it has been reported that activation of m2 receptors elicits an increase of MNs' excitability through to a reduction of their spike's AHP<sup>5</sup>.

However we have observed that, in young mice (P7-P10) lumbar spinal cord, the excitatory effect of muscarine (1-10 µM) on Fast Motoneurons (F-MNs) - characterized by their "delayed firing" pattern<sup>6</sup> - appears mostly mediated by m1-m3 muscarinic receptors <sup>see also 7</sup>. This effect is mediated by the reduction of a resting K<sup>+</sup> conductance. In contrast, Slow Motoneurons - with an "immediate firing" pattern<sup>6</sup> - are slightly hyperpolarized, through the activation of a m2 dependent K<sup>+</sup> conductance. The presence of a similar m2 dependent conductance increase in F-MNs can be revealed by applying muscarine after blocking the m1-m3 receptors. Furthermore, m2 receptors appear involved in a cholinergic presynaptic inhibition of the synaptic connection of MNs toward Renshaw cells. This inhibition - which resembles that described at the neuromuscular junction<sup>8,9</sup> - affects both the cholinergic and the glutamatergic components of the Renshaw cell response.

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**P2.018 Locus coeruleus reduces inhibition in the cerebellar input layer through noradrenergic modulation of Golgi cells**

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Golgi cells (GoCs), the main inhibitory interneurons in the input layer of the cerebellar cortex, provide feedforward and feedback inhibition to granule cells (GCs). Tonic inhibition arising from GoCs regulates the threshold for GC spiking while phasic inhibition contributes to the precision of spike timing. However, little is known about how GoC activity is regulated *in vivo*. Here we show that norepinephrine (NE) is a powerful modulator of GoC activity. Whole cell patch-clamp recordings from GoCs in acute brain slices revealed that NE induces a significant and reversible hyperpolarization of GoC resting membrane potential, and a decrease in their spontaneous firing. This effect was blocked by the alpha2-adrenergic receptor antagonist Idazoxan. In voltage clamp, bath application of NE induced the activation of an outward current mediated by the activation of GIRK channels. This current was not blocked by the mGluR antagonist LY341495. Retrograde tracing and immunohistolabelling for tyrosine hydroxylase in the cerebellum indicate that the locus coeruleus (LC) is the main source of noradrenergic projections. Optogenetic activation of ChR2-expressing LC projections labelled with a Th-Cre mouse line induced an outward current that was blocked by Idazoxan. Gap junction coupling between GoCs was decreased in the presence of NE and this effect was reversed by bath application of tetrodotoxin (TTX), suggesting that this effect is mediated by the modulation of persistent sodium channels ( $I_{NaP}$ ). Our findings show that NE release from axons from LC reduces the excitability of GoCs and their effective electrical coupling by modulating key ionic conductances. These results suggest that inhibition in the cerebellar input layer could be reduced during behavioral states, when LC is activated.

**P2.019 The role of microglia in the development of forebrain axonal tracts**

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Brain functioning relies on complex neural circuits that begin to assemble during embryogenesis and alterations of this process can lead to neurological or psychiatric disorders. Microglia, the brain resident macrophages, colonize the brain parenchyma during early embryogenesis and contribute to homeostasis in physiological conditions as well as in response to insults, through phagocytosis and secretion of a broad panel of factors. In addition to their immune functions, microglia have been identified over the past years as regulators of neural circuit formation and activity. For instance, postnatal microglia regulate synaptic remodeling and myelination whereas embryonic microglia contribute to corpus callosum fasciculation, dopaminergic axon outgrowth, as well as interneuron distribution in the neocortex. Remarkably, microglia display heterogeneous localization during development, in particular associating with specific forebrain axonal tracts. Using a cross comparative analysis of phenotypes induced by either an absence or perturbation of microglial activity combined with 3D and 2D imaging we examined on a large-scale the contribution of microglia to axonal tract formation and remodeling. Our ongoing work indicates that abnormal embryonic microglia activity may have a long-term impact on dopaminergic forebrain innervation. Furthermore, microglia are required for the remodeling of cortical axonal tracts during the first postnatal weeks. This study will highlight the contribution of embryonic and postnatal microglia to the development of long-range connections.

**P2.020**

**How direct thalamic inputs modulate hippocampal dynamics during development**

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In adult mice, the activity of hippocampal CA1 neurons is controlled by many converging inputs, including inputs from the hippocampus as well as other cortical or even subcortical structures. The CA1 region is therefore a highly integrative brain area. Among those various pathways, the ventral midline thalamus (VMT), composed by the nuclei Reuniens (Re) and Rhomboïd (Rh), directly projects to the CA1 *stratum lacunosum moleculare* (slm) and functions in modulating CA1 dynamics by acting on the excitation/inhibition balance (Dolleman-van der Weel et al., 1997). Through these interconnections with both the medial prefrontal cortex and the hippocampus (Vertes et al., 2007), Re is involved in many cognitive processes in adult mice. It was recently shown that the VMT is an anatomical and functional relay between the hippocampus and the medial prefrontal cortex as early as P8 in rats (Hartung et al., 2016). It therefore suggests that the VMT may shape early hippocampal dynamics and contribute to the establishment of functional circuits. However, the impact of VMT on CA1 dynamics at cellular level remains unknown.

To address this issue, we have developed injections of a virus inducing the restricted expression of the opsin chronos in the thalamus (AAV8-Syn-Chronos-tdTomato) in P0 mice. Then, by using *in vitro* electrophysiological recordings and calcium imaging coupled with optogenetic stimulations, we have probed the effect of photostimulating thalamic afferents on the activity of hippocampal neurons. We report that the stimulation of thalamic afferents as early as postnatal day 5 induces direct monosynaptic responses onto CA1 GABAergic neurons located in the *stratum lacunosum moleculare*. In addition, we observe that the same photostimulation evokes polysynaptic responses in pyramidal cells. These preliminary results suggest that thalamic afferents may contribute in shaping early hippocampal dynamics as early as the first postnatal week through a direct drive of GABAergic neurons.

**P2.021 Brain activity during transitive and social action observation in adults and adolescents**

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The Action Observation Network (AON) is a set of brain areas consistently engaged during the observation of other's actions. While the core nodes of the AON are present in childhood and early adolescence, it is not known to what extent they are sensitive to different features of the observed action. In particular, as social cognitive abilities continue to mature during adolescence, we would expect that the AON response to socially oriented action would be different in adolescents and adults, respectively. In contrast, we would not expect any age difference for object-related actions. To test this hypothesis, we implemented an action observation paradigm using social (i.e. directed towards another person) and transitive (i.e. involving an object) actions as stimuli. Twenty-five typically developing adolescents (age 13-17 years;  $M_{age} = 15.0$ ,  $SD = 1.2$ ; 10 females) and twenty adults (age 24-33 years;  $M_{age} = 26.4$ ,  $SD = 2.1$ , 12 females) were enrolled in the study. They were asked to passively observe videos of hand actions varied along two factors: sociality (social/non-social) and transitivity (transitive/intransitive). We found that observing actions recruits similar fronto-parietal and occipito-temporal networks to the same extent in both adults and adolescence. While observing social actions activates the bilateral posterior superior temporal sulcus, the right temporo-parietal junction, the left V5/MT+, the bilateral precentral gyrus and the left superior frontal gyrus, observing transitive actions activates the bilateral superior parietal lobe, the bilateral fusiform gyrus, the right superior frontal gyrus, the left anterior cingulate cortex and the right supramarginal gyrus. These results replicate those from Wurm et al. (2017) and further extend them to adolescents. We show for the first time, that adolescents (13 to 17 years old) have the same level of activation in the AON as adults. In addition, the modulation of activation by the content of the action is similar in adolescents and adults. Thus, contrary to our expectations, the adolescent brain is as sensitive as the adult brain to the social information conveyed by the action.

**P2.022 Plasticity of thalamic axons and cortical areas is regulated by embryonic and birth-sensitive checkpoints**

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Functional areas of the neocortex are characterized by their pattern of connectivity with thalamic nuclei. For instance, distinct first-order (FO) thalamic nuclei innervate specific primary sensory areas. In the embryonic brain, thalamocortical axons (TCAs) are oriented towards their cortical targets by intermediate targets located on the axonal trajectory. If TCAs are initially misrouted, they show an extraordinary capacity to reorient within the neocortex after birth, thereby correcting prenatal guidance defects. The role of these sequential targeting steps in cortical area map formation, however, remains to be fully understood. Here, we addressed this issue using a mutant mouse model in which the trajectory of embryonic TCA is initially shifted. We found that the prenatal guidance of TCAs regulates FO thalamic cell survival and, consistently, the size of the primary sensory areas that these neurons innervate. We furthermore showed that the postnatal rewiring of TCAs occurs in a discrete postnatal time window, which is sensitive to levels of the neurotransmitter serotonin and to preterm birth. Indeed, serotonin depletion during this time window or preterm birth alters TCA rewiring and disrupts the formation of cortical areas. Overall our study reveals distinct embryonic and postnatal TCA checkpoints that control the size of FO thalamic nuclei as well as a remarkable plastic adaptation of the cortical area map.

P2.023

**The Microtubule-severing enzyme katanin is required for embryonic survival and regulates adult dentate gyrus neurogenesis**

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Microtubules (MTs) are involved in a variety of cellular functions, including cell division. Katanin is an enzyme that forms a hexameric ring and severs MTs in an ATP-dependent manner. It is formed by p80, the regulatory subunit; and p60, the catalytic subunit and although previous data indicates that katanin is involved in cell division and brain cortical formation, little is known about the impact of this enzyme *in vivo*. Here, we created a constitutive knockout mouse for p60 katanin to investigate the role of katanin in brain development. Consistent with a function of p60 katanin in cell division, homozygous knockout embryos did not survive. Besides, p60 heterozygous knockout mice displayed an accumulation of cells in the lateral ventricle during corticogenesis, and young-adult animals show a significant reduction of newly generated neurons in the subgranular zone of the dentate gyrus, resulting in an accumulation of neuronal progenitors. However, we did not observe *in vivo* behavioral phenotypes in multiple non-cognitive, and cognitive tests and dentate gyrus LTP showed comparable results among genotypes, indicating that reduced adult neurogenesis was not sufficient to impair overall hippocampal function. Altogether, our data indicate that p60 katanin is fundamental for embryonic survival and is involved in embryonic and adult neurogenesis most likely via its MT-severing function. As supported by previous studies about p60 katanin function in cell division, p60 katanin might modulate cell proliferation in the adult brain.

**P2.024 Cooperative interactions between retinal ganglion cells from the same eye shapes the connectivity of the visual system**

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The development of a wide range of neuronal connections involves competitive mechanisms. Pre-synaptic neurons with correlated activity with their synaptic partners stabilize their connections, in contrast to synapses with uncorrelated pre- and post-synaptic activity. In most connectivity maps including retinal projections, post-synaptic neurons receive inputs from multiple neurons. The interactions between pre-synaptic terminals and their partners have been extensively studied in contrast to the interplay between pre-synaptic axons. In the visual system, retinal ganglion cell (RGC) axons from both eyes form a binocular map in their brain targets. This map is initially exuberant before its refinement involving cyclic AMP-dependent (cAMP) competitive mechanisms. We investigated whether interactions between RGC axons from the same eye are involved in the development of precise projection maps.

We developed a molecular tool (Zaïc) enabling to trace unaffected neurons adjacent to RGCs with altered cAMP signaling. Blocking cAMP in a subpopulation of RGCs perturbs the projection pattern of their neighbors, demonstrating that RGCs cooperate to shape their axonal arbor. We further investigated the mechanisms involved. We show that developmental cell death does not contribute to the reported phenotype, using TUNEL staining on early post-natal retinas. We evaluated whether the cAMP-dependent alteration of axon interactions reflects defects in axon guidance or in refinement terminal arbors. No alteration of dLGN invasion by Zaïc-expressing axons was detected, demonstrating that axon cooperation arises during the pruning of exuberant branches. Other retinal cell types, including starburst amacrine cells, are critical for the development of retinal connectivity. They regulate the propagation and frequency of spontaneous waves of activity in the developing retina, which correlates the firing of neighboring cells. Restricting cAMP in a subset of RGCs using a cell type-specific promoter was sufficient to recapitulate the alteration in axon pruning detected in neighboring neurons, demonstrating that other retinal cell types are not involved.

Our findings highlight a cAMP- and RGC-dependent interaction between retinal axons that might be key to regulate neuronal connectivity.

**P2.025 Synaptic function of 3S-HS and HS3ST2 in physiologic conditions and during Alzheimer's disease-related tauopathy**

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Strong evidence has emerged showing that tauopathy centrally affects the synapses in Alzheimer's disease (AD), and that synaptic changes may be critical on the onset and development of the AD neurodegenerative process. Heparan sulfates (HS) are known to play pivotal role during synaptic decline. Moreover, they have shown to play a critical role during the early events leading to tauopathy and to accumulate in post-synaptic regions in AD neurons. In physiological conditions, HS interact with many ligands and participate to the regulation of biological processes at the cell surface. Interestingly, HS are internalized and accumulate in the AD neurons several years before the apparition of amyloid plaques and neurofibrillary tangles (NFTs). Previously, we demonstrated that HS 3-O-sulfotransferase (HS3ST2), an enzyme that produces rare 3-O-sulfated HS chains (3S-HS), is critically involved in the mechanisms leading to the abnormal phosphorylation of tau in AD. Accordingly, inhibition of *hs3st2* expression in a zebrafish model of tauopathy resulted in disease arrest and animal functional recovery. However, at the synaptic level the implication of HS3ST2 and 3S-HS during the tauopathy is not known.

To investigate whether HS3ST2 and 3S-HS participate to synaptic plasticity dysregulation in the context of tauopathy, we evaluated if HS3ST2 expression can alter synaptic function in hippocampal primary cultures and in synaptosomes isolated from WT mice compared to those from the mice model of tauopathy rTG4510. We showed the abnormally phosphorylated tau accumulation at the synapse is strongly correlated with accumulation of 3S-HS, that HS3ST2 plays key regulating roles in the plasticity and stability of the synapse under physiologic and pathologic conditions. Our results suggest that HS3STs are new potential targets for AD and related synaptopathies.

**P2.026 Role of dietary n-3 polyunsaturated fatty acid in memory and hippocampal synaptic plasticity in male and female mice**

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**Background:** The brain is rich in docosahexaenoic acid (DHA, 22:6 n-3) and arachidonic acid (AA, 20:4 n-6), which are n-3 and n-6 polyunsaturated fatty acids (PUFAs) respectively, with distinct biological activities. PUFAs are provided through the diet and start to aggregate in the brain during the perinatal period. Some epidemiological studies suggest that diets poor in n-3 PUFAs increase the risk of developing cognitive deficits. Our preliminary data show that perinatal dietary n-3 PUFAs deficiency leads to decreased amount of DHA in the hippocampus, altered spatial memory and impaired hippocampal neuronal plasticity assessed by long term potentiation (LTP), in male mice at weaning (P21). However, the mechanisms underlying the role of n-3 PUFAs on memory are poorly understood. Here, we aim at deciphering whether 1) long-term exposure to a diet poor in n-3 PUFAs induces the same alterations at adulthood; 2) a n-3 PUFAs-enriched diet reverses the effect of perinatal dietary n-3 PUFAs deficiency; 3) diet effect is sex dependent.

**Methods:** Male and female mice were fed with n-3 PUFAs deficient or sufficient diets from pregnancy until P21. At P21, half of the n-3 PUFAs deficient mice were switched to n-3 PUFAs sufficient diet until adulthood. In all animals, we assessed spatial memory abilities (Y-maze task), the composition in fatty acids of the hippocampus and synaptic plasticity in hippocampal slices (High Frequency Stimulation- HFS- protocol).

**Results:** N-3 PUFAs deficiency impaired spatial memory, lowered DHA levels and altered hippocampal neuronal plasticity at adulthood, as compared to balanced diet animals. Switching animals to n-3 PUFAs sufficient diet at P21 restored DHA levels and LTP in the hippocampus, up to control levels. Notably, spatial memory was restored only in female mice.

**Conclusion:** According to our preliminary data, exposing animals to n-3 PUFAs sufficient diet from weaning reversed neurobiological alterations induced by perinatal n-3 PUFAs deficiency, in a sex-dependent manner. Further analysis are now required to understand the mechanisms underlying the differences observed in male and female.

**P2.028 Neuroprotective effects of PACAP against paraquat-induced oxidative stress in the *Drosophila* central nervous system**

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Parkinson's disease is a progressive neurodegenerative movement disorder that can arise after long-term exposure to environmental oxidative stressors, such as the herbicide paraquat (PQ). Here we investigated the potential neuroprotective action of vertebrate pituitary adenylate cyclase-activating polypeptide (PACAP) against PQ-induced oxidative defects and lethality in *Drosophila*. In mammals, PACAP is known as a powerful antioxidative, anti-apoptotic and anti-inflammatory agent. We found that pretreatment with this neuropeptide applied to the ventral nerve cord (VNC) at low doses markedly extended the survival of wild-type decapitated flies exposed to neurotoxic levels of PQ. In contrast and interestingly, application of a PACAP receptor antagonist, PACAP-6-38, had opposite effects, significantly decreasing the resistance of flies to PQ. PACAP also reduced PQ-induced caspase activation and reactive oxygen species (ROS) accumulation in the VNC. We then searched for the endogenous neuropeptide receptor potentially involved in PACAP-mediated neuroprotection in *Drosophila*. The receptor Han/PDFR of the neuropeptide pigment-dispersing factor (PDF) is homologous to the mammalian vasoactive intestinal polypeptide (VIP)/PACAP receptor VPAC2-R and it has binding affinity for PACAP. Interestingly, both PACAP and PDF are circadian neuropeptides that play important roles in the regulation and entrainment of circadian rhythms in mammals and insects, respectively. We found that knocking down the gene encoding the receptor PDFR in all neurons conferred to flies higher resistance to PQ, whereas PDFR downregulation restricted to PDF or dopamine neurons did not increase PQ resistance, but remarkably suppressed the neuroprotective action of PACAP. Further experiments performed with PDF and PDFR-deficient mutants confirmed that PDF and its receptor are required for PACAP-mediated neuroprotection in flies. We also provide evidence using split-GFP reconstitution that PDF neurons make synaptic contacts onto dopamine neurons in the abdominal VNC. Our results therefore suggest that the protective action of PACAP against PQ-induced defects in the *Drosophila* nervous system involves the modulation of PDFR signaling in a small number of interconnected neurons.

**P2.029 Impact of Cx30 overexpression on astroglial and neuronal networks**

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Glial cells, and more importantly astrocytes play an important role in cognitive functions, behavior states and cerebral pathologies. They are indeed involved in brain information processing via the modulation of neuronal excitability, synaptic activity and plasticity. A typical feature of astrocytes is their prominent interconnection via gap junction channels formed by connexins, i.e. connexin 30 (Cx30) and connexin 43 (Cx43), which provide direct electrical and metabolic coupling. Remarkably, Cx30 is expressed postnatally in the CNS and mostly by astrocytes, and not only controls the functional extent of astroglial networks, but also modulates synaptic transmission. However, the impact of a temporally- and spatially-restricted modulation of astroglial connectivity on astroglial network and neuronal activity is yet unknown.

**The aim of our study is to investigate the impact of increased Cx30 levels specifically in astrocytes on hippocampal synaptic efficacy.**

For this purpose, we used stereotaxic injections of adeno-associated viruses (AAVs) to increase Cx30 in astrocytes from the CA1 hippocampal area of juvenile wild-type mice (P15). Using this strategy, we investigated the impact of Cx30 overexpression on the size of the astroglial network, cellular properties and on neuronal network compare to wild-type mice injected with AAV-GFAP-GFP as control. In particular, we show that injections with CX30- AAVs lead to : (1) the increased of the levels of Cx30 expression visualized by immunolabeling and western blot; (2) the increased of the size of astroglial networks, highlighted by dye coupling experiments with biocytin locally injected in one astrocyte and diffusing to connected astrocytes by gap junctions, (3) change of astroglial and neuronal properties of pyramidal cells and parvalbumin (PV) interneurons highlighted by patch clamp recordings; and (4) the decreased of field potentials at CA1 Schaffer collateral synapses in hippocampus slices.

Altogether, these results provide new insights into the role of Cx30 overexpression in the modulation of astrocyte and neuronal networks.

**P2.030 A new mouse model to explore the role of glycine and D-serine as NMDAR co-agonists in neuronal and brain function**

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NMDA receptors (NMDARs) are ionotropic glutamate receptors involved in multiple aspects of brain physiology and pathology. Unlike other neurotransmitter receptors, the activation of NMDARs requires simultaneous binding of two distinct agonists, L-glutamate plus the co-agonist glycine or the atypical neuromessenger D-serine. The unique co-agonist dependence of NMDARs may render these receptors highly sensitive to the activity of their surrounding microenvironment. Decades after the discovery that D-serine and glycine act as NMDAR co-agonists, their availability, and dynamics at excitatory synapses remain controversial.

Canonical NMDARs are tetrameric assemblies composed of two GluN1 subunit, binding glycine or D-serine, and two GluN2 subunits binding glutamate. Although wild-type GluN1 subunits do not discriminate between glycine and D-serine, we recently identified a single point mutation in the GluN1 agonist-binding domain that strongly decreases glycine affinity (>50 fold increase in EC<sub>50</sub>) without affecting D-serine affinity (and all other properties tested including glutamate affinity and channel open probability). Taking advantage of this mutation, we generated genetically-modified inducible knock-in animals (GluN1-KI) harboring glycine-insensitive GluN1 subunits. Here, we present an initial set of results obtained with this original mouse model.

First, we show that sensitivity to glycine, but not D-serine, of native brain GluN1-KI NMDARs is markedly decreased as observed on recombinant mutant receptors. Second, GluN1-KI mice survive birth, develop and reproduce normally, indicating that glycine is not the sole endogenous NMDAR co-agonist even at early developmental stages. Third, using acute hippocampal slices, we show that GluN1-KI mice display striking alterations in long-term synaptic plasticity, although basal synaptic transmission is minimally affected. The impact on synaptic plasticity differs in a synapse-type-specific manner. Overall, these results indicate that NMDAR co-agonist identity is diverse and dynamically regulated both in time and space (in an activity-dependent and synapse-dependent manner). We expect our GluN1-KI mouse model to help elucidate key aspects of NMDAR co-agonist regulation at the cellular, network and behavioral levels.

**P2.031 Alteration of neuron morphology and type I mGlu signaling by a missense mutation of the GluD1 glutamate receptor causing intellectual disability**

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Glutamatergic neurotransmission mediated by ionotropic (iGlu) and metabotropic (mGlu) receptors plays an essential role in learning and memory. Intellectual disabilities (ID) are associated with altered glutamatergic transmission. Among iGlu, the GluD subunits are involved in synaptogenesis, long term plasticity and their channel is gated by the activation of group I mGlu. A rare missense mutation in the *Grid1* gene coding for GluD1 has been recently identified in patients with combined ID, spastic paraplegia and glaucoma. In this study we examine the possible impact of this mutation on GluD1 functions. HA-tagged mutant protein expressed in primary hippocampal neurons or HEK293T cells exhibits a normal membrane distribution when compared to wild type GluD1. We observed that GluD1 and mGlu receptors expressed in HEK293T co-immunoprecipitate suggesting that both proteins form a signaling complex. This interaction is not altered by the ID mutation. However, when the GluD1 mutant is expressed in primary cultured neurons, neurite length and number are reduced. Spine density and maturity are also significantly altered. Besides, the mutation alters mGlu induced ERK signaling but not the ability of GluD1 to bind cerebellins. These results show that the mutant GluD1 impairs the development and the maturation of neurons and synapses possibly by dysregulating type I mGlu intracellular signaling pathways.

**P2.032 Molecular analysis of distinct populations of central synapses in physiology and pathology in mice**

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The brain connectome is made of several functional classes of synapses (excitatory, inhibitory, modulatory) each category may be further classified in subcategories (GABAergic, glycinergic ...). In the end, synapses within each brain circuit may present molecular distinctions relevant to support specific functional network features. Since the pioneering work of Whittaker in the 1960's, neuroscientists have used enriched preparations of synaptic particles called synaptosomes to gather a wealth of knowledge about synapse structure, composition, and function. Yet, our current view of the molecular synapse is largely biased to an average synapse mostly contributed by the 2 major populations (glutamatergic and GABAergic).

We recently established Fluorescence Activated Synaptosome Sorting (FASS) that substantially improves conventional synaptosome enrichment protocols and enables high-resolution biochemical analysis of specific synapse subpopulations. Here I will expose results gathered through the mass spectrometric analysis of VGLUT1 glutamatergic synapses in physiology and pathology. I will also present new developments that allow the refinement of the FASS approach to more discrete populations of synapses of diverse phenotype and origin.

**P2.033 Microglial motility during sleep and wakefulness**

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Microglia, the resident CNS immune cells, are highly ramified and their dynamic processes transiently contact synaptic elements. The properties and function of microglia process' dynamics has been attributed to surveillance purposes but remain unclear. Several studies in vitro and in anesthetized animals have suggested that neuronal activity could control, at least partly, microglial motility. Nonetheless, data is lacking on the fluctuation of microglial motility in physiological conditions and through different states of consciousness. Using transcranial two-photon time-lapse imaging of microglia in the somatosensory cortex *in vivo*, we first examined the influence of neuronal activity during sleep and wakefulness on microglial motility and morphology. We then studied the interaction of microglial processes with dendritic spines during these different vigilance states. Our results indicate that the morphology and motility of microglia were modulated by sleep and wakefulness. More specifically, overall quantitative morphometric analysis showed a reduction of motility and shrinking of microglial arbor area within minutes of sleep. We also found that the duration of contact between microglial processes and dendritic spines was correlated with spine activity and more especially during wakefulness. These results provide valuable insight into the potential distinct instructive role of neuronal activity during wakefulness and sleep on microglial process dynamics and their interactions with dendritic spines.

**P2.034 Measurement of ATP release from single dorsal horn spinal cord glial cells and its modulation by noradrenaline**

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ATP release from cultured postnatal dorsal horn spinal cord (DH) glial cells was studied using an improved biosensor system. This system consisted of human embryonic kidney 293 cells (HEK-293 cells) stably expressing ratP2X2 receptors. We took advantage of the fact that P2X2-receptors display an increased affinity for ATP in the presence of progesterone (De Roo et al (2010), *Neuropaharmacology*, 58, 569-577) to improve the detection of extracellular ATP. The EC<sub>50</sub> of ATP in this system was 0.1 µM, allowing for the detection of extracellular ATP concentrations in the low nanomolar range. Moreover, the system detected ATP release from single cells with excellent spatial and time resolutions. ATP release could be evoked by noradrenaline and phenylephrine (Phe), an agonist of alpha1 adrenoceptors. This release was calcium dependent since it was blocked when glial cells were loaded with the calcium chelator BATA. Phe-induced ATP release was also blocked when glial cultures were incubated with Bafilomycin A1, an inhibitor of the proton pump of secretory vesicles. A comparable blockade of ATP release was obtained when the cells were pretreated with glycyl-L-phenylalanine-2-naphtylamide (GPN), that induces a selective lysis of secretory lysosomes. These results indicate that activation of alpha 1 adrenoceptors on DH glial cells induced a calcium-dependent vesicular release of ATP that involved secretory lysosomes.

Our results also show that the improved biosensor system that we developed should represent a valuable tool for the study of glia to neuron communication in the spinal cord as well as in other structures of the central nervous system.

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**P2.035 Specific downregulation of MCT2 in neurons and MCT4 in astrocytes using the AAV2/DJ in the rat barrel field of the somatosensory cortex to investigate their role in synaptic plasticity**

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Traditionally, neurons were considered to consume essentially glucose as their main energy substrate. This view has been challenged 25 years ago by the Astrocyte-Neuron Lactate Shuttle hypothesis, which proposed that a major part of glucose is taken up by astrocytes and transformed into lactate before being transferred to neurons. Lactate release by astrocytes is facilitated by the monocarboxylate transporter 4 (MCT4). Its uptake by neurons is facilitated by MCT2. The implication of MCT4 and MCT2 in lactate metabolism has been demonstrated *in vitro*. However, their involvement is not clear yet *in vivo*. Viral vectors were produced to induce a specific downregulation of MCT2 (AAV2/DJ-mCherry-miR30E-shMCT2) in neurons and of MCT4 (AAV2/DJ-mCherry-miR30E-shMCT4) in astrocytes.

Efficiency of these vectors was tested in primary cultures of rat. At the highest dose, the shMCT2 vector in neurons decreased MCT2 mRNA expression by 74% and MCT2 protein expression by 92%, MCT1 and MCT4 remaining constant. At the highest dose, the shMCT4 vector in astrocytes decreased MCT4 mRNA expression by 71% and MCT4 protein expression by 84%, MCT1 and MCT2 remaining constant.

Then, those vectors were tested *in vivo*, in the rat somatosensory cortex. After assessing their diffusion and cellular specificity, the downregulation efficiency was analyzed. The shMCT2 vector decreased MCT2 mRNA expression by 26% and the protein expression by 54%, MCT1 and MCT4 remaining constant. The shMCT4 vector decreased MCT4 mRNA expression by 34% and the protein expression by 37%, MCT1 and MCT4 remaining constant.

To investigate the putative role of lactate shuttling in synaptic plasticity, those vectors will be injected in the somatosensory cortex. After 3 weeks, the whiskers will be trimmed on one side of the snout and the animal will be placed in an enriched environment for 24h. It was shown that whisker trimming decreased cFos on the trimmed side (Landers et al, 2011) and that enriched environment increased cFos in intact animals (Dolan et al, 1996). The combination of both should lead to an important difference between the trimmed and non-trimmed side, allowing us to highlight the importance of metabolic interactions between neurons and astrocytes in neuronal activation and plasticity.

**P2.036 Spinal CSF-contacting neurons: properties of their protrusion in contact with the CSF**

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Around the central canal (CC), spinal neurons in contact with the CSF (CSF-cNs) exhibit a morphology conserved in all vertebrate. Their soma is under or within the ependymal layer and project a single dendrite to the CC ending with a protrusion or 'bud' in the lumen. CSF-cNs selectively express the polycystin isoform (PKD2L1) of 'Transient Receptor Potential' (TRP) channels acting as a sensory receptor. Based on their morphology, localization and expression of chemo/mechanoreceptors, CSF-cNs represent a novel sensory system intrinsic to the CNS; a function further supported by the localization of the 'bud' in contact with molecules circulating in the CSF and its potential role as a receptor pole for CSF-cNs. However, to date little is known about the bud properties or its functional relationship with the soma.

Using transmission electron microscopy, we show that the 'bud' is attached to neighboring ependymal cells through tight junctions and has numerous villi in the CC lumen. Further, a cilium formed by 9 microtubule doublets extends from the 'bud'. Interestingly, the cytoplasm presents many mitochondria and small vesicle-like structures suggesting secretory capabilities. Our confocal immunohistofluorescence imaging shows that the 'bud' is MAP-2 positive with an acetylated alpha-tubulin microtubule network. At the somatic level, PKD2L1 has a plasma membrane localization while in the bud it is present in the cytoplasm potentially associated with intracellular organelles.

Next, using the whole-cell patch-clamp technique, we show that the characteristic PKD2L1 channel activity can be recorded and voltage-dependent currents elicited from the bud. However, soma and 'bud' paired-recordings performed from the same CSF-cN suggest that this activity has a somatic origin and propagates to the 'bud'. Surprisingly, preliminary recordings obtained from isolated 'bud' indicate that *per se* this structure is devoid of any current activity.

Our study provides for the first time the unique organization of the bud in the mouse, indicates potential secretory properties that need to be demonstrated. At the functional level it appears to be connected to somatic activity nevertheless the mechanisms or pathways for such a relationship need to be further investigated.

P2.037

### Boc is implicated in myelin repair in the brain

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The type I transmembrane receptor Boc (Brother of Cdo) is related to cell adhesion molecules of the immunoglobulin superfamily and was initially implicated in the positive regulation of myogenic differentiation (Kang et al. 2002). Besides this role, Boc is a target and signaling component of the Sonic Hedgehog (Shh) pathway. By binding Shh with high affinity, Boc transduces Shh signal in the guidance of commissural axons in the embryonic spinal cord and in the segregation of ipsilateral retinal ganglion cell axons at the optic chiasm (Yam and Charron, 2013). Later during postnatal development, Boc forms a Shh receptor complex with the main receptor Patched1 and is required for Shh-mediated cell proliferation of cerebellar granule neuron progenitors (Izzi et al. 2011). Finally, the strong expression of Boc in neurons of the cerebral cortex revealed its requirement for circuit-specific synapse formation (Harwell et al. 2012).

In the adult brain, Shh signaling is required for the establishment of the adult stem cell niches (Ferent and Traiffort, 2015). We have also characterized Shh as a positive regulator of myelin repair in a mouse model of demyelination of the corpus callosum induced by stereotaxic injection of lysolecithin (Ferent et al, 2013). Here, we have investigated the role of Boc in the spontaneous regeneration of myelin. By using the model of CNS demyelination induced by the local injection of lysolecithin, we found impaired myelin repair in the Boc mutant mice partially reminiscent of the phenotype observed when Shh signaling is inhibited. Remarkably, morphological differences of microglial cells observed in the mutant suggest an inability for these cells to switch from a highly- to a faintly ramified morphology. Altogether our data identify Boc as a new regulator of remyelination.

**P2.038 A new role of astrocytes in the central amygdala neuronal network modulation by oxytocin**

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Oxytocin orchestrates social and emotional behaviors through known modulation of neural circuits in brain structures such as the central amygdala (CeA). Given the central role of astrocyte-neuron interactions in neuronal networks functions, we hypothesize that oxytocin effects on CeA neuronal network activity might be relayed by astrocytes. We discovered in the lateral and capsular part of the CeA (CeL) a subpopulation of astrocytes that expresses the oxytocin receptor and responds to its activation by long-lasting oscillatory calcium transients. Those responses are both sufficient to drive the activity of projection neurons of the medial part of the CeA (CeM) and necessary for their modulation by oxytocin. Within the CeL, astrocyte neuron communication is mediated by recruitment of neuronal NMDA receptors that conveys the oxytocinergic modulation of pain- and anxiety- related behaviors. Thus, CeL astrocytes play a pivotal role in the oxytocinergic modulation of CeL→CeM neuronal circuits and their behavioral correlates.

**P2.039 Identifying the MVP/vault neuronal function at the autism-associated 16p11.2 locus**  
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Copy Number Variation (CNVs) causes genomic variations that can lead to syndromes involving macro- and microcephaly associated with cognitive disorders such as intellectual disability (ID) and autism spectrum disorders (ASDs). The 16p11.2 deletion underlying 30 genes has a prevalence of ~0.05% in the general population and is one of the most frequent known aetiologies of ASDs and related neurodevelopmental disorders. Yet the specific gene(s) affecting brain function in this locus remain(s) to be identified.

Neuroanatomical characterization of 18 candidate genes at the autism-associated 16p11.2 locus identified *Major Vault Protein (Mvp)* as the main driver of brain size phenotypes associated to the 16p11.2 syndrome. These phenotypes are characterized by a reduction of the size of the corpus callosum, the hippocampus and the cingulate and somatosensory cortices, are specific to male mice, and appear postnatally. Concomitantly, a decrease of cell size is observed both in cortical and hippocampal neurons, as well as a reduction of the size of the growth cone. Moreover, the morphological abnormalities are reduced in double-heterozygous *Mvp<sup>+/−</sup>-Erk1<sup>+/−</sup>* mouse models, while these double mutants revealed behavioral abnormalities which were not present in single genes mutants.

To conclude, these data unravels the role of MVP, the main component of the vault organelle, in neurons and shows its interaction with Erk1. This opens up new mechanistic insights in understanding the biology of 16p11.2 genes and their interactions as well as shedding light on the pathophysiology of autism spectrum disorders.

**P2.040 Extracellular vesicles from human tauopathies CSF contains pathological competent tau species**

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**Background:** Intraneuronal accumulation of tau protein aggregates is one of the common feature of a group of heterogeneous neurodegenerative diseases called tauopathies. In some of them, the pathology will first affect a region or a subpopulation of cells before spreading to other cells following specific neural pathways; the best described being the Braak stages in Alzheimer disease. It has recently been considered that this staging could be linked to a prion-like propagation of pathological tau species (1); a concept of seeding in which the misfolding tau protein is released into the extracellular space by diseased neurons and transferred to healthy neurons to induce the aggregation of normal tau proteins. Whereas the pathological forms of tau that are spreading are not yet well known, several mechanisms mediating their transfer (secretion and capture) have been highlighted. Among them, we demonstrated that tau is secreted in extracellular vesicles (EV's) (2). In this context, we now sought to determine if these vesicles are able to transport seeds to recipient cells to convert normal endogenous tau.

**Methods:** EV's from transgenic mice brain or human tauopathies post-mortem CSF were purified and characterized using size-exclusion columns. These EV's were then transferred by lipofection to recipient cells expressing soluble tau fused to CFP or YFP. When seeds are taken up by these cells, tau aggregation produces a FRET signal (energy transfer between CFP and YFP) that is measured by flow cytometry.

**Results and conclusion:** FRET flow cytometry assay show significant FRET-positive cells treated with purified vesicles from transgenic murin ISF and recombinant tau fibers in comparison to cells treated with PBS. More importantly, when vesicles were recovered from human tauopathies CSF, converted cells were also detected. Together, these results strongly support that EV's present in the human CSF of patient suffering from tauopathies contain toxic seeds that might participate to the spreading of the human pathology.

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**P2.041**

**Modulation of POMC neuronal activity by lactate in the hypothalamus**

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Whole-body energy homeostasis is controlled by orexigenic neuropeptide Y (NPY) neurons and anorexigenic proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. These neurons are able to detect changes in extracellular glucose concentration to co-ordinate hunger and satiety. It has recently been proposed that specialized hypothalamic glial cells lining the walls of the third ventricle and named tanycytes, could contribute to these mechanisms of detection. It is suggested that lactate, produced from glucose by tanycytes, could act on POMC neurons to inform them about glycaemia. Thus, we investigated if POMC neurons could use endogenous lactate as an energy substrate regulating their electrical activity. To this end, through whole cell-patch clamp, we evaluate changes in action potential frequency of POMC-Cre:Rosa-tdTomato neurons in response to a inhibition of lactate metabolism and lactate membrane transporters. We show that POMC neurons respond to exogenous glucose deprivation by decreasing firing and that this effect is prevented by the application in the bath of lactate for the majority of the neurons (63%). The inhibition of lactate membrane transporters by α-cyano-4-hydroxycinnamate (4-CIN) is seen to reduce the spontaneous electrical activity in the majority of POMC neurons (75%). The application of oxamate, the inhibitor of the lactate dehydrogenase (LDH), the enzyme which converts lactate into pyruvate, is also found to cause a reduction in the firing rate in most POMC neurons (63%). The application of pyruvate prevents this effect. Overall, our study shows that the majority of POMC neurons uses endogenous lactate, which they metabolize into pyruvate, as an energy substrate to maintain their electrical activity. This use of lactate may be of great functional importance, since it could be used as a glial messenger produced from glucose by tanycytes in order to modulate the activity of POMC neurons to adapt physiological responses according to metabolic status.

**P2.042 Deciphering the molecular mechanisms of LRRTM2 trafficking and stabilisation at synapses**

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Synaptic Cell Adhesion Molecules (CAMs) are responsible for synapse formation, specification, and stabilisation during neuronal development. These transmembrane proteins are localised at the pre- and post-synapse where they interact across the synaptic cleft to maintain contacts between neuronal cells and participate to the control of synapse maturation, function, and plasticity. The Neurexin-Neuroligin complex is one of the most extensively studied and has been shown to play important roles in synapse specification and plasticity. However, new Neurexin ligands have been recently described, adding complexity to this model. In particular, LRRTM2 (Leucine Rich Repeat Trans Membrane) competes with Neuroligin for Neurexin binding, is highly enriched at excitatory synapses, and is required for LTP *in vivo*. At the molecular level, LRRTM2 has been shown to interact with PSD-95 and AMPARs, and we have demonstrated that LRRTM2 is highly confined at synapses and immobile in the plasma membrane. However, little is known about the molecular mechanisms that govern LRRTM2 trafficking and stabilisation at the plasma membrane, and how these mechanisms are involved in synapse formation and function. In this project, we investigate these molecular mechanisms by studying interaction- and trafficking-deficient LRRTM2 mutants. We show that WT-LRRTM2 is highly enriched at excitatory synapses where it colocalises with synaptic markers. We also show that LRRTM2 C-terminal domain controls its synaptic clustering and surface expression. Finally, we demonstrate that LRRTM2 is strongly colocalised with PSD-95 at the nanoscale level using super-resolution microscopy, while LRRTM2 mobility is controlled by PDZ binding domain-independent interactions. These results indicate that LRRTM2 trafficking and stabilisation are highly controlled, presumably through its C-terminus domain.

**P2.043 Use of Zif::CreERT2 transgenic mice for long-lasting tagging of neurons activated by epileptic seizures or cocaine injection**

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To identify neuronal ensembles activated in precise experimental situations, we used genetic tools to permanently tag relevant neurons that express an activity-dependent immediate-early gene (IEG). We created transgenic mice, called Zif::CreERT2, in which the expression of CreERT2 is activity-dependently driven by the promoter of the IEG *zif268* (also known as *Egr1*). CreERT2 recombinase is only active in the presence of tamoxifen (TAM) or 4-hydroxy-tamoxifen (4OH-TAM). Thus, in these mice, CreERT2 activity requires two conditions:

- 1) induction of the *zif268* promoter and
- 2) 4OH-TAM or TAM. Here, the Zif::CreERT2 mice were crossed with different Rosa26 locus reporter mice, Cre-dependently expressing GFP (RCE), tdTomato (Ai14) or GFP fused to L10a ribosomal subunit (EGFP-L10a).

Without 4OH-TAM/TAM, no or few tagged neurons were observed in the brain of double transgenic mice. When pilocarpine (70 mg/kg) or pentylenetetrazol (37.5 mg/kg) producing seizures and transient inductions of *zif268* in the dentate gyrus of hippocampus was combined with TAM (100 mg/kg) treatment, we observed numerous positive neurons in this region one week later, showing the persistent tagging of activated neurons. Mice from the same crossings were treated with cocaine (20 mg/kg) or saline in the presence of 4OH-TAM (50 mg/kg). One week later, the number of tagged neurons in the dorsal striatum was significantly higher in the cocaine-treated group than in the saline group, but the effect magnitudes depended on the reporter lines (+74%, +178% and +12% for RCE, Ai14 and EGFP-L10A, respectively). Pretreatment with SL327 (50 mg/kg), a MEK inhibitor blocking ERK activation, showed that the cocaine-induced tagging of striatal neurons depend on ERK activation. Using this persistent tagging approach, we provide evidence that the striatal neurons that are activated by a first cocaine injection exhibit a higher ERK activation following a second cocaine injection one week later, suggesting that similar neuron ensembles are activated by cocaine following repeated administration. Collectively, these experiments demonstrate the validity of this tagging approach that could provide a valuable tool to study the long term physiological and morphological changes in "activated" neurons.

**P2.044 Impact of neuronal activity on calcium signals of oligodendroglia during remyelination**

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The fast conduction velocity of action potentials in the central nervous system (CNS) depends on myelin sheaths produced by oligodendrocytes (OL) and enwrapping neuronal axons. In demyelinated diseases such as Multiple Sclerosis, a production of OLs and a partial myelin repair can occur. This OL regeneration in response to injury depends mostly on the ability of oligodendrocyte precursor cells (OPCs) to proliferate and differentiate into the damaged site. Although it is known that neuronal activity impacts the fate of OPCs and modulate myelination, the underlying signaling mechanisms linking neuronal activity with OPC fate are still poorly understood. Calcium, a key intracellular signal for OPC proliferation and differentiation, is a major candidate able to encode neuronal information and transduce it into these cellular processes. Our team recently showed that neuronal activity *in vivo* increases OPC proliferation and differentiation as well as myelin production by OLs in lysolecithin (LPC)-induced demyelinated lesions. Our goals are to assess the main signaling mechanism linking neuronal activity with calcium activity of OPCs and OLs in this model and test its remyelination potential. We combine epifluorescence and two-photon microscopy to analyze calcium signals in acute slices of transgenic mice expressing the fluorescent calcium-sensitive proteins GCamp5 and Gcamp6, specifically in OPCs and their progeny. Our results show that high levels of spontaneous calcium signals occur in both OPCs and OLs at different stages of the remyelination process. These signals are independent on basal neuronal activity and are insensitive to antagonists of ionotropic and metabotropic glutamate receptors. However, they are consistently modulated by an increase in neuronal activity. We presently investigate the signaling mechanism allowing neuronal activity to modulate these calcium transients in OPCs. This project should seed the basis to find new potential molecular tools to impact activity-dependent oligodendrogenesis and remyelination.

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**P2.045 Deciphering functional networks of ion channels in *substantia nigra pars compacta* dopaminergic neurons**

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Our aim is to understand the molecular mechanisms underlying robustness of electrical activity in *substantia nigra pars compacta* dopaminergic neurons. Previous studies have suggested that coordinated regulation of functionally-overlapping ion channels plays an important role in the stability of activity patterns (Chan et al., 2007; Amendola et al., 2012). To understand the mechanisms of coordinated regulation of ion channels, we are deciphering the interaction network of Ca<sub>v</sub>1.2, Ca<sub>v</sub>1.3, HCN2, HCN4, K<sub>v</sub>4.3 and SK3 ion channels, using a combination of cell biology and biochemical approaches.

By analyzing protein complexes co-purifying with these ion channels in midbrain tissue by mass spectrometry, we describe new interactants of each ion channel. Furthermore, we found that the HCN4 and SK3 channels are present in the same protein complex. To ascertain that these interactions indeed take place in *substantia nigra pars compacta* dopaminergic neurons, we then use proximity-ligation assay.

Furthermore, we are evaluating HCN4 expression in SK3 knock-out mice (KCNN3<sup>-/-</sup>) to search for possible expression compensation. These data confronted with electrophysiological recordings of dopaminergic neurons will help us better understand the molecular mechanisms involved in robustness of neuronal activity.

**P2.046 LINGO-1, a major player of myelination and neuronal survival forms heteromeric complexes: a new signaling platform**

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LINGO-1 is a single transmembrane protein displaying a large extracellular region consisting in 12 LRR motifs (leucine-rich repeat) and one Immunoglobulin domain. LINGO-1 is selectively expressed in brain and spinal cord in both oligodendrocytes (OLs) and neurons. It is characterized as a negative regulator of neuronal survival, axonal regeneration and OL precursor cell (OPC) differentiation into mature myelinating OLs. Molecular mechanisms involved in these processes implicate a ternary receptor complex comprised of LINGO-1, the p75 neurotrophin receptor and the Nogo Receptor (NogoR) that bind several myelin associated inhibitors. Consequently, it was shown that the blockade of LINGO-1 functions using anti-LINGO-1 antibodies (LINGO-1-Fc) or its dominant negative form (DN-LINGO-1) increases neuronal and oligodendroglial survival, axonal growth and myelination. In the last decade, dysregulation of LINGO-1 expression and signaling was reported in a wide range of neurological and psychiatric disorders, underlying the interest of LINGO-1 as a novel therapeutic target for these diseases. Interestingly, three homologs of LINGO-1 named LINGO-2, LINGO-3 and LINGO-4 have been described, however, their relative expression and functions remained unexplored. In this study, we show by *in situ* hybridization and quantitative PCR analysis that LINGO homologs are differentially expressed in the central nervous system and that each LINGO possessing a specific and partially overlapping expression pattern. Using biochemical methods, we demonstrated that LINGO proteins form homo- and hetero-complexes not only in heterologous systems but also in cortical neurons. In addition, BRET (bioluminescence resonance energy transfer) analysis allowed us to demonstrate that LINGO proteins can physically interact with each other's with a relatively similar affinity in order to form these oligomeric states. Considering the role of LINGO-1 signaling in pathophysiology, its ability to form constitutive heteromeric complexes reveals a new level of complexity in its signaling and opens the way for new strategies to achieve diverse and nuanced LINGO-1 regulation.

**P2.047 Robustness to axon initial segment variation in rat and mouse substantia nigra dopaminergic neurons**

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In many neuronal types, axon initial segment (AIS) geometry critically influences neuronal excitability. Interestingly, the axon of substantia nigra pars compacta (SNC) dopaminergic (DA) neurons displays a highly variable location and most often arises from an axon-bearing dendrite (ABD).

We combined current-clamp somatic and dendritic recordings, outside-out recordings of dendritic sodium and potassium currents, morphological reconstructions and multi-compartment modelling on rat and mouse SNC DA neurons to determine cell-to-cell variations in AIS and ABD geometry and their influence on neuronal output (spontaneous pacemaking frequency, AP shape).

Both AIS and ABD geometries were found to be highly variable from neuron to neuron. Surprisingly, we found that AP shape and pacemaking frequency were independent of AIS geometry. Modelling realistic morphological and biophysical variations clarify this result: in SNC DA neurons, the complexity of the ABD combined with its excitability predominantly define pacemaking frequency and AP shape, such that large variations in AIS geometry negligibly affect neuronal output, and are tolerated.

P2.048

**Identification of an axon-resident pool of vesicles regulated by neuronal activity**

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During postnatal development, long-range axonal projections reach their target to form branches and synaptic contacts. This process highly depends on neuronal activity and requires large amounts of secretory materials. Axonal transport of secretory vesicles is responsible for addressing these cargoes to high demand sites. However, mechanisms that control the preferential targeting of axonal vesicles to active sites are unknown.

Here, we identify an axon-resident reserve pool recruited upon neuronal activity to rapidly distribute secretory materials to presynaptic sites. Using an *in vitro* system compatible with high-resolution videomicroscopy that combines microfluidic chambers and microelectrode arrays (MEA), we reconstituted a physiologically-relevant cortico-cortical network in which neuronal activity can be controlled. Using this approach, we showed that neuronal activity instantly recruits a pool of anterograde vesicles tethered along the axon shaft. We found that neuronal activity induces Calcium-Induced Calcium Release from ryanodine receptor after activation of Voltage Gated Calcium Channel in the axon, which triggers the recruitment of tethered vesicles. We are now investigating the precise molecular mechanism responsible for vesicle recruitment.

Using 2-photon live microscopy of cortical axons in acute slices, we confirmed that a pool of axon-resident static vesicles is recruited by neuronal activity *in vivo* with similar kinetics. We are now investigating the functional relevance of this axonal reserve pool to promote fast supply of synaptic materials during axon branching and synaptogenesis.

**P2.049 The Microtubule-associated protein Tau as a new putative therapeutic target in brain cancer**

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The microtubule-associated protein Tau is highly expressed in the central nervous system. In neurodegenerative diseases Tau accumulates to form pathological neurofibrillary tangles inducing cytotoxic effects. In cancer, Tau contributes to cell invasiveness such as sarcoma, neuroblastoma, gastric cancer, non-small cell lung cancer. In our study, we investigated the effect of Tau expression in glioblastoma (GBM), a brain tumor of astrocytic origin. By using a shRNA approach to deplete Tau in U87 cells (U87shTAU cells), we demonstrated defective migration of cells from multicellular spheroids settled onto fibronectin and collagen matrices. Surprisingly, we also observed that spheroids of U87shTAU cells were completely disassembled over 24 hours, which was associated to relocation of the junctional N-cadherin protein. Using Pathscan® Intracellular Signaling Array, we highlighted a significant reduction of the phosphorylation state of the survival kinase AKT in U87 shTAU cells, which correlated with decreased cell proliferation. Moreover, we examined the impact of Tau depletion in GBM growth in orthotopic xenograft models. Nude mice intracranially injected with U87shTAU cells presented significant longer survival compared to mice injected with control cells (median survival: 26.5 for U87shctrl vs 58 days for U87shtau), suggesting that Tau protein is strongly implicated in glioma cells aggressivity. Beside to complete knowledge about its role in regulating microtubule assembly in migrating cell, we suggest a role for Tau in linking N-cadherin cell adhesion to the regulation of cell survival via AKT activation. In summary, Tau may be a new putative therapeutic target in GBM.

**P2.050 Identification of somatosensory mechanotransducer(s) by functional genomics approach**

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Mechanotransduction is the conversion of mechanical stimuli into biological signals within the cell. It regulates a broad diversity of physiological functions including mechanosensation. Mechanosensation constitutes one modality of the somatosensory system and refers to the perception of touch, mechanical pain and proprioception, the sense of body position and movement.

At the molecular level, mechanosensors involved in mechanosensation are mechanically activated (MA) ion channels. Indeed, mechanical stimulation of dorsal root ganglia (DRG) neurons, the receptor cells of the somatosensory system, can elicit at least three types of excitatory MA currents distinguishable by their adaption kinetics to prolonged stimuli. These currents result from the activation of MA ion channels.

Piezo2 is an excitatory MA channel expressed in a subset of sensory neurons. It plays a crucial role in innocuous touch sensing and proprioception. However, Piezo2 is not involved in acute mechanical pain sensing, suggesting the existence of other(s) -still unknown- MA channel(s). Accordingly, Piezo2 knock-out abolishes only a fraction of MA currents in sensory neurons. The identification of other(s) MA channel(s), especially those involved in mechanical pain, constitutes one of the most important questions in the field of sensory transduction.

To unravel molecular components of MA channels, we used mechano patch-sequencing, *i.e.* single-neuron RNA-sequencing after electrophysiological characterization of neuronal mechano-phenotype. We successfully generated the gene expression profiles of 48 distinct single DRG neurons covering the different types of MA currents. Based on transcriptome comparisons, *in silico* analysis (edgeR, DESeq2) provided lists of differentially expressed genes which potentially code for molecular components of MA channels. The implication of these candidate genes in the distinct types of MA currents was tested by patch-clamp recordings in freshly isolated mouse DRG neurons after siRNA-mediated knock-down. So far, two candidate genes significantly alter the mechanical responses of subsets of DRG sensory neurons.

These data could lead to the identification of new MA channel component(s) or modulator(s), and to a better understanding of mammalian mechanosensation.

P2.051

**Development of neurotensin analogues conjugated to a brain penetrant peptide that induce hypothermia and promote efficient neuroprotection *in vivo* and *in vitro***

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Mild to moderate hypothermia (HT) is a potent neuroprotective approach against brain damage occurring in situations such as brain ischemia associated with sudden cardiac arrest and stroke, seizures, perinatal hypoxia/ischemia, traumatic brain and spinal cord injuries, or heart surgeries. Reduction of hyperthermia to normothermia is also warranted in situations of elevated body temperature such as intracranial hypertension, hemorrhagic stroke, or infections. To date, therapeutic HT is induced by body or head cooling using different medical devices. However, these methods activate physiological responses that may counteract the potential benefits of HT and necessitate pharmacological adjuncts. Pharmacological approaches have been suggested to induce HT, in particular using neurotensin (NT) or its analogues, which induce a potent effect when administered directly into the brain. However, the clinical use of NT is hampered by rapid proteolytic cleavage in plasma and poor blood brain barrier (BBB) permeability. We describe the development of conjugates that encompass brain penetrant peptide vectors to promote drug delivery into the CNS, different linkers, and proteolytically stable analogues of NT. Upon systemic administration, these conjugates demonstrate significant hypothermia with rapid onset of action and tunable central HT upon 24-hour intravenous slow infusion. In rodents, the vector-NT conjugates demonstrate efficiency in different pathophysiological conditions, including hyperthermia, and have potent neuroprotective effects in situations of excitotoxicity and neuroinflammation *in vivo*. Vector-NT conjugates administered as a slow 6-hour intravenous infusion also induce HT in new-born piglets, as a human-related non-rodent species, opening new avenues for the treatment of perinatal hypoxia/ischemia. Finally, we show that in addition to hypothermia-based neuroprotection, the vector-NT conjugates also elicit neuroprotection in cultured neurons submitted to excitotoxic agents. We have thus developed centrally acting pharmacological agents that induce HT in rodent and non-rodent species, that reduce neurodegeneration and neuroinflammation, and that also have intrinsic neuroprotective properties independent of HT.

**P2.052 Expression and distribution of Neurotensin receptors in wild-type and epileptic conditions in relation to the neuroprotective effects of vectorized Neurotensin (VH-NT)**

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Moderate **therapeutic hypothermia** (HT) is neuroprotective in situations of exacerbated neuronal death, including sudden cardiac arrest, perinatal hypoxia/ischemia, and traumatic brain injury (TBI). Selective brain cooling has also broad-ranging anti-inflammatory effects and decreases seizure burden in animal models of post-traumatic epilepsy. To date, therapeutic hypothermia is induced with medical devices.

We have shown that systemic administration of the neuropeptide neurotensin (NT) can elicit HT when conjugated to brain penetrant peptide-based vectors, in contrast with non-conjugated NT that has poor blood-brain barrier (BBB) permeability. HT induced by vectorized NT (VH-NT) **reduced epileptic seizures, neuroinflammation** and **neurodegeneration** of pyramidal hippocampal neurons in a mouse model of epilepsy, and also showed neuroprotective properties in cultured neurons that are not HT-mediated. In order to better understand these effects of VH-NT, we studied the expression, distribution and role of the main NT receptor subtypes (**NTSR1, 2 & 3**) in cultured hippocampal neurons and in non-neuronal cells, and *in vivo* in a rat model of epilepsy induced by pilocarpine, with characteristic neurodegeneration and neuroinflammation.

Immunohistochemical studies on rat brain sections and cultured hippocampal neurons showed that NTSR1 is localized at the cell membrane and within dendritic spines. NTSR2 is also expressed to some extent in pyramidal neurons and its **expression is induced** in astrocytes and distinct vulnerable neuronal subtypes at **different time points following seizure induction**. Treatment of primary astro-microglial cultures with pro-inflammatory factors induced NTSR2 expression levels, while transfection-mediated overexpression of NTSR2 in neuronal and non-neuronal cells induced **cell death that could be prevented by VH-NT treatment**. This effect of VH-NT is independent of HT.

Altogether, our findings suggest that:

- 1) VH-NT is involved in the neuroprotection effect *in vivo* and *in vitro*;
- 2) inflammation can modulate NTSR expression levels and
- 3) NTSRs represent interesting targets to modulate neuroinflammation and neurodegeneration.

**P2.053 Pathological low frequency oscillations of the subthalamic nucleus predict compulsive-like cocaine seeking in rats**

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Identifying vulnerable individuals before they transition to pathological seeking and taking behaviors remains a key challenge in the addiction field. Addiction does not solely result from the mere consumption of a drug of abuse but it involves more complex behaviors. In rats, compulsive-like cocaine seeking despite negative consequences (e.g. a foot-shock) can be observed in some individuals that had previously lost control of their drug intake (i.e. escalation). Interestingly, during the process of escalation, we observed a progressive increase of very low-frequency oscillations (~6-12 Hz) in the subthalamic nucleus (STN). This pathological activity was only present in animals that will subsequently exhibit compulsive-like seeking behavior when facing its negative consequences. This suggests that increased oscillatory activity in STN low frequency oscillations could be a predictive biomarker of resistance to punishment (i.e. compulsion). Indeed, 8-Hz stimulation of the STN of sensitive rats, applied during the process of escalation, switches their sensitivity to punishment towards compulsive-like cocaine seeking. Finally, we show that low (~30 Hz), but not high (~130Hz), frequency deep brain stimulation (DBS) of the STN progressively diminishes cocaine seeking in compulsive rats with no effect in sensitive animals. Here, we thus characterize a causal biomarker that allows identification of animals that will display compulsive-like cocaine seeking behaviors. Furthermore, our results highlight the critical role played by the STN in processes underlying transition to cocaine addiction and confirm that STN DBS represents a promising surgical strategy for the treatment of addiction.

**P2.054**

**Primary cilium: a new target for remyelination ?**

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The primary cilium (PC) is considered as a cellular sensory antenna present at the surface of many cell types. It coordinates several molecular pathways that control cellular proliferation and differentiation. In the central nervous system (CNS) the presence and the role of PC have been documented in neurons and astrocytes; however very little is known about PC in oligodendrocytes, the myelinating cells in the CNS. Oligodendrocytes originate in the ventricular zone from oligodendrocyte precursors cells (OPCs) before differentiating in myelinating cells. In neurons, PC length is modulated by extracellular cues and *in vitro* by drugs, such as Lithium Chloride (LiCl).

We used three types of cultures: an oligodendrocytic cell line (158N), olfactory ensheathing cells (OEC) (peripheral glial cells able to myelinate axons when transplanted in the CNS) and OPCs purified from mixed glial cell cultures established from neonatal plp-eGFP mouse cortices. Purified OPCs were analyzed at three time points (24, 48 and 72h). We show that the PC is present in these cell types, as observed by immunofluorescence and electron microscopy; in the oligodendroglial lineage, however, PC disappears in differentiated cells (MPB positive). LiCl was able to lengthen the PC in the three types of cultures. In neurons, inhibition of adenylyl cyclase type 3 (AC3) is believed to support the effect of LiCl on PC lengthening. We detected AC3 in OPCs and OECs but not in 158N cilium. Inhibition of AC by 3'AMP had no effect in 158N cells but lengthened the cilium in OECs. In OPCs cultures, the effect was dependent on the culture medium and on the time point analyzed.

To test a possible relationship between cilium length and OPCs differentiation, we compare the effects of LiCl and of two cilium shortening drugs: chloral hydrate and ciliobrevin on cell morphology.

This study opens a new field of investigation to increase the ability of OPCs to remyelinate in demyelinating diseases such as multiple sclerosis. Accelerating remyelination and preventing axonal and neuronal degeneration is currently an important issue in this pathology.

**P2.055 Chronic administration of sodium bromide relieves behavioral deficits in three different mouse models of autism**

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Autism spectrum disorders (ASD) are complex neurodevelopmental diseases whose diagnosis lies on the detection of impaired social interaction and communication together with restricted and repetitive behavior and interests (DSM-5). Although the etiology of ASD remains mostly unknown, increased excitation/inhibition ratio appears as a common mechanistic feature between these pathologies. Consistent with this, molecules that decrease neuronal excitability, such as diuretics antagonizing the NKKC1 chloride transporter, were shown to ameliorate autistic symptoms in animal models as well as in patients with ASD. Bromide ions can reduce neuronal hyperexcitability, possibly by competing with chloride ions at channels and transporters, and hyperpolarizing the cells, accounting for their powerful anticonvulsant properties. Here we first evaluated the therapeutic potential of chronically administered sodium bromide to relieve autistic-like behavioral deficits in three different mouse models of ASD, the *Oprm1*, *Fmr1* and *Shank3<sup>Δex13-16</sup>* knockout mouse lines. In the former, sodium bromide (125, 250 and 500 mg/Kg) dose-dependently improved social interaction and preference, reduced stereotypies and decreased anxiety. Bromide administration was significantly more effective than bumetanide (0.5 and 2 mg/Kg) in restoring social parameters. In *Fmr1* and *Shank3<sup>Δex13-16</sup>* mutant animals, sodium bromide (250 mg/Kg) produced similar and consistent improvements in autistic-like behavior. Then, we tried to shed light on the molecular mechanisms involved in bromide effects. In differentiated sH-sy5y, we used calcium imaging to evaluate the effects of bromide at different concentrations on cell excitability. The beneficial effects of bromide administration in three unrelated genetic murine models of ASD and its impact on neuron-like cell neurophysiology predicts high translational potential in patients with autism, despite high heterogeneity in etiology and symptoms.

P2.056

### Detecting brain diseases via plasma profiling

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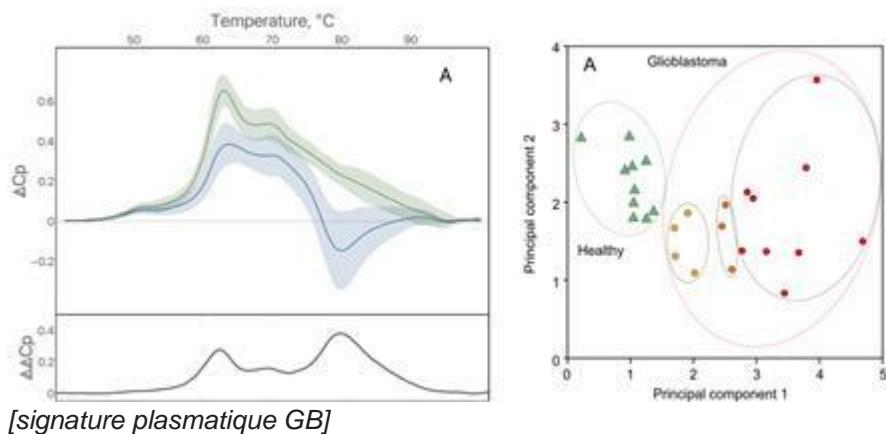
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Several pilot studies have previously hypothesized that Differential Scanning Calorimetry (DSC) could be used as a potential diagnostic tool for a number of pathologies by providing disease-specific calorimetric denaturation profiles of blood plasma (1). Recently, we have shown that this approach can be also used in Glioblastoma, the most frequent and aggressive primary brain tumor in adults (2). Comparing the DSC denaturation profiles of plasma samples from patients with glioblastoma with the ones from healthy individuals revealed the existence of a glioblastoma signature despite the blood brain barrier, pointing to a potential easy-to-use non-invasive monitoring tool for glioblastoma patients.

Unfortunately, there are several obstacles inherent to the DSC itself that make this approach non-transferable to the clinics. To circumvent these limitations, we proposed to use differential scanning fluorimetry (DSF) rather than DSC to obtain denaturation profiles of plasma samples. Using nanoDSF Prometheus NT instrument, we were able to obtain denaturation profiles of human plasma similar to the ones registered by DSC. The ability of this instrument to run up to 48 disposable capillaries with only 10 µL of undiluted plasma samples makes it not only more suitable for the large-scale experiments necessary for statistically robust results but also transferable to clinic. In order to develop an effective diagnostic tool based on nanoDSF, it is necessary to perform the complex analysis of large amount of multiparametric data extracted from these profiles. In collaboration with data scientists specialized in Artificial Intelligence solutions, we are developing a classification method of the plasma denaturation profiles based on deep learning algorithms to make this profile analysis automatic and applicable to a wider range of nervous system pathologies.



**P2.057 Concomitant modification of synaptic activity by IL-1 $\beta$  and metalloprotease MT5-MMP in primary cortical cultures**

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IL-1 $\beta$ [SR1]contributes to neurodegenerative disorders, including Alzheimer disease (AD) but the underlying pathogenic mechanisms are not well understood. Synaptic loss is among the first signs of AD pathogenesis and precedes neuronal death. IL-1 $\beta$ signaling mainly occurs through its receptor IL-1R1, which is enrichedpost-synaptically[A2]. IL-1R1 is sequentially cleaved first by TACE (TNF alpha converting enzyme, ADAM-17) and then by  $\gamma$ -secretase within the plasma membrane, releasing a C-terminal fragment that triggers IL-1 $\beta$ signaling and the consequent inflammatory cascade. Published and unpublished data from our laboratory indicate that MT5-MMP may modulate IL-1 $\beta$  signaling in mixed (neuron/astrocyte) primary cortical cultures, through a yet unknown mechanism. Here, we used whole-cell patch clamp in mixed cortical primary cultures to investigate the role of IL-1 $\beta$  at modulating synaptic activity and how this is influenced by MT5-MMP and  $\gamma$ -secretase. Our preliminary results suggest that IL-1 $\beta$  favors GABA transmission and lowers the NMDA-induced excitation, along with fewer synapses on dendrites of pyramidal cells. The inhibition of g-secretase and MT5-MMP differentially impacts onto the balance of excitation/inhibition mediated by IL-1 $\beta$ , as well as the number of synapses. These data open the way to further explore the functional interplay between IL-1 $\beta$ and MT5-MMP and the consequences for early pathophysiological events in the brain[A3].

[SR1]Vérifier si les symbols grecs sont acceptés dans l'abstract.

[A2]At the post-synaptic level

[A3]In the WT and AD brain

- P2.058 TP53INP1 deficiency exacerbates age-related and alpha-synuclein-induced degeneration of nigral dopaminergic neurons in mice**
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Parkinson's disease (PD), the second most common neurodegenerative disorder, is characterized by the progressive degeneration of nigrostriatal dopaminergic (DA) neurons. These neurons are also more prone to degeneration during normal ageing, which remains the biggest risk factor for developing idiopathic PD. Specific patterns of neuronal loss are reported, consistent with DA neuron heterogeneity. The mechanisms underlying neuron death include neuroinflammation, oxidative stress and mitochondrial dysfunction. Interestingly, the stress response protein TP53INP1 acts as a molecular nexus at the crossroad of metabolic pathways essential for reversing stress-induced alterations in cellular homeostasis: it interacts with the PD-linked proteins PINK1 and Parkin and its deficiency has been linked with metabolic syndrome via mechanisms common to those involved in neurodegenerative diseases. Here we investigated the unexplored role of TP53INP1 in the maintenance of neuron homeostasis under stress conditions, by focusing on DA neurons in the context of age and PD-related neurodegeneration. For this purpose, we performed comparative regional analysis of mesencephalic DA neuron loss and behavioral testing in WT and *Trp53inp1*-KO mice at different ages in unlesioned animals and at different time points of the degenerative process in a PD model based on viral vector-mediated overexpression of human  $\alpha$ -synuclein. In the nigra, the age-related DA neuron loss predominates in the rostral part in WT mice and it is worsened specifically in the caudal part in KO mice. In the PD model, DA neuron loss predominates in the rostral nigra and is worsened in both rostral and caudal nigral parts. This stronger neurodegeneration is accompanied by aggravated motor deficits. Furthermore, in both conditions, the calbindin-positive subpopulation of nigral DA neurons appears to be the most affected by TP53INP1 deficiency. In the ventral tegmental area, age and PD-related DA neuron loss does not differ between WT and KO mice. These data provide the first evidence for a neuroprotective role for TP53INP1 and emphasize the heterogeneity of responses to cellular stress among DA neurons.

Supported by CNRS, Aix-Marseille Univ and Fédération pour la Recherche sur le Cerveau.

**P2.059 Influence of Quercetin-loaded magnetic nanoparticles on kainate-induced epileptiform activity in the CA1 field of the rat hippocampus**

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Approximately 1% of people suffer from epilepsy and 35% is drug-resistant form. Treatment strategies have been focused on flavonoids. Despite the positive pharmacological effects of Quercetin poor bioavailability limits its use. The loading of drugs to the nanoparticles facilitates their delivery and impact on the target locus. Magnetic nanoparticles drug delivery system could be controlled by magnetic field.

The purpose of our research was to detect behavioral/morphological/electrophysiological effects of Quercetin-loaded magnetic nanoparticles (Q-MNP) and to investigate its influence on Kainic-Acid (KA)-induced epileptiform activity in the hippocampus.

In ketamine-anesthetized rats Q-MNPs were injected in the tail vena. Unilateral magnetic field exposure to the brain was executed. Behavioral experiments were performed in open field/T-maze tests. To detect the Fe inserts in the cortical structures Perl's blue stain was used. The brain slices from two groups of animals with the right and the left-side magnetic field-exposure were prepared. In electrophysiological experiments electrodes were implanted bilaterally in to the hippocampus. Unilateral 5-fold KA administration were performed in the CA3-field for the generation of epileptiform activity. Q-MNP injection were carried out under condition of 60 min magnetic field exposure. Registration/analyses of obtained data were performed by Chart5.5 software. Software PRIZM was used for statistics.

The experiments demonstrated that magnetic field, as well as MNP alone, does not change the behavior of animals. However Quercetin and/or Q-MNN improves learning ability of the rats. Morphological experiments revealed that the number of Fe inserts is significantly higher in the magnetic field-exposure site in comparison with the untreated contralateral site, suggesting that the exposure of magnetic field improves target-delivery of the Q-MNP to the brain. Electrophysiological experiment showed that Q-MNP as well as magnetic field alone did not change significantly the mean amplitude/frequency of neuronal activity, although preliminary administration of both factors statically reduced the frequency/amplitudes of KA-induced repetitive epileptiform discharges.

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**P2.060 Assessment of neurodegeneration and  $\alpha$ -synuclein pathology in clarified brain slices in animal models of Parkinson disease**

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Parkinson's disease (PD) is the second most common neurodegenerative disorder and leads to slowness of movement, tremor, rigidity, and, in the later stages of PD, cognitive impairment. Pathologically, PD is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta and the appearance of protein  $\alpha$ -synuclein aggregation in inclusions named Lewy bodies. While  $\alpha$ -syn aggregates have been shown to induce multimodal cellular dysfunctions, propagation of  $\alpha$ -syn pathology mechanisms remain unclear. Using clarity approach on sagittal sections, we here define the kinetics of dopaminergic neurodegeneration and  $\alpha$ -syn pathology induced by either overexpressing mutated form of synuclein and human-derived  $\alpha$ -syn aggregates.

In our study, we analyzed two well-characterized animal models of PD: a rAAV2/9-expressing human A53T  $\alpha$ -syn into the substantia nigra in rat and a mouse model obtained after intranigral inoculation of human-derived samples containing pathological  $\alpha$ -synuclein. For the rat model, we selected two time-points: one and three weeks after stereotactic injection corresponding to the onset and progression of the neurodegeneration, and regarding the mouse model, we have chosen 24 hours, 1 month and 4 months after nigral inoculation. All the brains were treated by CLARITY technique which enables three-dimensional visualization and quantification of immunostained-tissue. Extensive analysis was performed to assess qualitatively, quantitatively and spatially in clarified sagittal slice brain the extent and pattern of lesion as well as the occurrence of synucleinopathy using immunohistochemical procedures. This study highlights for the first time a new methodological approach by using a clarification process to appreciate the occurrence of  $\alpha$ -synuclein-induced neurodegeneration in two different animal models.

**P2.061 Rare PAK3 mutations responsible for severe intellectual disability and callosal dysgenesis inhibit cell migration**

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Mutations of numerous genes are involved in intellectual disability (ID) which is often associated with a wide clinical spectrum generating a complexity in the etiopathological relationship. Indeed, ID is in various cases associated with morphological brain anomalies. Another degree of complexity lies in the fact that mutations for a given gene produce a broad clinical outcome, raising the question of the relationship between genotype and phenotype. We explore this question by studying the p21-activated kinase 3 (*PAK3*) gene, previously characterized as a X-linked non-syndromic ID gene. Indeed, mutations in the *PAK3* gene lead to intellectual disability of various severities and in some cases associated with psychiatric traits and morphological alterations. The *PAK3* kinase encoded by this gene controls synaptic plasticity and dendritic spine dynamics, however its implication in neurodevelopmental disorders is less well characterized. We report here a novel *PAK3* missense mutation responsible for severe ID, microcephaly and callosal dysgenesis. Thanks to a lentiviral inducible expression system, we analyse biochemically and biologically this new variant and compare it with less severe mutations. This mutation which is located in the activation segment of the catalytic domain totally suppresses kinase activity, without affecting protein stability. Furthermore, this mutation increases interaction between *PAK3* and the guanine exchange factor  $\alpha$ -PIX encoded by the *ARHGEF6* gene, and the expression of this mutated variant disturbs focal adhesion dynamics, cell spreading, and severely impacts cell migration. Our findings highlight for the first time a molecular mechanism linking *PAK3* mutations to brain neurodevelopmental defects and suggest that severity of the pathology may be due to the cumulative and/or synergistic effects of several molecular defects.

**P2.062 Impact of hormone-therapy used in CRPC patients: evaluation of abiraterone acetate/prednisone or enzalutamide on activity and cognitive functions in aged castrated mice**

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Prostate cancer (PC) is a major public health problem and represents the most frequent cancer in elderly male patients. Although most patients initially respond to androgen deprivation therapy (ADT) through inhibition of gonadal testosterone biosynthesis, the majority of these patients will progress to metastatic castration-resistant PC (mCRPC). Novel oral agents targeting androgen signaling axis, abiraterone acetate (AA)+prednisone (P) and enzalutamide (ENZ) are available and used in mCRPC patients in addition to ADT, but their impact on cognition is not well understood. Recently, the AQUARiUS study (Thiery-Vuillemin et al., ESMO Open, 2018) showed that after treatment, median Quality of life score improved with AAP. Additionally, results from a phase 2 trial showed that a worsening of depression symptoms were more often detected in ENZ- than in AAP-treated patients (Khalaf et al., Eur Urol, 2018). Here we developed a preclinical animal model to clarify the potential impact of AAP or ENZ on emotional reactivity and cognitive functions including spontaneous activity, anxiety-like and depression-like behaviors or spatial memory and learning.

In aged castrated mice receiving *per os* vehicle or AAP or ENZ, we showed that, in contrast to AAP, exposure to ENZ reduced spontaneous activity and increased depressive-like behaviors. AAP-treated mice displayed diminished self-grooming suggesting lower arousal in a novel environment. None of the treatments provoked anxiety-like behavior, learning and memory deficits. However, the swimming strategies (Morris-water maze) in AAP and ENZ groups were slightly altered. Analysis of plasma from treated mice revealed a detectable level of corticosterone only in AAP group.

These data establish the impact of ENZ on emotional reactivity and of both ENZ and AAP on subtle cognitive functions in castrated aged male subjects. It paves the road for future effective research that could lead to better management of quality of life in mCRPC.

**P2.063 A new procedure to quantify cortical vascular autoregulation in mouse models of epilepsy**

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Epilepsy affects more than 50 millions of persons worldwide. Three generations of antiepileptic drugs have been developed, nonetheless their efficacy are comparable and the rate of pharmaco-resistant patients stays has remained around 30% and could reach 100% for severe acquired epilepsies like the Dravet syndrome or Dravet. It is important to identify novel therapeutic targets. The overall mechanism maintaining Cerebral Blood Flow (CBF) homeostasis during changes in blood pressure is called "cerebral autoregulation". Some clinical studies show that epileptic foci are interictal focus is hypoperfused during interictal activity and ictal focus is hyperperfused during ictal activity, demonstrating an abnormal autoregulation. Other studies regarding the effects of epileptic seizures on cerebral autoregulation show that patients with partial epilepsy have higher variation in blood pressure during tests that challenge autoregulation, and that defaults of autoregulation default observed in epilepsy can be reversed after temporal lobe surgery. Studies of autoregulation on animal models of epilepsy are sparse. CBF autoregulation is considerably impaired in a piglet model after seizures induced by bicuculline and also in a rat genetic model of epilepsy. We propose that CBF autoregulation can be a target of antiepileptic therapy, and we are currently studying the impact of induced seizures on cerebral autoregulation in mice mouse models of epilepsy. Cerebral autoregulation is evaluated using a new procedure that we developed. Cortical blood flow is assessed with laser speckle imaging, arterial pressure is measured and drugs are injected through vascular catheters, all on awake and moving animals. There are some examples of some drugs that act on , acting on the renin-angiotensin system, are able to restore a normal cerebral autoregulation. We tested the effects of these drugs on seizures frequency and severity. The demonstration that a pharmacological intervention on the vasculature can lead to an improvement in seizures consequences and/or frequency would be a major advance for the treatment of epileptic diseases.

**P2.064 The potential of motor cortical neurons derived hiPSC transplantation for brain repair following traumatic brain injury**

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Traumatic brain injury (TBI) constitutes a leading public health concern, with limited treatment options available. Cell transplantation is a potential strategy to repair the injured brain. The recent discovery of human-induced pluripotent stem cells (hiPSC) offers an opportunity to generate patient-specific stem cells for cell-based replacement therapies. The goal of our project is to generate cortical neurons from hiPSC and use these cells in transplantation experiments to investigate the capacity of hiPSC-derived cortical neurons to induce repair in animal model of cortical lesion in adult mice and to explore the ability of transplanted neurons to functionally integrate into the cortical pathway.

We induced the expression of GFP in hiPSC to distinguish the grafted cells from the host and induced hiPSC into motor cortical neurons using culture of embryoid body-like aggregates in the presence of WNT inhibitor. We generated brain spheroids-aggregates expressing anterior cortical markers SP8 and PAX6. Motor cortical projection identity of the neurons was examined by the expression of CTIP2 (marker of layer V cortical neurons) and the absence of the expression of COUP-TF1 (marker of posterior cortex). The generated neurons display markers of cortical layers including FOXP2, CTIP2 and SATB2. Additionally, the generated cells expressed markers of oligodendrocytes (OLIG2<sup>+</sup>) and astrocytes (GFAP<sup>+</sup>). Aggregates at day 46 were grafted into the motor cortex of adult NOD/SCID mice seven days after cortical impact injury. At 2 months post-transplantation (mpt) grafts were well integrated within the host cortex and the majority of the grafted neurons were still immature and expressed doublecortin (DCX). At 2 mpt, axons of the transplanted neurons were detected mostly close to the site of the graft in the ipsilateral cortex, with few GFP<sup>+</sup> axons extending to the corpus callosum and in the striatum. In contrast, at 8 mpt, axons of grafted neurons were found in the most target of motor cortex including striatum, thalamus and pontine nuclei down to the pyramidal tract. Moreover, grafted neurons expressed layer-specific cortical pyramidal neuronal markers including Foxp2, Ctip2 and Cux1. Ongoing experiments are in progress to address the functionality of the grafted neurons.

**P2.065 Effect of myelin remodeling on axons and oligodendrocytes in pathological conditions**

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Axonal myelin allows rapid and efficient neural processing. Throughout life, precursor cells generate new oligodendrocytes, which play a critical role in the tuning of neuronal network activity. The newly generated myelinated oligodendrocytes improve motor learning and reinforce active pathways. However, the dynamics of myelin remodeling in different microenvironmental conditions and how it impacts the pathological demyelination insults remain poorly understood. Using high-resolution, intravital multimodal non linear microscopy (CARS and two-photon fluorescence) in mouse spinal cord, we highlighted and described pathological subcellular demyelinating events in living subjects over several days. Sensitivity was sufficient to detect changes in oligodendrocytes and myelin densities induced by a sensory enrichment protocol. Finally, we shown that experiment-induced myelination protects neurons from demyelination and from subsequent degeneration. Such myelin remodeling potentially plays a critical role in pathological conditions.

**P2.066**

**Contribution of reactive astrocytes to myelin repair**

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Myelin speeds up action potential transmission, allowing efficient functional integration in the central nervous system (CNS). Myelin is lost in several CNS area in demyelinated diseases, such as Multiple Sclerosis (MS). After a demyelinated insult, there is a spontaneous repair process (remyelination) characterized by the migration, proliferation, and differentiation of oligodendrocyte precursor cells (OPC) into remyelinating oligodendrocytes (OL). In addition to this dynamic response of the oligodendroglia population, a highly conserved hallmark of demyelinated lesions is the recruitment of reactive astrocytes. Astrocytes release several molecules that can modify OPC proliferation and differentiation, potentially affecting OL production and subsequent myelin synthesis. Current evidence indicate a role for reactive astrocytes on the demyelination/remyelination process. However, the precise cellular mechanisms and the contribution of reactive astrocytes to myelin repair are not completely understood.

To decipher the role of reactive astrocytes at different stages of the remyelination, we use the lysolecithin (LPC) model of demyelination in the mouse corpus callosum (CC). Thirty days before LPC stereotaxic injection into the CC, astrocytes are infected with a lentivirus encoding SOCS3 (lenti-SOCS3) to inhibit the JAK-STAT3 pathway and prevent astrocyte reactivity. The effects of this genetic inactivation of astrocyte reactivity are being analyzed by the quantification of OPCs and OLs at different time points of the remyelination process by immunohistochemistry and confocal microscopy on post mortem sections. Longitudinal magnetic resonance imaging (MRI) of mice injected with LPC and lenti-SOCS3 are also performed to image and quantify myelin loss and repair. Finally, electron microscopy will help quantify the effects of reactive astrocytes on myelin properties. Our results will shed light on glia-glia interactions involved in myelin disorders such as MS.

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**P2.067**

**Rescue of intrinsic excitability in CA3 neurons from LGI1-deficient mice**

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Leucine-rich Glioma Inactivated 1 (LGI1) is a soluble glycoprotein extracellularly secreted by neurons, which deletion induces Autosomal Dominant Lateral Temporal Lobe Epilepsy and that is targeted by antibodies associated with Limbic Encephalitis (LE). Lethal epileptiform activity is observed in LGI1 knock-out mice model (Boillot et al., 2014). The mechanisms by which this phenotype occurs has recently been elucidated. It has been shown that LGI1 deficiency leads to a decrease in axonal Kv1.1 channel density, a voltage-gated potassium carrying  $I_D$  current that dampens intrinsic excitability and glutamate release (Seagar et al., 2017).

In order to test whether LGI1 controlled intrinsic excitability through expression of Kv1 channel-mediated  $I_D$  current, we rescued LGI1 expression in LGI1 KO cells by single cell electroporation of LGI1-GFP gene. Patch-clamp recordings were obtained from CA3 pyramidal neurons to check whether wild-type electrophysiological phenotype was recovered 3 days after electroporation. Intrinsic excitability and sensitivity to dendrotoxin-K (DTX-K, a selective Kv1.1 subunit blocker) were measured in current-clamp mode and compared between KO and electroporated cells. Voltage-clamp recordings were used to measure  $I_D$  current in both conditions. As expected, we observed a reduction in intrinsic excitability and a higher sensitivity to DTX-K in electroporated KO cells compared to KO LGI1 cells, associated to the rescue of the  $I_D$  current. We conclude that reintroducing the LGI1 gene is sufficient to rescue normal intrinsic excitability in LGI1-deficient neurons through the re-expression of the Kv1 channel-dependent D-type current.

P2.068

## **Adenosine A<sub>2A</sub> receptor dysregulation in Alzheimer's disease impact of astrocytic A<sub>2A</sub>R upsurge in a mouse model of Tauopathy**

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Neuronal accumulation of hyperphosphorylated and aggregated Tau proteins is correlated with cognitive decline in Alzheimer's disease but mechanisms underlying Tau-induced memory deficits remain unclear. Previous epidemiological and experimental studies pointed out that chronic caffeine consumption reduces AD risk and associated cognitive deficits. These protective effects were ascribed to the blockade of adenosine A<sub>2A</sub> receptors (A<sub>2A</sub>Rs), which are found upregulated in the brain of AD patient's brains in correlation with Tau pathology development and cognitive deficits. These post-mortem observations suggest a link between A<sub>2A</sub>R dysregulation, Tau pathology and memory in AD. Both neuronal and astroglial A<sub>2A</sub>R appear to be dysregulated in AD. To get insights towards this relationship, we aimed at evaluating the pathophysiological impact of neuronal (see abstract from Kevin Carvalho, this meeting) and astrocytic (this abstract) A<sub>2A</sub>R upsurge in a transgenic model of AD-like Tauopathy (THY-Tau22 mice)

To address the role of astrocytic upsurge, we have developed a conditional model (Tet-Off) allowing A<sub>2A</sub>R overexpression in GFAP-positive astrocytes. This model was crossed with THY-Tau22 mice, who develop a progressive hippocampal Tau pathology associated with cognitive decline. In the different groups of animals, we evaluated Tau pathological changes (phosphorylation, aggregation) and functional impairments (learning and memory) at 5-6 months of age, when pathology is expressed but not maximal in the THY-Tau22 model.

We found that astrocytic A<sub>2A</sub>R overexpression worsens spatial memory impairments of THY-Tau22 mice. These effects were associated to an increased of Tau phosphorylation and aggregation as well as to the upregulation of hippocampal neuroinflammatory processes induced by Tau pathology.

Altogether, these data suggest that neuronal A<sub>2A</sub>R dysregulation seen in the brain of AD patients contributes to the development of Tau-induced cognitive impairments by modulating Tau pathology and neuroinflammation.

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P2.069

### Retinal alterations and visual dys-sensitivity in the Fragile X syndrome

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Fragile X syndrome (FXS) is the most common monogenic intellectual disability (ID) in men (1/4000 births). In addition to ID, patients present autism-like spectrum disorders as well as sensory disturbances, including impaired visual functions. Indeed, they display a decreased sensitivity to contrasts, textures and motions. FXS is caused by the absence of the FMRP protein, RNA binding protein involved in the regulation of neuronal and glial proteins' translation, due to the silencing of the *FMR1* gene. Consequently, the loss of FMRP induces cerebral molecular and cellular abnormalities leading to structural and functional synaptic abnormalities. This cerebral phenotype is considered as the origin of the clinical phenotype of ID, but also of the anomalies of visual functions since it concerns cerebral structures responsible for visual integration.

However, we have shown that in physiological conditions Fmrp is also expressed in the retina, the key structure of the visual system responsible for visual perception. As the retina is a sensory nervous tissue with the same embryologic origin than brain, the loss of Fmrp also impacts this "peripheral" part of the visual system. We have recently shown that the retina of the murine model of the FXS (the *Fmr1* KO mouse) displays protein deregulation as well as neuronal immaturity similar to those observed in brain, leading to major electrophysiological alterations. Besides, this retinal phenotype is settled at birth, and remains stable until the adulthood. Moreover, the behavioral response of *Fmr1* KO mice to several visio-spatial tests, involving both perception and integration of visual stimuli, is impaired.

Thus, the whole of our results indicates that the "peripheral" part of the visual system as well as its central part are altered, giving rise to impairments in visual abilities. We provide evidence that altered peripheral perception is a crucial component of the sensory processing defects of *Fmr1* KO mice. Both peripheral and central dys-sensitivity are involved in sensorial defect in the FXS pathology, therefore it becomes necessary to understand the involvement of each of these two parts in the visual clinical phenotype.

**P2.070 Network effects of cerebellar non-invasive stimulation: an MEG study on dystonic patients and healthy controls**

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Dystonia is a movement disorder characterized by abnormal muscular contractions and motor planning (Gallea et al., 2016). The cerebellum plays a critical role in dystonia (Lehéricy et al., 2013; Gallea et al., 2015) representing a potential therapeutic target (Tewari et al., 2017). However, the role of the cerebellum within the neuronal networks involved in movement planning is unclear. This study aims at investigating the network effects of cerebellar non-invasive stimulation during motor preparation. To this aim, 16 focal hand dystonia patients (FHD) and 19 healthy volunteers (HV) were included in the study with sham and cerebellar stimulation (transcranial magnetic for HV and transcranial alternating current stimulation for FHD). Participants performed a visuo-motor adaptation (VMA) task triggering cerebellar activity, before and after stimulation, while brain activity was recorded with magnetoencephalography. Participants moved a joystick to reach a target with a cursor presented on a screen, under two different conditions. In the control condition, joystick's movements and visual feedback were related directly to the cursor's motions. In the deviation condition, visual feedback was rotated inducing trajectory error (curved), which participants had to correct to produce trajectories as straight as possible. While both sham and cerebellar stimulation significantly reduced errors in both groups, cerebellar stimulation induced a significantly greater effect. The trajectory-correction learning rate was different in the two groups (slower in patients) and both group benefitted more from cerebellar, compared to sham, stimulation. Coherence measures between cerebellum and motor cortex for the beta frequency band correlate negatively with the learning rate. While the amplitude of trajectory errors was comparable between groups, HV adjusted their motor trajectories faster than patients and this learning rate was boosted by cerebellar stimulation compared to sham stimulation, more efficiently than in patients. This effect is likely due to a modulation of the coherence between the cerebellum and the motor cortex, in the beta frequency band. Cerebellar stimulation improved participants' learning rate, which depends on cerebellum-motor cortex communication.

**P2.071 LINE-1 retrotransposon repression attenuates neurodegeneration in adult dopaminergic neurons**

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LINE-1 (L1) retrotransposons comprise one fifth of the human genome and mobilize in the genome through a copy-and-paste mechanism termed retrotransposition. While L1 retrotransposition has led to a massive expansion and reshaping of mammalian genomes throughout evolution, their mobilization can threaten genome integrity. Independent of retrotransposition, L1 activity can also lead to genomic instability through DNA strand breaks induced by the encoded endonuclease.

We find that the three main active L1 families are expressed in dopaminergic neurons of the mouse *substantia nigra pars compacta*, a class of ventral midbrain neurons that degenerate in Parkinson's disease. The progressive degeneration of dopaminergic neurons in mice heterozygous for the homeodomain protein *Engrailed 1* (*En1-het*), starting at six weeks of age, is paralleled by an increase in L1 expression and signs of DNA damage. Similarly, DNA damage and cell death induced by oxidative stress applied either to embryonic midbrain neurons in culture or to mDA neurons *in vivo* is accompanied by enhanced L1 expression. Following these observations, we demonstrate that L1 overexpression is key to oxidative stress-induced DNA damage and induces neuronal death. Reduction of L1 activity through direct transcriptional repression by a siRNA directed against L1, the nucleoside-analogue reverse transcriptase inhibitor stavudine or viral *Piwil1* expression protects against DNA damage and neurodegeneration. We show that *Engrailed* directly binds to the promoter of L1 elements and reduces L1 expression levels in conditions of oxidative stress. Reducing L1 expression via *Piwil1* overexpression in *En1-het* mice partially prevents dopaminergic cell death. Our data suggests that L1 overexpression is a source of oxidative stress-induced genomic instability and subsequent cell death and that the protection of mDA neurons by *Engrailed* is in part through the repression of L1. L1-mediated genomic instability might be a driver of cell death in Parkinson's disease and potentially also in other age-related and neurodegenerative diseases.

- P2.072 MT5-MMP affects the stability of β-CTF of amyloid precursor protein, which may constitute a new potential pathophysiological mechanism in Alzheimer's disease**
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The γ-secretase-driven accumulation of the A<sub>β</sub> peptide (A<sub>β</sub>) is central to neurodegeneration in Alzheimer's disease, but growing evidence also points out the neurotoxic features of the A<sub>β</sub> immediate precursor generated by β-secretase processing of APP, known as β-CTF. We recently demonstrated that APP is an *in vivo* substrate of MT5-MMP and that MT5-MMP deficiency in 5xFAD mice strongly reduced brain β-CTF and A<sub>β</sub> levels, along with neuroinflammation, in parallel with improved synaptic efficacy and learning. We want now to gain further insight into the mechanisms underlying MT5-MMP/APP pathogenic interactions. To address our aim, we studied the impact of different MT5-MMP functional domains on β-CTF and A<sub>β</sub> levels in HEK cells and induced pluripotent stem cell (hiPSCs)-derived neurons. We found that MT5-MMP may promote amyloidogenesis in a catalytic independent manner. Moreover the lack of MT5-MMP C-terminal domains interfered with the proteolytic activity of the enzyme and drastically reduced the levels of β-CTF and A<sub>β</sub>. In order to place these experiments in a human neuron-like context, we use hiPSCs-derived neurons from Alzheimer's and non-demented patients, as well as CRISPR/Cas9 to generate isogenic MT5-MMP knockout cells. MT5-MMP deficient neurons exhibited a reduction in the levels of β-CTF and A<sub>β</sub> peptides. Our data further confirm the impact of MT5-MMP on APP metabolism to modulate Alzheimer's disease pathogenesis and further highlight the interest of MT5-MMP as a potential therapeutic target.

**P2.073** **Argon neuroprotection in a non-human primate model of transient cerebral ischemia**  
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**Introduction:** Stroke is known as a leading cause of long term adult disability. Stroke patients suffer from various neurological deficits with variable recovery. We have recently observed that a cost-efficient and easily available gas, the noble gas argon, can be used to reduce the size of ischemic damage and improve the motor recovery in rats subjected to transient middle cerebral artery occlusion. Our goal was to confirm this neuroprotective effect on a model of transient cerebral ischemia in a species closer to humans: the macaque rhesus.

**Material and methods:** We performed a transient and focal endovascular brain ischemia in 6 rhesus macaques randomized into 2 groups. Briefly, selective transient occlusion of the distal M1 segment of the right middle cerebral artery (MCA) was accomplished under general anesthesia by the technique of endovascular microcoil placement. The correct endovascular microcoil placement to block the MCA was determined by angiography to confirm interruption of blood flow through the vessel. A CONTROL group ( $n = 3$ ) and an ARGON group ( $n = 3$ ) for which Argon was applied 30 minutes after the onset of ischemia and for 90 minutes. For all animals, high resolution MRI scans (3DT1, DTI, Flair) were acquired with a 3T Prisma Siemens scanner right after the ischemia and analyzed to estimate the lesion volumes.

**Results:** In the CONTROL group, the lesion was large and encompassed the parietal, temporal and frontal lobes (fig.1). On average, the lesion volume was significantly smaller in the ARGON group when compared to the CONTROL group.

**Conclusion:** These preliminary data confirm the neuroprotective effect of Argon inhalation and its impact on the lesion volume. In the next part of the project, we will analyze the long-term effect of Argon neuroprotection on functional recovery following reversible cerebral ischemia.

**P2.074 Repair strategy for traumatic spinal cord injury; an advance in bioengineering-based preclinical approaches**

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Recovery from traumatic spinal cord injury (SCI) usually fails due to a cascade of cellular and molecular events that compromise neural tissue reconstitution by giving rise to glial scarring and cavity formation. We designed a scaffold material for SCI treatment containing only chitosan and water as fragmented physical hydrogel suspension (Chitosan-FPHS), with defined degree of acetylation (DA), polymer concentration, and mean fragment size. As a proof of concept, we previously demonstrated (Chedly et al., 2017) that implantation of Chitosan-FPHS alone into rat spinal cord immediately after a bilateral dorsal hemisection promoted reconstitution of spinal tissue and vasculature. Fibrous glial scarring was diminished, allowing the border between lesion site and intact tissue to become permissive for regrowth of numerous axons into, and for some even beyond the lesion site. This structural remodeling was associated with significant, long-lasting gain in locomotor function recovery. We are now investigating our strategy in a rat model of contusion injury, which is even more severe than the bilateral dorsal hemisection used in the initial study, and above all a much more common type of SCI in humans. Our data show that also after a contusion injury Chitosan-FPHS, now implanted 24 hours post-injury, is highly effective in that it improves functional locomotor recovery and tissue restoration. A major contribution of the biomaterial to tissue repair appears to be its modulation of the inflammatory response, favoring inflammation resolution through macrophage polarization towards the anti-inflammatory M2 phenotype. Thus, our tissue engineering approach seems very promising, as it promotes a highly dynamic tissue restorative process by favoring cell survival and axon growth, and by modulating the immune response. Our perspective for a follow-up of the present study is to determine the suitable time window for the biomaterial implantation to test the relevance of the strategy in a chronic lesion model.

**P2.075 Delayed brain development in a mouse model of intellectual disability in Coffin-Lowry syndrome**

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Coffin-Lowry syndrome (CLS) is a rare genetic disorder characterized by severe intellectual disability (ID) associated with physical and neurological abnormalities (facial dysmorphism, growth retardation, psychomotor disorder). It is caused by mutations of the *RPS6KA3* gene that encodes the RSK2 protein kinase in the MAPK/ERK signaling pathway. Magnetic resonance imaging (MRI) studies in a few CLS children have shown markedly reduced total brain volume, with a particular impact of the pathology on cerebellum and hippocampus. However, there was variation in the profile of these regions, with individuals showing disproportionately enlarged or reduced volumes, that may be linked to specific interfamilial mutations. Our previous characterization of the behavioral phenotype of the *Rsk2*-KO mouse model of CLS revealed a panel of cognitive deficits, suggesting hippocampal dysfunction. Although ID is often associated with developmental disorders, there is as yet no study of postnatal brain development of this model. Two studies using neuronal cultures have suggested a role of RSK2 in neuronal precursor differentiation, neuronal maturation and neurite outgrowth. Here, we used *Rsk2*-KO mice to better understand the role of the RSK2 protein in postnatal brain development. Using MRI, we focused on volumetric analyzes of total brain and of the hippocampus, a structure that plays a key role in cognition. This unveiled a profound delay in brain and hippocampus development in juvenile *Rsk2*-KO mice from their 14th day of postnatal life. However, total brain volume was recovered in adulthood. Using immunohistochemical approaches, we also explored postnatal neurogenesis. Our first investigation in the hippocampus highlighted a role of the RSK2 protein in cell proliferation during brain development. Together, these results suggest that RSK2 plays a crucial role in the first weeks of postnatal development. This delayed maturation of brain structures might reflect some abnormalities of the functional development of neuronal circuits during this period, which could be at least in part responsible for the cognitive deficits associated with ID in CLS. Supported by Fondation Jerome Lejeune to SL and RP and a PhD fellowship from Fondation pour la Recherche Médicale (FRM) to LG.

**P2.076 PM20D1 quantitative trait locus association with Alzheimer's disease: chromatin-mediated genetic-epigenetic interaction and disease progression**

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The chances to develop Alzheimer's disease (AD) result from a combination of genetic and non-genetic risk factors, the latter likely mediated by epigenetic mechanisms. In the past, genome-wide association studies (GWAS) have identified an important number of risk loci associated with AD pathology, but a causal relationship thereof remains difficult to establish. In contrast, locus-specific or epigenome-wide association studies (EWAS) have revealed site-specific epigenetic alterations and thereby provide mechanistic insights for a particular risk gene, but often lack the statistical power of GWAS. Combining both approaches, we have found that *PM20D1* is a methylation/expression quantitative trait locus (mQTL/eQTL) coupled to an AD-risk associated haplotype, which displays enhancer-like characteristics and contacts the *PM20D1* promoter via a haplotype-dependent, CTCF-mediated chromatin loop. Furthermore, *PM20D1* is increased following AD-related neurotoxic insults, at symptomatic stages in the APP/PS1 mouse model of AD and in human AD patients, who are carriers of the non-risk haplotype. Importantly, genetically increasing and decreasing the expression of *PM20D1* reduces and aggravates AD-related pathologies, respectively. These findings suggest that in a particular genetic background, *PM20D1* contributes to neuroprotection against AD.

**P2.077 Teashirt 3 haploinsufficiency impacts the functioning of the fear/defense circuitry in mice**

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The *Teashirt 3* gene (*Tshz3* in mice, *TSHZ3* in human) codes for a zing-finger transcription factor which is thought to be important for the proper development of different structures of the nervous system. Moreover, in human, *TSHZ3* deletion may lead to autistic traits. Autism spectrum disorder (ASD) is a neurodevelopmental disorder which symptoms (impaired social interactions, repetitive behaviors and restricted interests) appear in infancy. While studying the exploratory behavior of *Tshz3<sup>+/lacZ</sup>* adult mice we found that on top of the core autistic traits [Nat Genet. 2016 Nov;48(11):1359-1369], they also display exacerbated fear of lit and elevated spaces. Exacerbated fear of elevated spaces is already present at P8. We are now investigating if this may be due to a developmental defect of the fear/defense circuitry, concentrating first on the amygdala, a hub structure in the fear/defense circuitry. Interestingly, these defects may also be relevant to autism as specific phobia is the main comorbidity of ASD.

**P2.078 Robustness of behavioral and electrophysiological phenotypes of SK3KO mice in Parkinsonian conditions**

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Parkinson's disease (PD) is a common neurodegenerative disorder whose motor symptoms are largely attributable to the loss of dopaminergic (DA) neurons from the substantia nigra pars compacta (SNpc) innervating the dorsal striatum. DA neurons display spontaneous pacemaking activity which relies upon many different intrinsic conductances. Notably, calcium-dependent potassium SK channels - especially the SK3 subtype - contribute to the regularity of firing of these neurons by gating the transition to a bursting firing pattern. A previous study showed that SK2/3 channel blockade with apamin alleviates non-motor symptoms in a 6-OHDA rodent model for PD (Aidi-Knani, 2015). In the present study, we questioned to what extent 6-OHDA bilateral partial lesions of the nigrostriatal pathway correlates with altered motor control and modified intrinsic excitability of DA SNpc in WT and SK3KO mice. At a behavioral level, we quantified spontaneous exploration, motor-learning on a rotarod and dopamine 'supersensitivity', measured by stereotyped responses to repeated cocaine injections. Our results suggest that partial DA lesions produce behavioural impairment in WT animals compared to sham, which is not observed in the SK3 KO mice. In particular, exploratory behavior as well as motor-learning are more impaired in lesioned WT animals than in lesioned SK3 KO animals. Post-lesional changes in the electrical phenotype of DA SNpc neurons have also been assessed using patch-clamp in brain slices of sham or lesioned WT and SK3KO groups of animals after completion of behavioral testing. We measured spontaneous and evoked activity in response to current steps and a first observation is that pacemaking and excitability are conserved in WT and SK3KO neurons spared by the lesion. Further analysis of these properties as well as of underlying conductances (ISK, Ih) could shed light on compensatory mechanisms that maintain the intrinsic excitability of these neurons. These preliminary results suggest that in SK3 KO animals, SNpc DA neurons exhibit electrophysiological remodelling following partial DA lesions that allow them to counteract the motor disruption produced by DA neuronal degeneration.

**P2.079 Sex-dependent behavioral deficits and neuropathology in different ASD mouse models**

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Autism spectrum disorders (ASD) is a psychiatric disease, difficult to diagnose and with no curative treatment. A wide range of symptoms have been identified in ASD patients.

Among them, motor disorders are often observed but are surprisingly not included within the diagnosis criteria. Determination of cellular disturbances in the brain regions responsible for motor function (cerebellum, nigro-striatal pathway and motor cortex) could help to develop new therapeutic approaches.

In our study, we aimed at investigating whether ASD mouse models manifest motor impairments and thrived to determine the neuronal network involved in these deficits. Secondly, we were interested in the identification of differences between males and females as the sex ratio in ASD is 3 boys for 1 girl.

We used both environmental and transgenic (Shank3) mouse models to characterize different aspects of their behavior and determined the neurohistological readouts underlying deficits. Environmental mouse models were prenatally exposed to either valproic acid, an anticonvulsant drug, or poly I:C, a double stranded RNA that provokes a maternal immune activation.

Our results demonstrate a decrease of the sociability, fine motor disorders and neuronal loss in ASD mice models. These deficits were present in a sex and model-specific manner. Additionally, a correlation analysis revealed relationships among motor difficulties, low social interactions and decreased number of neurons in the cerebellum. This is of importance because it points out that motor disorders in ASD could be used as a marker of severity and that the cerebellum could be targeted in therapeutic strategies.

**P2.080 Microglial diversity in Alzheimer's disease early stages: a key to understand the disease initiation**

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Alzheimer's Disease (AD) is the most common form of dementia. It is characterized by behavioral deficits (e.g. memory loss) and histological features (e.g.  $\beta$ -amyloid deposits). Neuroinflammation is another important hallmark of the disease. When brain homeostasis is compromised, microglia, brain main immune cells, become reactive thus contributing to neuroinflammation. Almost all AD risk genes are highly expressed in microglia demonstrating their crucial role in this disorder. Whether microglia play beneficial and/or detrimental roles to the disease progression remains heavily debated and, in addition, their role at early stages of the pathology is still poorly understood.

This study was designed to investigate the microglial reactivity at early stage of AD. The main objectives were to: (1) characterize whether early (prior to plaques seeding) microglial reaction occurs; (2) identify genes and pathways dysregulated in this early phase; and (3) determine whether these genes may represent potential early biomarkers. Using an AD mice model in which microglia express GFP (APP<sup>swe</sup>/PS1<sup>de9</sup>.CX3CR1<sup>+/eGFP</sup> mice), we isolated the parenchymal microglia at an early phase of the disease. RNA sequencing revealed significant remodeling of the microglial transcriptome and led to the identification of early markers of the pathology. We then focused on two genes representing potentially early biomarkers and investigated their expression in brain tissue from early stage AD mice. Using in-situ hybridization and immunohistochemical approaches, we demonstrate their upregulation in discrete microglial subpopulations. In parallel, we also demonstrate that, at this disease's stage, synaptic modifications, microglial phenotypic reactivity and subtle cognitive alterations occur.

As a whole our data support an early contribution of microglia to AD progression and point to specific genes that may represent potential early biomarkers and/or therapeutic targets.

**P2.081 Translocation of TDP-43 and FUS in SOD1 Tg and WT spinal cord motor neurons injured with glutamate or A $\beta$ 1-42 peptide: an *in vitro* model of ALS**

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Amyotrophic lateral sclerosis (ALS) is a rare motor neuron disease, (~5000 case per year in France), affecting people between 50 and 70 years old, and is characterized by degeneration and loss of upper (motor cortex) and lower (spinal cord and brainstem) motor neurons. The loss of spinal motor neurons in ALS is caused by complex and multifactorial pathological events. Some familial cases (fALS) are linked to gain-of-function mutations of superoxide dismutase type-1 (SOD1), an antioxidant enzyme whose activity is preserved in most mutant forms. Owing to the similarities in sporadic and fALS forms, mutant SOD1 animal and cellular models are useful tool to study the disease. In addition, mutations on genes involved in RNA metabolism (e.g. tarbp/TDP-43, fus) are found in inherited and sporadic forms of ALS. TDP43 and FUS proteins are abnormally translocated from the nucleus to the cytoplasm. Aggregates of TDP43 and FUS are found in the motor neurons of the majority of ALS patients.

Glutamate excitotoxicity is known to participate in neuronal death in ALS and A $\beta$  1-42 peptide was shown to accumulate in the spinal cord of ALS patients which exacerbated neuronal loss.

Here, we investigated the kinetic of TDP43 and FUS cytoplasmic translocation and neuronal degeneration, following glutamatergic stress or A $\beta$  1-42 intoxication in WT and SOD1(G93A) Tg spinal motor neurons.

Glutamate and A $\beta$  1-42 triggered neuronal cell death on a time- and dose-dependent manner. The accumulation of TDP-43 and FUS was detected few hours after the injuries and preceded neuronal loss. Neurodegeneration and abnormal translocation of TDP43 and FUS were more pronounced in the SOD1 neurons.

Altogether, our results linked an exacerbated cytoplasmic mislocalization of TDP43 and FUS to the gain of function of the G93A mutation in SOD1. Abnormal translocation of TDP43 and FUS was an early event in cellular models that may directly contribute to neuronal cell death.

**P2.082 Respective contribution of parenchymal and plaques associated microglia during Alzheimer's Disease progression**

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Microglia cells are the main immunocompetent cells in the brain and play key homeostatic and supportive roles in the CNS. Through the course of neurodegenerative diseases, they adopt reactive states characterized by loss of their homeostatic molecular signatures and acquisition of immune phenotypes. Recent genetic studies have underlined the key roles of microglia in Alzheimer Disease (AD), however their contribution to the disease progression is still poorly understood. In particular, whether microglia play beneficial and/or detrimental roles to the disease progression remains heavily debated. One hypothesis is that this duality of effects is carried by different subtypes of reactive microglia having either beneficial or detrimental effects on neuronal functions. Interestingly, in AD, microglia clustered around plaques have marked different phenotypes than those away from plaques underlining microglia diversity in this disease.

In this study, we used a laser microdissection approach to separately isolate parenchymal and plaque associated microglia in the APP/PS1 AD mouse model. Using RNA-seq, we then investigated the remodeling of the transcriptome in these two microglial subtypes at different stage of the disease. As expected from their phenotype, our results demonstrate profound transcriptome changes in microglia clustered around plaques. However, although microglia from the parenchyma exhibited typical ramified homeostatic morphology, significant transcriptomic remodeling were also evidenced in this microglia subtype.

Interestingly, we demonstrated transcriptomic changes in four months old APP/PS1 mice that is when plaques barely form and identified potential early biomarkers. Gene ontology and pathways analyses were performed to highlight the differential contributions of the two microglial subtypes during the progression of the disease.

As a whole our data support a strong involvement of microglia during AD progression and highlight the differential contribution of parenchymal and plaques associated microglia. In addition, they point to a contribution of microglia in the early stage of the disease.

**P2.083 Cingulate overexpression of MKP-1 as a key factor for depression**

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**Background:** Depression is frequently associated with chronic pain or chronic stress. Among cortical areas, the anterior cingulate cortex (ACC) appears to be important for mood disorders and constitutes a neuroanatomical substrate for investigating the underlying molecular mechanisms. The current work aimed at identifying ACC molecular factors subserving depression.

**Methods:** Anxiodepressive-like behaviors in C57BL/6J male mice were induced by neuropathic pain, unpredictable chronic mild stress, and optogenetic ACC stimulation and were evaluated using novelty suppressed feeding, splash, and forced swim tests. ACC molecular changes in chronic pain-induced depression were uncovered through whole-genome expression analysis. Furthermore, the causal link between molecular changes and depression was studied by using knock-out mice, pharmacological antagonism, and local viral-mediated gene knockdown.

**Results:** Under chronic pain-induced depression, gene expression changes in the ACC highlighted the overexpression of a regulator of the mitogen-activated protein kinase pathway, mitogen-activated protein kinase phosphatase-1 (MKP-1). MKP-1 overexpression is also observed with unpredictable chronic mild stress and repeated ACC optogenetic stimulation and is reversed by fluoxetine. A knockout, an antagonist, or a local silencing of MKP-1 attenuates depressive-like behaviors, pointing to an important role of this phosphatase in depression.

**Conclusions:** These data point to ACC MKP-1 as a key factor in the pathophysiology of depression and a potential target for treatment development.

**P2.084 Effects of 6-hydroxydopamine lesions of the substantia nigra, the dorsal striatum, the medial accumbens and the lateral accumbens on food choice (regular chow, fat, sucrose)**

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Dopamine influences feeding behavior. Reciprocally, feeding can affect dopamine systems. Among these reciprocal impacts, it has for example been observed that increased intake of dietary fat leads to diminished dopamine function, and to compensate this lowered dopamine function, food intake may increase. To further explore the impact of dopamine systems on food preference, we used 6-hydroxydopamine (6-OHDA) to deplete these systems in male Sprague Dawley rats; and we tested the food preference by providing a free choice access to a fat source, sugar water, tap water and regular chow. In this food choice procedure, rats with lesions of the substantia nigra (which also offer a model of Parkinson's disease) displayed a decrease in total kcal intake that was related to a decrease in regular chow intake, whereas fat intake increased and sucrose intake was not changed. To test which of the projection areas may contribute to these effects, we next compared specific 6-OHDA lesions of terminals in the dorsal striatum, the medial nucleus accumbens and the lateral nucleus accumbens. Results highlighted that only the 6-OHDA lesion of the lateral nucleus accumbens led to increased fat intake. These findings suggest a role for dopamine signalling in the lateral nucleus accumbens in regulating food preference, in particularly fat intake.

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**Keywords:** nucleus accumbens; 6-OHDA; fat; sugar; dopamine; food preference; Parkinson

**P2.085 Investigating the physiological function of the amyloid precursor protein and its relevance to Alzheimer's disease**

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Alzheimer's disease (AD) is a neurodegenerative disorder characterised by memory loss and cognitive decline. AD is present in an ageing population and is associated with reduced neuronal survival. Post-mortem AD brains show an accumulation of amyloid  $\beta$  (A $\beta$ ) plaques, aggregates of A $\beta$  oligomers. These A $\beta$  oligomers are products of the cleavage of the amyloid precursor protein (APP) by  $\beta$  secretase. Current dogma stipulates that the cause of AD is the formation of these "toxic" A $\beta$  plaques. However, thus far no drugs targeting the formation of A $\beta$  plaques, that have reached the clinical trials phase, have been shown to improve cognitive decline and memory loss. In this project, we are using *D. melanogaster*, as the model organism, to examine the physiological function of APP and the potential that its loss of function might be the real cause of AD.

APP is a functionally and structurally conserved transmembrane protein and its fly homologue is the APP Like (APPL). Studies on *D. melanogaster* have shown that APPL has a role in a variety of aspects of neuron biology, such as axonal transport, outgrowth and injury response, but most of the loss of function phenotypes are very mild. Therefore, we hypothesize that APPL is a homeostasis factor and we suggest that germline or somatic mutations of APPL can disrupt the cellular homeostasis causing organelle stress, apoptosis like cell death and the appearance of age-associated disorders, such as Familial AD or AD respectively.

We propose to study this by 1) Studying the effect of the deletion of APPL on lifespan and neuronal health and 2) discovering the molecular mechanism of APPL function. Our observations thus far point to deficits in the neuronal endo-lysosomal degradation pathway, aberrant neuro-glial interactions, increased critical-period neuronal death, and reduced lifespan, in APPL mutant flies. We are now investigating the precise mechanistic links between these deficits.

P2.086

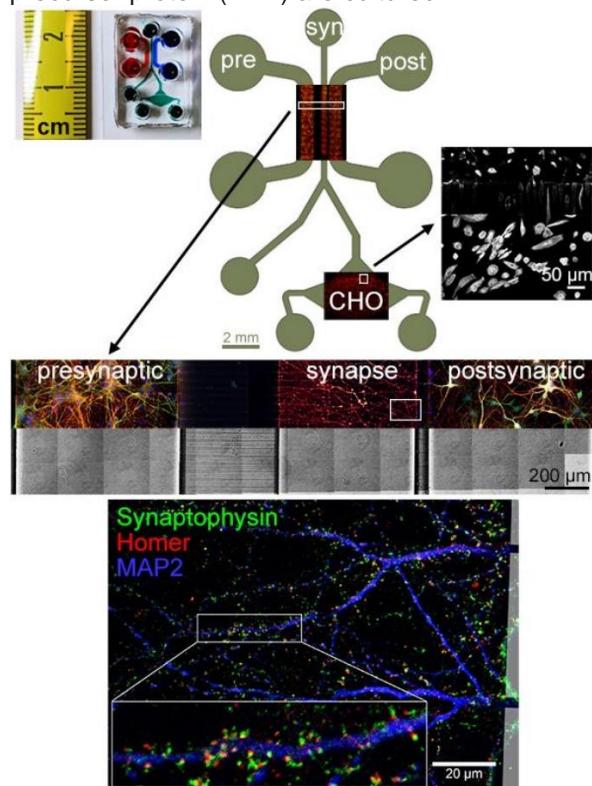
## Microfluidic primary neuron co-culture to expose fluidically-isolated synapses to CHO cell-secreted oligomeric A $\beta$ 42 to decipher the role of Pyk2 in Alzheimer's disease

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**Introduction:** Our genome-wide association studies identified genetic risk factors for Alzheimer's disease (AD); however, the mechanisms by which they contribute to the disease are poorly understood. One such gene (*PTK2B*) expresses Pyk2, a tyrosine kinase closely related to FAK, which regulates synapse function and plasticity in the hippocampus via mediating dendritic spine remodeling.

**Methods:** To specifically analyze Pyk2 at postsynapses and in AD context, we developed a microfluidic device that isolates synapses and pre- and post-synaptic neurons. The device employs microchannels of varying length to allow axons and dendrites (or only axons) emanating from distant chambers to reach the "synapse" chamber. The synapse chamber is directly accessible to introduce toxic oligomeric Amyloid- $\beta$  (A $\beta$ ) or potential therapeutic compounds and is also connected to another chamber, where Chinese Hamster Ovary (CHO) cells overexpressing wild-type or mutant (V642I; London) amyloid precursor protein (APP) are cultured.



[Fig. 1 Microfluidic co-culture of rat postnatal hippocampal neurons and CHO cells at DIV14 (top). Mature synapses form in the synapse chamber (bottom)]

**Results:** CHO cell-secreted A $\beta$  forms diffuse into the synapse chamber at nanomolar concentrations and form low molecular weight oligomers. Cells with mutant APP secrete a higher ratio of A $\beta$ <sub>1-42</sub> over other A $\beta$  forms, which correlated with decreased synaptic connectivity, as quantified by assigning postsynaptic puncta to presynaptic. Treatment with anti-A $\beta$  antibodies blocked the increase in A $\beta$ 42 ratio and blocked the decrease in synapse connectivity. Preliminary data indicated phospho-Pyk2 (Tyr<sup>402</sup>) puncta localize to postsynaptic densities and is associated with A $\beta$ -resistant synapses.

**Discussion:** CHO cell secretion provides long-term exposure to pathologically-relevant levels of A $\beta$ , thus mimicking disease conditions. Experiments where we selectively under- or overexpress Pyk2 in postsynaptic neurons to dissect its role in synapse plasticity and failure are under way.

**P2.087 Unravelling alpha-synuclein aggregates nature to model and understand the diversity and variability among synucleinopathies**

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Synucleinopathies, such as Parkinson's disease (PD) and multiple system atrophy (MSA) are neurodegenerative diseases characterized by the presence of cerebral alpha-synuclein (a-syn) positive intracytoplasmic inclusions. Due to commonalities with prion diseases, these pathologies are now proposed as prion-like. Indeed, a-syn shares key features with prions such as misfolding, seeding or cell-to-cell transmission and spreading. Despite intensive research in the field, the links between a-syn aggregation and disease phenotype, seeding potential, propagation or toxicity remain elusive.

To this end, we have developed a novel procedure for extraction and isolation of a-syn aggregates from human post-mortem brain tissue by adapting the published SarkoSpin method (harsh solubilization of brain homogenate, and sedimentation) to a-syn.

Using velocity and density sedimentation, we found that PD and MSA aggregates show distinct size and density. These results highlight disease-dependent differences in a-syn aggregates structure, reminiscent of prions strains. We can also analyse their composition by mass spectrometry.

In order to assess the seeding capacity of each aggregated a-syn population, we have adapted the *in vitro* prion replication method (PMCA). This technique amplifies the aggregation from minutes amount of seeds (here brain-extracted aggregates) in a normal a-syn substrate (recombinant a-syn) through a growth/fragmentation mechanism. We also model its aggregation by performing fibrilization of recombinant monomeric a-syn.

Lastly, to assess the spreading and toxicity of extracted aggregates and recombinant assemblies, we treat primary neuronal cultures with SarkoSpin pellets from synucleinopathies samples, or fibrils, and analyse their biological activity by measuring aggregation and phosphorylation of the endogenous murine a-syn. We also plan in the future to inoculate these assemblies intracerebrally in mice and primates.

More than a physical characterization of the pathological a-syn aggregates, this study will help us to better understand synucleinopathies pathogenesis and to model the pathogenic mechanisms and processes, allowing us to move towards the development of therapeutic approaches.

P2.088

**Validation of a cerebral chemoattractant local trap based on a "smart" hydrogel in a mouse model of glioblastoma resection**

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Glioblastoma (GBM) is the most common and aggressive primary tumor of the central nervous system and represents the third cause of death in cancer adult patients, who have a median survival of around 15 months after the standard treatment. This poor prognosis is mainly due to invasiveness of glial tumor cells through blood vessels and myelinated axons, specific zones spared by the surgical resection. We develop a methodology for resection of intrastriatal xenografted human and murine GBM cells in Nude and C57BL/6 mice, to study invasion pathways, tumor recurrence and capture of glioma cells by means of a biocompatible hydrogel filling the cavity and containing the chemoattractant peptide urotensin II (UII).

First, the invasive properties of human GBM U87 and 42MG or murine GL261 cell lines were established into different hydrogels in Boyden chambers towards a UII gradient concentration. In Nude and C57BL/6 mice, we validated an intrastriatal orthotopic xenograft and tumor resection model and compared survival between Tumor, Resection, Resection+hydrogel and Resection+hydrogel+UII mouse groups. Resection+hydrogel+UII mice ( $n=8$ ,  $p=0.0002$ ) survived longer than animals with only hydrogel (80% still alive after 2 months). Brain analysis revealed expression of the UII receptor mainly in hypoxic (CA9)-positive GBM cells, migrating along tortuous CD31-positive tumor vessels, in metalloprotease (MMP9)-expressing areas. In resection cavity containing the hydrogel+UII, glioma cells (GFP) were detected into the hydrogel whereas GFAP-positive reactive astrocytes edged the margin of the cavity, in contact with NeuN-positive neurons.

Interestingly, parenchymal brain vessels likely converged towards the cavity suggesting neoangiogenic tube formation. This plasticity and survival benefit were evaluated through behavioral studies before and five days after resection. GBM mice showed cognitive deficits compared with GBM+resection or GBM+resection+hydrogel+UII mice, suggesting cognitive improvement.

Together, this original work validates a trapped strategy of glioma cells in a resection cavity containing a hydrogel filled with a chemoattractant, preventing cognitive deficits and mortality in mice.

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P2.089

**Absence of interleukin 33 impaired axonal outgrowth of grafted cortical neurons**

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Loss of cortical neurons is a common characteristic of numerous neuropathological conditions. We have previously reported that embryonic cortical neurons grafted into adult mouse motor cortex immediately after a cortical lesion allowed restoration of the damaged motor pathways. Recently, we have shown that a delay between cortical lesion and cell transplantation can enhance graft vascularization, survival and projections associated with better functional recovery. We have also shown a modulation of post-traumatic inflammation after introducing a one-week delay between lesion and transplantation. As a novel cytokine of the interleukin-1 family, Interleukine-33 (IL-33) is involved in inflammatory responses following brain injury. Here we investigated for the first time the impact of IL-33 expression on the development of the grafts at the anatomical and functional level. For this, we have transplanted embryonic motor cortical neurons expressing GFP into the motor cortex of adult mice (C57BL/6 and IL-33 deficient mice) immediately or 7 days after cortical lesion. We have then analysed the impact of IL-33 on the vascularization, axonal projections and the functionality of the graft. We have shown an upregulation in the expression of IL-33 in the cortex of C57BL/6 mice seven days after the cortical injury. By using IL-33 KO mice, we have shown for the first time that the absence of IL-33 impaired axonal outgrowth of transplanted neurons. We have previously shown that vascularization of the graft mainly originates from the graft in one week delay transplantation. Here, we have showed, in one week delay transplantation, that the depletion of IL-33 induced a reduction of angiogenesis originating from the graft. At the functional level, our results highlighted a delay of functional motor restauration in the absence of IL-33 expression. Cell transplantation in combination with IL-33 treatment may lead to novel therapeutics for cortical injury.

**P2.090 Chronic oxytocin administration relieves social deficits in the mouse model of Fragile X syndrome**

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Autism spectrum disorders (ASD) are complex neurodevelopmental diseases whose diagnosis lies on the detection of two types of symptoms: deficient social interaction and communication together with stereotyped behaviors (DSM-5). Oxytocin plays a crucial role in controlling many aspects of social behavior and has been identified as a promising target to relieve symptoms of autism, notably social deficits. The therapeutic potential of this molecule in the context of Fragile X syndrome (FXS), however, has not been much explored, although this genetic disease is the most common single gene cause of ASD. Interestingly, we found in *Fmr1* knockout (*Fmr1*<sup>-/-</sup>) mice, the murine model of FXS, a marked decrease in oxytocin transcripts in the nucleus accumbens and prefrontal cortex, two key brain regions for social behavior and reward. In this context, we tested whether acute or chronic intranasal administration of oxytocin would improve social behavior in *Fmr1*<sup>-/-</sup> mice and possibly relieve other symptoms associated to FXS, such as repeated behavior, anxiety or cognitive deficit. Furthermore, we assessed whether beneficial effects of oxytocin administration would be maintained over time, including after cessation of treatment. Together, our results confirm the interest of the oxytocin/vasopressin system as a therapeutic target to relieve deficient social abilities in patients with ASD.

**P2.091 Therapeutic effects of ADAMTS-4 and exercise in a mouse model of traumatic brain injury**

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A growing body of evidence indicates that chronic neuroinflammation contributes to progressive neurodegeneration and subsequent long-lasting sequelae which include cognitive decline and locomotor dysfunctions after traumatic brain injury (TBI). A disintegrin and metalloproteinase with thrombospondin motifs type 4 (ADAMTS-4) has been shown to exert therapeutic effects on neuroplasticity and neuroinflammation in preclinical models of spinal cord injury and ischemic stroke. The aim of this study was to investigate the therapeutic potential of ADAMTS-4 to modulate the extracellular matrix towards a permissive environment for neurorepair in order to efficiently accompany physical rehabilitation with the objective to aid functional recovery after TBI. For that purpose, adult mice were subjected to a controlled cortical impact (CCI) onto the right sensorimotor cortex. Injured mice were treated with an intracerebroventricular injection of saline or a recombinant ADAMTS-4 in the contralateral hemisphere fifteen minutes after the trauma. At one month post-injury, half of the mice were trained daily on a treadmill for 4 weeks. Spontaneous locomotor activity (open-field) and gait pattern (treadmill) were studied at several time points up to 2 months post-injury. Brains and spinal cords were collected afterwards for immunohistochemistry. The combination of ADAMTS-4 and exercise reduces the lesion volume at 2 months post-injury compared to exercised saline-treated CCI mice. Furthermore, the spontaneous locomotor activity of exercised ADAMTS-4-treated CCI mice was increased in the open-field (total distance, average speed). We have previously shown that CCI induces a remote activation of microglia and astrocytes in the spinal cord, pathological changes contributing to the modulation of gait function after TBI. Interestingly, ADAMTS-4 decreases microgliosis in the spinal cord at 3 days post-injury. We are now further investigating the effects of ADAMTS-4 and exercise on neuroinflammation-induced neurodegeneration in the brain and on spinal/cerebral neuroplasticity, and their impact on gait function recovery. By having synergistic therapeutic effects, the combination of ADAMTS-4 and exercise may represent a promising strategy to aid recovery following acute CNS injuries.

**P2.092 Nav1.2 haploinsufficiency in *Scn2a* knock-out mice results in self-limited autistic-like phenotype, with dysfunctions that are attenuated in adult compared to young mice**

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Mutations of the *SCN2A* gene, encoding the voltage gated sodium channel Nav1.2, have been associated to a wide spectrum of epileptic disorders ranging from benign familial neonatal-infantile seizures to early onset epileptic encephalopathies such as Ohtahara syndrome. These phenotypes may be caused by either gain of function or loss of function mutations. More recently, loss of function *SCN2A* mutations have also been identified in patients with autism spectrum disorder (ASD) without overt epileptic phenotypes.

The aim of our study was to characterize the behavioral phenotype of heterozygous *Scn2a* knock-out (*Scn2a<sup>+/−</sup>*) mice during the juvenile/adolescent phase of development and in adulthood. A previous report has shown that these mice display a very mild epileptic phenotype (infrequent absences). We used a battery of tests to identify a possible autistic-like phenotype and the different comorbidities that are frequently found in ASD. The results show that whereas young *Scn2a<sup>+/−</sup>* mice display a clear autistic-like phenotype associated to impaired memory and reduced reactivity to anxiety- and stress- stimuli, adult mice showed much milder behavioral abnormalities, consistent with a partial rescue of the autistic phenotype after adolescence.

Thus, *Scn2a<sup>+/−</sup>* mice are a model of self-limited autism induced by mutations of the *SCN2A* gene.

**P2.093 Uranium, an environmental factor that accelerates and/or worsens the Alzheimer's disease?**

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**Background:** Uranium (U) is a radioactive heavy metal that can be found naturally in soils and rocks, as well as in waters. A better knowledge of its effects on the living beings is necessary since population can be chronically exposed. Experimental studies have shown that chronic exposure of healthy rodents by low doses of U lead to moderate metabolic changes that did not cause real pathologies. However, it is conceivable that some individuals predisposed to illness could respond differently than the healthy ones to chronic exposure. Alzheimer's disease (AD) is the most common neurodegenerative disease among senile dementia. Numerous factors are involved in the development of AD, such as cholesterol metabolism and in particular the apolipoprotein E (ApoE) that plays a role in the formation of β-Amyloid burden. AD is also affected by environmental factors, such as metals and could include U.

**Objective:** So the aim of this study was to determine if a chronic low dose exposure to U could influence the development of the AD. For that, the ApoE-deficient mice were exposed during 3 or 9 months by a dose of 20 mg / L of natural U via drinking. The study of the oxidative stress and cholesterol and acetylcholine metabolisms was performed. A behavioral analysis was also made.

**Findings:** After 3 months, the exposure to U of ApoE-/- mice impaired working memory, but had no effect on anxiety like behavior, in comparison to control ApoE-/- mice. The exposure of ApoE-/- mice to U induced also a trend toward higher total cholesterol content in the cerebral cortex (+15%) compared to control ApoE-/- mice. After 9 months of U exposure, any significant effect has been found at behavioral and molecular levels on ApoE-/- mice compared to control ApoE-/- mice.

**Conclusion and perspectives:** The present study established for the first time that U induced a precocious cognitive impairment of ApoE-/- mice after an exposure of 3 months, suggesting that uranium could accelerate, but not worsen, the development of the AD. These results confirm that environmental factors can be associated with an increase of the risk and the development of neurodegenerative diseases. The effects of U on female ApoE-/- mice should be also tested since ApoE-induced deficits are critically influenced by gender.

P2.094

**PET imaging of functional 5-HT<sub>1A</sub> receptors in hemiparkinsonian rats**

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The gold-standard treatment for Parkinson's disease (PD) is L-DOPA but long-term treatment leads to dyskinesia. Raphe-striatal serotonergic neurons are responsible for dyskinesia, taking up and converting L-DOPA into dopamine and releasing it as a 'false neurotransmitter' while lacking the autoregulatory mechanisms. Previous studies showed that the stimulation of 5-HT<sub>1A</sub> receptors (5-HT<sub>1AR</sub>) can reduce involuntary movements following the administration of L-DOPA in dyskinetic subjects but this mechanism is poorly understood. Although the serotonergic system is impacted in PD, changes occurring at the level of 5-HT<sub>1AR</sub> have been little explored. This study aimed to investigate the functionality of 5-HT<sub>1AR</sub> in PD and the antidyokinetic mechanism of 5-HT<sub>1A</sub> agonists, using *in vivo* molecular imaging in hemiparkinsonian rats (unilaterally lesioned with 6-OHDA), some of which were treated with L-DOPA. Rats underwent two different studies: a microPET study with [<sup>18</sup>F]MPPF, a 5-HT<sub>1AR</sub> antagonist (which labels the whole population of receptors) and [<sup>18</sup>F]F13640, a 5-HT<sub>1AR</sub> agonist (which labels receptors in high-affinity state). There were slight bilateral decreases in [<sup>18</sup>F]MPPF binding in parkinsonian rats compared to control rats, that were restricted to cortical areas. In dyskinetic animals, changes were even slighter but also found in raphe and brainstem. In contrast, the uptake of [<sup>18</sup>F]F13640 was differently altered. In the striatum, there was a bilateral decrease that was more pronounced in the lesioned side. In the insula, the hippocampus and the amygdala, [<sup>18</sup>F]F13640 binding was increased in the non-lesioned side. In dyskinetic animals, the binding of [<sup>18</sup>F]F13640 was generally increased in cortical and limbic areas, especially in the non-lesioned side, while a significant decrease was still found in a small part of the striatum. These data indicate that changes in 5-HT<sub>1AR</sub> expression are detected using the agonist radiotracer that are not detectable using the antagonist radiotracer. In addition, the data suggest that induction of dyskinesia is associated with marked changes in 5-HT<sub>1AR</sub> expression in cortical and limbic brain regions. Taken together, these observations support the development of 5-HT<sub>1AR</sub> agonists for treatment of L-DOPA-induced dyskinesia in PD patients.

**P2.095 Does cooperative parent mediated therapy modify parentese prosody and improve the interaction between parent and child with autism? An Italian pilot study**

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Following Bearss' Parent Training taxonomy, The Cooperative Parent Mediated Therapy (CPMT) is an individual parent coaching program for young children with Autism Spectrum Disorder (ASD) based on Naturalistic Developmental Behavioral Interventions with specific attention to the promotion of cooperative interactions.

The aim of CPMT is to improve parental skills and to enable parents to promote in their child the following seven target skills: Socio-emotional Engagement, Emotional Regulation, Imitation, Communication, Joint Attention, Play and Cognitive Flexibility, and Cooperative Interaction. The coaching is created in order to develop specific strategies related to the main topics of the session, provide live modeling and feedbacks and promote and facilitate the child's acquisition of specific skills.

Literature supports the hypothesis that appropriate use of parentese enhances infant's attention, emotional bonding with the parents and child's language learning capacities.

The present study intends to evaluate if CPMT really modifies the parentese prosody in dyads of parent-infant with ASD and improves parents' effectiveness.

The CPMT was performed in a playroom at the Hospital; Each weekly core session had a specific focus and intervention strategies based on active parent coaching by a trained therapist.

Using a software for prosody analysis we looked at the modification of the prosodic patterns in 5 parents of infants with ASD (22 months mean age), during 6 months of CPMT.

Child's behavior was evaluated considering the frequency of vocalizations and gaze to parent.

Our findings indicate that after intervention there is a functional modification of the parentese, and an increase in child's interactive behaviors.

This suggests that during the therapy, parent had positive communicative feedbacks from the child that encouraged him to modify his prosody during the interaction; also the improved communication with the child promoted parent's self efficacy.

These results show that modification of parental prosody can be assumed like a mediator of CPMT effectiveness.

Further investigation will use NIRS and biofeedback technologies in order to test the progresses of dyads of parent-infant with ASD during therapy and prosody elaboration in ASD.

**P2.096 Distorted own-body and self representations in patients with vestibular disorders and in healthy participants during caloric vestibular stimulation**

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There is increasing evidence that vestibular disorders evoke deficits reaching far beyond imbalance, oscillopsia and spatial cognition. Yet, how vestibular disorders affect own-body representations, in particular the perceived body shape and size, has been overlooked. Here, we explored vestibular contributions to own-body representations using two approaches. *Study 1* measured the occurrence and severity of distorted own-body representations in 60 patients with dizziness and 60 healthy controls using 6 items from the Cambridge Depersonalization Scale. 12% of the patients have experienced distorted own-body representations (their hands or feet felt larger or smaller), 37% reported abnormal sense of agency, 35% reported disownership for the body, and 22% reported disembodyment. These proportions were larger in patients than controls. *Study 2* aimed at testing whether artificial stimulation of the vestibular apparatus produced comparable distortions of own-body representations in healthy volunteers. We compared the effects of Right-warm/Left-cold caloric vestibular stimulation (CVS), Left-warm/Right-cold CVS and sham CVS on internal models of the left and right hands using a pointing task. The perceived length of the dorsum of the hand was increased specifically during Left-warm/Right-cold CVS, and this effect was found for both hands. Our studies show a vestibular contribution to own-body representations and should help understand the complex symptomatology of patients with dizziness.

**P2.097 Ketamine-induced behavioural and dopaminergic responses in the core part of the nucleus accumbens in adult rats are increased following postnatal ventral subiculum functional inactivation**

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For about two decades now schizophrenia is considered as a functional disconnection disorder. This functional disconnectivity between distributed cerebral regions might have a neurodevelopmental origin. Among these regions, the parahippocampal structure subiculum (SUB), appears as a particular target region for neurodeveloppemental disturbances in schizophrenia as established by post-mortem data showing molecular, cellular, and morphological anomalies characteristic of developmental impairments. Moreover, recent neuroimaging studies have shown that marked changes are observed with the progression and onset of the schizophrenia psychosis in the SUB in the left brain hemisphere. A striatal dopaminergic (DA) dysregulation in schizophrenia is commonly acknowledged and may be dependent of a subiculo-striatal disconnection involving glutamatergic NMDA receptors.

The present study was designed to investigate, in adult rats, the effects of the non-competitive NMDA receptor antagonist ketamine on DA responses in the ventral striatum, more precisely in the core part of the nucleus accumbens (Nacc), following a postnatal functional inactivation of the left ventral subiculum (SUB). Functional inactivation of the left SUB was carried out by local tetrodotoxin (TTX) microinjection at postnatal day 8 (PND8), i.e. a critical time of the neurodevelopmental period. DA variations were recorded using in vivo voltammetry in freely moving adult rats (11 weeks). The locomotor activity was recorded simultaneously with the extracellular levels of DA in the core part of the Nacc before and after administration of ketamine.

The following results were obtained: 1) For locomotor activity and DA variations, dose-effects were observed for the two microinjected groups (PBS and TTX) at PND8; 2) DA increases in the core part of the Nacc in adult animals after the administration of ketamine were more elevated in TTX microinjected animals than in PBS microinjected animals. These data suggest that animals microinjected with TTX in the left SUB at PND8 present a more important reactivity to ketamine than animals microinjected with PBS (solvent). In conclusion, these findings may provide new insights regarding the involvement of NMDA glutamatergic receptors in the pathophysiology of schizophrenia.

**P2.098 GABAergic inhibition in dual-transmission cholinergic and GABAergic striatal interneurons is abolished in Parkinson disease**

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We report that half striatal cholinergic interneurons are dual transmitter cholinergic and GABAergic interneurons (CGINs) expressing ChAT, GAD65, Lhx7, and Lhx6 mRNAs, labeled with GAD and VGAT, generating monosynaptic dual cholinergic/GABAergic currents and an inhibitory pause response. Dopamine deprivation increases CGINs ongoing activity and abolishes GABAergic inhibition including the cortico-striatal pause because of high  $[Cl^-]_i$  levels. Dopamine deprivation also dramatically increases CGINs dendritic arbors and monosynaptic interconnections probability, suggesting the formation of a dense CGINs network. The NKCC1 chloride importer antagonist bumetanide, which reduces  $[Cl^-]_i$  levels, restores GABAergic inhibition, the cortico-striatal pause-rebound response, and attenuates motor effects of dopamine deprivation. Therefore, most of the striatal cholinergic excitatory drive is balanced by a concomitant powerful GABAergic inhibition that is impaired by dopamine deprivation. The attenuation by bumetanide of cardinal features of Parkinson's disease paves the way to a novel therapeutic strategy based on a restoration of low  $[Cl^-]_i$  levels and GABAergic inhibition.

**P2.099 Repurposing of FDA-approved pro-myelinating drugs for the treatment of glioblastomas**

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Glioblastomas (GBMs) are the most common and aggressive primary brain tumors in adults. GBMs still represent a major cause of cancer-related death, due to their resistance to standard chemotherapy and radiotherapy treatments. Recent advances in molecular characterization of gliomas have contributed to a better understanding of the pathophysiology of gliomas but there is a need to find new therapeutic strategies.

GBMs are thought to originate and be driven by cells with features of neural stem cells. However, accumulating evidence indicates that cells with features of oligodendrocyte precursor cells (OPCs) may be key drivers of tumor development. Indeed, GBMs display morphological and transcriptomic features of OPCs, and in glioma mouse models, OPC-like cells are the main proliferating cells and are impaired in their differentiation process. Therefore, the OPC nature of these tumor progenitors constitutes an attractive therapeutic target.

Since OPC differentiation is also defective in other diseases such as multiple sclerosis, we reasoned that pro-myelinating drugs that have been shown to induce oligodendrocyte differentiation in multiple sclerosis models could induce the differentiation - or at least induce cell cycle arrest - of OPC-like cells in gliomas.

We selected FDA-approved drugs that were previously demonstrated to have a potent effect on oligodendrocyte differentiation. We tested these drugs on patient-derived glioma cell lines (PDGCLs) established in the laboratory. Our initial observations show that some of these drugs can induce cell death and differentiation *in vitro*. These drugs are now being tested, in an orthotopic xenograft model of glioma, for their capacity to reduce tumor growth *in vivo*.

**P2.100**

**Metabolic characterization of different phases of Parkinson's disease**

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Parkinson's disease (PD) is the most common neurodegenerative disorder after Alzheimer's disease, affecting almost 1% of the population beyond the age of 60. Currently, its diagnosis relies on the expression of the well-known motor symptoms (akinesia, rigidity, and tremor) which appear in the late stage of the disease. Detecting the disease earlier represents a key step to develop curative treatments which are so far only symptomatic. Long considered as a purely motor disease, PD is nevertheless also characterized by neuropsychiatric disorders (apathy, depression, anxiety...) that can develop during the early stages of the disease as well as later on.

In this context, our aim is to find specific molecular markers of early phases of PD, when only the neuropsychiatric symptoms are expressed. Proton NMR-based metabolomics (Nuclear Magnetic Resonance) is applied to serum samples and brain tissues of a rodent model allowing investigation of different phases of PD.

The animal model is based on a specific, partial, bilateral 6-OHDA-induced lesion in dopaminergic neurons. For each rat, motor functions and apathetic-like behaviors were assessed using a stepping test and operant sucrose self-administration, respectively. Serum samples were analyzed by liquid NMR at 950 MHz (IBS Grenoble) and intact tissue by HRMAS-NMR (High Resolution Magic Angle Spinning) at 500 MHz (CEA Grenoble). Data were submitted to multivariate statistics in order to investigate whether behavioral and histological data can be predicted from metabolomics.

In our animal cohort we observed a gradation in the symptoms, from only neuropsychiatric, to the expression of neuropsychiatric associated with motor symptoms. This gradation is well in line with PD progression from early to late phases of the disease. For more precise evaluation, a scale integrating behavioral performances and the striatal dopaminergic denervation was determined. Serum and tissue spectra analysis showed a good correlation between metabolic profiles and score gradation, i.e. with the different phases of PD.

In both samples, the energetic pathway seems to increase with the progression of the disease, while some amino acids, like alanine and serine, are also dysregulated prior to the appearance of motors symptoms.

**P2.101 A spatial code in the dorsal lateral geniculate nucleus**

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Hippocampal place cells along with other spatially tuned neurons (e.g. grid cells, head direction cells) are thought to provide the basis of episodic-like memory in mammals. In recent years, visual structures (e.g. primary visual cortex, V1) were suggested to play an important role in navigational abilities in rodents additionally to their well-known function in visual processing. We therefore thought to investigate, in the rat, neuronal correlates of a topological representation of space in a thalamic structure located one synapse upstream of V1, the dorsal Lateral Geniculate Nucleus (dLGN), and discovered that a substantial proportion (ca. 30%) of neurons exhibits spatio-selective activity. These cells maintain their spatial selectivity in the absence of visual inputs and across sessions in a familiar environment whereas contextual modifications yield separated representations. Our results show that dLGN place cells are likely to participate in spatial cognition processes, creating as early as the thalamic stage a comprehensive representation of one given environment.

**P2.102 Medial entorhinal cortex neurons signal relevant positions in a distance estimation task**

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Path integration is a navigational strategy based on self-motion cues that requires the animal to estimate the distance and orientation relative to a starting location. Based on their firing properties, grid cells in the medial entorhinal cortex (MEC) have been hypothesized to represent the neural substrate of path integration. Grid cells display a striking hexagonal grid-like firing pattern within an open field. Their activity is modulated by running speed and heading direction suggesting that they integrate self-motion cues to signal distance and direction information necessary for path integration. Animal and human studies point to a role of the MEC in distance estimation. However, how MEC cells participate to such process remain largely unknown. In this study, we recorded MEC neurons and local field potential while animals were trained to estimate three distances on a linear track (30, 60, and 90 cm) in darkness. We found that both grid cells and non-spatially tuned cells in the MEC show a spatial activity that is located at the three distances learnt by the rat, and at the limits of the linear track. Overall, these results indicate that the MEC hosts a population of neurons that works as an internal odometer, signaling discrete distances during self-motion-based navigation.

**P2.103 Diversity of spatially tuned neurons in dorsal lateral geniculate nucleus**

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Place cells are spatially tuned neurons found in the mammalian brain and are thought to reflect the memory trace of the subject's place for a given environment. Unlike other spatially tuned cells such as grid and head direction cells found in various brain regions, very few hippocampal related structures showed 'place cell'-like firing patterns, thus reinforcing the central role of the hippocampus in spatial memory. However, visual and navigational systems are known to closely interact in both rodent and primate brains, and the boundaries between these two systems are becoming less and less clearly delimited. We recently reported, in the rat, place cell like activity in the dorsal lateral geniculate nucleus (dLGN), a thalamic structure classically known to be an essential component of the visual pathway between retina and the primary visual cortex. Interestingly, we also recorded dLGN cells which activity appeared tightly bound to the presence of objects. We also found numerous putative border cells in this region but no head direction or place-by-direction cells. These preliminary data suggest that spatial cognitive mapping occurs very early in the processing of sensory information.

P2.104

**Spatial goals locally modify the grid-like firing pattern of the grid cells**

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Grid cells are spatially selective neurons whose firing fields form a regular hexagonal pattern across the 2D environment. This activity is primarily generated by the integration of self-motion cues. However, environmental cues are able to control to some extent the grid cell activity. Here we asked whether the presence of a goal in space influences their activity. We recorded mEC neurons while rats were performing a continuous goal directed navigation task. In this task, the animals have to reach and stay for two seconds in an unmarked goal zone within a circular arena, in order to receive sugar pellets that are randomly scattered on the floor. We show that the grid-like firing pattern is locally expanded around the goal area. This major modification is not accompanied by any changes in head-direction cells or border cells activity. This result indicates that grid cell activity signals the presence of a goal by locally varying the scale of the grid, without altering the global structure of the map. This mechanism may allow to distinguish a salient area within a global map of the space.

**P2.105 Processing of allothetic and idiothetic cues by the medial and lateral entorhinal cortex**

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The entorhinal cortex (EC) has been shown to play an essential role in the processing of spatial information in rodents. In addition, electrophysiological and lesion data suggest that the two sub-regions of EC, the medial entorhinal cortex (MEC) and the lateral entorhinal cortex (LEC) have different functions. However, their respective contribution remains unclear. In the present study we examined the implication of the MEC and LEC in the processing of two categories of cues, external (i.e. environmental, allothetic) and internal (i.e. movement-related, idiothetic) cues. In the first experiment, rats with MEC ( $n = 8$ ) or LEC ( $n = 8$ ) NMDA lesions and SHAM rats ( $n = 7$ ) were trained in two place navigation tasks in the Morris water maze in which they had to use allothetic cues to locate a submerged platform. One task involved the use of room, distal, cues and the other the use of intramaze, proximal, cues that were objects directly located in the pool. In a second study, the same rats were submitted to an object exploration task in total darkness in which they had to detect a spatial change (displaced object) and a non spatial change (novel object) using idiothetic cues. In the distal cue condition of the place navigation task, MEC rats exhibited impaired acquisition of the platform location and were not able to remember the goal location during the probe test. In the proximal cue condition, MEC rats exhibited impaired acquisition but were able to remember the platform location during the probe test. No deficit in either condition was found in LEC rats. In the object exploration task, MEC rats were impaired to detect the spatial change in light but the deficit was unexpectedly reversed in darkness. LEC rats were not likewise impaired in darkness. All groups were able to detect the novel object. Overall, these results show a dissociation between MEC and LEC for the processing of information. We conclude that 1) the MEC but not the LEC plays an important role in navigation based on the use of allothetic, in particular distal cues, 2) the MEC and LEC are not necessary for the building and use of a spatial representation based on idiothetic cues.

**P2.106 Hippocampal LTP modulation and glutamatergic receptors following vestibular loss**  
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Vestibular dysfunction strongly impairs hippocampus-dependent spatial memory performance and place cell function. However, the hippocampal encoding of vestibular information at the synaptic level, remains sparsely explored and controversial. We investigated changes in *in vivo* long-term potentiation (LTP) and NMDA glutamate receptor (NMDAr) density and distribution after bilateral vestibular lesions (BVL) in adult rats.

At day 30 (D<sub>30</sub>) post-BVL, the LTP of the population spike recorded in the dentate gyrus (DG) was higher in BVL rats, for the entire 3 h of LTP recording, while no difference was observed in the fEPSP slope. However, there was an increase in EPSP-spike (E-S) potentiation in lesioned rats. NMDArs were upregulated at D<sub>7</sub> and D<sub>30</sub> predominantly within the DG and CA1. At D<sub>30</sub>, we observed a higher NMDAr density in the left hippocampus. NMDArs were overexpressed on both neurons and non-neuronal cells, suggesting a decrease of the entorhinal glutamatergic inputs to the hippocampus following BVL. The EPSP-spike (E-S) potentiation increase was consistent with the dorsal hippocampus NMDAr upregulation. Such an increase could reflect a non-specific enhancement of synaptic efficacy, leading to a disruption of memory encoding, and therefore might underlie the memory deficits previously reported in rats and humans following vestibular loss.

**P2.107 Deciphering the neural code of the motor cortex with a multidirectional reaching task in mice**

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In spite of being a longstanding neuroscience question, a unified vision of the role of the motor cortex is debated. Although advances in rodent research have shed light on this subject, the majority of rodent tasks lag behind those of primates, limiting the potential of circuit dissection with recording, manipulating and genetic tools available in mice. Thus, behavioral paradigms for mice that offer well-controlled, tractable and versatile skilled movements are necessary.

We have recently described a reaching task in which head-fixed mice reach and grasp water droplets presented at different spatial locations. Mice learned the task rapidly and efficiently performed hundreds of trials to three different target locations, demonstrating a higher degree of dexterity and behavioral flexibility than generally assumed. Optogenetic inactivation of the motor cortex impaired reaching supporting the notion of the motor cortex involved in motor control.

Moreover, two-photon imaging of layer 2/3 and layer 5a cortical neurons revealed task-related activity in different regions of the frontal cortex, with prominent activity in the secondary motor cortex. Cortical neurons responded at different phases of the task ranging from target presentation to reaching-onset and reward consumption. The majority of these neurons were differently recruited depending on the position of the target, suggesting encoding of different motor plans. Interestingly, while layer 2/3 activity was typically selective for only one target location, layer 5 neurons showed target selectivity with graded responses to more than two target locations. However, what these neurons are actually coding for (e.g. motor commands or target-related information) remains unanswered.

To unveil this question, we introduced another dimension to the task: mice were trained to initiate reaching alternatively from two starting points providing different motor outputs for the same reaching target. Interestingly, the activity of cortical neurons remained insensitive to changes in the reaching starting point, indicating that superficial layers of the motor cortex do not encode lower-order motor commands. Further recordings of corticospinal and subcortical neurons will be necessary for dissecting the underlying neural circuit.

P2.109

**Respiration-based synchronization in the brain: bottom-up and top-down influences**

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Inter-area communication requires the different brain rhythms to be coordinated across areas. As others, we hypothesized that the respiratory rhythm could act as a central clock for cerebral rhythms coordination. If true, neuronal activity should be influenced by respiration across a large brain network. We tested this hypothesis by recording respiration and neuronal activity in different brain areas (olfactory areas, V1, S1, CA1, DG, prefrontal cortex) in freely-moving rats during various vigilance states. In agreement with recent publications, we observed that all structures could be modulated by breathing. We provided the additional observation that such a modulation varies according to the vigilance state, each state being associated with a specific respiratory regime. Particularly, we observed a large-scale synchronization across areas on the breathing rhythm mainly during quiet state, where animal's breath is around 2Hz. We then sought to decorrelate brain state from respiratory regime. To do so, animals were recorded while breathing a CO<sub>2</sub>-enriched air, which changes the respiratory regimes but not the vigilance state. We demonstrated that the across-areas respiratory synchronization observed in quiet state can be extended, under CO<sub>2</sub> condition, to other vigilance states (REM and non-REM) and to higher respiratory frequencies (3-4 Hz). We thus evidenced that amplitude and spatial extent of breathing-related modulation is mostly dependent on the respiratory regime (volume). However, the question of whether this respiratory modulation was under bottom-up (air volume in the nasal cavity) or under top-down influence (central respiratory center) was remaining. To answer this question,

we collected data in urethane anesthetized tracheotomized rats where nasal airflow can be precisely controlled. We showed that large-scale brain activity can be entrained by the respiratory rhythm when:

1) airflow is by-passed in the nasal cavity,

2) brain activity is in slow-wave regime so that nasal influence is shut down.

We thus evidenced a top-down influence of respiration on the brain rhythms that was woefully underestimated until now. Data are still under process.

**P2.110 Role of somatosensory cortical feedback in a sensorimotor brain-machine interface**  
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Invasive brain-machine interfaces (BMIs) use single neuron activity to control prostheses, with the long term goal of restoring motor abilities of impaired subjects. So far, these interfaces did not include a somatosensory-like feedback. We hypothesize that sensory feedback will favor rapid and accurate control of movements. We have developed a BMI by combining online recordings of neurons in the motor cortex (M1) and simultaneous real-time delivery of patterned optogenetic feedback over the somatosensory cortex (S1). This is to our knowledge the first invasive motor BMI that includes a short-latency, intracortical, somatosensory-like feedback.

Using this innovative system, we have developed two complementary projects. The first one aims to study the impact of the spatial organization of S1 feedback on the BMI performance. Towards this aim, we carried out behavioral experiments where a head-fixed transgenic mouse uses M1 activity to bring a virtual bar to a rewarded location, while receiving either biomimetic or randomized patterns of S1 optogenetic feedback. Our data show that animals perform significantly better under biomimetic feedback versus non-structured feedback. These results emphasize the importance of providing somatosensory-like feedback in the context of a BMI. They also show for the first time that the structure of the feedback neuronal activity can have an impact on its integration in a BMI task.

The second project consists in extending our BMI system towards the control of a model of a real prosthesis, in order to explore learning mechanisms during a fine control task in a realistic environment. To this end, we interfaced the M1 readout with a robotic simulation software, and developed a task that requires the mice to precisely control the angular position of an arm prosthesis. Motor commands are generated using a fixed mapping between firing rate and acceleration, while information on the state of the arm is continuously delivered to S1 as a rotating bar following the motion of the controlled joint. Preliminary experiments indicate that the animals are able to quickly learn a simplified, ballistic version of the task.

**P2.111 Does midcingulate cortex encode choice difficulty?**

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The frontal cortex is considerably developed in primates. It contributes essentially to explore and adapt decisions in complex and changing environments. Assessing the difficulty of decisions, in terms of similarity of choices, effort or required cognitive resources, in a given context, might be essential to adjust cognitive control in such environments. Difficulty encoding has been associated to midcingulate cortex (MCC) activity especially in functional magnetic resonance imaging studies (Shenhav et al., 2014), but these results are largely debated. In fact, an effect of difficulty on MCC activity was rather shown in association with responses than with decision itself, appearing only at the end of decision periods (Kolling et al., 2016).

We addressed this issue of whether MCC neural activity reflect difficulty in monkeys and compare to the lateral prefrontal cortex (LPFC) which is known to be involved in cognitive control and to have strong functional relationships with the MCC. We trained 2 rhesus monkeys to perform a categorization task (instructed decision task) which includes three levels of difficulty adjusted to the performance of each animal. We analysed the variation of local field potentials in MCC (101 and 179 recordings in monkeys A and H respectively) and LPFC (63 and 103 recordings in LPFC) at specific time in relation to 5 parameters of the task: movement planning (decision), reaction time, motivation and performance monitoring, and the level of difficulty.

The analyses show modulations of LFP amplitude in relation to all parameters but difficulty. These results confirm the role of these regions in behavioural adaptation but belie the role of the MCC in difficulty encoding even at the end of the response period. More generally, we emphasize that the definition of difficulty is often too vague and misleading, and should be discussed precisely in regards of variable to which it correlates or to which it is associated.

**P2.112 Integrating information from both nostrils - random or not?**

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In most sensory systems, neuronal connections from the periphery to the brain occur in a spatially organized manner, giving rise to topographic maps. By contrast, in olfaction, these connections appear to be spatially distributed and disordered, which has led to the postulate that they are random. Inter-hemispheric cortical projections that arise from the olfactory cortex will, in principle, add even further disorder when integrating information from both nostrils.

To gain insight into bilateral integration of information in cortical neurons, we developed a method for selective unilateral odor delivery in awake mice and to record the spiking activity of neurons in three cortical areas - anterior olfactory nucleus, anterior piriform cortex, and posterior piriform cortex. A vast majority (>85%) of neurons in all three areas could be activated by odors presented selectively to either the ipsilateral or contralateral nostril, but their odor tuning arising from the two sides were largely mismatched.

Population activity in all three areas could be used to accurately decode whether the left or right nostril was stimulated, independent of odor identity. Our data suggest that olfactory cortical neurons integrate distinct information from the two nostrils, which might increase coding capacity in each hemisphere, but also allow detection of spatial gradients near the nose.

**P2.113 Glial endozepines reverse high fat diet-induced obesity by increasing hypothalamic sensitivity to peripheral leptin**

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Endozepines (EZ), a family of peptides encoded by the gene diazepam binding inhibitor, are expressed by glial cells and exert potent anorexigenic action. Up to now, the mechanisms underlying EZ anorexigenic effect remained unknown. The hypothalamus and the dorsal vagal complex (DVC) of the hindbrain, the two main structures involved in the homeostatic regulation of food intake, are strongly enriched in EZ-immunoreactivity, expressed by astrocytes and ependymoglia cells in both structures, including hypothalamic tanycytes. We show here that the intracerebroventricular administration of EZ enhances satiety by activating anorexigenic neurocircuitry, such as POMC neurons in these structures. Interestingly, we observed that EZ induce a strong STAT3 phosphorylation, a hallmark of leptin signaling, in hypothalamus and DVC. Strikingly, EZ were completely ineffective in reducing food intake and activating STAT3 in leptin-deficient mice (*ob/ob*), as well as in wild type mice treated by a leptin antagonist. In *ob/ob* mice, EZ potentiated the reduction in food intake and body weight induced by treatment with low dose of exogenous leptin. We also observed that EZ potentiated the transport of fluorescent leptin into hypothalamus, suggesting a possible stimulation of LepR-ERK-dependent tanycytic leptin shuttle. In accordance, EZ induced ERK activation in cultured tanycytes and selective *LepR* deletion in tanycytes, via the stereotaxic infusion of the TAT-Cre protein into the third ventricle of *LepR<sup>LoxP/LoxP</sup>* mice, abolished the EZ-induced STAT3 phosphorylation. Given these results, we targeted EZ as potential anti-obesity compound and we observed that high fat diet (HFD) significantly reduced DBI mRNA expression in the hypothalamus and DVC. In diet-induced obese mice, EZ reversed the obese phenotype by reducing food intake. In summary, our data indicate that glial EZ expression is dysregulated during obesity. Exogenous EZ treatment exerts an anorexigenic action through a mechanism that involves leptin responsiveness. Chronic EZ treatment reverses obesity induced by a HFD and increases hypothalamic sensitivity to peripheral leptin. Altogether, these results suggest that the development of EZ analogs could hold therapeutic potential in obesity.

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**P2.114 The brain smells and tastes the self - lessons from the Allen Brain Atlas**

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Animals strongly rely on chemical senses to uncover the outside world and adjust their behaviour. Chemical signals are perceived by facial sensitive chemosensors that can be clustered into three families, namely the gustatory (TASR), olfactory (OR, TAAR), and pheromonal (VNR, FPR) receptors. Over the recent decades, chemoreceptors were identified in non-facial parts of the body, including the brain. In order to map chemoreceptors within the encephalon, we performed a study mainly based on data from the Allen Brain Atlas. We analysed, in 13 brain areas of healthy and demented human brains, the expression of members from the three chemoreceptor families and their canonical partners. We observed that the transcripts of all chemoreceptor families are expressed in the central nervous system, particularly in the limbic system. Their canonical transduction partners (G proteins, ion channels) are also expressed in all studied brain areas, reinforcing the suggestion that cerebral chemoreceptors are functional. In addition, we noticed that i) the brain displays a preference for bitterness and is equipped to sense trace amine and pheromonal cues and ii) chemoreceptor expression varies with age but not dementia or brain trauma. Extensive studies are now required to further understand how the brain makes sense of endogenous chemicals.

**P2.115      Distinct neuronal drives from locomotor circuits modulate breathing during exercise**  
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When animals walk or run, respiration increases to match the augmented energetic demand. Furthermore, breaths and strides can become synchronized. Yet, the neuronal bases for these adaptations are poorly understood. We address here the possibility that neuronal drives originating from both spinal and supraspinal locomotor centers directly modulate breathing during ongoing locomotion.

We monitored, on ex-vivo preparations from neonatal mice, locomotor and inspiratory activities simultaneously using ventral nerve roots recordings. We show that engagement in locomotor-like activity, triggered by pharmacological activation of the lumbar locomotor Central Patten Generator (CPG), results in an increase of the frequency of inspiratory-like activities yet without temporal coupling of the respiratory and locomotor rhythms. In contrast, short-latency inspiratory bursts can be evoked by, and phase-locked to, electrical stimulations of lumbar dorsal sensory roots. Furthermore, genetic deletion of the Retrotrapezoid Nucleus (RTN), an essential group of respiratory neurons, abolishes the locomotor entrainment of inspiration but not the sensory-evoked inspiratory bursts.

In addition, we performed optogenetics activation of the mesencephalic locomotor region (MLR, the prime supraspinal activator of locomotion), combined with chronic electromyographic recordings of respiratory and locomotor muscles in freely moving adult mice. We show that activation of the MLR upregulates breathing frequency prior to the onset and throughout locomotion and that the MLR projects onto the preBötziinger complex, the main inspiratory oscillator.

Altogether, our data indicate that locomotor circuits may send distinct drives to respiratory centers through

- 1) a central ascending drive from the spinal locomotor CPG to the RTN that may upregulate respiratory frequencies during locomotion
- 2) a RTN-independent ascending sensory drive that may couple respiratory and locomotor rhythms, and
- 3) a descending feedforward drive from the MLR that could help prime respiratory centers in anticipation of exercise.

**P2.116 Short-term impact of a western diet on the physiology of the peripheral olfactory system**

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Current feeding behaviors contribute to the epidemic levels of obesity and diabetes observed in Europe and worldwide. Both the quantity and the quality of ingested food are incriminated. Together with other sensory modalities, olfaction is involved in the control of food intake. Olfactory cues can influence eating behaviors, yet the nutritional status and diet can also alter olfactory abilities. Patients with metabolic disorders present impaired olfactory sensitivity which could in turn worsen their eating behaviors.

Here we examined the short-term impact of a Western diet enriched in fat and sugar (High Fat High Sugar, HFHS) on the anatomy and physiology of the olfactory epithelium of postnatal mice. We used a transgenic line of mice expressing GFP under the promoter of the SR1 odorant receptor in order to monitor the properties of a define population of neurons. After 8 weeks of diet, HFHS fed animals were glucose intolerant without any change in basal glycaemia and insulinemia. They presented higher adiposity but no overweight compared to control mice. We measured electro-olfactogram amplitudes in response to three ligands of the SR1 olfactory receptor. Detection thresholds estimated from the dose-response curves were higher after 8 weeks of a HFHS diet. Reconstruction of the cilia of SR1 olfactory sensory neurons revealed shorter cilia in HFHS mice compared to control animals. A buried food test indicated impaired olfactory capacities in the HFHS group. Reversibility of these alterations has been investigated by restoring standard diet conditions.

Our results demonstrate that diet enriched in fat and sucrose can rapidly alter the physiology of the olfactory epithelium. Anatomical changes of individual olfactory sensory neurons may participate to the reduced olfactory sensitivity. These olfactory dysfunctions appear early on after exposure to a Western diet and lead to altered olfactory behavior.

**P2.117 The breath whispers in the membrane potential**

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Complex behaviors implicate the collaboration of several brain areas, which could be distant from each other. This functioning assumes the temporal coordination of the involved areas activities. Brain activity displays rhythms ranging from 0.5 to 200Hz, in these, slow rhythms (< 12Hz) are thought to enable long-range communication between brain areas by providing a common temporal reference to all areas. The respiration-related rhythm (from 1.5 to 12Hz in awake rodent) is an electrical brain rhythm which could act as a coordinator rhythm. This rhythm is found in the extracellular activity almost all over the rat brain, and in several human brain areas. However, this brain-wide presence is contested because extracellular signal can be contaminated by an artifactual diffusion of a distant-generated signal. Therefore, we choose to perform intracellular recordings which allow to follow the precise evolution of membrane potential. We recorded neurons in different areas (V1, S1, CA1, Prefrontal) to verify the widespread distribution of respiratory rhythm. We are the first to show that the intracellular activity, the membrane potential as well as the spiking pattern, of non-olfactory neurons can be entrained by the respiratory rhythm. Furthermore, to better understand the neuronal synchronization function of the respiratory rhythm, we looked for relations between the respiratory modulation of a cell and the activity of the surrounding network. Finally, we showed that an increase in olfactory inputs (odor stimulation) can also modify the respiratory modulation even in non-olfactory structures. In summary, these findings support the assumption that the respiratory rhythm, by directly modulating the neurons activity, could be a common clock for the brain areas.

**P2.118 “Hearing the touch”: impact of sonification in the haptic perception of artificial textures and its modulation with aging**

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In everyday life, the perception of objects' properties (nature, shape, texture) is not only based on tactile information but also relies on visual, kinesthetic and, sometimes, auditory cues. The integration of multisensory information is known to enhance perception, especially among older people who are facing a decline in all their senses. While visuo-haptic integration in the exploration of objects has been widely investigated, little attention has been paid to audio-haptic interactions. Auditory signals occur frequently when we touch objects, and these sounds can convey useful information about the texture of the objects we explore.

The present study examined for the first time the impact of textured sounds on haptic exploration in healthy young and older adults. To this end, we developed an innovative approach combining a texture simulation device (ultrasonic tactile display) with synthetized textured sounds fully synchronised with haptic exploration. To give the sensation that the sound was actually produced by the haptic exploration, it was modulated in real time by the participant's movement velocity, a method called sonification. Participants had to explore with their right finger various simulated textures in a force choice discriminative task in presence of three distractive sounds (neutral, smooth or rough). Recordings of finger displacements on the surface showed that movements of all participants changed in presence of the textured sounds compared to the neutral sound. Surprisingly, psychophysical results revealed that young adults performed the task with the same ability, regardless of the sound added. By contrast, the elderly had a higher discriminative threshold than young participants and were more disturbed by the presence of the textured sounds with respect to the neutral sound condition.

These results show that, although textured sounds were taken into account by the young participants, as evidenced by the changes in movement exploration, they appropriately segregated irrelevant auditory information from tactile information. Older adults failed to segregate the auditory information, supporting the hypothesis of general facilitation of multisensory integration in the elderly, which may be a compensatory or a dedifferentiation phenomenon.

**P2.119 Intracellular dynamics of CA3 pyramidal cells in awake head-fixed mice during the theta rhythm favor sparse coding**

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Different behavioral states are associated with distinct brain states, which in turn influence ongoing neural computations. Studies from several brain areas show that changes in single cell properties correlate with and possibly result in these changes in brain state. While much work has characterized different brain states and their corresponding oscillations in the local field potential (LFP), the underlying cellular mechanisms and their effects on cellular computation are less known.

Area CA3 of the hippocampus, important in rapid encoding of one-trial memory, is of particular interest for this line of research because of its unique function and network structure. CA3 is the site where sensory and mnemonic information from the entorhinal cortex, dentate gyrus, and CA3 itself (via extensive recurrent connections) is compared and integrated before output to CA1. During quiet wakefulness, the hippocampal LFP displays large irregular activity punctuated by short oscillations known as sharp-wave ripples, which play a role in memory consolidation. During exploratory behaviors, when memory formation and recall are thought to occur, hippocampal LFP oscillates at both theta and gamma frequencies. Considering that specific brain states are supporting different memory stages, and the importance of CA3 circuit for rapid encoding and retrieval of episodic memories, we hypothesize that changes in intracellular properties of CA3 PCs may underlie the ability of CA3 to perform distinct memory functions.

To measure these changes, we made whole-cell patch-clamp recordings from CA3 pyramidal cells in awake head-fixed mice. In order to characterize brain states, we combined those recordings with measurements of pupil diameter and CA3 LFP. We find that during theta, most cells display a sustained change in the membrane potential, either a hyperpolarization or a depolarization, which results in a corresponding change in firing rate. In either case, the variance of the membrane potential is decreased, indicating lower synaptic noise. Taken together, these findings suggest that during the theta brain state, the CA3 network favors sparse coding. The observed changes may underlie the ability of this area to switch between different stages of memory processing.

**P2.120 Alteration of S1Bf cortical network during epileptogenesis in GAERS, a genetic model of absence epilepsy**

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Epilepsies are characterized by recurrent seizures caused by hyper-synchronization and hyper-excitability of neuronal networks. Although the dynamic of these networks has been studied during the chronic phase of epilepsy, little is known about these networks during epileptogenesis, in particular in idiopathic epilepsies. The study of this period is critical for a better understanding of cortical networks development in normal and pathological conditions. In the Genetic Absence Epilepsy Rat from Strasbourg (GAERS), spike-and-wave discharges (SWD) are initiated in the barrel field (S1Bf), the whisker-related part of the primary somatosensory. They first occur around the 25th postnatal day (P25) and are preceded by the emergence of abnormal oscillatory cortical discharges after P15. Our working hypothesis is therefore that S1Bf connectivity develops differently during brain maturation/epileptogenesis in GAERS rats. Here, using *in vivo* multichannel electrophysiological recordings of field potentials and multiunit activities, we showed that at P30, the initiation of SWD is associated with a co-activation of L2/3 and L5/6 layers that is different from the L5/6→L2/3→L4 propagation circuit of SWD shown previously in adult GAERS. This is in line with a progressive building of the epileptic network throughout the cortical layers in S1Bf. Additionally, when multi-whisker stimulations were performed to investigate the sequence of sensory processing across S1Bf cortical layers, the evoked responses were lower in GAERS at P30 and P15, as compared to controls, suggesting an anomaly in the functionality of the somatosensory circuit in GAERS. Finally, we mapped the functional projections in S1Bf, using *ex vivo* Laser Scanning PhotoStimulation with glutamate uncaging combined to patch-clamp recordings and observed stronger inhibitory circuits in GAERS at P30. Indeed, during this period of epileptogenesis the inhibitory projections to L2/3 pyramidal cells are stronger. Altogether, our data suggest an abnormal development of functional and structural S1Bf networks responsible for the emergence of paroxysmal activities in GAERS.

**P2.121 Modulation of corticostriatal transmission by striatal cholinergic interneurons in normal and parkinsonian conditions: electrophysiology and optogenetics *ex vivo***  
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Although striatal cholinergic interneurons (CINs) are few in number, they have morpho-functional features that place them as critical players in striatal functions. CINs contact the two populations of striatal output neurons (also called medium spiny neurons, MSNs) that express either D1 or D2 dopaminergic receptors. Correct execution of movement or habits requires a balanced activity between MSNs that is disrupted in Parkinson's disease (PD) in favor of D2 MSNs. Alteration in the strength of excitatory corticostriatal synapses contributes to this imbalance. *In vivo*, CINs exhibit a tonic activity that is inhibited in a synchronous manner (pause) during associative learning. This pause disappears in animal models of PD, suggesting that CIN inhibition rather than activation is the relevant message for striatal functions. What is still unknown is whether inhibition of CIN activity modulates corticostriatal transmission and contributes to the imbalance of striatofugal pathways in PD. To address this question, we combined electrophysiological recordings of corticostriatal transmission in D1 and D2 MSNs with optogenetic inhibition of CIN activity in brain slices from control and parkinsonian mice. We show that a brief pulse of light (589 nm) in halorhodopsine-expressing CINs induces a complete inhibition of their firing. The features of this optogenetically-induced inhibition are similar to the characteristics of the pause observed *in vivo* in terms of duration and synchronization. The light-induced inhibition does not modulate synaptic transmission in the two populations of MSNs in normal condition. Pharmacological experiments show that the absence of modulation of corticostriatal transmission is not due to an insufficient cholinergic tone in slices. In parkinsonian mice, CIN pause selectively potentiates corticostriatal transmission in D1 MSNs; we are currently investigating the cellular mechanisms underlying this cell-type specific potentiation. Our results suggest that CIN pause could counteract the hypoactivity of the D1 MSNs in PD and question the role of CINs in the physiology of the corticostriatal network in physiological condition. Supported by Fondation de France, CNRS and AMU.

**P2.122 Role of NMDA receptors in the inhibitory synaptic transmission plasticity in the dorsal horn of the spinal cord**

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In the dorsal horn of the spinal cord, excitatory and inhibitory interneurons surrounded by glial cells built up a complex network where nociceptive information is integrated and modulated before being transmitted to brain structures. Spinal inhibitory synaptic transmission, mediated by GABA and glycine, plays a key role in the processing of nociceptive information. This inhibition can display plastic changes linked with hyperalgesia (i.e. a nociceptive stimulus perceived as more painful) and allodynia (i.e. a normally non noxious stimulus eliciting a painful sensation) associated with neuropathic pain. In the DH, NMDA receptors are widely expressed and recruited following a nerve injury. Although their role in plastic phenomenon is well established, little is known about their involvement in modulation and plasticity of the spinal inhibition.

Our aim is to determine the effect of NMDA receptors activation on DH synaptic inhibition. To do so we used mice acute spinal cord slices to record inhibitory postsynaptic currents (sIPSC; mIPSC) and studied effect of NMDA receptors activation.

Activation of NMDA receptors led to an increase of GABAergic sIPSC and mIPSC frequency, but had no effect on glycinergic transmission. This modulation appears without change in the events amplitude showing a presynaptic potentiation of GABA release.

Interestingly, using GAD65 mice, we revealed a target specificity of this effect. By a pharmacological approach, we investigate the location and composition of NMDA receptors involved in the effect observed. Finally, to better understand the role of NMDA receptors activation effect on the inhibitory transmission plasticity underlying neuropathic pain, we performed recordings from neuropathic mice 1 and 2 weeks after nerve injury.

Altogether, our results bring new insights on the activity dependent plasticity of inhibition in the spinal cord network that could underlie the development and maintenance of neuropathic pain.

**P2.123 High resolution large volume multicolor imaging of brain tissue with chromatic multiphoton serial microscopy**

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Large scale microscopy approaches are transforming brain imaging, but currently lack efficient color contrast modalities. Here we introduce Chromatic Multiphoton Serial (ChroMS) microscopy, an approach combining trichromatic multiphoton excitation through wavelength mixing and microtome-based serial block-face image acquisition to image neural tissue marked with multiple endogenous fluorescent labels. This approach delivers micrometric imaging of spectrally distinct fluorescent proteins with constant resolution and sub-micron channel registration over the entire imaged volume. We demonstrate continuous 3D imaging over several cubic millimeters of neural tissue, and whole brain reconstructions by serial 2D acquisition. We illustrate the potential of ChroMS microscopy for several measurements relevant for region-scale or whole brain studies: color-based analysis of astrocyte morphology and interactions in the mouse cerebral cortex; color-assisted reconstruction of neuronal layout; and brain-wide mapping of axonal projections labeled with distinct tracers. ChroMS imaging enables for the first time to record large-scale images of multicolor-labeled tissue with the resolution and quality appropriate for color-based morphological, clonal and connectivity analyses and should find many applications for multiscale studies in neuroscience.

**P2.124 Astrocytes contribute to the trigeminal central sensitization and cephalic cutaneous hypersensitivity in rat model of chronic migraine**

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Repeated migraine attacks are associated with maladaptive neural plasticity and lead to chronic headache. Sensitization of pain networks play an important role in the transition to the chronic forms of the disorder. It is increasingly recognized that glial astrocytes are activated in the *medullary* dorsal horn (MDH) in response to peripheral tissue injury and are involved in central sensitization (Ji *et al.*, 2011, Lefevre *et al.*, 2015).

Combining behavioral and *in vivo* electrophysiological approaches, this study examined the contribution of astrocytes activity in trigeminal central sensitization and cephalic cutaneous hypersensitivity in a new model of chronic migraine (Dallez *et al.*, 2018). We investigated the effect of intracisternal (i.c.) application of D-Amino-Acid-Oxidase (DAAO), a D-Serine degrading enzyme, or L- $\alpha$ -Aminoadipic acid (LAA), a gliotoxin, on cephalic cutaneous sensitivity and on neuronal activation within the MDH in the rat evoked by recurrent administration of systemic administration of isosorbide dinitrate (ISDN), a nitric oxide donor.

Recurrent ISDN injections (10 mg/kg, 5 injections, 1 per day) induced a persistent cephalic mechanical allodynia that was prevented by DAAO-treatment or LAA. During *in vivo* electrophysiological unitary extracellular recordings performed in allodynic rats at day 5, ISDN administration facilitated C-fiber-electrically-evoked responses ( $144 \pm 3.4\%$  of baseline). This facilitation was abolished by preventive DAAO or LAA. This preventive effect was reversed when D-serine was injected together with ISDN. Present results suggest that astrocytes contribute to the trigeminal central sensitization and cephalic cutaneous hypersensitivity that characterize the migraine progression.

**P2.125 3D imaging of vertebral column lymphatic network in mouse**

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Cranial lymphatic vessels (LVs) are involved in transport of fluids, macromolecules and CNS immune responses. Little information about spinal LVs is available, because these delicate structures are embedded within vertebral tissues and difficult to visualize using traditional histology.

Here we reveal an extended vertebral column LV network using three-dimensional imaging of decalcified iDISCO-clarified spine segments. Spinal LVs are metameric circuits exiting along spinal nerve roots and connecting to lymph nodes and the thoracic duct. They navigate in the epidural space and the dura mater around the spinal cord, and associate with leukocytes, peripheral dorsal root and sympathetic ganglia. Spinal LVs are VEGF-C-dependent and remodel extensively after spinal cord injury. They constitute an extension to cranial circuits for meningeal fluids, but also a route for perineurial fluids and a link with peripheral immune and nervous circuits. Vertebral column LVs may be potential targets to improve the maintenance and repair of spinal tissues as well as gatekeepers of CNS immunity.

**P2.126 Effect of the long non-coding RNA Neat1 knock-down on the circadian transcriptome in a rat pituitary cell line**

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The long noncoding RNA nuclear-enriched abundant transcript one (Neat1), is the structural component of nuclear bodies called paraspeckles. These bodies have been shown to retain in the nucleus RNAs and proteins. We previously showed in the rat pituitary somatotrope cell line GH4C1, that Neat1 and other components of paraspeckles are rhythmically expressed and rhythmically retain RNAs in the nucleus leading to a rhythmic expression of the corresponding genes (Torres et al, eLife, 2016). To evaluate the contribution of Neat1 and paraspeckles to the circadian transcriptome in this cell line, we knocked-down this lncRNA using CRISPR-Cas9 technology. We then performed comparative high throughput RNA sequencing on wild type and Neat1 KO cells every 4 hours for 24 hours after synchronization of the cells by a fresh medium replacement. Expression levels were determined using Hisat2/FeatureCounts softwares, differential displays were assessed by DESeq2 analysis and circadian profiles were evaluated using MetaCycle.

Preliminary results showed that 1432 genes (9%) among 15242 expressed genes displayed a circadian expression pattern in wild type GH4C1 cells. 85% of these genes (1252) lost their rhythmic pattern in Neat1 KO cells. Surprisingly however, 2140 genes whose expression did not follow a circadian pattern in wild type cells were shown to display a circadian expression in Neat1 KO cells. It looks like if in addition to disrupting the normal circadian cycle, Neat1 knock-down caused an unexpectedly large-scale genesis of de novo oscillating transcripts. Further analyses are currently in progress to determine whether Neat1 knock-down actually causes the reprogramming of the pituitary circadian clock. Alternatively, knock-down of Neat1 may increase the amplitude of the oscillations of some transcripts allowing them to reach the threshold of significance in our analyzes. This is all the more conceivable as we observed a modified expression level of different core-clock-genes (Arntl, Per1, Per2, Nr1d1, Rora and Rorb) in the KO Neat1 cell line that could have profound impact on clock-controlled-genes. Whatever the mechanism involved, our results showed the crucial role the long non-coding RNA Neat1 played in the functioning of the pituitary circadian clock.

P2.127

### **Effect of an intranasal administration of ODN on mouse body weight**

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Due to their poor pharmacodynamic and pharmacokinetic properties, experimental and therapeutic delivery of neuropeptides or analogues to the brain has been hampered. When administered systemically, these compounds are rapidly degraded, do not readily pass the blood-brain barrier (BBB), and often evoke potent hormone-like side effects. Thus, it is mandatory to find an alternative route of neuropeptide administration to reach their parenchyma targets. Since more than a decade, the intranasal (i.n.) route has received considerable attention because of low proteolytic activity compared to the oral route, high vascularization and large absorptive surface, resulting in improved absorption. In addition, i.n. route offers a direct access to the brain to peculiar compounds. The DBI-derived peptide ODN acts as a potent anorexigenic compound in rodents when injected intracerebroventricularly (i.c.v.). However, intravenous injection of a high dose does not modify feeding behavior suggesting that ODN does not comply to systemic administration. Hence, we have evaluated the ability of ODN and 2 analogues, OP and cycloOP to induce anorexigenic effects in mice via i.n. administration. Preliminary results revealed that i.n. instillation (1 µg/twice a day/7d) of OP induces a significant reduction in body weight, while ODN and cycloOP do not modify body weight compared to the vehicle injected group. The effect of OP was settled after 3 days and lasted until the end of treatment. Neither rebound hyperphagia nor gaining weight was observed after treatment cessation. Investigation performed using qPCR revealed that i.n. administration of OP induces an increase in UCP1 transcript expression in brown adipose tissue, suggesting that OP stimulates energy metabolism via sympathetic activation. Additionally, OP increased mRNA levels of gene related to both lipid oxidation and lipid uptake, suggesting that OP i.n. administration enhances fatty acid β-oxidation in the liver. In conclusion, our data show that OP injected by i.n. route reaches the CNS by skirting around the BBB and then activates central anorexigenic pathways. Moreover, they provide evidence that the physicochemical characteristics of the compound govern its brain delivery. Supported by ANR EZICROM (ANR-16-CE14-0011).

**P2.128 The importance of infantile neuronal NOS-derived NO signaling for fertility, olfaction and cognition**

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The gonadotrophin-releasing hormone (GnRH) neurons are the key players in a complex neural network that is controlling sexual maturation, puberty onset and adult fertility in mammals. Interestingly, these GnRH neurons are not born inside the brain. They find their origin in the olfactory placode and migrate into the hypothalamic preoptic region during further embryogenesis. Defects in the migration of these GnRH neurons or the capacity to secrete their neurohormone result in a delay in puberty onset and fertility problems, and are related to genetic disorders like congenital hypogonadotropic hypogonadism (CHH) and Kallmann syndrome (KS). Neuronal nitric oxide (NO) synthase (nNOS or NOS1)-containing neurons have been suggested to interact with GnRH neurons and regulate their activity and neurosecretory capacity. Here, we report that mutations in the Nos1 human gene have been discovered in patients with CHH and KS, and it appears that several of them are associated with comorbidities. Similar to human, Nos1 deficient mice do not only show impaired minipuberty, pubertal delay and infertility, but also cognitive, auditory and olfactory impairments. Moreover, we demonstrate that the administration of inhaled NO during the late infantile period can reverse the defects in sexual maturation, olfaction and cognition in this mouse model. Our results identify a critical time window for Nos1 action and suggest a potential therapeutic for human.

**P2.129 Pregnancy is associated with the production of new glial cells in the rat hypothalamus**

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The success of pregnancy involves processes of brain plasticity ensuring its proper unfolding, lactation initiation and onset of maternal behaviour. Increased neurogenesis in the two main germinal zones of the adult mammalian brain, the subventricular zone/olfactory bulbs and the dentate gyrus of the hippocampus, has been shown to occur during pregnancy and has been implicated in maternal behaviour. The hypothalamus has recently emerged as a third germinal niche producing new neurons and glial cells in the post-natal brain. Given the central role of the hypothalamus in the control of reproduction and physiological adaptations to pregnancy, we explored whether cell neogenesis in this brain region may contribute to the mechanisms of plasticity used by the maternal brain. Analysis of cell proliferation using the thymidine analogue BrdU showed that proliferation in the female rat hypothalamus varies across the estrous cycle, with a peak in diestrus 2, which precedes the pre-ovulatory surge leading to ovulation. Cells born in diestrus 2 preferentially survived if females became pregnant compared to non-pregnant ones. This differential survival was selectively seen in the medial preoptic area (mPOA), which is located in the preoptic region and plays a key role as a hub in the onset of maternal behaviour. Co-immunofluorescent labelings showed that most BrdU<sup>+</sup> newborn cells in the mPOA expressed the oligodendroglial marker Olig2 but were negative for the astrocyte markers GFAP and S100b, and for the neuronal marker HuC/D. The fraction of BrdU<sup>+</sup> cells co-expressing Olig2 was higher in pregnant ( $76.1 \pm 2.3\%$ ) versus non-pregnant rats ( $56.8 \pm 5.6\%$ ). Moreover, BrdU<sup>+</sup> newborn cells were frequently found associated with neuron cell bodies, some of which expressed parvalbumin. Altogether, our data show that pregnancy is associated with the production of new oligodendroglial-lineage cells, which associate with neuron cell bodies, selectively in the mPOA. These observations raise the possibility that the addition of new glial cells contributes to modulating the activity of neuronal networks involved in the onset of maternal behaviour.

**P2.130 Development of metabolic disturbances in a mouse model of polycystic ovary syndrome**

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Polycystic ovary syndrome (PCOS) is a chronic complex disorder that affects more than one in ten women. Women with PCOS suffer symptoms of excess androgen, reproductive dysfunction and metabolic disturbances. Metabolic features include insulin resistance (IR), hyperinsulinaemia, impaired glucose tolerance, type 2 diabetes (DM2) and obesity. The true underpinnings of metabolic disturbances in PCOS remain complex and somewhat unclear.

We recently generated a new animal model which recapitulates the major PCOS cardinal neuroendocrine reproductive features, by exposing the animals to high concentration of Anti-Mullerian Hormone during their fetal life.

In this study, we examined the metabolic characteristics of the PCOS-like female mice across postnatal development and uncovered that they develop an age-related increase in body weight correlated with an increase in food intake as well as fasting glucose levels, impaired glucose tolerance and insulin resistance.

Furthermore, we checked the expression levels of key peptides involved in the central hypothalamic control of energy homeostasis and food intake. Interestingly, we detected a significant decrease of *anorexigenic* proopiomelanocortin (*POMC*) mRNA in the brains of PCOS females as compared to controls.

These results support the hypothesis that PCOS might originate *in utero* and that an altered hormonal milieu during early life could disrupt the hypothalamic neuronal circuits controlling reproduction and metabolism.

**P2.131 Dietary PUFAs immunomodulatory properties shape the neuronal network during development**

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During development, the many cells of the central nervous system (CNS) interact to allow the maturation of a functional network. Amongst the necessary remodeling events is the synaptic pruning, during which certain synaptic terminals are removed to guaranty the efficiency of the neuronal signaling. This elimination activity is performed by microglia, the innate immune cell of the brain which is capable of phagocytosis. Polyunsaturated fatty acids (PUFAs) are immunomodulators and key regulators of brain innate immune system processes. Our group showed that by changing the ratio of n-3/n-6 PUFAs in the diet, their levels in the brain and in the composition of the microglia membrane were altered.

Functional analyses and high-resolution imaging revealed that microglia-dependent synaptic pruning is inversely correlated to the n-3/n-6 PUFA ratio. Additionally, data obtained by protein and RNA quantification suggested a role of the complement system in the effect of microglial inflammation on the shaping of the neuronal network. The deleterious effect of dietary n-3/n-6 PUFA was inhibited by blocking microglial CR3 a key component of the complement pathway.

We used *in vitro* and *ex-vivo* models to better understand the mechanisms linking PUFAs and microglia inflammation. We present here new experiments investigating a pathway linking the PUFAs composition of the diet to the inflammatory status of microglia. Indeed, quantifications of the PUFAs derivatives in the microglia of animals fed with the low n-3/n-6 ratio have provided us with target lipids that were screened *in vitro*. We have identified a pro-phagocytic derivative of arachidonic acid (AA), synthesised from AA by the 12Lox enzyme. By modulating 12Lox enzymatic activity we chain the link between n-3 PUFA deficient diet and increased microglia inflammation during this key developmental period for the CNS.

**P2.132 The role and molecular mechanisms of the anti-FGFR3 antibody, a biomarker of sensory neuropathies inducing neuronal death**

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Dysimmune sensitive neuropathies (SSN) were characterized by neuron cell death in dorsal root ganglia (DRG). We have recently identified FGFR3 antibodies which recognized the intracellular domain (TRK) of FGFR3 as a biomarker of a subset of SSN patients. We submitted mice cortical neurons cultures to different concentrations of a rabbit polyclonal antibody recognizing the FGFR3 TRK domain. FGFR3 antibody induced neuron cell death in a dose dependent manner. The main downstream pathway associated with FGFR signaling is the RAS/MAP kinase pathway. In order to decipher molecular mechanism involved in neuronal death induced by FGFR3 antibodies, we submitted neuron cultures to FGFR3 antibodies with and without the presence of the p38 MAPK inhibitor or the ERK1/2 MAPK inhibitor. The expression of FGFR3, NR1, NR2A, NR2B subunit of NMDA receptor and GLUR1, GLUR2 subunit of AMPA receptor were analyzed by RT-qPCR. FGFR3 antibodies treatment increased FGFR3 receptor, NMDA receptor subunits and AMPA receptor subunits expression and this increase was prevented by ERK1/2 or P38 MAPK inhibitor. Treatment of neurons culture cells by Dovinitib, a FGFR3 kinase inhibitor, showed the same expression profil compared to neurons submitted to FGFR3 antibodies. These results suggest that cytotoxicity induced by FGFR3 antibodies increases NMDA and AMPA receptor expression through FGFR3 tyrosine kinase site blocking and RAS/MAP kinase pathway activation. A similar expression profil of FGFR3 and NMDA subunits was observed in SSN serum-treated cultures. Internalization of certain antibodies enhanced autophagy. We analyzed several autophagy markers expression. We showed that optineurin expression increased in neurons culture submitted to FGFR3 antibodies and this increase was prevented by ERK1/2 or P38 MAPK inhibitor suggesting that autophagy activation may also play a role in neuron degeneration.

**P2.133 Implication of the plasticity of the blood/arcuate nucleus interface during the establishment of obesity**

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Obesity is worldwide problem that beside impact human health, produces economic and social damages. Obesity is associated with a central resistance to leptin, a hormone secreted by adipose tissue. Indeed, an increase of adipose tissue is directly related with high plasmatic leptin levels. Beside this, and as a first step in the onset of the central leptin resistance induced by obesity, leptin is no longer able to reach the hypothalamic arcuate nucleus (ARC) to exert its anorexic effect. This strongly suggests impairments in the blood/ARC interface as a factor during the establishment of obesity.

Our group has previously shown that a modulation of the permeability of ARC vessels regulates the access of peripheral signals to the neurons controlling energy homeostasis in ARC. In fact, in a mice model, changes in the energetic status modulates the secretion of vascular endothelial growth factor a (VEGFa) by tanycytes. Tanycytes are specific ependymal cells lining the wall of the third ventricle and project their end-feet into the ARC to contacting endothelial vessels.

In this work we sought to determine whether an alteration in blood/tanycytes/ARC interface is produced in an obesogenic state contributing to the central leptin resistance.

For this purpose, obesity was induced by a high fat diet for 10 weeks and the architecture of endothelial vessels/tanycytes/ARC interface was studied by immunohistochemistry. Moreover the same studies will be carried out in mice for which the expression of VEGFa was specifically invalidated in tanycytes by using a VEGF<sup>loxp/loxp</sup> mouse.

Our preliminary results show that a high fat diet induces alterations in the plasticity of the blood / ARC interface.

**P2.135 SHANK3 downregulation in the BNST drives anxiety**

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Autism Spectrum disorders (ASD) have been characterized by a triad of symptoms, deficit in social interactions and communications and presence of repetitive or obsessive compulsive behaviors. Associated to these core domains, other symptoms have also been described such as anxiety which can affect up to 40 % of ASD patients. Anxiety is a physiological response but can be maladaptive if persistent and further turns into anxiety disorder.

Although the etiology of ASD is complex, there is a strong genetic component. In particular, mutation of post synaptic scaffolding proteins like shank3 has been identified as responsible of some forms of ASD. Different mouse models have been generated to mimic some aspect of ASD. Strikingly, some of them also present anxiety trait as in SHANK3 mutant mice.

Understanding which neuronal circuits drive anxiety is still a crucial question. The Bed Nucleus of the Stria Terminalis (BNST) has been recognized as a critical structure in exerting a powerful control on anxiety. Thus, we hypothesized that SHANK3 deficiency in the BNST may induce anxiety phenotype.

Here, to evaluate the consequences of SHANK3 gene downregulation in the BNST, we used a combination of cutting edge technologies and behavioural assay associated with SHANK3 gene silencing strategy. We demonstrate that SHANK3 insufficiency affects the excitatory transmission in the BNST as well as anxiety-related behaviour. Altogether, our study identifies novel molecular and anatomical targets for the development of future therapies for ASD and anxiety.

**P2.136 Lithium reverses mechanical allodynia through a mu opioid receptor-dependent mechanism**

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Lithium is used to treat bipolar disorders and painful cluster headache. Several research groups reported functional interactions between lithium and the opioid system. In particular, lithium affects morphine-induced analgesia and reduces morphine tolerance and dependence. In addition, lithium attenuates thermal hyperalgesia and mechanical allodynia in neuropathic rats via a naloxone-sensitive mechanism, suggesting a mu opioid receptor (MOR)-dependent effect.

By using a combination of genetic, pharmacological, behavioural and biochemical tools, we investigated the link between lithium analgesia and the endogenous opioid system in the mouse cuff model of neuropathic pain.

We show that acute injection of lithium alleviates neuropathic pain in a mouse model of sciatic nerve chronic constriction and demonstrate that the MOR is necessary for lithium analgesia. This confirms and extends data reported by other groups on rat neuropathic models. Notably, our results suggest that lithium analgesia involves the upregulation of beta-endorphin synthesis in the CNS. This would explain, at least in part, the MOR-dependent nature of the analgesic properties of lithium.

Weinsanto I & al. Lithium reverses mechanical allodynia through a mu opioid-dependent mechanism. Mol Pain. 2018 Jan-Dec;14:1744806917754142. doi: 10.1177/1744806917754142. Epub 2018 Jan 21. PubMed PMID: 29353538

**P2.137 What do we know about interference control in children with ADHD?**

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A deficit in "interference control" is commonly reported in children with Attention Deficit Hyperactivity Disorder (ADHD), which is characterized by inattention, hyperactivity, and impulsivity. This has mainly been interpreted as difficulties in inhibiting inappropriate responses but it could be due to at least two distinct processes involved in impulsivity: a larger susceptibility to trigger automatic responses and a deficit in suppressing them, two non-disentangled processes in most studies. We separately investigated these two processes by using sophisticated analyses of behavioral data (dynamic analysis of performance) (Experiments 1 and 2) complemented by electromyographic activity (EMG) (Experiment 3).

Our work had three main objectives. The first one was to more deeply understand processes impaired in ADHD (Experiments 1 and 3) by comparing children with ADHD and typically developing children when they were engaged in a conflict task known to involve interference control. Secondly, we investigated the effect of the most often prescribed medication (methylphenidate, MPH) (Experiment 1). MPH is supposed to act on DA system which is known to be involved in the control of interference. We therefore compared children with ADHD without medication versus children with ADHD under MPH. And thirdly, we evaluated the impact of a behavioral therapy on children with ADHD (Experiment 2) by comparing the performance of children with ADHD before and after they completed a 3-months intervention program. The main findings were that 1/ difficulties in interference control mostly reported in ADHD children were due to both a higher susceptibility to trigger automatic responses and an inhibition deficit, 2/ MPH improved interference control by improving the selective inhibition of automatic responses without modifying the strength of automatic responses, and 3/ the behavior intervention program improved interference control by improving both the ability to resist automatic actions and to inhibit them.

P2.138

**The role of new N-terminally truncated Tau species in Alzheimer's disease**

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**Introduction:** In Alzheimer's disease (AD), one of the hallmarks is the neurofibrillary degeneration (NFD), which is mainly composed of aggregated Tau proteins. Mechanisms leading to Tau aggregation are not clearly elucidated. Some studies indicated that Tau truncation could have an etiological role in the pathological process of AD. Recently, we have identified new N-terminally truncated Tau species. Our preliminary data have shown this new Tau species to be a signature feature of AD. Currently, we aim at demonstrating the instrumental role of this Tau species into the development of Tau pathology.

We have performed stereotaxic injections of lentiviral vectors (LV) in order to express full-length Tau and truncated Tau species, in the hippocampus of wild-type and Tau-transgenic mice. Our immunohistochemistry analyses of brain sections, performed 2 months post injections have showed that Tau proteins are stably expressed in neurons within the whole hippocampus and that the N-terminally truncated Tau species is detected in regions that are relevant to synaptic plasticity and memory. Moreover, this new Tau species is likely able to potentiate Tau aggregation.

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**P2.139 A neuronal population code for resemblance between drug and nondrug reward outcomes in the orbitofrontal cortex**

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The orbitofrontal cortex (OFC) is implicated in choice and decision-making in both human and non-human animals. We previously identified in the rat OFC a mechanism that influences individual drug choices and preferences between a drug and a nondrug (i.e., sweet) outcome that is common across different types of drugs (cocaine and heroin). Importantly, this research also revealed some intriguing drug-specific differences. Notably, the size of non-selective OFC neurons that indiscriminately encode both the drug and the sweet outcomes varies as a function of the drug outcome available (cocaine or heroin). Here we tested the hypothesis that the relative size of the non-selective OFC population somehow represents the degree of resemblance between the drug and nondrug reward outcomes. We recorded OFC neuronal activity *in vivo* in the same individual rats while they were choosing between two outcomes with varying degrees of resemblance: high (two concentrations of sweet), intermediate (sweet *versus* heroin) and low (sweet *versus* cocaine). We found that the percentage of non-selective OFC neurons dramatically increased with the degree of resemblance between choice outcomes, from 26% to 62%. Overall, these findings reveal the existence of a neuronal population code for resemblance between different kinds of choice outcomes in the OFC.

**P2.140 Type 2 diabetes alters emotional behavior, HPA axis and expression of stress and immune-related genes in the medial prefrontal cortex**

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A large literature documents the co-occurrence of type 2 diabetes (T2D) and anxiety and depressive disorders. In animals, emotional disturbances have been recursively reported in obese models of T2D. But these models do not adequately reflect the full clinical context of T2D which is not always associated with obesity. The Goto-Kakizaki (GK) rat is a spontaneous, non obese model of T2D established by inbreeding Wistar rats selected at the upper limit of normal glucose tolerance. Our study aims to explore emotional behaviors in diabetic GK rats. Since chronic activation of the innate immune system and hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis might play a role linking T2D and affective disorders, we also examined endocrine stress response and neuroinflammation in GK rats. Two months-old GK and control Wistar male rats were tested for anxiety-like behavior, social interaction and post-stress plasma corticosterone levels were determined.

Expression of glucocorticoid and cytokine-related genes was assessed in the medial prefrontal cortex (mPFC), amygdala and ventral hippocampus. Our results reveal that GK rats exhibited a marked hyper-anxiety and reduced social interaction behavior compared with Wistar rats. This emotional phenotype was associated with elevated plasma corticosterone levels in both basal and stress conditions, as well as significant up-regulation in the expression of key stress-related genes such as 11 $\beta$ HSD1 (11 $\beta$ -Hydroxysteroid dehydrogenase type 1), SGK1 (serum and glucocorticoid-regulated kinase 1) and Redd1 (regulated in development and DNA damage responses 1) in the mPFC.

Finally, we reported a 4-fold increase of the pro-inflammatory cytokine IL-6 and a decrease of SOCS3 (suppressor of cytokine signaling 3) in the mPFC of GK rats. Altogether, our study suggests that, independently of obesity, T2D leads to marked emotional disturbances, HPA axis hyper-activity and altered expression of glucocorticoid and cytokine-related genes specifically in the mPFC. Further experiments are needed to determine the causal role of glucocorticoids and neuroinflammation in the emotional disturbances reported in GK. Finally, our work highlights the importance to further explore the mechanisms linking T2D and affective disorders.

**P2.141 A novel environment-evoked transcriptional signature predicts reactivity in single dentate granule neurons**

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Activity-induced remodeling of neuronal circuits is critical for memory formation. This process relies in part on transcription, but neither the rate of activity nor baseline transcription is equal across neuronal cell types. In this study, we isolated mouse hippocampal populations with different activity levels and used single nucleus RNA-seq to compare their transcriptional responses to activation. We found that, one hour after novel environment exposure, sparsely active dentate granule (DG) neurons had a much stronger transcriptional response compared to more highly active CA1 pyramidal cells and vasoactive intestinal polypeptide (VIP) interneurons. Activity continued to impact transcription in DG neurons up to five hours, with increased heterogeneity. By re-exposing the mice to the same environment, we identified a unique transcriptional signature that selects DG neurons for reactivation upon re-exposure to the same environment. These results link transcriptional heterogeneity to functional heterogeneity and identify a transcriptional correlate of memory encoding in individual DG neurons.

**P2.142 Neural signature of musical preference during spontaneous auditory imagery**  
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Although one of the greatest motivations for listening to music is the pleasure elicited by this activity, little is known about the neural mechanisms that elicit our liking for a song. The ability to make predictions about the continuation of a song while listening to it is an important determinant of musical appreciation but is difficult to explore because the neural processing of ongoing music occurs at the same time as prediction processes are generated. To avoid this limitation, a possibility is to explore prediction processes not during the perception but during the imagination of music. We explored the neural mechanisms of musical appreciation in twenty healthy volunteers. As a first step, we asked them to listen to five unknown songs for two weeks. Subsequently, the songs judged to be the two most liked and the two least liked were selected. Neural correlates of musical preference were investigated by high-resolution electroencephalography whilst listening to these songs in which gaps of silence had been inserted. Several neuronal mechanisms related to the evaluation were highlighted. Throughout the period of silence, specific oscillatory activities appeared, resulting in changes in theta and alpha activity within particular brain structures such as the lower frontal and superior temporal gyri, known to be involved in music retrieval. This study shows how our knowledge of the incoming stimulus forms the basis of a preference judgment.

**P2.143 Mapping neurons and brain regions underlying sensorimotor decisions and sequences in *Drosophila***

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A single nervous system architecture can generate a wide variety of distinct motor patterns in response to sensory cues. A key step in understanding how the nervous system selects and controls the production of appropriate actions and behavioral sequences in response to sensory stimuli is identify neuronal substrates to which we can assign relevant behavioral functions. To do this, we developed an approach were we combined an automated behavioral classification method with large-scale behavioral screening. We analyzed behaviors from hundreds of thousands of larvae where we selectively silenced small subsets of neurons and individual neurons systematically across the nervous system in a library of *Drosophila* GAL4 lines using a machine-learning based approach. We determined and quantified the effect of these manipulations on larval behavior during responses to a mechanosensory stimulus: air-puff. The supervised machine-learning based approach that we developed is based on limited set of features and annotations of a small number of video frames to automatically classify behaviors. The different discrete behaviors emerge as different cluster in a feature space where the two dimensions are the shape change and angle change. This method allows the detections of six different behavioral categories. We applied it to characterize the response of *Drosophila* larvae to an air-puff and uncovered a probabilistic sequence of five elements : Hunch, Bend, Stop, Back-up and Crawl. Statistics of the automated behavior classification such as fraction of animals performing an action, as well as the transition probabilities between the different actions in a sequence for example allow the detection of subtle changes in behavior as a result of neuronal manipulations. By applying the automated machine-learning based behavioral classification and analysis to the dataset of the inactivation behavioral screen we identified neurons and brain-regions underlying *Drosophila* larva response to air-puffs selectively involved in sensorimotor decisions and sequence transitions between five different actions. These findings provide to groundwork for understanding how sensorimotor decisions and sequence transition are controlled by the nervous system control.

**P2.144**

**Role of neural circuitry of the insular cortex in anxiety-related behaviors**

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Despite high societal burden of anxiety disorders, efficient anxiolytics without side effects are unavailable. Most pharmacological treatments of anxiety disorders are targeting the serotonin system. Selective serotonin reuptake inhibitors (SSRI) are used as the first-line pharmacological treatment of anxiety disorders and buspirone, a partial agonist of serotonin 1A receptor, is also prescribed for anxiety disorders. However, those anxiolytics affect serotonin neurotransmission in the whole central nervous system, including the neural circuits irrelevant to anxiety, likely leading to the debilitating side effects. Therefore, to develop efficient treatments of anxiety disorders, it is necessary to understand the neural circuitry underlying anxiety.

Human neuroimaging studies revealed abnormal function of the insular cortex (IC) and amygdala in patients with anxiety disorders. Recent anatomical studies in animal models reported divergent connections between IC subregions and amygdala nuclei, including projections of the anterior IC to the basolateral amygdala (BLA) and projections from the posterior IC to the central nucleus of amygdala (CeA). The neural circuits of anxiety are well studied in the amygdala, whereas the function of the IC neurons on anxiety remains unclear. Therefore, we investigated the role of the anterior and posterior IC neurons in anxiety-related behaviors, along with the expression of serotonin receptors in those circuits.

First, to record the activity of anterior and posterior IC neurons, we used *in vivo* fiber photometry during well-established anxiety assays. We found that the activity of posterior IC neurons, but not anterior IC neurons is correlated with anxiety levels. Second, we characterized the topography of IC-amygdala projectors by injecting retrograde tracer in the BLA or CeA. Moreover, we quantified the proportion of anterior IC-BLA and posterior IC-CeA projectors expressing the serotonin 1A or 2A receptors. Lastly, we performed optogenetic activation of anterior and posterior IC terminals in the BLA and CeA during anxiety and valence assays. Altogether, our findings revealed a role of the IC neurons in anxiety-related behaviors.

**P2.145 A neuro-computational model showing the effects of ventral striatum lesion on the computation of reward prediction error in VTA**

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One of the earliest attempts to understand how animals learn involved pairing an unconditioned stimulus (US) with a cue or conditioned stimulus (CS) and observing that animals start responding to the CS after some point in time. This is the basis of pavlovian learning, a fundamental learning mechanism in animals, which has been addressed by several models of neural networks. We have developed a model focusing on the mechanism of reward prediction error within pavlovian learning and studied the effects of Ventral Striatum (VS) lesions to illustrate a fundamental dissociation of magnitude and timing replicating experimental studies.

The paradigm used to evaluate the model is a simple CS-US associative learning task and considers also how the expectation cancels out the dopamine peak at the time of the reward. The trial duration is 500 time steps with each time step corresponding to 1ms. The stimulus is presented at the 10th time step and is kept switched on till the arrival of the reward at the 400th time step (400ms). The reward and the stimulus have by default a magnitude of 1. The number of trials for the entire conditioning to happen was 16 trials. Virtual lesions of VS to VTA GABA was made by disconnecting the link between them. Two experiments were conducted where the time and magnitude were varied. In the first experiment, a reward magnitude of 2 is given instead of 1. The reward prediction error in VTA still shows a firing of 1 indicating the magnitude is conserved even after the VS lesion. In the second experiment, an early reward is delivered which doesn't show firing compared to the control scenario where firing exists thus replicating the studies done by Takahashi(2016).

The results show that there exists fundamental dissociation of magnitude and temporal when calculating reward prediction error (RPE) in the VTA. We propose this is achieved through magnitude being computed in the PPN FT neurons and time being computed in the ventral striatum (VS) respectively. The implications of this model bring into light new interpretations of dopamine firing extending to state prediction errors and creating a sensory representation before learning the reward fully.

**P2.146 Decoding the activity of amygdala-to-frontal cortex axons during decision making**

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Life is a chain of decisions and actions that shapes subject's behaviours. Individuals tend to choose the best action possible (known as 'action-selection') among different alternatives by using goal-directed decision making. We found previously that the frontal association cortex (FrA) is critical in organizing such action-selection. However, to achieve flexible behaviors in a dynamic environment, individuals must rapidly re-evaluate and update these alternatives according to the difference between the predicted and the obtained outcome. While many cortical and subcortical structures act in coordination to encode and process changes in the outcome value, how these different systems are interconnected and how they cooperate to implement action values remain unknown. To address this question, we first developed a new decision-making task during which head-restrained mice learn to associate lever press with reward delivery through a trial-error strategy. This behavioral task allowed us to monitor over days and weeks the activity of axons that project from the basolateral amygdala (BLA) to the FrA, during the entire course of learning and after change in reward contingencies. We found that a cluster of BLA buttons shows time locked activity during key periods of the task. In parallel, we also explored the effect of transient optogenetic inactivation of BLA-to-FrA neurons during the task. Our first results show that the BLA conveys task-related information to the FrA; thereby supporting the idea that BLA neurons would likely participate in setting a fine "online" action representation in FrA that quickly adapts to contingency changes.

**P2.147**

**Time-based expectancy in school-aged children with dyslexia**

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Increasing number of research reports timing abnormalities in children with developmental dyslexia including deficits in the estimation of time either the visual or the auditory domain. However, development of time-based event expectancy, that is essential aspect of human temporal cognition, has not been previously studied in this population. In the present study, we aimed to investigate the time-based event expectancy in school-aged children with dyslexia.

Eighteen children with dyslexia and eighteen age-matched (8-13 years) typically developing children completed a binary choice response task in which short (1000ms) or long (3000ms) duration of the visual cue (i.e. foreperiod) predicted the pointing direction of the centrally presented arrow with a probability of .9.

We found that children in both groups showed a significant opposite expectancy effect selectively at the long foreperiod, i.e. they responded slower to the frequent combinations of foreperiod and arrow's pointing direction than to infrequent combinations, suggesting that adaptation to time-based predictability is not fully developed in school-aged children. Yet, children in both groups responded faster to long than to short foreperiods, showing a stronger variable foreperiod effect. Thus, we found that children with dyslexia were able to differentiate between the different foreperiod durations. However, we found that children with dyslexia were characterized by slower total choice response time than typically developing children. This generally slowing, in children with dyslexia, was negatively correlated with the magnitude of expectancy effect.

In conclusion, we found no evidence that the ability of formation of the time-based expectancy in school-aged children with dyslexia differs from the same age typically developing children. However, it seems that in children with dyslexia, in contrary to typically developing children, the deficits in the time-based expectancy may be related to slowing in perceptual-motor processing speed.

**P2.148 Cognitive ability characterization of rat model with mutated alpha-synuclein overexpression**

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One third of Parkinson's disease (PD) patients suffer from cognitive impairments, sometimes becoming more severe than the classical motor symptoms with disease's progression with consequences on the quality of life. A recent model of AAV-mediated overexpression of mutated alpha-synuclein in midbrain dopamine neurons showed a progressive neurodegeneration associated with PD motor symptoms (Bourdenx et al, 2015). The present study aims to assess cognitive function in this model in order to determine whether behavior of AAV induced alpha-synuclein overexpression rats resembles those observed during early PD manifestations.

Twenty-four male adult rats were included in the cognitive function test (French ethical committee authorization). AAV2/9 vectors carrying the human mutant p.A53T alpha-synuclein were injected into both substantia nigra of fourteen rats and AAV-GFP marker in ten rats (as controls). A comprehensive behavioral battery of tests was performed every 4 weeks for motor skills, anxiety, working memory and object recognition for 4 months. In parallel, touchscreen based operant tasks were performed for visual discrimination and attention processes.

Behavioral parameters analysis revealed that AAV-ha-syn injections did not induce global locomotor alteration but affected sensorimotor skills within the first month. The spontaneous alternation and the novel object recognition tests remained in the normal range suggesting no major working or recognition memories alteration; however anxious behavior was detected within the first 2 months on the elevated plus maze and the open-field tests. Analysis of touchscreen based operant conditioning tasks revealed that AAV-ha-syn injected rats presented attentional and visuo-spatial discrimination deficits.

Response on the tactile screen and food collection latencies were delayed as compared to control rats but trial number performed and sucrose appetence for the liquid reward were not affected.

The early anxiety, attention and visuospatial alteration observed in this nigral hm- p.A53T alpha-synuclein rat model provide a relevant opportunity to study underlying physiopathological mechanisms and propose potential therapeutic target to improve PD patient's quality of life.

**P2.149 Peripersonal space perception in the eye of the hurricane**

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Recent studies have suggested that, to be accurate, judging if an object is reachable may imply a motor component. The seemingly associated changes in motor behavior and perceptual judgements in sensorimotor adaptation tasks are thought to be related to the updating of internal models which impacts in parallel both the motor commands and the prediction of their sensory consequences (Körding and Wolpert, 2004). Adaptation of internal models can be due to geometrical changes (Redding and Wallace, 1996; Rossetti et al., 2008), or to changes in the inertial properties of the environment with specific effects on the dynamics of the motor performances (Lackner and DiZio, 1994; Coello et al., 1996; Bourdin et al., 2001). However, the effect of adapting to new limb dynamics on the perception of reachability and the representation of peripersonal space has not been investigated so far.

In this context, the aim of the present study was to assess the effect of sensorimotor adaptation to a new force field environment (using a rotating platform), on the representation of peripersonal space. We conducted two experiments with participants seated on-axis of the rotating platform. In both experiments, participants performed in the PRE, PER and POST conditions a perceptual task consisting in judging the reachability of visual targets presented on their right side at different distances. In the first experiment, participants were asked to provide reachability estimates before, during and after the platform's rotation at constant velocity without performing any reaching movements. In the second experiment, participants completed the same perceptual task but were also requested to perform accurate reaching movements towards a visual target during the platform's rotation, which resulted in force-field adaptation.

Results show peripersonal space is reduced after the sensorimotor adaptation. Moreover, when no reaching movements were required, reachability estimates did not vary, suggesting that rotation of the platform did not, by itself, induced a change in the perception of the peripersonal space. On these grounds, we conclude about the role of limb dynamics' representation on the perception of peripersonal space.

**P2.150 Anatomical and functional characterization of the neural circuits controlling ejaculation**

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Sexual behaviour is fundamental for evolution and an important component of human well-being.

Ejaculation is a critical mechanism in male sexual function, which is hypothesized to be controlled by a neural circuit known as the 'spinal ejaculation generator' (SEG), located in the lumbar spinal cord. The SEG has also been hypothesized to control the post/ejaculatory refractory period, a phase of sexual satiety, through ascending projections to the brain. However, the exact mechanisms by which the SEG controls ejaculation and the refractory period remain elusive.

After having identified the anatomical position and molecular identity of the SEG cells we aim at expressing fluorescent probes in these neurons, which will enable us to obtain targeted electrophysiological recordings. With those we will characterize the intrinsic and synaptic properties of the SEG circuitry *in vivo*. Electrical stimulation of the SEGs cells will indicate us whether we can drive activity in the ejaculatory muscles.

**P2.151 A large scale brain network involved in fear conditioned response: a functional imaging study in rat using microPET**

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Initially developed for measuring brain activation in humans, functional imaging techniques such as fMRI and positron emission tomography (PET) are currently available in rodents, allowing examination of whole brain activity. While we succeeded in recording odor evoked BOLD response in the rat olfactory bulb (*Martin et al., Neuroimage, 2007*), fMRI studies in small animals remain a challenge and require the animal to be anesthetized or head fixed thus precluding assessment of behavioral related brain activation. In spite of its limited spatial resolution compared to fMRI,  $\mu$ PET overcomes above limitations since the animal is awake and freely-moving during radio-tracer uptake.

In a previous experiment (*Litaudon et al. Brain Struct Func, 2017*), we demonstrated that  $\mu$ PET is a powerful tool to investigate, in rodents, the neural processes underlying odor-induced response in a large-scale neuronal network as a function of behavioral response to the stimulus. In the present experiment, we took advantage of  $\mu$ PET imaging to analyze brain network involved in a paradigm developed to study emotional memory. Rats were trained in an odor fear conditioning paradigm. Briefly, the conditioned group received 12 pairings of odor and electrical shock while the control group received odor stimulation only.  $\mu$ PET imaging was performed during the test session, 24h following the conditioning session. After [18F]FDG injection, rats were placed in the test chamber and received 12 odor presentations. Freezing behavior and sniffing were monitored during the whole session. After FDG uptake, rats were anesthetized to perform the PET scan. The same procedure was used one month later for a long-term retention test. PET data processing was carried out using SPM12. After spatial normalization to a custom PET FDG template, a voxel based statistical analysis was performed. T-value maps were overlaid onto the MRI template to identify brain structures that showed significant changes.

A first analysis revealed that fear conditioned response is associated with activity in a large brain network including amygdala, hippocampus and olfactory areas. This experiment demonstrates that  $\mu$ PET imaging offers an original perspective for longitudinal behavioral neuroscience studies in rodents.

**P2.152 Circuits for opposite valences learning in auditory cortex studied by inference of plastic connectivity**

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Listening and understanding our sound environment is a behavior that requires training and relies on our past experience. Auditory-cued behavioral training can alter neural circuits in primary auditory cortex (A1), but the mechanisms and consequences of experience-dependent cortical plasticity are far from being fully understood. This work addresses the following open questions: is there a general pattern of changes in the neuronal properties of A1 local networks when a sound becomes behaviorally relevant? Does the representation of a sound depend on whether it is associated with reward or punishment? Are there different circuits recruited during these opposite motivation auditory learning, and can we identify them? We explore these issues with mice that learn to perform two tasks with the same acoustic discrimination but with differential reward valence—one with water reward and the other with shock punishment. By taking advantage of the imaging capability of two-photon microscopy, we follow the same GCaMP6f expressing neurons in A1 throughout successive learning. Awake head-fixed recordings provide a rich observation of A1 activity in its layer 2/3. We find that in A1 superficial layers, both learning tasks induce strong patterning of neuronal sound selectivity, with an increase of marked spatial contrasts between zones representing the target sound and the surrounding areas. Neuronal assemblies representing the target sounds after learning the two tasks are distinct but overlapping. Finally, we apply approaches inspired by statistical physics to analyze our optical recordings and infer the underlying functional connectivity. They suggest that internal connectivity within A1 and external connection onto A1 are both reshaped by learning, and contribute to the observed modifications of sound selectivity. This work will improve our understanding of the various circuits involved in learning associated with opposite values.

- P2.153 Brain functional connectivity dynamic is modified by sleep deprivation and correlated with cognitive performance**
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It is known that dynamic change in brain connectivity plays an important role in large-scale network integration and cognition in humans. On the other hand, sleep deprivation can be conceived as a model of cognitive dysfunction. However, still is little known about how cognitive changes after sleep deprivation relate to dynamic changes on large-scale networks. Functional connectivity dynamics appear as a useful tool to understand how cognition relates to the temporal reconfiguration of resting state networks. In this work, we sought to understand if cognitive changes after sleep deprivation emerge from a different dynamic reconfiguration of resting state networks. To do so, we developed a method to understand whether brain modular dynamics based on inter-edge correlations or meta-links relate to global brain dynamics and cognition. With this, we sought to characterize the link between local brain dynamics, global computations, and cognition. We found that the global brain dynamic slow-down after sleep deprivation and the temporal reconfiguration of a frontal-parietal meta-hubs is informative about performance on sustained attention. We conclude that cross-links dynamics are informative about cognition, while the global brain dynamic slowing-down is a marker of sleep deprivation state. This method could be useful to understand whether subtle cognitive changes during the pathological cognitive decline, relate to changes in dynamic brain coordination.

P2.154

**Absolute bottlenecks and incompatible dynamics during a dual-task paradigm**

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**Introduction:** During a dual-task (DT), performance can be notoriously impaired. An explanation is that both tasks neural activity overlaps in common neural population creating interference, and consequently processing bottlenecks (BNs). Although sources of interference are known, the nature behind them is still a mystery. We believe that a dual-task switching process without impaired performance could be possible if interference limits are understood. Thus, here we show the first recorded example of incompatible dynamics between two tasks experiencing interference with intracranial EEG, the only brain technique that can reveal precise neural activity within milliseconds and in different anatomical locations, with the hope to delineate the precise limits of dual-tasking.

**Methodology:** iEEGs recordings were obtained from 18 patients with intractable epilepsy during an attention-demanding task (T1). We measured T1 under two conditions: during a single task execution (ST), and during DT, with patients asked to perform T1 plus a Verbal Fluency Test or task two (T2), assessing the ability to generate words with phonemic and semantic characteristics. Consequently, High Frequency Activity [HFA 50-150 Hz] was computed and used as a marker of neural activity at the population level and analyzed in light of behavioral performance (ST and DT).

**Results:** Behavioral results showed a significantly worst performance during DT versus ST. Electrodes with the most consistent HFA during ST and DT where organized by anatomical location and 3D-modeled based on patients' fMRIs. Activity was modeled creating graphical analyses during DT on T1 and T2 by separate. Later, they were compared to seven different cognitive conditions (i.e. verbal memory, motor execution, etc), contrasted to their anatomical location, sorted by network belonging, and correlated, delivering a list of areas susceptible to interference.

**Discussion:** With these results we are starting to show how trait-specific BNs arise and interfere in a patient's brain activity, showing the real limits of attention and possibly delivering the first hints on how to develop compatible dynamics between several simultaneous tasks.

**P2.155 Activity of fast-spiking interneurons in the primate striatum during reaching movements performed under different degrees of reward uncertainty**

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The striatum integrates a wide range of excitatory afferents from the cerebral cortex and thalamus in order to perform appropriate behaviours. Among striatal neuronal populations, fast-spiking interneurons (FSIs), presumed parvalbumin-expressing GABAergic interneurons, are known to be the main cortical target and, by contributing to the local processing, have a strong influence on striatal output. FSIs' modulation in activity in opposite directions (activation / inhibition) allows them to emit two signals to striatal output pathways, either facilitating or suppressing actions. In a previous study we showed that FSIs modulate their activity according to the prediction of an action by an external cue. However, it is still unclear how these changes in activity could be modulated by a prediction that becomes uncertain. To address this issue, we recorded FSIs in two macaque monkeys performing a task combining reaching movements and uncertainty of reward outcomes. Monkeys explored by trial-and-error a set of three targets to find the one associated with the higher probability of reward and then exploited this knowledge by repeating the same target choice until the reward schedule was changed. The two different conditions of the task corresponded to two different sets of reward probability for all options, allowing us to modulate the uncertainty in stimulus-outcome association. Our behavioural results showed that monkeys were slower to make movement when reward uncertainty increased, possibly reflecting greater difficulties in choosing the "best" target, decreasing motivation, or differences in the amount of attention. At the neuronal level, we found that changes in FSI activity mostly occurred at the moment of action, with distinct groups that either increased or decreased their firing rate. Across conditions, the proportions of activated FSIs were quite similar, whereas the proportion of inhibited FSIs was the lowest when reward uncertainty was the highest. These results provide evidence that changes in FSI activity could make distinct contributions to processes involved in reward-based action selection. The variety of modulation types may reflect a mixture of different signals related to attention, action selection, movement generation, and reward uncertainty.

**P2.156 Dorsal periaqueductal gray and medial hypothalamus involvement in the panic-modulating effects caused by serotonergic activation of dorsal raphe lateral wings**  
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**Background:** A wealth of evidence indicates that the lateral wings (lwDR) subnucleus of the dorsal raphe is a key structure in the modulation of panic-associated behaviors, such as escape and flight. Pharmacological stimulation of serotonergic neurons in this subnucleus promotes a panicolytic-like effect. It has been hypothesized that this effect is due to serotonin release in two other major panic-associated areas, the dorsal periaqueductal gray (dPAG) and dorsomedial hypothalamus (DMH), where facilitation of 5-HT<sub>1A</sub> neurotransmission inhibits escape performance. However, there is scanty information on the neuroanatomical targets of the lwDR, and more specifically if it indeed projects to the dPAG and DMH. It is also unknown whether blockade of 5-HT<sub>1A</sub> receptors in the dPAG or in the DMH interferes with the anti-escape effect caused by lwDR serotonergic neurons stimulation.

**Methods:** The anterograde neural tracer biotinylated dextran amine was injected in the lwDR to verify its projections. Male Wistar rats (280-310 g) were stereotactically implanted with a guide-cannula directed to the lwDR and other to the dPAG or DMH. Local microinjection of a small volume of the 5-HT<sub>1A</sub> receptor antagonist WAY-100635 (0.74 nmol/50 nl) was used to indirectly stimulate serotonergic neurons in the lwDR. Ten minutes before the administration in the lwDR, rats were infused with the same drug into the dPAG (0.37 nmol/200 nl) or into the DMH (0.74 nmol/200 nl). Escape behavior was investigated in the elevated T-maze.

**Results:** lwDR sends serotonergic innervation to the dPAG and medial hypothalamus. Previous treatment with WAY-100635 in the dPAG or DMH fully blocked the anti-escape effect caused by the injection of this drug in the lwDR [interaction between dPAG and lwDR treatment factors: F(1,28)=6.40; p< 0.05], two way ANOVA; interaction between DMH and lwDR treatment factors: F(1,25)=5.67; p< 0.05], two way ANOVA].

**Conclusion:** Our results show that 5-HT<sub>1A</sub> receptors activation in the dPAG and DMH mediated the panicolytic-like effect caused by lwDR stimulation. Dysfunctions in the serotonergic pathways that connect the lwDR to the dPAG and to the DMH may be critically involved in the pathophysiology of panic disorder.

**P2.157 Freezing and shaking as distinct behavioural readouts of fear and anxiety**

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We recently designed a novel device (Phenotypix) which consists in an open-field platform resting on highly sensitive piezoelectric pressure-sensors, with which we could detect the slightest movements of freely moving rats and mice, such as individual heartbeats and breathing cycles during rest, or tremor and shaking in response to pain or fear. Here, we report on the potential of this platform for the behavioural readout of fear and anxiety. In rodents, anxiety is classically evaluated as the avoidance of innately aversive situations such as exposed or bright areas (e.g. center of an open field, open arms of a maze). Fear on the other hand, a behavioral reaction to a perceived threat, is classically quantified as freezing immobility. Using the Phenotypix to quantify freezing and shaking, we found that exposition to a novel environment induced very little freezing but significant expression of shaking during the first 10 min, which then disappeared with familiarization. Similar exposition preceded by injection of the anxiolytic diazepam eliminated the shaking behavior without any significant effect on freezing. After a protocol of contextual fear conditioning, associating a sound with a footshock, the emission of the sound alone triggered high level of freezing but little or no shaking. In contrast, exposition to the fear-conditioned environment (in the absence of the sound) produced little freezing but high levels of shaking. A similar behavioural reaction, combining high shaking but little freezing, was produced by exposing the animal to the presence of a rat, a natural predator of the mouse. We next investigated the behavioral effect of optogenetic activation of distinct populations of insular-cortex neurons projecting towards specific regions of interest in respect to human anxiety disorders. We observed that repeated stimulations over 10 days (40 minutes in total) of insular neurons projecting to the ventral hippocampus induced persistent shaking behaviour, while freezing response was rather phasic, only during the stimulation periods. We propose that high-frequency (80-120Hz) shaking is a sensitive index of fear responses and complementary to the classically used freezing measures to quantify fear-related and anxiety-related behaviors in mice.

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**P2.158 Orexin in the posterior paraventricular thalamus mediates hunger-related signals in the nucleus accumbens core**

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Animals constantly use stimuli perceived in the environment that have acquired, through experience and learning, the ability to predict available resources. These exteroceptive stimuli allow to engage in adaptive behaviors. Meanwhile, signals related to the internal state (e.g. hunger, satiety) arise from the peripheral system and inform about the current needs, modulating the ability of exteroceptive information to drive food-seeking behavior. At the neurobiological level, the nucleus accumbens core (NAcC) is essential in encoding the value of reward-predictive cues and in controlling the level of behavioral responding. However, how information related to the physiological needs are integrated in the NAcC remains to be clarified.

The posterior paraventricular thalamus (pPVT) neurons receive strong projections from feeding-related hypothalamic orexin (also called hypocretin) neurons, and are excited by orexins. Hence, Kelley *et al.* proposed that the PVT serves as an integrative relay, conveying hypothalamic energy-balance information to the NAc, through its glutamatergic projection. Here, we test whether NAcC neural encoding of reward-predictive cues is modulated by the integration of pPVT orexin-mediated hunger-related signals. Using a cue-driven reward-seeking task, we show that satiety decreases cue-evoked excitations in NAcC and pPVT neurons, the latter preceding that found in NAcC neurons. Furthermore, intra-pPVT injection of 1) orexin-2 receptor antagonist reduces cue-driven reward-seeking behavior in hungry rats, and 2) local orexin-A restores responding in sated rats. Finally, pPVT orexin positively controls reward-seeking by modulating NAcC neurons cue-evoked excitations, highlighting a circuit integrating reward-predictive cues perceived in the environment with the current metabolic status of the animal.

**P2.159 Connections of the laterodorsal tegmental nucleus with the prefrontal cortex and habenular-interpeduncular-raphe system**

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The laterodorsal tegmental nucleus (LDTg) is a hindbrain cholinergic cell group traditionally thought to be involved in mechanisms of arousal, the induction of REM sleep, and the control of the firing pattern of midbrain dopamine cells. Nowadays, there is increasing evidence that LDTg is also engaged in mechanisms of anxiety/fear and promotion of emotional arousal under adverse conditions. Interestingly, LDTg appears to be connected with other regulators of aversive motivational states, including the medial prefrontal cortex (mPFC), lateral habenula (LHb), medial habenula (MHb), interpeduncular nucleus (IP), and median raphe nucleus (MnR). However, the circuitry between these structures has hitherto not been systematically investigated. Here, we placed injections of retrograde or anterograde tracers into the LDTg, LHb, IP, MnR and mPFC of male Wistar rats. We also examined the transmitter phenotype of LDTg afferents to IP by combining retrograde tracing with immunofluorescence and *in situ* hybridization techniques. We found that the LDTg receives abundant inputs from all major subregions of the mPFC. Robust LHb inputs to LDTg mainly emerged from the medial division of the LHb (LHbM), which also receives minor axonal inputs from LDTg. The reciprocal connections between IP and LDTg displayed a lateralized organization, with LDTg inputs to IP being predominantly GABAergic or cholinergic and mainly directed to the contralateral IP. Moreover, we disclosed reciprocal LDTg connections with structures involved in the modulation of hippocampal theta rhythm including the MnR, nucleus incertus, and supramammillary nucleus. Our findings indicate that the habenula is linked with the LDTg either by direct bilateral projections from/to LHbM or indirectly via the MHB-IP axis. These findings support a potential role of LDTg in the processing of aversive information. Moreover, they further characterize LDTg as part of a classic state-setting neuromodulatory projection system, and LHb and PFC as master-controllers of such systems, exposing that both are settled to impact not only dopaminergic and serotonergic, but also cholinergic modulatory systems.

**P2.160 Impact of a working memory task in sustained attention on resting networks in healthy and traumatic brain injury subjects: an EEG study**

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Mental fatigue is a common long-lasting symptom in traumatic brain injury (TBI) patients, which is independent of the severity and the length of the trauma. It is a disabling symptom that interferes with rehabilitation processes and limits professional reinsertion.

This mental fatigue is induced by the demands of daily life. The TBI patient tries to reach an acceptable level of performance for everyday life and needs higher energy reserves because of his slower processing and cognitive deficits. Especially attentional and working memory impairments are closely linked to mental fatigue.

In this context, our goal is to study the impact of fatigue on neuronal resting networks in EEG via lagged phase synchronization (LPS) measurement. The LPS is calculated during a resting EEG performed before and after a one-hour sustained attention working memory task. This task aims to induce mental fatigue by maintaining a high mental load over time through a high demand for mental flexibility, inhibition and updating of the subject.

Subjective mental fatigue, i.e., the mental fatigue felt by the subject, is also quantified at the beginning and end of this task. This computerized questionnaire assesses the subjects' level of fatigue, anxiety and drowsiness on a scale of 0 to 10.

We conducted 4 case studies with chronic-phase head injury patients compared to a control group of 48 healthy subjects.

Subjective measurements indicate an increase in fatigue and drowsiness resulting from the cognitive task for patients and healthy subjects.

The EEG results show that the increase in mental load over a period of 1 hour causes certain connectivity changes (LPS) for TBI patients in 4 resting networks (AN, FN, SN, VN) distributed in the frequency bands ( $\theta$ ,  $\alpha$  and  $\beta$ ). While this same task has no impact on the resting networks of the control group.

**P2.161 Motion tracking and reward-based decision-making in healthy and Parkinson's disease participants**

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The efficient selection of one out of several options relies on the estimate of the consequences of this selection, such as a reward or a punishment. The Iowa Gambling Task (IGT, Bechara et al., 1994) has been widely used to test reward-based decision-making performance and it has allowed unveiling specific deficits in patients with Parkinson's Disease (PD), a pathology associated to severe motor deficits.

Voluntary eye movements efficiently adapt to the contextual requirements, including reward contingencies. Work from our group and others demonstrates that when tracking a visual moving target, smooth pursuit eye movements are dynamically modulated by reward already in the very early phases, including prediction-driven anticipation.

We designed a novel smooth pursuit task inspired by the IGT where participants had to track one of two moving targets associated with different random schedules of monetary gains or losses. Each target's direction was associated either with a globally advantageous, or disadvantageous schedule. In the baseline control condition, the target to be tracked was explicitly instructed (e.g. "Follow the black target") and the overall monetary gain did not depend on the oculomotor performance. Participants were patients diagnosed with Parkinson's disease (PD), tested both ON and OFF Dopamine medication. We also tested age-matched and young healthy controls.

We analyzed reward-based pursuit behavior during different epochs, namely the anticipation phase preceding target motion onset, the visually-guided initiation (which typically follows the vector-average of the two motion signals), and the steady-state tracking phase. In young controls, but not in the other groups, smooth eye movements were dramatically biased, in the main experiment, toward the selected direction, both during the anticipatory epoch and the vector-averaging initiation. PD patients' and age-matched controls' eye movements did not express target selection until after the vector-average phase, about 300ms after target motion onset. Finally, during the late pursuit epoch, PD patients showed larger instability and more frequent *changes of mind* about which target to be tracked. Overall, target selection strategy was strongly suboptimal for all groups.

P2.162

**Perception of cardiac interoceptive signals in bilateral vestibular failure**

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Bodily self-consciousness relies on the weighting and the integration of external as well as internal sensory signals. Vestibular signals from the inner ear, and interoceptive signals from the viscera, are crucial for a coherent sense of self. Does losing vestibular signals influence the perception of cardiac interoceptive signals? To study the relative implication of these two sensory modalities for self-consciousness, we recorded cardiac activity in 26 patients with an idiopathic bilateral vestibular failure engaged in a heartbeat counting task. They silently counted the number of perceived heartbeats for various intervals between 25 and 50 s, followed by a confidence rating. Interoceptive accuracy scores were calculated to represent the participant's ability to detect their heartbeat. We also used the Body Perception Questionnaire to measure interoceptive sensibility, the general attention given to interoceptive signals. Patients were compared to 26 age- and gender-matched healthy controls. Preliminary results show no significant difference between patients and controls regarding accuracy, confidence and sensibility. These results suggest that an idiopathic bilateral vestibular failure does not modify the perception of and focus to cardiac interoceptive signals.

**P2.163 Behavioural and metabolic consequences of *Dlx5* and *Dlx6* inactivation in GABAergic neurons**

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Brain activity depends on GABAergic inhibitory interneurons, a heterogeneous class of neurons distinguished by diverse anatomical, biochemical and physiological characteristics. GABAergic interneurons are found in the cerebral cortex and in most other brain regions, including the hypothalamus; their activity affects functions as diverse as, for example, cognition and feeding behaviour.

*Dlx5* and *Dlx6* are two closely related homeobox genes, organized in tandem, expressed in the telencephalic ganglionic eminences interneuronal lineage. In the adult brain, *Dlx5* is expressed in most adult GABAergic interneurons.

The role of *Dlx5/6* on adult GABAergic neurons has been, so far, difficult to analyze due to perinatal lethality of mice carrying null alleles. Nonetheless, grafting of immature, mutant, interneurons into wild type newborn brains results in the reduction of graft derived adult Parvalbumin (PV)-positive GABAergic neurons.

Here we analyse *Vgat*<sup>Δ*Dlx5-6*</sup> mice in which *Dlx5* and *Dlx6* are simultaneously and selectively inactivated in GABAergic interneurons. They present a striking behavioural phenotype characterized by strong reduction of neophobia, anxiety and obsessive compulsive behaviour. In the open field test, *Vgat*<sup>Δ*Dlx5-6*</sup> mice present an increased exploratory behaviour and a reduced latency before entering the central region, indicating reduced anxiety. In the "Marble burying test", related to anxiety and compulsive behaviour, whereas control mice bury in average 50% of the marbles over 10 minutes, *Vgat*<sup>Δ*Dlx5-6*</sup> mice bury fewer marbles and, strikingly, 44% of them only bury or displace one marble. The metabolism of *Vgat*<sup>Δ*Dlx5-6*</sup> mice is also modified: at 20 months, both male and female present a 25% body weight reduction deriving from a marked decline in white and brown adipose tissue. In the cerebral cortex of *Vgat*<sup>Δ*Dlx5-6*</sup> mice, we observed regionalized alterations of PV-positive neuronal density.

We conclude that *Dlx5/6*-dependent regulations in GABAergic neurons determine the psychophysiological status of the body and could be an entry point to understand the molecular and cellular mechanisms through which the brain affects body homeostasis.

P2.164

**Contribution of grid cells inputs to distance/position coding in CA1 place cells**

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Grid cells in medial entorhinal cortex exhibit a striking hexagonal grid-like firing pattern that tessellate the environment. Grid cells are supposed to be at the core of a path integration system, driven mainly by self-motion cues, in order to compute distance travelled. However, grid cells are also sensitive to allocentric cues (landmarks) so that the type of spatial information carrying by grid cells and fed to hippocampal place cells remains elusive. In order to clarify this point, we studied the effects of an inactivation of the medial septum, a manipulation known to affect hexagonal firing patterns of grid cells, on two types of spatial coding in CA1 place cells: position and distance coding. These types of coding were assessed in mice running back and forth in a virtual linear track deprived or enriched with proximal virtual 3D-objects (Bourboulou, Marti, et al, 2019). Interestingly, the paucity of visual landmarks favored distance coding (firing at the same distance from start in both directions) while the presence of 3D-objects favored position coding (firing at the same position relative to the external visual cues). The effects of septal inactivation are still under analysis. In a second experiment, we wondered whether the type of behavioral strategy used by the animal to navigate could also biased position VS distance coding. We trained animals in two different spatial memory tasks in a virtual linear track in which the animal can use only an allocentric strategy (to locate a hidden goal from any point in the maze) or in which it could rely on a path integration strategy (to locate a hidden goal from two fixed points in the maze). Mice were able to learn both tasks. Place cells firing characteristics in both tasks are still under analysis. Inactivation of the medial septum were also done in both tasks to assess grid cells contributions to place cells firing characteristics depending on the strategy used by the animal.

**P2.165 New translational procedure to study retroactive interference and memory updating mechanisms in mice**

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Memories are not fixed entities but change in a course of new experiences. Evidence that memories are subject to modification is supported by a large body of work in cognitive psychology demonstrating that presentation of new competing information at the time of retrieval can lead to distortion or impairment of old memories. Although the constructive nature of memory is now well established, the underlying cellular mechanisms remain poorly understood. Here, we introduce a new translation task for rodents that provides a way to study memory-updating mechanisms and retroactive interference phenomenon, the most common cause of forgetting. The task is conducted in an operant chamber and involves spontaneous discrimination of novel from familiar nose-poke modules that are distinguishable by their visual feature and spatial location. In the acquisition session, mice are exposed for the first time to the testing chamber with one blinking nose-poke module. In the choice session, a novel non-blinking nose-poke module is inserted into an empty spatial location and the preference for novel over familiar nose-poke modules (number of nose poking) is used as an index of recognition memory. We first demonstrate that recognition performance varies as a function of the length of the acquisition period and the retention delay and is sensitive to conventional amnestic treatments (muscarinic receptor and NMDA receptor antagonists scopolamine and MK-801, respectively). We next manipulated the features of spatial context during a brief reactivation episode (insufficient for acquiring a new context recognition memory) to study memory updating mechanisms. We show that presentation of new competing information during retrieval impairs subsequent recall of old memory as reported by studies in normal human subjects, and provide evidence that mnemonic integration can occur either by a consolidation or a reconsolidation mechanism to update pre-existing memory representation. We further demonstrate that both forms of memory updating do not overwrite previously stored information and that memory impairments are due to retrieval failure caused by retroactive interference.

**P2.166 Development of the handwriting network: a coupled fMRI and kinematics study in middle-age children**

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The handwriting network has been defined in adults but not in children. The acquisition of motor patterns leads to major changes. For children, writing is dependent on feedback and attentional resources. Adults switch to a proactive control mode and automate their writing. We measured the changes in the handwriting network between age 8/10 and adulthood. The adult network is formed of 5 key regions. We hypothesized that the memorization of motor and orthographic representations would lead to more focal and stronger activations. We also expected that handwriting automation would lead to a decrease of activation in extra visual, somatosensory and prefrontal regions.

65 right-handed participants (23 adults, 42 children) wrote the alphabet, the days of the week or draw loops in blocks. Writing kinematics were recorded on an MRI-compatible digitizing tablet, in the course of scanning. Structural and functional images were acquired on a 3-Tesla MRI scanner, processed with SPM12 and corrected for head motion and distortions. We created a common template using DARTEL to better account for anatomical differences between groups. 2nd-level analyses were carried out using GLMflex with factors condition (letters vs loops / words vs loops) and group (adult vs children).

The main effect of group showed that the handwriting network described in adults was activated in children. A quantification of the coordinates of the local maxima and of the extent of the clusters in the key regions indicated more anterior and more diffuse activation in 3 of the key regions in children. Primary motor cortices and the right anterior lateral cerebellum were more activated in adults. Finally, only children recruited prefrontal regions (anterior cingulate cortex, inferior frontal gyrus pars orbitalis) and the left anterior fusiform gyrus.

This constitutes the first investigation of the handwriting network in typical children. Results suggest that the handwriting network is already established in middle-childhood but slightly more anterior and less focalized, reflecting a general developmental trend. Results also highlight the role of prefrontal regions in learning this complex skill in children and confirm the role of the motor cortices and anterior cerebellum in overlearned movements in adults.

P2.167

**Learning-related plasticity of top-down information in auditory cortex layer 1**

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Sensory neocortex is a critical substrate of learning and memory, but the brain-wide afferents that underlie cortical plasticity as well as their integration in the local microcircuit are only starting to emerge. Theoretical work has proposed that memory formation may shift control over processing in the local circuit from bottom-up, sensory-dominated to top-down, internally generated activity representing the behavioral relevance of stimuli. Many of these top-down afferents are enriched in neocortical layer 1, where they converge and are ideally located to affect neuronal circuit elements from all cortical layers that send their dendrites to layer 1. In secondary auditory cortex (AuV), a prominent top-down projection derives from the higher-order auditory thalamus (MGm/PIN), a multimodal structure displaying learning-related plasticity. Here we employ discriminative auditory fear conditioning as a controlled paradigm to dissect the top-down thalamocortical interactions that enable associative memory. Using Calretinin (CR) as a specific marker for MGm/PIN combined with *in vivo* 2-photon calcium imaging of synaptic boutons, electrophysiology and optogenetics, we find that cortical regions critically implicated in associative memory are densely innervated by MGm/PIN input. Calcium imaging of individual MGm/PIN boutons in neocortical layer 1 of behaving mice revealed enrichment and potentiation of sound responses for stimuli with learned relevance, which correlates with the strength of the memory trace. MGm/PIN inputs arriving to layer 1 of AuV directly contact local interneurons and tuft dendrites of pyramidal neurons, locally recruiting long lasting excitation and inhibition. Thus, long-range MGm/PIN afferents to auditory cortex emerge as a key component of memory, conveying information on acquired relevance of sensory stimuli, which can in turn recruit cortical inhibitory and disinhibitory mechanisms as well as dendritic association mechanisms in principal cells to optimize the computations of the neocortical microcircuit.

**P2.168**

**Dyslexia and motion discrimination**

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Visual deficits are suspected to limit the reading skills in people with dyslexia and evidences suggest involvement of magnocellular system. Although neurological origin of dyslexia is evidenced, the underlying mechanisms of the disorder are not fully understood and are debated for a long time. The fact that vision is essential for reading is not questionable. Magnocellular system provides main visual input to dorsal visual pathway and deficit in that system affects visual attention, eye movements and movement discrimination. Letter identification and recognition takes place in ventral visual pathway but attention and accordingly magnocellular system is needed to correctly locate letter to build the word. Therefore, poorly developed magnocellular system in dyslexia have distinct importance. And motion discrimination deficits are also evidenced in dyslexia. We investigated discrimination of two different motion tasks and visual working memory in Georgian children with dyslexia and their age and IQ match typically developing children. Twenty-seven dyslexic and twenty-five typically developing children (8-12 years old) participated in experiments. The results showed no significant difference in performance of coherent motion task between children with dyslexia and typically developing children. We assume that magnocellular deficits in terms of coherent motion discrimination is not specific only for dyslexia and is observed in typically developing children. However, performance of biological motion task was significantly different for two groups and children with dyslexia performed the task worse. These results suggest that specific deficit in dyslexia can be related to more "object-selective" ventral rather than dorsal stream. This assumption was somehow proved by the results of visual n-back task. There was significant difference in performance between two groups children with dyslexia performing worst. We conclude that for reading deficit in dyslexia not only magnocellular pathway is responsible but also deficits in ventral pathways plays a role.

**P2.169 Effect of *Panax quinquefolius* and/or vitamin C on behavioural and neurobiological impairments induced by the 5-Fluorouracil chemotherapy in mice**

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The occurrence of cognitive impairments has been described recently in the cancer field. This new area of oncology addresses a current clinical situation, as patients often complain of impaired memory, concentration and thought processing capacities. These troubles, referred to "chemobrain or chemo fog", have a negative impact on their quality of life.

Fatigue, possibly related to loss of muscle strength, sleep disturbances or over-exertion, is also a common complaint of cancer survivors after chemotherapy. Preclinical research has a role to play in finding ways to prevent and treat chemotherapy-related cognitive impairment (CICI) and/or fatigue. In particular, some food complements such as *Panax quinquefolius* (*P.qfolius*), as some pharmacotherapies, were shown to reduce fatigue in cancer patients treated by chemotherapy. Here we develop a behavioral animal model to evaluate the potential beneficial impact of a solution of Qiseng® (Natsuca) (*P.qfolius*+vitamine C) on CICI or fatigue in C57Bl6 mice.

We show that the chemotherapy 5-Fluorouracil (5-FU, 60 mg/kg/week, 3 i.p. administrations) induced nearly 15% of mortality, drastically decreased spontaneous activity potentially associated with fatigue, and reduced motivation to explore an anxiety area. Long-term deficits in spatial learning, memory and behavioural flexibility have also been demonstrated 2 weeks after the end of the 5-FU treatment period. Co-administration of vitamin C (19 mg/kg, 5 per os administrations/week during 3 weeks) did not prevent the deleterious neurotoxic effects of chemotherapy on mortality, activity (fatigue) and cognitive functions. However, co-administration of Qiseng with 5-FU significantly reduced mortality (only 4%), and completely prevented the effects of 5-FU on wakefulness activity and locomotor skills and anxiety-like behavior. However, no beneficial actions were observed on CICI in mice.

Together, these results interestingly establish that oral administration of Qiseng compensates and prevents symptoms of fatigue induced by 5-FU in mice, and thus paves the road for future effective research in cancer management and patient support care.

**Keywords:** *Panax quinquefolius*, Chemotherapy, Fatigue, Anxiety

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**P2.170 Computing hubs in the hippocampus and cortex**

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Neural computation, which relies on the active storage and sharing of information, occurs within large neuron networks in the highly dynamic context of varying brain states. Whether such functions are performed by specific subsets of neurons and whether they occur in specific dynamical regimes remain poorly understood. Using high density recordings in the hippocampus, medial entorhinal and medial prefrontal cortex of the rat, we identify computing microstates, or discreet epochs, in which specific computing hub neurons perform well defined storage and sharing operations in a brain state-dependent manner. We retrieve a multiplicity of distinct computing microstates within each global brain state, such as REM and nonREM sleep. Half of recorded neurons act as computing hubs in at least one microstate, suggesting that functional roles are not firmly hardwired but dynamically reassigned at the second timescale. We identify sequences of microstates whose temporal organization is dynamic and stands between order and disorder. We propose that global brain states constrain the language of neuronal computations by regulating the syntactic complexity of these microstate sequences.

**P2.171 A Bayesian inference framework for visuomotor decisions: eye movements modeling and analysis**

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Visuomotor decisions allow to link visual information to an appropriate motor response. The study of decision-making in the visual domain must take into account a great number of variables at play, both externally and internally. As a consequence, a flexible and yet reliable multi-dimensional model is certainly needed. The theoretical approach we propose in the present work is known under the name of Bayesian Theory (BT) and is a method of statistical inference where the probability of an event is updated as more evidence or information related to that event becomes available. In other words, the fundamental idea is that at any given moment our brain combines the incoming (noisy) sensory evidence of a visual scene with any prior knowledge it already has about it. Such dynamic combination then leads to an up-to-date estimate of the current state of the world and help determine the subject's final decision. As demonstrated by an extensive and rich literature, the oculomotor system really seems to follow the above-described principles. Our aim is to show that this is indeed the case both for relatively simple visual processes such as the smooth pursuit of moving targets, and for more complex behavioural processes such as the discrimination of the global motion of a set of points at different levels of coherence. To support our claim, two experimental scenarios have been tested: a smooth pursuit task with targets moving along orthogonal directions and a random dot kinematogram discrimination task. On the basis of acknowledged results about the baseline behaviour of the oculomotor system in both paradigms and going a bit further, we introduced a probability-bias in the distribution of the target motion directions to validate our Bayesian inference hypothesis and demonstrated that anticipatory eye movements constitute a proxy for the internal representation of a Prior for motion direction and combine with the visual noisy input according to both the strength of the target direction Prior itself and the targets specific properties (contrast, level of motion coherence, etc..). Despite a strong inter-individual variability, our results suggest that eye movements provide faithful information about the inferential processes underlying visual motion processing.

**P2.172**

**Development of binocular vision through experience dependent plasticity**

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There is converging evidence supporting the claim that the visual systems of animals adapt their limited resources to the regularities of the surrounding environment. This efficient coding model has been shown to successfully predict units with Gabor-like receptive fields close to those observed in V1 simple-cells. However, most of these studies remain limited in their scope because they rely on 2-D statistics of natural images, while the scene is 3-D. Here, we propose a novel model based on a spiking neural network which uses a biologically inspired plasticity rule (spike-timing dependent plasticity or 'STDP') to simulate the learning of binocular properties from natural stereoscopic images. First, the stereoscopic images were convolved with ON/OFF centre-surround filters to characterize retinal ganglion cells and LGN activity. These responses were converted to spikes and thresholded such that only the most active units could fire.  $3^\circ \times 3^\circ$  spatial pools from this retina/LGN layer were then used to train an STDP based neural network composed of 300 integrate-and-fire neurons with lateral inhibition.

Our results show that for both eyes, most units develop Gabor-like receptive fields similar to those observed in binocular simple-cells of macaque V1. When tested with random-dot stereograms, the units were also found to show disparity-tuning curves close to those observed in single-cell recordings from macaque. Binocular disparity selectivity was principally observed along the horizontal dimension, where it ranged between -0.5° and 0.5°. Interestingly, statistics at the population level showed that selectivity in our neural network reflects biases observed in visual environment. Furthermore, we show that the receptive fields we obtain are closer in structure to electrophysiological data than those predicted by normative encoding schemes such as sparse coding or independent component analysis. Together, our modeling results suggest that Hebbian coincidence detection is an important computational principle and could provide a biologically plausible mechanism for the emergence of selectivity to natural statistics in the early sensory cortex.

**P2.173 A deep-learning-based toolbox for inferring *in vivo* large scale neuronal activity in the region CA1 of the developing hippocampus**

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Two-photon calcium imaging is now widely used to indirectly infer multineuronal dynamics from changes in fluorescence of a reporter protein or dye.

However, analyzing this kind of data can still represent a computational challenge. Part of the challenge is to offer an analytical tool that would be scalable to the wide variety of calcium imaging data while providing reliable analysis.

State of the art computational tools are still not optimized for the analysis of highly active neurons in densely packed regions such as the CA1 pyramidal layer of the hippocampus during early postnatal stages of development. Indeed, the accurate segmentation of the activity from overlapping neurons is not achieved by the latest analytic tools such as CalmAn. To meet this challenge, we have developed a method based on deep-learning. First, we have developed a graphical user interface (GUI) allowing for a precise manual detection of transients (from onset to peak) of all transients from detected neurons. We collected and combined a corpus of manual annotations from three human experts' analyses on 6 mouse pups from 7 to 12 days old. Part of the labeled data was used to train our model, while the rest was kept to benchmark the performance. Then, we processed our data using a convolutional neural network and a bidirectional long-short term memory network. The proposed method is capable of learning long term sequences and can process long videos. We find that our method achieves better performance than CalmAn to identify neural activity in the developing CA1 without any user intervention.

**P2.174 A stochastic model of postsynaptic plasticity based on dendritic spine calcium downstream proteins**

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Dendritic spines are small neuronal protrusions and the main structure in neuron-to-neuron excitatory communication, shaping synaptic plasticity and learning in neural circuits. The dominant model for synaptic plasticity induction assumes that high synaptic calcium influx induces long-term potentiation (LTP), and moderate levels lead to long-term depression (LTD). In contrast to this, recent *in vitro* experiments with spike time dependent plasticity (STDP) at adult rodent hippocampal synapses reveal that similar post-synaptic calcium profiles lead to different synaptic plasticity outcomes (Tigaret et al., 2016). Additionally, most current STDP models cannot explain other effects like cooperation between inputs, dependence on dendritic spikes, and non-Hebbian plasticity.

We seek to develop a plausible model of synaptic plasticity that can capture signals interacting at multiple timescales, specifically electrophysiology data (Kwon et al., 2017) and calcium downstream binding proteins (e.g., CaMKII and Calcineurin). To this end, we develop a dendritic spine model encompassing transient structural changes and AMPA and NMDA receptors occupancy (Coombs et al., 2017). Our model reproduces recent results on dendritic spine voltage and calcium compartmentalization. Also, we report that calcium alone is not capable of mapping the dendritic spine plasticity, whereas calcium downstream proteins dynamics have enough discriminative power to determine plasticity even under similar calcium influx. Our long-term goal is to derive a reduced version of this model that is compact enough to use in network simulations. Summarizing, the critical points of our model are that

- a) all the variables are dynamic and reactions are biologically plausible;
- b) expansion to a dendritic neuron is straightforward since the variables are locally declared;
- c) it has realistic intrinsic stochasticity based on the biophysics of molecular reactions.

**P2.175 A hierarchical, multi-layer convolutional sparse coding algorithm based on predictive coding**

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Sparse coding holds the idea that signals can be concisely described as a linear mixture of few components (called atoms) picked from a bigger set of primary kernels (called dictionary). This framework has long been used to model the strategy employed by mammals' primary visual cortex (V1) to detect low-level features, in particular, oriented edges in natural scenes.

Differently, predictive coding is a prominent tool used to model hierarchical neural dynamics: high-level cortical layers predict at best the activity of lower-level ones and this prediction is sent back through of a feedback connection between the layers. This defines a recursive loop in which prediction error is integrated to the sensory input and fed forward to refine the quality of the prediction. We propose a Sparse Deep Predictive Coding algorithm (SDPC) that exploits convolutional dictionaries and a feedback information flow for meaningful, hierarchical feature learning in static images. The proposed architecture allows us to add arbitrary non-linear spatial transformation stages between each layer of the hierarchical sparse representations, such as Max-Pooling or Spatial Transformer layers.

SPDC consists of a dynamical system in the form of a convolutional neural network, analogous to the model proposed by Rao and Ballard, 1999. The state variables are sparse feature maps encoding the input and the feedback signals while the parameters of the system are convolutional dictionaries optimized through Hebbian learning. We observed that varying the strength of the feedback modulates the overall sparsity of low-level representations (lower feedback scales correspond to a less sparse activity), but without changing the exponential shape of the distribution of the sparse prior.

This model could shed light on the role of sparsity and feedback modulation in hierarchical feature learning with important applications in signal processing (data compression), computer vision (by extending it to dynamic scenes) and computational neuroscience, notably by using more complex priors like group sparsity to model topological organization in the brain cortex.

P3.001

### Role of Netrin-1 in the guidance of the corticospinal tract and the lateralization of motor control

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Mirror movements are involuntary movements of one hand that mimic voluntary movements of the opposite hand. Congenital mirror movement disease (CMM) is a rare genetic disorder with autosomal dominant transmission. Patients are unable to perform pure unilateral movements or complex bimanual activities that require independent control of the two hands. Thus, CMM is a unique paradigm to study the lateralization of motor control. Our team recently identified *Netrin-1* as a gene responsible for CMM. We showed that CMM patients with *Netrin-1* mutations present an abnormal anatomy of the corticospinal tract (CST) at the level of the pyramidal decussation. Mice KO for *Netrin-1* die a few hours after birth, when the CST crosses the midline and enters the spinal cord, forming the pyramidal decussation. The group of A. Chédotal has generated a viable mouse model in which *Netrin-1* is depleted at the floor-plate (*Shh::Cre;Ntn1<sup>lox/lox</sup>*). We took advantage of this model to investigate the role of *Netrin-1* in the CST guidance at the pyramidal decussation. We show that, the CST midline crossing is dramatically affected, leading to massive ectopic ipsilateral and reduced contralateral projections in the spinal cord. In keeping with this anatomical observation, unilateral cortical stimulation evokes substantial abnormal ipsilateral motor potentials in the mutants, indicating that these ectopic projections are functional. Interestingly, recent descriptions of this mutant revealed that hindbrain and spinal cord commissural axons were mostly preserved. Our result enlightens an original guidance mechanism for CST midline crossing with a critical dependence to floor-plate Netrin-1. Using retrograde tracing, we demonstrate that the proper lateralization of the rubrospinal and reticulospinal tracts is mostly preserved in these mutants, allowing to use them as a relevant model to assess the contribution of the CST in mirror movement. Last, the mutants show a specific loss of lateralization of the motor control when submitted to a voluntary motor task. This loss of motor control lateralization inversely correlates with the laterality index of the CST projections, highlighting the contribution of the CST projections in the occurrence of mirror movement.

**P3.002 Theta-burst firing induces a homeostatic depression of intrinsic excitability**

**involving Kv1.1 channels in CA1 pyramidal neurons in vivo**

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It is becoming increasingly apparent that intrinsic excitability plays an important role in memory and the creation of engrams, but how it is regulated to support such a role is not clear. Although many studies have described plasticity of intrinsic excitability *in vitro*, few have examined how, or if, it is expressed *in vivo*. Here, using whole-cell patch-clamp recordings we have examined how theta-burst firing, induced via the patch pipette, affects the intrinsic excitability of CA1 pyramidal neurons *in vivo*. We found that TBS induced a homeostatic decrease in firing in response to current injections, and that the magnitude of this decrease correlated with a decrease in input resistance and an increase in first spike latency. These effects were prevented by addition of the calcium chelator BAPTA to the intracellular solution. *In vitro*, plasticity of intrinsic excitability following similar stimulation protocols has been associated with the hyperpolarization-activated cation current,  $I_h$ . However, we found that *in vivo* the effect was independent of  $I_h$ , and rather involved Kv1.1 channels, as the effect was reduced in the presence of dendrotoxin-K, a Kv1.1 channel-specific antagonist. As Kv1.1 expression is restricted to the axon initial segment in CA1 pyramidal neurons this provides a mechanism by which they can regulate their excitability without disrupting synaptic integration.

P3.003

### Functional dynamics of the infant brain

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Study of brain functional responses is challenging in human infants. It is not possible to rely on an informed behaviour to sort trials by "task performance". Compared to adults, infant event related potentials (ERP) are highly variable, both in terms of latency of the components as well as ERP topographies across trials. This variability makes it difficult to define adult-like ERP components for infants. Hence, decoding the stages of stimulus-driven cognitive processing becomes an unsupervised problem. While the traditional ERP studies focus on the mean activity -- discarding the across-trial variability as noise -- this variability is important; especially in case of infants since it is highly prevalent even after averaging across trials. Here we investigate the across-trial variability in 2-5 months old infants while they process lateralized face stimuli, passively looking at the fixation. Using multivariate topographic analysis, we defined a measure of dissimilarity across trials and observed the time-evolution of this measure to understand the stimulus driven differences (variability) across trials. We found that moments of transient similarity with well known ERP components (e.g. P1, P400) can be observed even in single trials and that their timing tend to cluster at specific latencies after stimulus presentation, which become faster and better determined through early development. Furthermore, we find that the variability across trials also tend to reduce in specific epochs relative to stimulus time, which we call 'Variability Quenching Events' (VQE). We show that this reduction of variability cannot be fully explained by an improved signal-to-noise ratio and it may thus be a signature of specific neural processing stages. Remarkably, VQEs seem to be associated to ERP component maturation, since they match P1-like latencies until when the P1 topography is maturing (~ < 4 months) and shift then to P400-like latencies, when P1 maturation is completed and P400 maturation is still completing. Investigating single-trial dynamics while it "liquidly flow" through loosely structured sequences of internal states will allow understanding the genesis and development of cognitive responses in infants and the role played in their emergence by response variance.

**P3.004 Beyond the receptor: new strategies to study the dynamic interactions between the AMPAR and their auxiliary subunits**

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In the central nervous system, fast excitatory synaptic transmission is mainly mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR). AMPAR are homo-tetrameric or hetero-tetrameric receptors assembled from different combinations of four core subunits, GluA1-4. These pore-forming then form a macromolecular complex with several interacting proteins, the AMPAR auxiliary subunits. To date, more than 30 different auxiliary subunits have been identified<sup>[1]</sup>. Those are known to exert a wide range of functions on the receptor: from receptor stabilization, ER-export, trafficking, synaptic anchoring, to channel gating modulation. Despite their relevance in proper receptor function and synaptic transmission, there is still a lack of knowledge on how these proteins interact and regulate AMPAR. In particular, it is unknown whether a given AMPAR can interact with different auxiliary subunits during its lifetime and what would be the modalities and role of such an exchange between different auxiliary subunits. Here, we report the development of two new approaches that will allow us to study the dynamic of the interaction between AMPAR and different auxiliary subunits. 1) the interaction between AMPAR and the ferric-chelate reductase 1-like protein (FRRS1L), thought to play a critical role during AMPAR biogenesis<sup>[2]</sup>, using fluorescence-lifetime imaging microscopy (FLIM)-based Förster resonance energy transfer (FRET), and 2) the combination of unnatural amino acid with click-chemistry to surface-label the transmembrane AMPA receptor regulatory proteins (TARP) family of auxiliary proteins, key mediators of AMPA receptor trafficking and channel gating<sup>[3, 4]</sup>.

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P3.005

**Deletion of CB<sub>1</sub> receptors in D1-positive cells impairs object recognition memory and synaptic plasticity**

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*Via modulation of neuronal and glial activity by cannabinoid receptor type-1 (CB<sub>1</sub>), the endocannabinoid system is a major brain modulatory system controlling memory functions. We observed that a mouse line lacking CB<sub>1</sub> in cells expressing dopamine receptor type-1 (D1-CB<sub>1</sub>-KO) displayed impaired long-term, but not short-term, novel object recognition memory (NOR). D1-CB<sub>1</sub> positive cells are mainly present in the striatal GABAergic neurons although recent evidence suggests that hippocampal D1-positive cells also express CB<sub>1</sub> receptors. Interestingly, re-expression of CB<sub>1</sub> in D1-positive cells in the hippocampus of D1-CB<sub>1</sub>-KO mice, but not in the striatum, reversed the NOR impairment present in these mice. GABA<sub>A</sub> receptor inhibition rescued the memory impairment of D1-CB<sub>1</sub>-KO mice, suggesting that excessive inhibition is part of the mechanism involved in the D1-CB<sub>1</sub>-KO memory phenotype. Moreover, we found that *in vivo* long-term potentiation (LTP) in the CA3-CA1 pathway of the hippocampus is modulated by learning the NOR task. Notably, D1-CB<sub>1</sub>-KO mice displayed normal hippocampal plasticity in basal conditions, but they lacked the learning-induced increase of LTP, indicating that CB<sub>1</sub> receptors expressed in hippocampal D1-positive cells are required for this form of *in vivo* plasticity. Overall, these results provide functional evidence for the involvement of specific hippocampal circuits in endocannabinoid-dependent long-term memory processes.*

P3.006

### Exploring the role of FLNA in cortical development and function

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Mutations in the actin-crosslinking protein FLNA are the main cause of Nodular heterotopia (NH). NH is caused by defective neuronal migration that results in ectopic neuronal nodules lining the walls of the lateral ventricles and is highly associated with epilepsy, intellectual disability and, occasionally, with ASD. Patients have seizures and their cognitive level varies from normal to moderate. No correlation between the extent of NH and epilepsy severity was found suggesting that aberrant cortical circuitry rather than nodules is responsible of the disease. The main objective of this work is to assess the impact of FLNA damage on cortical development and activity. The hypothesis is that Flna regulates the morphological and functional maturation of pyramidal neurons and that the presence of the nodules in patients could represent only the “tip of the iceberg” of a global cortical circuitry. We found that FLNA regulates the morphological- functional maturation of pyramidal neurons support the hypothesis (Falace et al. manuscript in preparation). Considering the electrophysiological data where we found an increase of inhibition in Flna-cKO glutamatergic neurons, we suggest that gabaergic neurons may participate to the adaptation of the network. To address the contribution of GABAergic neurons in NH pathogenesis, we crossed homozygote Flna conditional females to Nestin Cre male animals. This cross grants the ability to remove Flna from both glutamatergic and gabaergic neural progenitor cells from an early age, which gives to our model a closeness to the situation found in patients. We target specific subsets of interneurons through immunohistochemistry, in order to quantify interneurons and its distribution along the Cortex. Along with gabaergic neuronal distribution, the electrophysiological properties will be tested through local field excitatory/inhibitory postsynaptic potentials (fEPSPs/fIPSPs) in the Somatosensory Cortex.

P3.007

**Consuming a balanced diet from weaning reverses the inappropriate food preferences in offspring of low protein-diet fed rat dams but modifies the glutamatergic and dopaminergic circuits in hypothalamus and reward pathway**

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The perinatal period is a critical window in which different stresses (nutritional, inflammatory, infectious,...) could condition the occurrence of eating behaviors like to promote metabolic disorders in adulthood. It is now clearly established that dopaminergic function is impaired during an obese diet in both humans and animals. This dopaminergic function is also impaired in animals born with IntraUterine Growth Retardation (IUGR) that could be at the origin of the modification of the food preferences observed in these models. Since the dopaminergic circuits evolve and grow over the perinatal period, we still do not know clearly the impact of early malnourished perinatal diet on the organization of dopaminergic networks and functions?

The objectives of this study are to understand the impact of perinatal diet on evolution of dietary preferences and to correlate this longitudinal study with the measurement of the activity of the brain reward circuitry.

This study has been done on a rat model of IUGR. Different experiences have been done on pups at 3 stages: PN25 (childhood), PN50 (adolescence), and PN100 (young adult), using a combination of techniques : free choice preference for fat, immunochemistry of dopaminergic neurons, molecular biology (RNA-seq) and electrophysiology (patch clamp of MSN neurons in the Nucleus Accumbens (Nacc)).

When compared with control rats, first results showed that perinatal protein restriction lead to a higher preference for fat at PN25 (altered food behavior), a lower preference for fat at PN50 (protective mechanisms?) and no difference of preference for fat at PN100 (compensation mechanisms?). To understand these behaviors, cerebral molecular and functional signatures have been searched in brain structures controlling food behavior (hypothalamus and mesolimbic system). Food preference could be correlated with modification of dopaminergic transcripts. Moreover, electrophysiological properties of MSN in the Nacc (which is a target area of dopamine neurons and play a central role in the reward system) are differently affected at the 3 stages.

To conclude, a perinatal protein restriction has an impact on fat preference later in life with a long effect on remodeling and information processing of brain reward circuitry.

P3.008

**Neuronal integration in the adult olfactory bulb is a non-selective addition process**

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Adult neurogenesis is considered a competition in which neurons scramble during a critical period for integration and survival. Moreover, newborn neurons are thought to replace preexisting ones that die. Despite indirect evidence supporting this model, systematic *in vivo* observations are still scarce. We used 2-photon *in vivo* imaging combined with low dose thymidine analog pulse chase experiments to study neuronal integration and survival in the olfactory bulb (OB). We show that cell-loss in the OB occurs only at low levels.

Neuronal death resembling a critical period was induced by standard doses of thymidine analogs, but disappeared when low doses of Edu were used. Finally, we demonstrate that the OB grows throughout life. This shows that neuronal selection during OB-neurogenesis does not occur during integration and argues against the existence of a critical period for survival. Moreover, the OB is not a turnover system but shows lifelong neuronal addition.

P3.009

**The Punctin-Neuroligin partnership regulates the *C. elegans* inhibitory synapse; investigating the synaptic interactions of Punctin**

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Synaptic defects can lead to neuropsychiatric impairments, highlighting the need for understanding the molecular mechanisms responsible for correct synapse function. Many synaptic organizers have been identified, among which the membrane-linked cell adhesion proteins Neuroligin (NLG) and Neurexin, whose mutations are associated with synaptic malfunction and whose mode of interaction is well documented. In *C. elegans*, the secreted multidomain protein Punctin was identified as a novel NLG partner, critical for postsynaptic recruitment of GABA<sub>A</sub> receptors, and hence, the regulation of the inhibitory *versus* excitatory synapse identity. The human gene encoding a Punctin orthologue has been identified as a susceptibility gene for schizophrenia.

To characterise the molecular determinants and binding parameters involved in the Punctin-NLG partnership, we combined cell biology, biochemical and structural approaches. Spontaneous cleavage of Punctin toward a shorter form, observed both in vitro during recombinant protein production and in vivo, suggested occurrence of a physiologically relevant maturation process. The Punctin domain primarily involved in NLG recognition was identified, albeit other domains may provide secondary contact points to stabilise the complex. Cross species analysis of Punctin specificity revealed absence of binding to a mammalian NLG but instead, binding to a fish cholinesterase, a feature possibly related to the suspected role of these enzymes in cell adhesion. To compare the molecular determinants at the surface of these three structural relatives, we solved a crystal structure of *C. elegans* NLG, whose comparison with available structures of the other two is underway. In parallel, by assaying the effect of heparin, a mimic of extracellular matrix proteoglycans, on the Punctin-NLG interaction, we found the presence of heparin to be deleterious for complex formation. Further investigation of the Punctin interaction network in *C. elegans* will document how other synaptic molecules and/or extracellular matrix components are involved in neuronal communication, and expectedly provide information transposable to the regulation of the human neuronal synapse.

**P3.010 Impact of a Fragile X syndrome missense mutation on the neuronal function**  
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Fragile X syndrome (FXS) is the most frequent form of inherited Intellectual Disability (ID) and a leading monogenic cause of autism. FXS results from mutations within the *FMR1* gene causing the loss-of-function of the Fragile X Mental Retardation Protein (FMRP). FMRP is an RNA-binding protein that transports several mRNAs along dendrites to the base of active synapses for local translation in an activity-dependent manner. In FXS, the loss-of-function of FMRP leads to a hyper-abundance of immature dendritic protrusions, resulting from abnormal translation events at the synapse. Such defects lead to altered postsynaptic maturation and pruning and, consequently, synaptic communication and plasticity deficits. We recently demonstrated the activity-dependent SUMOylation of FMRP *in vivo*, which is critical to the neuronal function. Interestingly, several *FMR1* missense mutations identified in FXS patients lead to amino-acid changes that are close to the active SUMO sites of FMRP. This raises the exciting hypothesis that these mutations directly affect the SUMOylation state of FMRP and, consequently, its function, leading to FXS. Thus, we successfully engineered a Knock-In mouse model expressing one of these *FMR1* mutations. Using this unique FXS model and a combination of state-of-the-art approaches, we are currently dissecting the impact of this FXS mutation on the FMRP function with particular attention to its activity-dependent SUMOylation and synaptic regulatory role.

**P3.011 Glutamate imaging reveals co-operative release sites in the CA3 giant mossy fiber boutons**

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One of the most studied central synapses which have provided fundamental insights into cellular mechanisms of neural connectivity is the ‘giant’ excitatory connection between hippocampal mossy fibers (MFs) and CA3 pyramidal cells. Its large presynaptic bouton features multiple release sites and is densely packed with thousands of synaptic vesicles, to sustain a highly facilitating ‘detonator’ transmission. However, whether glutamate release sites at this synapse act independently, or rather in a co-operatively and synergistic fashion, remains unknown. This knowledge is critical for a better understanding of mechanisms underpinning presynaptic plasticity and postsynaptic signal integration rules. Here, we use the optical glutamate sensor SF-iGluSnFR and the intracellular  $\text{Ca}^{2+}$  indicator Cal-590 to monitor spike-evoked glutamate release and presynaptic calcium entry in MF boutons. Multiplexed imaging reveals that distinct sites in individual MF giant boutons can release glutamate generally independently, in a probabilistic fashion. However, low release probability events tend to be synchronized in adjacent release sites. This observation argues for a co-operative presynaptic mechanism of release synchronization in the giant mossy fiber bouton.

**P3.012 Death of Cajal-Retzius cells is required for developmental pruning of synapses and for the maturation of cortical circuits**

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Programmed cell death (PCD) is emerging as a key player in the wiring of cortical circuits. Cajal-Retzius cells (CRs) are among the first born cortical neurons and reside in the most superficial layer of the developing cerebral cortex from where they coordinate multiple crucial steps in the construction of functional circuits. At embryonic stages CRs comprise at least three distinct subtypes which differ for their generation site (septum, ventral pallium and hem), molecular signature, distribution at the cortical surface and function. The vast majority of CRs are thought to be transient as they disappear during early postnatal life in mice as well as in primates and their abnormal persistence is associated with pathological conditions in humans.

Here we show that subtype-specific features persist at postnatal stages. Using genetic fate mapping our work revealed that CR subtype-specific differences exist in the distribution and timing of disappearance in the postnatal brain. We showed that all CR subtypes undergo cell death although, surprisingly, through at least two molecularly distinct pathways. Conditional inactivation of the pro-apoptotic factor *Bax* prevented death of septum but not hem-derived CRs. Surviving CRs are integrated in neural circuits and keep the electrophysiological properties of immature CRs. Furthermore, we found that CRs survival promotes exuberance of dendrites and spine density in upper layers pyramidal neurons. This results in imbalanced Excitatory/Inhibitory (E/I) ratio due to an increase in excitatory drive in the network.

These results strongly suggest that CRs demise is a novel player in developmental pruning of dendrites and synapses and provide the first mouse model to test the relevance of altered PCD in human pathologies. We will discuss the effects of maintaining immature neurons in the mature cortex and the role of a subtype-specific control of CR programmed cell death in the construction of cortical functional and dysfunctional circuits.

**P3.013 Studying neuronal network genesis to understand neurodegenerative diseases: role of VPS35, a sub-unity of the retromer**

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An ever-increasing number of people are afflicted with neurodegenerative diseases, becoming clearer that adulthood neurodegenerative disorders are likely due to early defects in embryonic neuronal development. Therefore, a better understanding of the role of genes implicated in development and demise of neurons will be key to a better comprehension of these diseases. It has been shown that VPS35, a member of the protein complex named “retromer”, is involved in familial forms of neurodegenerative diseases such as Parkinson’s. The retromer is involved in protein recycling, thus, defective VPS35 may trigger premature protein degradation, or accumulation of toxic proteins leading to neuronal cell death. VPS35 is expressed in the developing mouse cortex but little is known about its role. The present project is aimed at deciphering in detail the activities of VPS35 during brain development and brain wiring. We already have data implicating VPS35 conditional deficiency in cortical development and in several forebrain axon main tracts. As at the level of the somatosensory cortex, where the entire barrel sensory map is absent. The results will be significant to understanding novel regulatory mechanisms controlling neural development and their biological basis.

**P3.014 Disruption of the transcription factor NEUROD2 causes a spectrum of neurobehavioral phenotypes in mice and humans**

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The transcription factor NEUROD2 is a recent candidate for neuropsychiatric disorders and epilepsy. It is strongly expressed in pyramidal neurons in the forebrain and involved in synapse differentiation and integration but its exact functions in development and adulthood remain elusive. We set out to understand the functions of NEUROD2 in the developing forebrain and found that losing this factor results in hyperactivity, altered social interactions, stereotypic behaviors and spontaneous epileptic seizures as well as abnormal dendritic and synaptic maturation, laminar positioning and physiology of cortical projection neurons. Informed by these neurobehavioral features in mouse mutants, we identified several individuals with de novo heterozygous truncating mutations and copy number variations in NEUROD2 who share similar clinical features, including intellectual disability, epilepsy and autism spectrum disorders. Our findings support the importance of NEUROD2 in development and functioning of cortical circuits and its implication in neuropsychiatric disease.

**P3.015 Long-term plasticity of intrinsic excitability in dorsal lateral geniculate nucleus**  
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Although the dorsal Lateral Geniculate Nucleus (dLGN) is classically considered as a relay of visual information, recent work has shown that dLGN neurons may be subject to experience-dependent plasticity (Rose & Bonhoeffer, 2018). While activity-dependent plasticity of synaptic transmission has been shown, little is known regarding the possible modulation of intrinsic excitability by neuronal activity.

In our study, we performed whole-cell patch-clamp recordings of dLGN neurons in acute brain slices to check whether plasticity of intrinsic excitability may occur in these neurons following activity increase. dLGN neurons were recorded in current clamp in P19-P20 Long Evans rats and their excitability was assessed by current injections designed to elicit a few action potentials. In order to induce long-term potentiation of intrinsic excitability (LTP-IE), trains of action potential were elicited by 40 Hz current pulses injection to mimic visual drive, and excitability was then checked.

Surprisingly, we found that these trains of stimulations resulted in a persistent (>25 minutes) increase in excitability in 12 out of 15 cell tested. No change in intrinsic excitability was observed without stimulation. The induction and expression mechanisms are being characterized. We conclude that dLGN neurons express intrinsic plasticity during development that might be tuned by visual experience.

P3.016

### Dopamine triggers Long Term Potentiation

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Long Term Potentiation (LTP) is an increase in synaptic transmission dependent on neuronal activity that can be triggered in the hippocampus using high frequency stimulations. LTP is considered as one major mechanism of learning and memory. It can actually be triggered by learning. However, high frequency stimulations are not compatible with the physiology of hippocampal neurons and the Hebbian model of LTP cannot account for everyday memory. Since dopamine neurons are activated by salient and novel unpredicted stimuli, we hypothesized that learning-induced LTP could be triggered by dopamine release.

We used optogenetic stimulation of dopamine cells of the ventral tegmental area (VTA) coupled with electrophysiological recording in the hippocampus. We showed that co-activating dopaminergic neurons and glutamatergic transmission in the hippocampus was sufficient to cause an increase in glutamatergic synaptic transmission which partially occludes LTP induced by high frequency stimulations. This plasticity is blocked by a D1 antagonist. These results demonstrate that dopamine is able to trigger LTP in the hippocampus.

We propose dopamine as a learning signal which would trigger LTP and thus, the formation of long lasting memory upon encounter of a salient and novel stimulus.

**P3.017 Study of the etiology of a rare form of mental retardation linked to autism, associated with mutations in the TRIO gene**

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Intellectual Disability (ID) and Autism Spectrum Disorders (ASD) are neurodevelopmental disorders with large genetic components. Thanks to the recent massive sequencing of patient exomes, a small group of children has been identified with potentially deleterious *de novo* mutations in the TRIO gene and presenting a rare form of ID, associated with ASD. TRIO is a Rho-Guanine Nucleotide Exchange Factor (RhoGEF), which activates the GTPase Rac1 to modulate actin cytoskeleton remodelling. It is an important regulator of neuronal migration, axon growth and guidance, and synaptogenesis. It is highly expressed in many areas of the developing brain and pathogenic variants in this gene are now recognised as an important cause of autosomal dominant mental retardation with or without microcephaly.

The clinical phenotypes of patients with TRIO mutations are quite heterogeneous, and clear phenotype/genotype correlations are difficult to make at this stage. Analysing the TRIO missense mutations found in patients, we identified two mutational hotspots in the TRIO sequence. We found that mutations in Hotspot 1 (GEF1 domain) associated to ID and microcephaly dramatically inhibit the activation of Rac1, the main target of TRIO to control actin cytoskeleton remodelling (Pengelly R./Greville-Heygate S./Schmidt S. et al, 2016). We further show that patients with mutations in Hotspot 2 present a stronger developmental delay with macrocephaly, sometimes associated to ASD. At a molecular level, we found that mutations in Hotspot 2 induce an overactivation of Rac1, and dramatically perturbed the formation of dendritic spines in cultured hippocampal neurons and affected neuronal development in zebrafish (unpublished data).

All together, these data show that mutations targeting different domains of TRIO induce either a hypo- or a hyper-activation of TRIO, as monitored by the levels of Rac1 activation. This may explain the heterogeneity of the phenotypes. We are currently evaluating in more detail how the different TRIO mutations disrupt the functioning of the nervous system.

P3.018

**Fast unsupervised generation of oriented vascular graphs**

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The vasculature of the brain is a complex network of arteries, capillaries and veins that provide nutrients to neurons and glia. Ischemia, trauma or neuroinflammation are known to trigger rearrangements of this network through plastic remodeling of the organization of endothelial cells, pericytes or smooth muscle cells. However, the rules that govern the homeostatic reorganization of the topology of this network are unclear. The challenge in deciphering those rules lie in our current limited capacity to reconstruct the organization and orientation of blood flow through the brain in 3D with accuracy at a large scale. We present here tools for the reconstruction and analysis of the oriented graph of the cerebral blood vessels based on light sheet microscopy and tissue clearing. We designed a novel way to immunolabel intact filled blood vessels, optimized conditions to image at 1.6µm/px iDISCO+ cleared brains with light sheet microscopy and developed a high-performance toolbox including a novel non-rigid stitcher, advanced structural filters and a deep convolutional neuronal network to generate oriented, atlas-registered and annotated graphs of the vasculature from terabyte sized datasets in a few hours. The analysis of these graphs provides insights into the variations, consistency and dynamic adjustments of the brain vasculature under various conditions.

**P3.019 A primary cilium-dependent cAMP-rich zone at the centrosome is necessary for proper saltatory neuronal migration in the postnatal mouse brain**

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cAMP is crucially involved in brain development. However, its role in neuronal migration is still unclear. To analyze cAMP dynamics in migrating cells, we performed live imaging of a cAMP-specific FRET biosensor in newly-formed migrating cells of the postnatal Rostral Migratory Stream (RMS). These cells display a cyclic saltatory mode of migration with alternation of nucleokinesis and pausing phases and stereotypical movement of the centrosome.

We observe a cAMP-rich small dynamic zone surrounding the centrosome of migrating cells during nucleokinesis. The centrosome is located at the basis of the primary cilium, a small rod-shaped organelle important for neuronal migration. We observed that genetic ablation of the primary cilium in RMS migrating cells leads to a slowing-down of migration, with reduced distance of nucleokinesis and increased pausing phases. Centrin-RFP imaging during migration revealed concomitant defects in centrosomal dynamics.

Interestingly, the centrosomal cAMP-rich zone disappears in cilium-ablated neurons, suggesting an essential role for the cilium in its formation. Accordingly, immunocytochemistry for Adenylate Cyclase 3 (AC3) shows its ciliary localization. Moreover, AC pharmacological inhibition leads to similar defects in migration and centrosomal movement as cilium ablation, suggesting the importance of ciliary cAMP production for normal migration. We hypothesized that the cAMP-rich zone could act on a centrosomal cAMP-dependent Protein Kinase A (PKA). Indeed, immunocytochemistry against PKA showed its almost exclusive centrosomal localization in migrating neurons. Moreover, expression of a non-centrosomally located dominant-negative form of PKA delocalizes PKA and also recapitulates the migratory phenotype of primary cilium ablation and AC pharmacological inhibition.

Our data thus unveil a new mechanism regulating neuronal saltatory migration through ciliary production of cAMP diffusing as a cAMP-rich zone around the centrosome, which locally activates PKA. We are currently investigating the role of this cAMP-rich zone on microtubule dynamics through PKA activation of the Lis1/Dynein microtubule motor complex, shown to be essential for saltatory migration.

**P3.020 Morphological and electrophysiological characterization of CSPNs in a mouse model of fine motor skill impairments**

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The mammalian neocortex, responsible for high brain functions such as voluntary movements and sensorimotor integration, is subdivided into functionally distinct areas and composed of six layers. This peculiar structure mirrors the function of each area, with a primary motor cortex (M1) containing a large number of layer 5 subcerebral projection neurons (SCPNs) and a primary somatosensory area (S1) mainly composed by layer 4 sensory neurons. These neurons connect themselves up into dynamic networks that generate and maintain stable activity patterns via a fine-tuning of intrinsic excitability, synaptic strength and network excitability and inhibition.

Our lab has previously shown that loss of COUP-TFI (Nr2f1) cortical expression leads to affected neocortical arealization, impaired SCPNs specification and ultimately to altered voluntary movements, recapitulating symptoms observed in human patients. In this work, we investigate whether or not these mis-specified neurons are able to reach morphological and electrophysiological maturity, despite changes in environment and connectivity.

We first generated a topography map of SCPNs targets in the pontine nucleus (PN) to assess if a change in cortical areal identity may influence PN spatial organization. We then analyzed morphological and intrinsic electrophysiological properties of SCPNs to evaluate maturation and functionality of mutant cells.

Our data show that SCPNs lacking COUP-TFI tend to project more peripherally in the PN, in areas that normally receive projections from M1. Moreover, we observe that SCPNs from both M1 and S1 are characterized by an increased intrinsic excitability and a reduction of basal dendritic arbor complexity at juvenile stages and a reduction in dendritic spine density at adult stages.

Overall, our work shows that cortical area patterning genes, such as COUP-TFI, besides controlling specification of distinct neuronal subpopulations, play a key role in directing their maturation both in term of morphological and electrophysiological features. Moreover, we show that cortical arealization modifications are also reflected in the temporal and spatial organization of subcerebral targets, such as the PN.

P3.021

**The lack of spatacsin (SPG11) disrupts postnatal synaptogenesis in mouse**

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Hereditary spastic paraplegias are neurodegenerative motor neuron diseases characterized by rigidity and progressive paralysis of the lower limbs. Spastic paraplegia type 11 (SPG11) is the most common recessive autosomal paraplegia, accounting for 21% of autosomal recessive forms. The severe motor conditions were often associated with cognitive disorders including mental retardation (low IQ < 70), learning disabilities, short-term memory impairment.

We have generated a SPG11 knockout mouse which perfectly mimics the clinico-pathological features of the human disease. Indeed, the mice have a motor deficit and a cognitive deficit resulting in relatively early spatial and emotional memory disorders (Branchu *et al.*, 2017).

We investigated, by morphometric approaches, the cellular basis of this cognitive deficit. We used photonic and electron microscopies on well-fixed and Epon included hippocampus. We analysed the early post-natal developmental stages of hippocampus of *Spg11<sup>-/-</sup>* mice at P10, P14, P20 and P60 since the memory impairment manifest early. First, the number of pyramidal neurons in CA1 area of the hippocampus was quantified and the thickness of the SR measured. Then, with electronic microscopy, we quantified the synapses of the SR in CA1 area. Finally, to complete the study, we realized a morphological characterisation of the dendritic spines.

We showed: I) Neither modification on neuronal density of CA1 nor on the thickness of SR; II) Decreased number of synapses in the SR of the CA1.

No developmental alteration of the hippocampus was observed, but the study highlights a clear delay of synaptogenesis in *Spg11<sup>-/-</sup>* mice which reach 20% in comparison with *Spg11<sup>+/+</sup>* mice. Further studies could decipher the molecular mechanisms of this synaptogenesis delay.

P3.022

**Genetic and environmental factors shape the brain development**

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The balance between excitatory and inhibitory system plays a crucial role during the programming period with long-term effects. In the rat adult offspring, the perinatal stress (PRS) environmental model exhibits an important effect of early life stress on glutamatergic system characterized by a massive reduction in the glutamate synapse release. In the aged PRS rats, we showed a decreased risk-taking behavior, spatial memory and gross and thin motor skills. As for the adult PRS rats, these behavioral alterations in aged rats are associated with large reductions in the levels of synaptic vesicle-related proteins (Rab3a, SNAP25 and syntaxin) in the ventral hippocampus. Moreover, in aged PRS rats we also found a decrease in the protein expression of GluR2/3 and mGluR5 in the ventral hippocampus, as previously observed in adult PRS animals. Notably, both sexes present a reduction of mGluR2/3 expression in the ventral hippocampus at adulthood and aging. Hence, we hypothesized that Group II mGlu receptors could be a good candidate to understand the interaction between genetic and environmental factors in the brain development. There is evidence that mGlu3 receptors could be involved in the GABAergic interneurons development which play a key role in the early brain maturation. Thus, we examined whether mGlu3 receptors influence the developmental trajectory of interneurons and cortical GABAergic transmission in the postnatal life. We found that mGlu3<sup>-/-</sup> mice display substantial changes in the expression of interneuron-related genes in the prefrontal cortex (PFC) and hippocampus in the early postnatal life, when interneurons undergo their final differentiation. These changes include large reductions in the transcripts encoding for specific biochemical markers of GABAergic interneurons, such as parvalbumin, somatostatin, and vasointestinal peptide, as well as changes in the transcripts encoding for the GluN1 subunit of NMDA receptors and the CB1 receptor. These and other results suggest that both genetic and environmental factors shape the developmental trajectories of glutamatergic and GABAergic transmission. Current studies with mGlu3<sup>-/-</sup> mice exposed to perinatal stress aim to elucidate the interplay between genetic and environmental factors.

P3.023

**The Kv7.2 (KCNQ2)-mediated M-current tunes the locomotor rhythm**

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The locomotion is a complex behavior consisting in a coordinated sequence of muscle activation promoted by a Central Pattern Generator (CPG). To gain insight into the function of the CPG, it is important to characterize individual ion channels in locomotor-related neurons and determine their roles in generating rhythmic and coordinated movements during locomotion. Our previous studies for the biophysical basis for rhythmogenesis has identified the persistent sodium current ( $I_{NaP}$ ) as contributing to rhythmic bursting in locomotor-related interneurons. The immediate conclusion was that the locomotor rhythm generation could emerge from excitatory circuits incorporating  $I_{NaP}$  as a “pacemaker” current. In a “push-pull” organization of the spinal locomotor network, the present study investigates the role of a persistent potassium current mediated by Kv7.2 (KCNQ2)-channels, also called M-current ( $I_M$ ), into the operation of the locomotor CPG. As a first result, *in vivo* intraperitoneal injection of Kv7.2 channel blocker (XE991) lengthens the step duration of juvenile rats whereas the opener (Retigabine) shortens it. These data are consistent with the drugs effects on the NMA-induced fictive locomotion observed with the *in vitro* isolated spinal cord preparations of neonatal rats. The early postnatal expression of Kv7.2 channels in the spinal locomotor network has been confirmed with confocal imaging and electrophysiological recordings. We demonstrated that Kv7.2 channels expressed in the axon initial segment contributes to oscillatory processing in the locomotor CPG. The Kv7.2 pharmacological blockade, as well as the KCNQ2<sup>T274M/+</sup> mutation, leads to a decrease of the duration of (1) autorhythmic activities in interneurones and (2) NMA-induced voltage oscillations in motoneurones. Opposite effects is obtained with KCNQ enhancers. In conclusion, our study provides evidence that the locomotor rhythm may be modulated by balancing the relative contribution of  $I_M$  and  $I_{NaP}$ .

P3.024

### **Musical sonification for the rehabilitation of Parkinsonian dysgraphia**

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Parkinsonian dysgraphia is characterized by a motor deterioration of handwriting that oversteps the pure reduction of writing size, namely micrographia. Music has been shown to activate a pathway that may compensate for the defective cortico-striatal networks in patients with Parkinson disease (PD), leading to motor improvements. In this study, we tested an original strategy of musical sonification in PD dysgraphia. This method changes music as functions of handwriting kinematics in such a way that velocity distortions generate music distortions. Twelve PD patients (on medication) and 12 healthy controls were recruited for a “pre-test/training/post-test” experiment design. Three training sessions were compared for which participants were asked to produce graphomotor exercises. Each session was conducted under one of the following three experimental conditions: background music (unrelated to handwriting), musical sonification (related to handwriting), and silence. The trainings were counterbalanced between participants. All participants were tested just before and after each training. During the tests (all in silence), participants were required to draw loops, to write the French word “cellule” (cell), and to make their own signature. Prior to the first training, both groups performed similarly, except for the signature that was slower for the PD patients. The performances during the training were better with musical sonification than under silence or background music, for both groups. In fact, loop velocity, height and frequency were improved under musical sonification, while background music increased loop frequency. Significant improvements of the velocity of the loop production and words were found for both groups after the training with musical sonification, but not after training with background music. This study established a proof of concept highlighting the specific effect of musical sonification on the motor control of handwriting. The interest of this study goes beyond the rehabilitation of Parkinsonian dysgraphia: it provides a novel argument to use musical sonification as an original, simple and easy to reach auditory guidance strategy for movement rehabilitation in PD patients.

P3.025

**Reorganization of brain networks following long-term sensory loss**

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Large-scale rearrangements of axonal projections in the post-natal brain are gradually restricted during development as networks mature and are refined, to a point of being largely undetectable in the adult age. However, studies of neuronal activity at different scales suggest that functional adaptations in adult brain networks can take place under certain circumstances. For instance, lasting modifications in sensory inputs trigger homeostatic changes to the receptor fields of cortical neurons in the adult brain. This could be explained by local remodeling of dendritic spines or the addition/pruning of axonal branches. It is unclear however whether more extensive changes across distant brain areas are still possible at this stage. We seek to test the hypothesis that long-term changes to sensory experience in adult brains can lead to long-range structural rearrangements of neuronal connectivity. Using a model of permanent denervation of the mystacial pad in the mouse, we analyzed the effects of peripheral deprivation on exploration-evoked whole-brain activity over several weeks. Automated mapping of Fos expression by iDISCO+ tissue clearing and ClearMap analysis revealed modifications over time in activity patterns throughout the brain affecting many functionally distinct regions. We could document expected adaptive changes to neuronal activity in primary sensory areas but also in distant motor, associative and neuromodulatory regions. To better understand the cellular processes underlying these changes in activity, we studied the associated changes to the translatome and connectivity of the barrel field in the primary somatosensory area. The translatome of active cells was analyzed by ribosome capture followed by RNA-seq. This points to the possible implication of inflammatory, vascular and neuronal players in the response to long-lasting modifications in the somatosensory cortex. Finally, we mapped the connectivity of the candidate regions undergoing changes in their activity patterns. This study provides a brain-wide view of the molecular, functional and structural changes elicited by long-term changes to sensory experience in the adult brain.

P3.026

### Role of Huntingtin in the maturation of cortical neurons

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Huntington's disease (HD) is a devastating neurodegenerative disorder characterized by the dysfunction and degeneration of striatal and cortical neurons during adulthood. Clinical features of HD include progressive motor, psychiatric and cognitive symptoms. The mutation that causes HD is an abnormal polyglutamine expansion in the huntingtin (HTT) protein. Since HD is characterized by an adult onset, most studies have focused on the toxic effects elicited by mutant HTT in adult neurons. Nevertheless, it is now widely accepted that part of HD pathological events is also attributable to the loss of functions of HTT. Thus, understanding the normal functions of this protein is crucial to elucidate the mechanisms underlying the pathogenesis.

Growing evidence shows that HTT is essential during development as revealed by the early embryonic lethality of the complete *huntingtin* knock-out mice. During cortical development, HTT is known to regulate the division of progenitor cells, the migration of excitatory newborn neurons and their dendritic morphogenesis. Nevertheless, little is known about the normal cellular function during later steps of cortical development. In this context, I study the role of HTT during the maturation of excitatory cortical neurons. For this purpose, by using genetic mouse models and *in utero* electroporation, I determine *in vivo* the consequences of HTT loss on: (i) the morphogenesis of dendritic spines, (ii) the formation of functional synapses and (iii) the neuronal activity of cortical neurons. Finally, I aim to identify the molecular mechanism by which HTT regulates these events.

**P3.028 Serotonin Receptors-Associated Networks: role in non-amyloidogenic processing of APP**

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Alzheimer's Disease (AD) is the most common form of dementia worldwide and has become a major public health problem. This pathology is characterized by the presence of two main features in the brain: neurofibrillary tangles (NFTs) composed of hyperphosphorylated Tau and amyloid plaques, dense aggregates of hydrophobic  $\beta$ -amyloid peptide (A $\beta$ ). A $\beta$  peptide formation results from the amyloidogenic degradation of the Amyloid Precursor Protein (APP) by  $\beta$ - and  $\gamma$ -secretases mainly in early/sorting and late endosomes. On the other hand, the non-amyloidogenic proteolysis of APP, within the A $\beta$  sequence by  $\alpha$ -secretase, releases the extracellular fragment of APP (sAPP $\alpha$ ), which is neurotrophic and neuroprotective. Non-amyloidogenic APP processing mainly occurs at the plasma membrane level. The most active  $\alpha$ -secretase in the brain is ADAM10. We have demonstrated that the serotonin type 4 receptor (5-HT<sub>4</sub>R) physically associates directly or indirectly with ADAM10 and APP, modulates their trafficking and maturation, and thereby constitutively promotes the non-amyloidogenic cleavage of APP. Our objectives are to decipher the protein networks underlying the trafficking of the 5-HT<sub>4</sub>R/ADAM10/APP complex to the plasma membrane in order to propose innovative targets to reduce amyloid production in the context of AD. Using an unbiased proteomic approach, we identified candidate proteins able to interact with this complex. By co-immunoprecipitation, we validated the interaction of selected proteins of interest with 5-HT<sub>4</sub> receptors. Interestingly, a series of 5-HT<sub>4</sub>R-interacting partners belongs to the insulin signalling pathway. These proteins could be of particular relevance in the context of Alzheimer's Disease, because of their impact on the two main aspects of the disease: the APP trafficking and the Tau phosphorylation. We are decrypting their role in the trafficking of the 5-HT<sub>4</sub>R/ADAM10/APP complex and exploring their ability to promote the non-amyloidogenic processing of APP.

**P3.029** **Live super-resolution studying of AMPARs intracellular transport in brain slices**  
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AMPARs intracellular transport is a key mechanism fundamental for the maintenance of a tightly dynamic equilibrium of the number and/or type of AMPARs at the plasma membrane responsible to tune synaptic efficacy. Here we explored for the first time, the properties and contribution of GluA1-AMPARs intracellular vesicular transport to basal transmission and to long term synaptic plasticity in the CA1 region of the hippocampus in organotypic slices. We use a unique combination of 1- innovative molecular tools, 2- high-resolution, cutting-edge imaging methods which allowed us to record video of vesicles in live cells with *the Lattice Light Sheet Microscope (LLSM)*, 3- electrophysiology. We knocked out endogenous GluA1 in a small number of CA1 cells by expressing Cre recombinase into neurons from GluA1-floxed animals. We studied the intracellular transport of different AMPAR pools, *newly synthetized* and *internalized* receptors, taking advantage of two different approaches: the ARIAD system which allows TdTomGluA1-AMPAR to leave simultaneously the endoplasmic reticulum (ER) on demand and follow *newly synthetized* vesicles in dendrites; and BirA/mSA system to look at the *internalized* biotinylated GluA1-AMPAR. We detected single vesicles transport of *newly synthetized* and trafficking of *recycled* AMPARs thanks to LLSM. In parallel, we recorded AMPAR currents during basal transmission and after LTP from transfected cells with the final aim to correlate vesicular transport and synaptic activity.

Thus, our findings shed new light on the dynamic of different pools of AMPARs in brain slices, pushing the frontier in neuroimaging and discovering new insights on the delivery of AMPARs over their journey to and from the PM and the role such properties play in neuronal plasticity.

**P3.030 Study of the pathogenic mechanisms of Lesch-Nyhan disease in relation to the dopaminergic system in the *Drosophila* model**

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The purine salvage pathway is an essential component of cellular metabolism that allows the recovery of free purine bases derived from the diet or the degradation of nucleic acids and nucleotides, thus avoiding the energy cost of *de novo* synthesis. The two enzymes involved in this pathway in mammals are adenine phosphoribosyltransferase (APRT) and hypoxanthine-guanine phosphoribosyltransferase (HGPRT). In humans, inherited mutations that suppress HGPRT activity are associated with Lesch-Nyhan disease (LND), a rare metabolic disorder affecting children, characterized by hyperuricemia and severe neurobehavioral disturbances such as dystonia, spasticity and compulsive self-injury. Studies have shown that LND patients have markedly reduced dopamine levels in the brain's basal ganglia, but the mechanisms linking purine recycling and the dopaminergic system have not been elucidated to date. Furthermore, HGPRT knockout in rodents did not induce neurobehavioral defects comparable to those observed in patients. We are studying the relation between purine metabolism and the dopaminergic system in *Drosophila*, in the hope of finding new clues about the mechanisms involved in LND pathology. No HGPRT homologue is present in the *Drosophila* genome, which suggests that the APRT homologue is the only purine-recycling enzyme in this organism. We observed that an *Aprt-null* *Drosophila* mutant showed defects partly comparable to those associated with HGPRT deficiency in humans, notably an increase in uric acid levels, as well as alterations in dopaminergic markers and locomotor behaviour. Conversely, mutants with altered dopaminergic systems exhibited specific changes in APRT expression and activity levels. We have also constructed transgenic flies expressing native or mutant human HGPRT and started to analyse consequences of these expressions on dopaminergic markers and locomotion. Overall, our current results highlight a link between purine metabolism and the dopaminergic system in an invertebrate organism and provide new models to better understand the function of purine recycling in health and disease in the human brain.

**P3.032 Differential modulation of excitatory synaptic inputs on dopamine neurons by group I metabotropic glutamate receptors**

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Activation of group I metabotropic glutamate receptors (mGlu1/5) induces long term depression (mGlu-LTD) at glutamatergic synaptic transmission onto midbrain dopamine (DA neurons). However, DA neurons receive excitatory inputs from several brain structure such as anterior cortex, subthalamic nucleus (STN), pedunculopontine nucleus and lateral hypothalamus. These inputs are endowed with different synaptic properties and susceptibility to neuromodulators. Thus it is unclear whether mGlu-LTD is present at all excitatory synapses on to DA neurons or only at a specific subset. Using midbrain acute slices and a combination of whole cell patch-clamp recording and optogenetics, we examined the sensitivity of cortical and STN glutamatergic inputs to the mGlu1/5 agonist DHPG. To probe cortical synaptic transmission, we crossed the Emx1Cre mouse line that expresses Cre recombinase in all excitatory cortical neuron, with the Cre dependent reporter line Ai32 encoding channelrhodopsin2 in fusion with YFP. To target STN inputs, we injected an adeno-associated virus encoding the opsin Chronos in fusion with GFP. Using voltage clamp recording of DA neurons in presence of the GABA A antagonist gabazine, we observed that bath application of RS-DHPG (100 µM) caused a significant amplitude reduction of light evoked excitatory synaptic currents in Emx1Cre:Ai32 mice (-33.2 ± 6.1%, n=9). This mGlu-LTD of cortical EPSC was associated with an increase of paired pulse ratio (PPR, +30.3 ± 8.5%) and with an increase of the failure rate (from 2.2 ± 0.9% to 30.6 ± 4.7%). Unlike cortical inputs, DHPG had no effect on the amplitude of STN EPSC and PPR (n=10). These data suggest that mGlu-LTD occurs via a presynaptic mechanism at cortex-DA neurons synapses and is not present at the STN-DA neuron synapse. We are currently investigating the DHPG sensitivity of other excitatory inputs using optogenetics and the molecular mechanisms of the mGlu-LTD at cortex-midbrain synapse.

P3.033

**Astrocytes modulate synaptic efficacy as a function of incoming activity**

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Data accumulated over the two last decades have demonstrated that astrocytes play key roles in the regulation of synaptic transmission and plasticity. This is due to their capability to detect and regulate synaptic transmission by expressing receptors and releasing gliotransmitters, respectively. Importantly, we have shown that a single astrocyte is able to detect and in turn up-regulate basal synaptic transmission at individual synapses in juvenile rats. Whether this upregulation is still present in adults and whether it is affected by the synaptic activity occurring at neighboring synapses present within the same astroglial domain is unknown.

Using STED imaging on fixed tissue and electrophysiological recordings on acute hippocampal slices of adult male rats we here show that the upregulation pathway previously described in juvenile rats is also present in adults. Indeed, as in juvenile, astrocytes detect basal glutamatergic transmission at individual synapses through mGluR5 and in turn upregulate it by releasing purines through the activation of presynaptic A2A receptors. More importantly, our data suggest strongly that an individual astrocyte is able to adapt its purine-mediated regulation of glutamatergic transmission as a function of the number of synapses activated in its domain. When the number of afferent inputs activated is small, astrocytes facilitate synaptic efficacy through a purine-mediated process. Interestingly, this process is no longer present when a higher number of afferences is activated, suggesting the astrocytes integrate the incoming information and adapt its response in terms of purine release.

P3.034

### Regulation of the SUMOylation balance at the mammalian synapse

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Sumoylation is a very dynamic post-translational modification that consists in the covalent but reversible attachment of the Small Ubiquitin like MOdifier SUMO to specific lysine residues of target proteins. Sumoylation regulates the activity, stability, subcellular localization and protein-protein interactions of many target proteins. This protein modification is also essential to the regulation of synaptic transmission and plasticity. A tightly regulated equilibrium between the sumoylation and desumoylation processes is therefore critical to the brain function and its disruption has been associated with several neurological disorders. The sumoylation / desumoylation equilibrium is governed by the mutual enzymatic activities from the sole SUMO-conjugating enzyme Ubc9 and a group of desumoylases called SENPs. We previously demonstrated that the activation of mGlu5 receptors transiently increases the postsynaptic residency time of Ubc9 in a PKC-dependent manner (Loriol et al., 2014 Nature Communications). This transient synaptic trapping of Ubc9 increases synaptic sumoylation levels, which in turn, modulates neuronal excitability. However, the mechanisms regulating the desumoylation pathway are still unknown. Using a combination of advanced live-cell imaging as well as biochemical and pharmacological approaches, we have investigated the diffusion properties of the SENP1 enzyme in individual hippocampal spines. We have also uncovered the regulatory mechanisms driving the neuronal diffusion of SENP1. Altogether, our work provides additional insights into the sequential activity-dependent regulatory mechanisms driving the homeostasis of protein sumoylation at the mammalian synapse.

**P3.035 Novel role of type III sodium-phosphate co-transporters in regulating hippocampal-dependent cognitive functions**

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Inorganic phosphate (Pi) plays a critical role in various metabolic processes and is a fundamental component of many biological structures. It is well established that dysregulation of the Pi/Ca<sup>2+</sup> homeostasis has important impact on neuronal survival, neurodegeneration, and inflammatory processes. However, the physiological role of Pi homeostasis in neurons remains still unclear.

Pi transport in eukaryotic cells is mediated by sodium-dependent phosphate co-transporters (NaPiTs), which are essential for the maintenance of intracellular Pi homeostasis. Interestingly, the type III, including PiT-1 (*Slc20a1*) and PiT-2 (*Slc20a2*), are the only NaPiTs expressed in the brain. In addition to their transport activity, these proteins show Pi transport-independent signaling in different tissues. However, the functional relevance of PiT-1 and PiT-2 in the brain has not been explored yet.

After demonstrating that PiT-1 and PiT2 are expressed in the hippocampus, we investigated their physiological role(s) in regulating the activity of this brain structure, critical for learning and memory.

We analyzed the neuronal morphology of primary hippocampal neurons transfected with *Slc20a1* or *Slc20a2* shRNAs, and we generated mouse models of selective hippocampal downregulation of PiT-1 or PiT-2, obtained after stereotactic injections of AAV expressing shRNAs. Different behavioral tests allowed us to evaluate hippocampal-dependent functions in those mice, such as anxiety-like behavior and memory.

We first observed that downregulation of PiT-1 or PiT-2 in primary hippocampal neurons reduces dendritic spines density and neuronal branching complexity, suggesting a role of these co-transporters in regulating hippocampal neuronal plasticity. This is supported by our *in vivo* data, obtained by selective PiT-1 or PiT-2 downregulation in the hippocampus, that leads to severe hippocampal-dependent memory impairments.

The drastic phenotypes observed in hippocampal neurons and in our mouse models lacking PiT-1 or PiT-2 demonstrate the physiological importance of these NaPiTs in the brain. Our data strongly suggest that both type III NaPiTs are novel players in the control of hippocampal synaptic plasticity and neuronal network function.

**P3.036 Neuropeptide S inhibits sleep-promoting neurons into the VLPO to favor wakefulness**

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Regulation of sleep-wake cycles is crucial for brain's health and cognitive skills. Among the various neurochemicals known to control different states of alertness, neuropeptide S (NPS) would play an important role in promoting awakening. However, NPS signaling pathways remain elusive.

In this study, we characterized the effects of NPS in the ventrolateral preoptic nucleus of hypothalamus (VLPO), one of the major brain structures regulating non-rapid eye movement (NREM) sleep. Using polysomnographic recordings, we demonstrated that in mice, local and bilateral infusion of NPS into the VLPO significantly increases awakening while reducing both quantity and quality of NREM sleep.

At the cellular level, we demonstrated by patch-clamp recordings that NPS hyperpolarizes VLPO sleep-promoting neurons, indirectly via the depolarization of local GABAergic neurons. Moreover, we have established that the application of NPS on acute brain slices induces a strong and reversible TTX-sensitive constriction of blood vessels in the VLPO. This vasoconstrictor effect suggests that NPS down-regulates the activity of VLPO neural networks.

Altogether, our results highlight for the first time in the VLPO that NPS exerts a direct role by controlling local neuronal activity. Following the depolarization of local GABAergic neurons, NPS indirectly causes a feed-forward inhibition onto sleep-promoting neurons, which translates into a decrease in NREM sleep to favor arousal.

**P3.037 Characterization of CRMP4 as a partner of the MAP6 protein in the semaphorin-3E signaling pathway during brain wiring**

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During embryonic development, the establishment of specific neural networks depends on the regulation of axonal growth. This is mediated by cytoskeleton dynamics, composed mainly of actin and microtubules, that will induce elongation or retraction of the axon.

Studying the mechanisms involved in the stabilization of neuronal microtubules has led our team to discover Microtubule Associated Protein 6 (MAP6). More recently, we identified a new function for MAP6 that is independent of its cytoskeleton binding function and crucial for neuronal connectivity during embryonic development. Indeed we have shown that MAP6 is necessary for axonal growth of subicular neurons mediated by a guidance molecule, semaphorin 3E. MAP6 KO presents an absence of fornix development, a structure onto which subicular neurons project.

To better understand the formation of the fornix and the semaphorin 3E signaling pathway, we have studied a MAP6 interactor called collapsin response mediator protein 4 (CRMP4). We first demonstrated, *in vitro*, that CRMP4 is involved in axonal growth mediated by semaphorin 3E and we observed abnormal development of the fornix in CRMP4 KO mice. We were then able to identify, in the N-terminal portion of MAP6, 2 domains necessary for its interaction with CRMP4. We would now like to define the functional domains of CRMP4 needed to stimulate axonal growth. CRMP4 has, like MAP6, the ability to bind microtubules and actin. This property could make it the missing link in Sema3E signal mediation via dynamic regulation of the cytoskeleton resulting in axonal elongation.

Bearing in mind that disorders in the formation of the fornix are associated with schizophrenia, a better understanding of this structure's growth may provide new evidence for the neurodevelopmental origin of psychiatric diseases.

**P3.038 *In situ validation and spatial mapping of diverse striatal cells identified by scRNA-seq in the mouse brain at single-cell resolution***

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Characterizing the molecular transcriptomic profiles of individual cells has become exceedingly important for understanding how cells and tissues develop and function, revealing new cell types, and ushering in a new era of precision medicine with highly targeted treatments. This has proven to be especially important in complex organs with high cellular heterogeneity, such as the mammalian brain. Current single-cell transcriptomic tools such as single-cell RNA sequencing (scRNA-seq) utilize dissociated cells and result in the loss of spatial organization of the cell population. Validation and spatial mapping of scRNA-seq results can be obtained using assays that retain spatial organization, such as RNA *in situ* hybridization (ISH). In this study, we sought out to validate and spatially map the diverse cell populations in the mouse striatum that have been identified by scRNA-seq (Gokce et al, *Cell Rep*, 16(4):1126-1137, 2016). Employing the RNAscope technology, we developed a multiplex fluorescent RNA ISH assay to simultaneously detect multiple genes at single cell resolution in the tissue context. We validated the major gene signatures identified by scRNaseq, including discrete D1 and D2 medium spiny neuron (MSN) subtypes: Drd1a/Foxp1, Drd1a/Pcdh8, Drd2/Htr7, and Drd2/Synpr. Further cellular heterogeneity within the MSN subpopulations was marked by a transcriptional gradient, which we could spatially resolve with RNA ISH. Lastly, we validated heterogeneity within non-neuronal striatal cell types, including vascular smooth muscle cells (Myl9/Tagln), endothelial cells (Pecam1/Pltp/Ly6c1), microglia (Olfml3/Cx3cr1/Mlxipi), macrophages (Mrc1/Dab2), and oligodendrocytes (Klk6/Nfasc). Taken together, we have demonstrated the capabilities of a multiplexed transcriptomic *in situ* approach for the validation and spatial mapping of scRNA-seq results in the highly complex and heterogeneous mouse striatum. Single-cell transcriptomics combined with spatial mapping with RNA ISH holds great promise in resolving heterogeneous tissues at cellular resolution and providing insights into cell type-specific aspects of brain function in healthy and disease states.

**P3.039 Evaluating the quinolinone GSA-10 during CNS demyelination**

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Neural stem cells (NSCs) located within the subventricular zone (SVZ) of the lateral ventricle generate neural precursors giving rise to increased number of new oligodendrocytes after demyelination. Pharmacological inhibition of Gli1, a transcription factor associated with the Hedgehog (Hh) pathway, promotes SVZ-derived NSC recruitment to the corpus callosum and their differentiation into oligodendrocytes, ultimately enhancing remyelination (Samanta et al, *Nature*, 2015). Smoothened (Smo), another molecular target for modulators acting on the Hh pathway, also plays a major role in NSC maintenance (Ruat et al, *Top. Med. Chem.*, 2015). We have recently identified the quinolinone GSA-10 as a Smo agonist acting through an AMPK non-canonical pathway associated with inhibition of Gli1 transcription (Manetti et al, *EJMC*, 2016; Fleury et al, *Sci. Rep.*, 2016). We have now demonstrated the pro-myelinating properties of GSA-10 and determined its efficacy in inducing the expression of the Myelin Basic Protein (MBP) in the mouse immortalized oligodendrocyte precursor cell line (Oli-neuM) expressing the Myelin Regulatory Factor (Porcu et al, *PlosOne*, 2015). Therefore, GSA-10 may have therapeutic value for demyelinating diseases by acting on NSCs or their progeny.

To further investigate the contribution of NSCs to remyelination, we performed *in vivo* genetic fate mapping by using the GLAST<sup>CreERT2-YFP</sup> mouse reporter strain in which YFP is expressed in GLAST<sup>+</sup> (astrocyte- and astrocyte-like NSC specific glutamate transporter) cells upon tamoxifen administration (Daynac et al, *Stem Cell Reports*, 2016). We have investigated the behavior of these cells in the corpus callosum of mice demyelinated by the stereotaxic injection of lysophosphatidylcholine (LPC) alone or in the presence of GSA-10. Experiments are underway to characterize GLAST fate-labeled cells in the corpus callosum of these mice and to identify Hh signaling implicated in this process. Altogether, these experiments should bring novel strategies and tools for developing active drugs for demyelinating diseases.

P3.040

**Implication of nuclear calcium signaling in cocaine-evoked adaptations**

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Addiction is a form of pathological memory in which mechanisms engaged in normal learning and memory processes are “highjacked” by exposure to drugs of abuse. These pathologic memories are robust, long-lasting and require changes in gene expression in specific neuronal populations. Drugs of abuse modify the reward system by increasing dopamine (DA) in the mesolimbic system, especially in the striatum, resulting in alterations of glutamate (Glu) transmission-dependent plasticity. The integration of DA and Glu inputs in the striatum is achieved by striatal projection neurons (SPN), which comprise two distinct populations: the “direct pathway” (dSPN), expressing DA D1 receptors (D1R) and promoting reward processes, and the “indirect pathway” (iSPN) that express DA D2 receptors (D2R) and inhibits reinforcement. The team showed that the interaction of D1R with Glu NMDA receptors (NMDAR) controls some cocaine-evoked alterations. We showed that the disruption of D1R/NMDAR heteromers, which alters cocaine-induced long-term behavioral responses, also impacts on calcium influx towards the nucleus. Nuclear calcium (nucl-Ca<sup>2+</sup>) signaling is a key route linking neuronal activity to gene transcription in multiple models of long-lasting neuroadaptation, but its role in addiction is unknown. This project aims at unravelling the dynamics and functions of nucl-Ca<sup>2+</sup> signaling in dSPN and iSPN in cocaine-mediated molecular, cellular and behavioral adaptations. By using an ex-vivo model of cocaine exposure, nucl-Ca<sup>2+</sup> dynamics was studied by two-photon imaging on acute striatal slices owing to viruses expressing the Ca<sup>2+</sup> indicator GCaMP3 fused to a nuclear localization signal either in dSPN or iSPN. To study the roles of nucl-Ca<sup>2+</sup> signaling in dSPN and iSPN, we used a viral-based approach to achieve a cell type-specific expression of nucl-Ca<sup>2+</sup> blockers. This will allow us characterize the specific implication of nucl-Ca<sup>2+</sup> signaling in dSPN and iSPN on cocaine-evoked transcriptional, morphological and behavioral alterations.

P3.041

**Spatial Ca<sup>2+</sup>sensing of vesicles determine their directionality along microtubules**

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Mutation of huntingtin (HTT) leads to Huntington disease (HD), a neurodegenerative disorder characterized by the preferential dysfunction of cortical and striatal neurons. Whereas death of striatal neurons is linked to a defect in the anterograde transport of BDNF to the striatum, the mechanism leading to the degeneration of cortical neurons remains unclear. One potential mechanism could involve the retrograde axonal transport of endosomes in cortical neurons that is known to induce survival of projecting neurons in various paradigms. The *in vitro* reconstitution of cortico-striatal network using microfluidics, allowed us to analyze distal-axonal TrkB trafficking in response to synaptic BDNF infusion. We observed that BDNF leads to a massive but transient retrograde flow of TrkB vesicles in cortical neurons, which requires receptor activation, the subsequent induction of the PLC $\gamma$  pathway and CaN activation. Interestingly, we previously reported that vesicular HTT regulates transport directionality via its dephosphorylation of S421 by CaN, thus promoting retrograde transport. We found that CaN is present on vesicles positive for HTT and TrkB, suggesting that calcium release upon TrkB activation would be sufficient to drive the endosomal retrograde flow. Next, we showed that TrkB re-routing requires HTT dephosphorylation using neurons derived from mice carrying point mutations on HTT at the S421.

To test the possibility that vesicles directly respond to calcium and modify the activity of the molecular motors we purified vesicles purified from mouse brains that we perfused on *in vitro* polymerized microtubules. We next recorded their movements after calcium uncaging. We observed a change in vesicles directionality upon calcium uncaging that was absent in vesicles from mice in which HTT cannot be dephosphorylated. In conclusion, the data obtained suggest that vesicles are able to sense calcium-rich environments, activate CaN on-board of vesicles leading to HTT dephosphorylation and to the reversion of trafficking directionality, revealing that the BDNF-TrkB-PLC $\gamma$ -CaN-HTT signaling acts as a major pathway for the retrograde routing of axonal TrkB signaling endosomes with potential implication in HD.

**P3.042 Inhibitor of apoptosis proteins determine glioblastoma stem-like cells fate in an oxygen-dependent manner**

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In glioblastomas, apoptosis inhibitor proteins (IAPs) are involved in apoptotic and non-apoptotic processes. We previously showed that IAPs inhibition induced a loss of stemness and glioblastoma stem cells differentiation by activating nuclear factor- $\kappa$ B under normoxic conditions. Hypoxia has been shown to modulate drug efficacy. Here, we investigated how IAPs participate in glioblastoma stem-like cell maintenance and fate under hypoxia. We showed that in a hypoxic environment, IAPs inhibition by GDC-0152, a small-molecule IAPs inhibitor, triggered stem-like cell apoptosis and decreased proliferation in four human glioblastoma cell lines. We set up a 3D glioblastoma spheroid model in which time-of-flight secondary ion mass spectrometry analyses revealed a decrease in oxygen levels between the periphery and core. We observed low proliferative and apoptotic cells located close to the hypoxic core of the spheres and glial fibrillary acidic protein<sup>+</sup> cells at their periphery. These oxygen-dependent GDC-0152 anti-tumoral effects have been confirmed on human glioblastoma explants. Notably, serine-threonine kinase activation analysis revealed that under hypoxic conditions, IAPs inhibition activated ataxia telangiectasia and Rad3-related protein signaling. Our findings provide new insights into the dual mechanism of action of IAPs inhibitors that depends on oxygen level and are relevant to their therapeutic application in tumors.

**P3.043 Role of mGlu3 / PICK1 interaction in hippocampal theta rhythm and implications for neuropsychiatric disorders**

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Hippocampal theta rhythm (7-15 Hz) is suggested to support wide-ranging neural processing. We recently demonstrated that theta rhythm is disrupted in mGlu3 receptor deficient mice *in vitro*, but the underlying mechanisms remain unclear. A variety of studies have indicated that protein-protein interactions are critical for transduction pathways associated with metabotropic glutamate receptor intracellular signaling. In this study, we showed by co-immunoprecipitation and pull-down experiments that PICK1 (protein interacting with C Kinase1) interacts specifically with mGlu3. Immunofluorescence experiments in primary cultures revealed that the PICK1/mGlu3 receptor interaction targets the receptor to the surface of hippocampal neurons. Thus, PICK1 appears to act as an essential element to stabilize the mGlu3 receptor at the membrane of neurons.

The next step was to examine the role of the mGlu3/PICK1 interaction in the hippocampal theta rhythm *in vitro* and *in vivo*. We showed that the frequency of theta oscillations and theta episodes was reduced significantly in both mGlu3<sup>-/-</sup> and WT hippocampal neurons treated with the dominant-negative TAT peptide (TAT mGlu3 SSL) *in vitro*. Theta rhythm is associated in rodents with rapid eye movement sleep (REM) which is known to be involved in memory formation. Interestingly, increasing evidence implicates mGlu2/mGlu3 receptors in REM sleep. Using EEG recording, we showed that cerebro-ventricular injection of the TAT mGlu3 SSL peptide decreased the time spent in REM sleep and is associated with a decrease of theta power. Together our results suggest that disruption of the mGlu3-PICK1 complex is sufficient to alter theta rhythmicity during REM sleep in the hippocampus. mGlu3 receptor expression is downregulated in schizophrenic patients who present alteration of the sleep /wake cycle. Characterization of a functional role of the mGlu3/PICK1 complex in hippocampal neurons may provide novel insights into the processes underlying this psychiatric disorder.

**P3.044 Linking robustness of neuronal activity and topology of ion channel expression in midbrain dopaminergic neurons**

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How neurons can maintain their electrical activity despite external and internal perturbations is a substantial open question. Functional redundancy of ion channels with overlapping or degenerate properties has been proposed as one of the mechanisms underlying this robustness. However, precisely tuning neuronal activity might rely on co-regulating the expression and/or function of functionally-overlapping ion channels. In a recent study using single-cell transcriptomics (Tapia et al., 2018), we demonstrated that several somato-dendritic voltage- and calcium-gated ion channels supporting the autonomous activity of midbrain dopaminergic neurons might be co-regulated at the genetic level. Moreover, the levels of expression of these ion channels seem to be genetically coupled with the definition of neurotransmitter identity.

In order to understand the role of these co-regulation patterns in maintaining the electrical phenotype of midbrain dopaminergic neurons, we combined patch-clamp recordings with single-cell microfluidic RT-qPCR from hundreds of neurons from wild-type and ion channel knock-out animals. Therefore, we define in parallel the cell-to-cell variations in neuronal activity induced by the deletion of ion channels and the changes in ion channel expression induced by these genetic perturbations. Our results bring new insights into the compensatory mechanisms generating multiple solutions to sustain a stable pattern of activity in these neurons.

**P3.045 Analysis of Glast expressing cells by 3D imaging of transparent adult mouse hypothalamus**

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Emerging evidence indicates that active neurogenesis occurs in the adult mammalian hypothalamus (HPT), and that new neurons are added to the appetite and energy-balance regulating centers (Prevot et al, *End. Reviews*, 2018). Tanyocytes, ependymocytes, subventricular astrocytes and parenchymal glial cells that are located next to the median eminence (ME) represent potential stem and progenitor cell candidates. To study the plasticity of this neurogenic niche, we have used GLAST<sup>CreERT2</sup>-YFP mouse line where YFP is expressed in GLAST<sup>+</sup> cells (astrocyte- and astrocyte-like NSC specific glutamate transporter) upon administration of tamoxifen (Daynac et al, *Stem Cell Reports*, 2016). In these mice and upon activation, the reporter is detected in ME tanyocytes and in parenchyma astrocytes as shown by immunohistochemistry (IHC). These results are in agreement with the expression of GLAST transcripts in these cells. Immunolabelling for YFP of a slice encompassing the HPT region from these mice followed by iDISCO and light-sheet laser scanning microscopy (Alpha3 Light Sheet Microscope, PhaseView), provided high resolution imaging of immunofluorescence signals along the third ventricle in the HPT. We have developed an automated quantification method to analyze YFP signals within ME tanyocytes and have studied the plasticity of these cells over time. Interestingly, we further identified expression of the Hedgehog receptor Patched (Ptc) by ME tanyocytes and parenchymal astrocytes, both by *in situ* hybridization and IHC experiments conducted on brain sections from wild type or Ptc<sup>+/−</sup>-LacZ adult mice. Thus, experiments are in progress to further investigate the effects of a short and long term genetic activation of Hh signaling on tanyocyte plasticity after the conditional deletion of Ptc in GLAST<sup>CreERT2</sup>-Ptc<sup>−/−</sup>-YFP mice (Ferent et al, *Stem Cell Reports*, 2014). Altogether, these experiments should bring novel tools for studying the plasticity and regulation of tanyocytes at the level of the ME, and for further understanding their potential role in hypothalamic neurogenesis and in metabolic diseases.

**P3.046 The AlphaLISA technique: an innovative approach for studying CB1-intracellular signaling pathway in brain tissue lysates**

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The cannabinoid receptor of type-1 (CB1), the target receptor of marijuana active compound Δ9-Tetrahydrocannabinol, is one of the most abundant G protein-coupled receptors in the mammalian brain and regulates a plethora of different cellular and behavioral activities. To understand this receptor impact on cell functions and behaviors, it is imperative to understand the CB1 intracellular signaling pathway in depth. Studying intracellular signaling cascades in the central nervous system is a particularly complex task due to the heterogeneous nature of the brain tissues, which consists of many embedded sub-structures. The most common technique to analyze protein phosphorylation in cells or tissue lysates is the western blot. However, even if the western blot is a reliable technique, very often it is not sufficient due to the relatively low throughput and high sample consumption. To overcome this degree of complexity, it is required a technique, economical in the amount of biological material and with a higher and more proficient throughput. A suitable method for this task is the AlphaLISA (Amplified, Luminescent, Proximity, Homogeneous Assay). However, to date, AlphaLISA has been used for cell lysates only. The present study aims to demonstrate the Alpha principle and its superior throughput; the validity of the technique in both cell lines and murine brain tissue lysates; the compatibility of Alpha technology with the most commonly used RIPA buffer and the compatibility of Alpha buffer with the western blot technique; the high reproducibility of Alpha technology; how to fine-tune this technique. Altogether these results point that Alpha technology is particularly well adapted to study brain signaling pathways by allowing rapid, sensitive, reproducible and semi-quantitative detection of phosphoproteins from individual brain tissue homogenates, representing a powerful tool to investigate the CB1 signaling pathway.

**P3.047 Huntingtin phosphorylation at serine 421 regulates axonal transport of synaptic vesicle precursors and mouse behavior**

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Huntingtin (HTT), the protein that when mutated causes Huntington's disease is a large protein interacting with more than 300 partners. These interactions are responsible for HTT physiological roles and are modulated by post-translational modifications, such as phosphorylation. One of HTT function is to facilitate the axonal transport of the main brain neurotrophic factor, Brain Derived Neurotrophic Factor (BDNF). HTT-mediated BDNF transport is crucial for the maintenance of corticostriatal network, altered in HD, resulting in a reduced trophic support and striatal degeneration. Interestingly, HTT phosphorylation at serine 421 (S421) promotes BDNF vesicle anterograde transport. Here we investigated whether HTT capacity to transport vesicles is restricted to BDNF vesicles. We found that HTT also regulate the axonal transport of synaptic vesicle precursors (SVPs). Using microfluidics reconstituting corticostriatal network on-a-chip, we showed that axonal transport of SVPs depends on HTT S421 phosphorylation: while neurons carrying S421A mutation, that mimics the absence of phosphorylation, promotes retrograde transport of SVPs, S421D that mimics constitutive phosphorylation promotes their anterograde transport. We found by electron microscopy that synaptic vesicle (SVs) quantity changes according to S421 phosphorylation status. We also found by electrophysiology that S421 phosphorylation regulates synaptic transmission and facilitation in the striatum. Interestingly, SVPs contain neurotransmitters that are crucial for neuronal plasticity and memory. Interestingly, we found that procedural memory is altered in mutant S421D mice. We are now investigating the consequences of specific modulation of axonal transport of SVPs in the corticostriatal network *in vivo* using viral-mediated expression or silencing of specific molecular motors and of phosphorylated HTT on this behaviour.

P3.048

**Boc, a new regulator of developmental myelination in the brain**

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Boc belongs to a subgroup of the Ig/fibronectin superfamily of cell adhesion molecules which bind directly and with high affinity the Hedgehog proteins, major regulators of tissue patterning and homeostasis in vertebrates (Ferent and Traiffort, 2015). Boc is expressed in the developing nervous system where it is necessary for Shh-mediated guidance of commissural axons in the neural tube (Okada et al., 2006) and segregation of ipsilateral retinal ganglion cell axons in the developing optic chiasm (Fabre et al., 2010). Moreover, at periods of peak cortical synaptic development, Boc mediates Shh-dependent synapse formation of a specific cortical circuit (Harwell et al., 2012). Recently, a dorsal Shh-dependent domain in the ventricular-subventricular zone was reported to produce large numbers of oligodendroglial lineage cells in the early postnatal brain (Tong et al, 2015). However, Boc involvement in such Shh-mediated activity had not yet been addressed. Here, we used the Boc knockout mice (Okada et al, 2006) in order to investigate the role of this critical Shh receptor in the postnatal production of oligodendroglial lineage cells and in the subsequent myelination of axons. We found that Boc can be detected in progenitors arising from the dorsal forebrain and fated to the glial cell lineage. Moreover, the Boc mutant displays a transient decrease in oligodendroglial cell density and delayed myelination. Despite recovery of oligodendroglial cells at later stages, the adult Boc mutant still exhibits a lower production of myelin basic protein correlated with a significant decrease of axon caliber. Altogether our data identify Boc as a new regulator of developmental myelination.

**P3.049 Is Ih responsible for mitral cells respiratory-driven slow oscillations?**

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We are interested in understanding respiratory information coding in olfactory bulb (OB). When recorded in anaesthetized animal, mitral cells of the OB display respiratory-driven membrane potential slow oscillations around 2 Hz (MPSO) which are highly variable depending on the recorded cell. In fact, mitral cells can display depolarization during animal inspiration (MPSO+), hyperpolarization during inspiration (MPSO-) or no respiratory-driven oscillation (noMPSO) (Briffaud *et al.*, 2012). Moreover, amplitude of MPSO varies from 1 to 15 mV. This variability of MPSO induces a variability of mitral cells spiking synchronization on the respiratory cycle. Mitral cells displaying MPSO+ present an increase of their spiking during inspiration (S+ pattern) while mitral cells displaying MPSO- present a decrease of their spiking during inspiration (S- pattern). Furthermore, we showed that the strength of the spiking synchronization on respiratory cycle is determined by the amplitude of the MPSO. Therefore, MPSO occurrence is of great importance in olfactory bulb information processing.

Hyperpolarization-activated cationic current (Ih) expression is widely heterogeneous among mitral cells (Angelo *et al.*, 2012). Ih is known to create a membrane potential resonance at low frequencies (2-6 Hz) which may increase the propensity of mitral cells to oscillate at MPSO frequency. Besides, Ih increases spiking precision during membrane potential oscillations in various neurons types. Therefore, we questioned if the Ih expression variability in mitral cells explain the variability of their response to respiration including MPSO type (MPSO+, MPSO-, noMPSO), MPSO amplitude and spiking synchronization to respiratory cycle. To address this question, we performed both *in vitro* and *in vivo* recordings of mitral cells using respectively patch clamp on OB slices and sharp electrodes intracellular recordings. In *in vitro* recordings, we tested if Ih expression produced a membrane potential resonance at MPSO frequency. We used *in vivo* recordings to explore the effect of Ih expression on mitral cell response to respiration. Our preliminary results seem to reveal no correlation between Ih expression and MPSO type or spiking synchronization of mitral cells.

**P3.051 Implication of vitamin A in neuroprotection of dopaminergic neurons in a rat model of Parkinson's disease**

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Parkinson's disease (PD) is caused by a loss of dopaminergic neurons in the substantia nigra pars compacta (SNc), leading to strong motor impairments. Dopaminergic neurons from the SNc project to the striatum which allow the control of voluntary movements.

Vitamin A, through the action of its active metabolite, retinoic acid (RA), is involved in the development, differentiation and neuroprotection of SNc dopaminergic neurons.

Additionally, retinaldehyde dehydrogenase (RALDH), the synthesis enzyme of retinoic acid, is involved in cellular detoxification. However, the cerebral bioavailability of retinoic acid decreases with aging, which downregulates RALDH expression. This may precipitate neurodegenerative processes such as those observed in Parkinson's disease. Here we hypothesize that nutritional supplementation with vitamin A normalizes brain levels of retinoic acid and thus RALDH, which exhibit a neuroprotective effect on dopaminergic neurons, to delay the progression of the disease.

To test our hypothesis, we modeled Parkinson's disease with unilateral injection of 6-hydroxydopamine (6-OHDA), a toxin that selectively destroys dopaminergic neurons, into rats' striatum. Rats were supplemented or not with dietary vitamin A (20 UI/g) for 5 weeks before the lesion. Motor impairments induced by 6-OHDA and protective effect of vitamin A were quantified with the step test, cylinder test and rotarod. Extend of dopaminergic neurons degeneration was assessed with stereological analysis of tyrosine hydroxylase, the production enzyme of dopamine, staining in the striatum. To evaluate the functionality of the dopaminergic system, levels of dopamine and its metabolites were measured in the striatum with HPLC. Finally, to precisely interrogate the impact of vitamin A supplementation on RALDH enzyme, its expression and localization will be assessed with immunostaining, western blot and RT-qPCR analyses.

These experiments that are still in progress will allow a precise assessment of the neuroprotective effects of vitamin A supplementation on dopaminergic neurons in a rat model of Parkinson's disease. This work may open therapeutic strategies to prevent neurodegeneration.

**Keywords:** Parkinson's disease, vitamin A, nutritional supplementation, animal models

**P3.052 Identification of new biomarkers of posturo-locomotor instability in a rodent model of vestibular pathology**

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Vestibular system plays a crucial role in maintaining postural balance. Unilateral vestibular lesion results in a typical syndrome characterized by postural imbalance, an alteration of locomotion and gaze stabilization as well as cognitive and neurovegetative disorders. One of the main difficulties encountered in the development of new anti-vertigo drugs is the lack of sensitivity in the evaluation of this syndrome. Qualitative assessment of vestibular syndrome exists (Péricat et al. 2017) but there is a critical lack of quantitative evaluations. Recently, the use of a dynamic weight-bearing device (DWB®, Bioseb) has revealed postural alterations in rats with unilateral vestibular neurectomy (UVN) (Tighilet et al. 2017). Our team is evaluating a new version of this device capable of quantifying additional parameters of postural and locomotor equilibrium. The objective of this study is to use this device to validate these new parameters on our rat model of vestibular pathology. The biomarkers extracted from this device are: the barycenter, the support surface and the weight distribution of rats when they are in motion or stationary. Before UVN, rats show a symmetric distribution of their weight along the lateral axis and put more weight on their hindlimbs. In the acute phase after UVN, rats distribute more weight on the right and then they favor a distribution of their weight on the left side. For the anteroposterior axis, rats distribute more weight forward and quickly regain a preoperative weight distribution pattern. These results corroborate our previous study (Tighilet et al., 2017). After UVN, the support surface of the rats increased from 1 to 30 days and the barycenter distribution respects the weight distribution. In addition, our results show a less altered weight distribution when UVN animals are in motion. This study provides new information on the static and dynamic postural balance pattern observed after vestibular loss in rats. These data are relevant : they allow to quantify the postural disorder as well as the compensatory strategies used after a vestibular loss. These results could guide us on rehabilitation protocols in the vestibular patient but also on the validation of pharmacological compounds favoring the restoration of equilibrium.

**P3.053 Oxytocin rescues atypical thermosensory reactivity during the neonatal period in a mouse model of ASD**

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To survive, neonates have to undertake innate behaviors such as nipple-searching and calls in response to olfactory, tactile, thermal sensory cues coming from their environment or their mother's body. Animal models of sensory depletion during *early life* period demonstrate that sensory integration is detrimental for normal neurodevelopment and brain *functions*. Despite injury models, early life dysfunctions of sensory integration have been unexplored in models of neurodevelopmental disorders while atypical sensory reactivity is observed in Autistic patients. We hypothesized that animal models of autism spectrum disorder (ASD) might present sensory alteration during neonatal period. We thus explored thermosensory-evoked call reactivities to coolness environment (15°C) in mice knock-out for Magel2. This gene is mutated in Schaaf-Yang patients presenting a high prevalence (75%) of ASD. We found that coolness exposure decreases the latency to emit the first calls (sensory reactivity) in WT, while this latency is clearly elevated in Magel2 KO neonates. This lack of reactivity is temperature-dependent since WT and mutant neonates behave similarly when isolated at room temperature. The responsive rate to coolness (i.e. the proportion of pups responsive to cooling) is markedly lower in Magel2 KO than WT neonates and gets worse from P1 to P6. Investigations of body surface temperature and brown adipose tissue reveal normal nonshivering thermogenesis in mutant pups. In addition, thermosensory neurons of the Grueneberg ganglion (a main thermosensor region located at the tip of the nose of neonate) are normally active when exposed to cool stimuli. However, biochemical and electrophysiological analyses demonstrate abnormal activities in the preoptic area; a main central region that integrates peripheral thermal information. Interestingly, intranasal injection of oxytocin can rescue this sensory deficit. Moreover, inactivation in WT neonates of hypothalamic oxytocin neurons through DREAAD technique reproduces the coolness response failure observed in mutants. All together these results highlight impairments of thermal reactivity in a mouse model of ASD during early life period and reveal that the oxytocinergic system regulates this innate sensory-motor behavior.

**P3.054 Interaction of ApoE-ε4 and acquired risk factors on the development of synaptic impairments in a mice model of Alzheimer's disease**

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Alzheimer's disease (AD) is an irreversible neurodegenerative disorder characterized by progressive cognitive and memory dysfunction associated with the loss of glutamatergic synapses, beta-amyloid peptide accumulation and neuronal death. Increasing evidence indicates that the combination of genetic and acquired risk factors could be determinant for the initiation and progression of AD. In fact, apolipoprotein ε4 (Apoe-ε4) is the strongest genetic factor for the development of late-onset sporadic AD, the most common form of AD. However, it is still not clear how Apoe-ε4 contributes to AD pathogenesis. One hypothesis is that Apoe-ε4 modifies the function of glutamate receptors responsible for the maintenance of glutamatergic synapses and the induction long-term synaptic plasticity (LTP), thought to be the cellular basis of learning and memory. In addition to genetics, recent data suggest that acquired risk factors like western-diet consumption increases the risk to developing AD. However, whether western-diet interacts with Apoe-ε4 to disturb synaptic function in AD is not known.

We propose that the interaction between genetic familial (APP-PS1), sporadic (Apoe-ε4) and acquired (age and western-diet) risk factors is crucial for the initiation and progression of synaptic dysfunction in AD. To investigate this hypothesis we are evaluating the impact of the human ApoE-ε4 isoform in an APP/PS1 mouse model of AD, with or without western-diet. Extracellular field excitatory postsynaptic potentials were elicited and recorded on acute hippocampal slices from 5 to 11 months mice. Our preliminary data indicates that Apoe-ε4 genotype exacerbates the degree of impairment of basal synaptic transmission and LTP in APP/PS1 mice at 9 and 11 months. In addition, western-diet intake selectively precipitates the adverse effect of Apoe-ε4 on LTP impairment in APP/PS1 mice from 9 to 7 months. Therefore, the interactions between a sporadic AD genetic risk factor (Apoe-ε4) with an environmental risk factor (Western-diet) exacerbate and accelerate, respectively, LTP impairment on APP/PS1 mice. Further studies may be critical to understand and devise novel therapeutic strategies against this devastating disease.

**P3.055 The pathophysiology of Fragile X Syndrome: molecular deregulations in interneurons**

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Fragile X syndrome (FXS), the most common form of inherited intellectual disability, is due to the functional deficiency of the Fragile X Mental Retardation Protein (FMRP), an RNA-binding protein involved in the translational regulation and in the transport of many mRNAs involved in synaptic morphology and plasticity (1,2). To date, no effective treatment for FXS is available. We searched for FMRP targets by HITS-CLIP during early development of multiple mouse brain regions (cortex, hippocampus and cerebellum) at a time when FMRP is most highly expressed and synaptogenesis peaks. We identified the largest dataset of messenger RNA targets of FMRP available in the rodent brain and we defined their cellular origin. Remarkably, we have recently validated the functional role of two prominent targets of FMRP in the pathophysiology of FXS, PDE2A and CACNA1A resulting in the identification of a new therapeutic target for FXS (3), a new cellular biomarker for neurons, lacking FMRP (4). These data demonstrate the validity of our approach and the robustness of our *in vitro* results. To get more insights into the molecular and cellular mechanisms that ultimately lead to the pathology, we have optimized a prototype called aiFACS (Agonist Induced Functional Analysis and Cell Sorting) that enables the simultaneous stimulation, recording and sorting of cells according to their response to a pharmacological stimulation (5). We used aiFACS with AMPA stimulation on freshly dissociated neurons followed by single-cell RNA sequencing. This allowed us to reveal the global impairment of AMPA response in *Fmr1*-KO *Meis2* interneurons, the precursors of striatal medium spiny neurons. Given the significant overlap between striatum-associated deregulated behaviors and clinical features of FXS patients, this suggests that we have identified a new *Fmr1*-KO cellular phenotype, likely involved in FXS physiopathology. Findings concerning the molecular role of FMRP in this neuronal population will be presented.

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**P3.056 Stimulating vesicular glycolysis to restore fast axonal transport of BDNF in Huntington's disease**

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Huntington's disease (HD) is a genetic neurodegenerative disorder caused by the abnormal expansion of a CAG repeat in the huntingtin (HTT) gene. This pathology is characterized by the dysfunction and death of neurons in the cortex and striatum. The survival of neurons in the striatum depends on the supply of BDNF (Brain-Derived Neurotrophic Factor), a growth factor produced by neurons in the cortex. HTT is a scaffolding protein involved in the axonal transport of vesicles containing BDNF. When HTT is mutated, the resulting altered trafficking of BDNF leads to a reduction in the amounts of BDNF provided to the striatum, which in turn leads to death of both striatal and cortical neurons. BDNF vesicles are driven by molecular motors that require energy in order to function. Recently, the team discovered that glycolytic enzymes are attached to vesicular membranes and that glycolysis occurs locally on vesicles to provide ATP necessary for transport. The objectives of this study are to identify the mechanisms underlying glycolytic enzyme targeting to vesicles, to investigate how these mechanisms may be altered in HD and finally to correct BDNF transport deficits in HD by specifically stimulating vesicular glycolysis. Through co-immunoprecipitation, we found that HTT interacts with at least one of the glycolytic enzymes, glyceraldehyde-3-phosphate dehydrogenase (GAPDH). We are now investigating how HTT specifically regulates vesicular glycolysis. In order to stimulate vesicular glycolysis in HD and test if this can rescue BDNF transport, we expressed an artificial transmembrane form of GAPDH (TM-GAPDH) that is specifically targeted to vesicular membranes in WT and HD neurons. We used microfluidic chambers to recreate *in vitro* a cortico-striatal connection. Our results demonstrate that the addition of TM-GAPDH to neurons expressing mutated HTT completely restores BDNF transport *in vitro*. We are now developing delivery approaches to selectively enhance vesicular glycolysis *in vivo* and will assess neurodegeneration in HD mouse models. These studies should provide a better understanding of the mechanisms underlying vesicular transport and provide a proof of concept that restoring energy supply for vesicular transport may represent a new therapeutic strategy to treat HD.

**P3.05 K-means clustering in the identification of autistic-like trait subgroups with differing cortical features**

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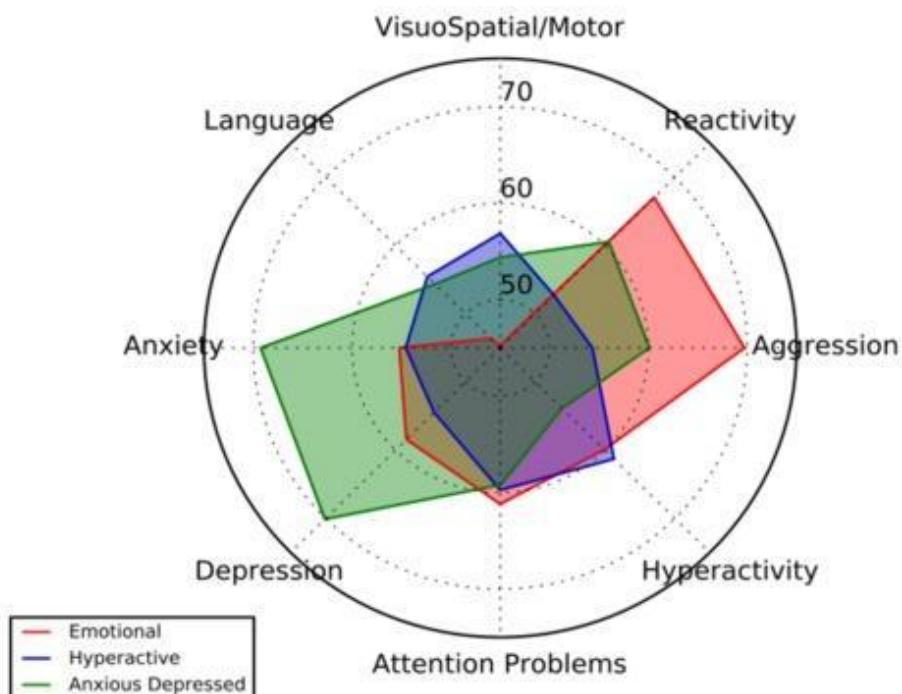
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Autism Spectrum Disorder (ASD) is a heterogeneous disorder defined by sociocommunicative impairments and repetitive/restrictive behaviors. To disentangle this heterogeneity, dimensional and multivariate approaches are well suited in isolating subtypes by considering ASD's widespread variability across biological and behavioral phenotypes. To study this disorder, we use the Social Responsiveness Scale (SRS) as a measure of autistic-like traits. A k-means analysis on behavioral and cognitive traits was conducted on the at-risk Healthy Brain Network cohort ( $n=1552$ ), yielding thirteen clusters. Of these clusters, three had a clinically significant level of SRS (Fig. 1). The three subgroups can be defined as follows:

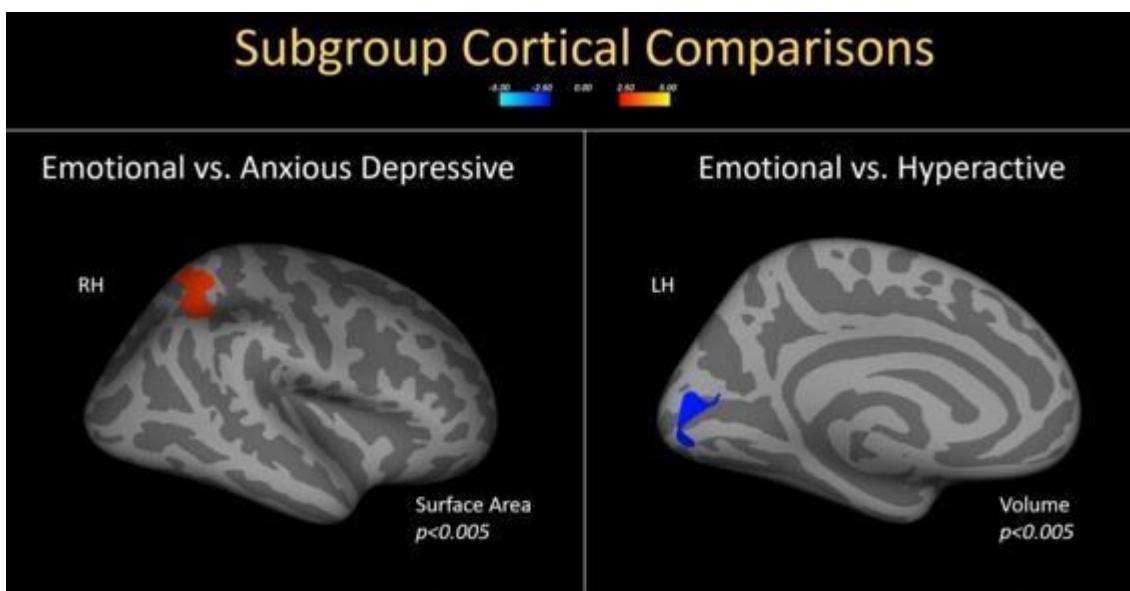
- 1) *Emotional* ( $n=80$ );
- 2) *Hyperactive* ( $n=57$ ); and
- 3) *Anxious Depressed* ( $n=55$ ).

We used FreeSurfer to run a vertex-wise statistical analysis using a general linear model on cortical thickness, volume, and surface area between all three subgroups. Results revealed structural differences between the *Emotional* and *Anxious Depressed* subgroups in the inferior parietal region ( $p< 0.005$ ; Fig. 2); and between the *Emotional* and *Hyperactive* subgroups along the pericalcarine region ( $p< 0.005$ ; Fig. 2). Since studies aiming to characterize ASD biological phenotypes have been quite varied, particularly within the cerebral cortex, our work further validates the necessity of defining subgroups versus using heterogeneous groups of ASD patients.

## Autistic-Like Trait Subgroups



**Fig.1 Radar Plot of Resultant Subgroups.** The *Emotional* subgroup shows higher levels of reactivity and aggression; the *Hyperactive* subgroup displays better cognitive abilities coupled with significant levels of hyperactivity; and lastly the *Anxious Depressed* subgroup shows exceptionally higher levels of anxiety and depression. All groups experience significant levels of attention problems.  
[Autistic-Like Trait Subgroups]



**Fig.2 Cortical Differences Between Autistic-Trait Subgroups.** We revealed that participants from the *Emotional* subgroup exhibit a right hemisphere inferiorparietal increase in surface area relative to the *Anxious Depressive* subgroup (left). Additionally, we observed a volume decrease in the left hemisphere pericalcarine region in the *Emotional* subgroup compared to the *Hyperactive* subgroup (right).

[*Subgroup Cortical Comparisons*]

**P3.058 The mitochondrial system of hippocampal adult-born neurons is altered in the Tg2576 mouse model of Alzheimer's disease**

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A large number of studies indicate that mitochondria are involved in neuroplasticity and their dysfunctions participate in neurodegenerative diseases, particularly in Alzheimer's disease (AD). In parallel, alterations of hippocampal adult neurogenesis have been described in AD patients and in several mouse models of AD. Using the Tg2576 (APPswe) transgenic mouse model of AD, we reported that alteration of hippocampal adult-neurogenesis occurs early in the course of the disease, suggesting that impaired neurogenesis could contribute to the defects in hippocampal function associated with this pathology (Krezymer et al 2013). The present study was designed to decipher whether altered mitochondrial system in adult-born neurons of Tg2576 mice could participate to impaired hippocampal adult neurogenesis in these mice. We examined for the first time, the mitochondrial network of adult-born hippocampal neurons in Tg2576 mice. We used a retroviral vector expressing the enhanced green fluorescent protein (GFP) to birth-date and follow developing adult-born hippocampal neurons in Tg2576 and non-Tg mice, as well as a retrovirus expressing MitoDsRed that stains mitochondria. Confocal images allowed quantifying dendritic spines and mitochondrial content of adult-born neurons in these mice. Our results showed that new neurons of Tg2576 mice display lower mitochondrial content both in their soma and dendritic compartments, which might be either due to a decreased number and/or size of the mitochondria, compared to non-Tg mice. These findings suggest that mitochondria may be pertinent and innovative targets for enhancing or rescuing neurogenesis-dependent hippocampal plasticity, thus opening new avenues for early therapeutic intervention to fight AD, and possibly other neurodegenerative diseases.

**P3.059 Depression and therapeutic resistance: complementary models to study inflammatory versus non-inflammatory depression in mice**

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Depression represents a major public health concern. Its prevalence is continuously rising, notably in patients exposed to chronic stress or suffering from medical conditions associated with low-grade chronic inflammation, such as obesity. These patients also often display increased resistance to conventional antidepressants (AD). There is growing evidence that inflammation plays a role in depressive disorders. Interestingly, recent clinical findings suggest that it may also contribute to therapeutic resistance, although the underlying mechanisms are still poorly understood. A relevant preclinical model of depression allowing to assess the specific features of inflammation is therefore urgently needed. The present study aims to model inflammatory vs. non-inflammatory depression in mice.

To address this issue, we compared depressive-like behaviors and peripheral and brain inflammation in mice exposed to diet-induced obesity (DIO) (60% Kcal from fat, 6 months from weaning), a procedure known to induce inflammation, or to unpredictable chronic mild stress (UCMS, 7 weeks), known to induce depressive-like behaviors responding to classical antidepressants. Peripheral inflammation was assessed by measuring plasma concentrations of inflammatory factors by bioplex.

Both DIO and UCMS induce depressive-like behaviors, as indicated by increased coat state score, latency to feed in the novelty suppressed feeding test, and immobility in the forced swim test. In contrast, systemic inflammation is only detected in DIO mice, as revealed by higher plasma concentrations of cytokines and chemokines, such as interleukins 6 and 10 (IL-6, IL-10), interferon gamma induced protein 10 (IP-10) and interferon gamma induced monokine (MIG). Detailed analysis of associated activation of brain inflammatory processes is still in progress, but the present data suggest that the preclinical approach reported here can be useful to deeply study the mechanisms underlying inflammation-driven depression and therapeutic resistance, comparatively to non-inflammatory depression.

**Keywords:** Depression, inflammation, behavior, animal models, therapeutic resistance

**P3.060 Development of a new nanobody-based MRI contrast agent of pTau for early diagnosis of AD**

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Alzheimer's disease (AD) is a neurodegenerative disease characterized by the presence of extracellular amyloid deposits and intracellular neurofibrillary tangles (NFTs) composed of highly-phosphorylated tau proteins. AD is a progressive disease that begins more than twenty years before the emergence of clinical symptoms, underlining the need to develop early diagnostic methods. The aim of our work is to develop a new *in vivo* MRI marker of NFTs, which are a strong predictor of subsequent cognitive decline, using nanobody-based contrast agents for early diagnosis of AD. Radioactive tracers specific to NFTs for positron-emission tomography (TEP) have been developed but lack selectivity and specificity and have cost, logistic and safety issues. Magnetic resonance imaging (MRI) on the other hand, is non-invasive and has a better spatial resolution and availability for clinical use. We recently designed a new highly sensitive and specific antibody targeting hyperphosphorylated Tau (A2), using a camelid single-domain antibody (VHH or nanobody). VHHs display several properties that make them very good candidates for imaging intracellular brain targets.

The A2 VHH was conjugated with ultrasmall superparamagnetic iron oxide (USPIO) as a potent MRI contrast: commercial USPIOs were functionalized with maleimide groups, conjugated with A2, and then purified by magnetic separation. ELISA assay showed a good affinity towards phospho-tau (pS422). Histology controls on brain tissue from transgenic P301S mouse model underlined the potential of A2-USPIO to detect NFTs. These results were obtained following anti-VHH immunohistochemistry (detection of the antibody moiety) compared to the standard AT8 antibody, or PERLS staining (detection of the iron nanoparticles). Best results were obtained with conjugates presenting an optimized size (hydrodynamic radius: 53.3 nm) and VHH/iron ratio (27.2 µg protein/mg Fe). Relaxometry properties of the A2-USPIO are currently performed and will be compared to standard contrast agents before initiating *in vitro* MRI acquisition on postmortem brain tissue. In parallel peripheral administration of A2-USPIO in transgenic P301S mice will be carried out to assess passage of the blood-brain barrier and diffusion in brain parenchyma.

- P3.061 Chronic stress in middle-age mice has consequences on behavioral emotionality and cognitive aging: relationships with changes in brain methylated H3K27**  
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Data showed that chronic stress exposure during middle-age induces persistent stress symptoms such as increased anxiety and depression state leading to long-lasting emotional disorders that can extend to cognitive deficits. Changes in epigenetic regulations, such as histones acetylation and methylation, have been identified as a key mechanism through which stress exposures induce emotional and cognitive alterations. In this study, we investigated the long-lasting behavioral impacts of chronic stress exposures and their epigenetic correlates with aging. C57bl/6 mice underwent an unpredictable chronic mild stress procedure (UCMS) for 6 weeks at either 6 month- (adult) or 11-month old (middle-age) while age-matched controls remained undisturbed (non-stressed groups). All mice underwent a battery of behavioral testing when getting the age of 18 months and then, were killed for immunohistochemical detection of the transcriptional repressive histone H3 tri-methylation at lysine 27 (H3Kme<sup>3</sup>). Trait anxiety in the elevated plus-maze, but not reactive anxiety in the marble burying test, as well as despair in forced-swimming and tail suspension tests were increased in mice that had experienced UCMS at 11 month as compared to controls. Spatial memory in water-maze and working memory were also further impaired. Principal component analysis confirmed a clear-cut separation of the behavioral patterns in these two groups of mice. These behavioral impairments were associated with changes in histone H3K27me<sup>3</sup> in CA1 area of the ventral hippocampus, the prefrontal cortex and lateral nucleus of the amygdala. In contrast, mice exposed to UCMS at 6-month old, did not display any persistent deficits nor any epigenetic changes when getting aged. In conclusion, these results indicate that chronic stress stronger impacts on behavioral emotionality and cognitive aging in association with epigenetic regulatory changes in middle-aged adults. Although adulthood has been associated with an increase in stress resistance, a second phase of vulnerability to stress emerges at midlife and interferes with brain aging.

**P3.062** **Engineering pharmacology active nanobodies to target mGlu2 receptor in the brain**  
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The metabotropic glutamate receptors (mGluRs) modulate transmission at many synapses, and are interesting therapeutic targets for the treatment of several neurological disorders and psychiatric diseases. A new strategy to modulate the glutamatergic transmission is the use of nanobodies. Nanobodies are single-domain antibodies derived from the variable regions of Camelidae atypical immunoglobulins constituted of heavy chains only. They show promise as high-affinity reagents for research, diagnostics and therapeutics owing to their high specificity, small size ( $\approx 15\text{ kDa}$ ) and straightforward bacterial expression. But nanobodies are small molecules that are quickly eliminated by the kidney, and they do not cross the blood brain barrier (BBB). Here we focus on three nanobodies (DN1, DN10 and DN13) that decrease the release of glutamate by activating the mGlu<sub>2</sub> receptor with high affinity and specificity. Our aim is to optimize these nanobodies for *in vivo* experiments by 1) increasing their affinity/avidity; 2) improving their half-life and 3) promoting the BBB penetration. We concatenated nanobodies and showed that the affinity and potency for mGlu<sub>2</sub> was improved (1-2 logs). In addition we generated a bivalent nanobody that was still detected after 7 days in the blood. We are currently assessing BBB penetration.

P3.063

### The epigenetic landscape of Alzheimer's disease: chromatin acetylation changes in the ThyTau22 mouse model

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Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized by the accumulation of amyloid- $\beta$  plaques and tau tangles, which leads to neuronal cell death and cognitive decline. The epigenomic alterations associated with AD, particularly the chromatin acetylation is thought to be implicated in the disease progression. Our group has shown previously that ThyTau22 mice, a tauopathy model, displayed a robust decrease of H2B but not H3K27 acetylation levels in the hippocampus (Chatterjee et al., EMBO Mol Med 2018). Excitingly, treatment with CSP-TTK21, an activator of CBP/p300 histone acetyltransferases, was able to increase H2B acetylation levels at decreased peaks, especially at transcription starting sites and CBP enhancers, restoring spatial memory and plasticity deficits. However, it remains unclear whether the epigenomic alterations associated with Tau are mainly neuronal or occur predominantly in glial cells. Thus, our aim is to investigate epigenomics changes associated with Tau in specific cell populations, neuronal and non-neuronal hippocampal cells. We isolated nuclei of the hippocampus of 12-month-old ThyTau22 mice and controls and performed FACS sorting of NeuN (neuronal marker) positive and negative cells. Next, we carried out Chromatin Immunoprecipitation Sequencing (ChIP-seq) of H2BK20ac and H3K27ac in the two different cell populations. Preliminary analysis has shown that the H2Bac decrease observed in whole hippocampal tissue of Tau mice is associated with both cell populations since a similar number of peaks was found in NeuN+ and NeuN- cells. Additionally, we observed that the decreased H2Bac peaks related to neuronal genes were associated with cAMP signaling and calcium ion binding pathways, while non-neuronal H2Bac decreased peaks were linked to transcription, DNA repair and cGMP signaling pathway. Lastly, we are currently assessing the effect of CSP-TTK21 treatment on the epigenomic profiles of both neuronal and non-neuronal cells. Overall, our data suggest that the cognitively impaired ThyTau22 mice share epigenomic alterations in both neurons and glial cells, opening new insights on the use of epigenetic therapeutics, such as CSP-TTK21, in AD-related disorders.

P3.064

### Importin alpha-5 regulates anxiety through MeCP2 and sphingosine kinase 1

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MeCP2 (Methyl-CpG binding Protein 2) is a multifunctional and activity-dependent modulator of the epigenome of critical importance in the nervous system. Alterations in MeCP2 gene dosage are implicated in devastating and complex neurological disorders such as Rett syndrome (RTT) and MeCP2 duplication syndrome (MDS). As a transcriptional regulator, MeCP2's subcellular locus of action is the nucleus, however nuclear import pathways for MeCP2 have not been targeted *in vivo* as yet. Importins (also known as karyopherins) mediate transport from synapse to soma and from cytoplasm to nucleus, suggesting that perturbation of importin-dependent pathways should have significant neuronal consequences. During the course of comprehensive behavioral analyses of a battery of importin alpha mouse mutants, we identified an importin alpha-5 knockout line with a significant reduction of anxiety levels. Re-expression of importin alpha-5 in ventral hippocampus of alpha-5 deficient animals increased anxiety behaviors to wild-type levels. Hippocampal slice recording from importin alpha-5 knockouts showed changes in presynaptic plasticity while RNA-seq analyses highlighted modified expression of MeCP2-regulated genes, including sphingosine kinase 1 (Sphk1). Immunohistochemistry and image analysis revealed changes in the nucleocytoplasmic distribution of MeCP2 in importin alpha-5 knockout hippocampal neurons. Pharmacological inhibition of Sphk1 reverses anxiolysis in the importin alpha-5 knockout mouse, while modulation of sphingosine signaling through the S1P receptors has robust anxiolytic effects in wild-type animals. Our investigation highlights the influence of importin alpha-5 on sphingosine-sensitive anxiety pathways by regulating MeCP2 nuclear import in hippocampal neurons.

**P3.065 Acupuncture effect on chronic stress-induced depression and its central neural mechanism**

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Depression is a serious psychiatric disorder with an enormous socioeconomic burden, and it is commonly comorbid with pain, chronic fatigue, or other inflammatory diseases. Recent studies have shown that acupuncture is an effective therapeutic method for reducing depressive symptoms; however, the underlying mechanism remains unknown. In this study, we investigated the effects of acupuncture on chronic stress-induced depression-like behavior and its central neural mechanisms in the brain.

We induced chronic restraint stress (CRS) in male C57BL/6 mice and acupuncture treatment was performed at KI10-LR8-LU8-LR4 or control points for 1 or 2 weeks.

Acupuncture treatment at KI10-LR8-LU8-LR4 points rescued the depressive-like behavior, while control points (LU8-LR4-HT8-LR2) and non-acupoints on the hips did not. The activation of c-Fos, a marker of neural activity was changed in the hippocampus, cingulate cortex, motor cortex, insular cortex, thalamus and hypothalamus after acupuncture treatment.

In conclusion, acupuncture treatment at KI10-LR8-LU8-LR4 was effective in alleviating the depressive-like behavior in mice, and this therapeutic effect was produced through central brain neural activity.

P3.066

### Physiological role of APP during aging: behavioral and molecular study in a new model of knock-out rat

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The *Beta-Amyloid Precursor Protein* (APP), precursor of the amyloid-beta (A $\beta$ ) peptide, is implicated in Alzheimer disease (AD). In early onset AD, the *App* gene is mutated, resulting in increased production of A $\beta$  peptide. Intraneuronal accumulation of A $\beta$  results in amyloid plaques, one of the characteristics of AD. APP has been mostly studied in the context of AD. However, this protein has also many physiological functions for which the mechanisms are not understood. Different models of knock-out mice (KO) for *App* showed an implication of APP in synaptic plasticity, neuronal morphology, but also in cognitive functions. Since inter-species differences may exist, it is interesting to confirm these results in an organism as the rat. Thus, we created a new model of rat KO for the *App* gene. At 2 and 12 months, we evaluated anxiety, locomotion and sensorimotor coordination. We also tested spatial memory and behavioral flexibility in the Morris Water (MWM) and Double H (DHM) mazes. The expression of cellular markers and synaptic proteins was assessed by western blot in the hippocampus and medial prefrontal cortex (mPFC), 2 brain structures involved in memory.

Our results show a decrease in body and brain mass at 2 and 12 months in homozygous rats and the emergence of cognitive deficits with aging. At 12 months, homozygous rats exhibited a slower learning in the MWM, and a flexibility deficit in both MWM (extinction deficit) and DHM (altered strategy shift). Therefore, the APP protein seems to be important during central nervous system development and participates in the maintenance of cognitive functions over aging. At the molecular level, there was no significant impact of the KO on the expression of APLP1, a protein of the same family as APP. Surprisingly, the expression of APLP2, another protein of this family, was decreased in the hippocampus at 12 months. The lack of APP had also an impact on the expression of the synaptic marker PDS-95, with an increase at 2 months in the mPFC, and a decrease at 12 months in the hippocampus. GFAP tended to be decreased in the hippocampus of homozygous rats at 2 months. These data point to relatively subtle cognitive alterations in APP KO rats, in parallel with weak alterations of the molecular markers we assessed.

P3.067

**Metabotropic glutamate receptor mGlu4 in the amygdala differentially inhibits sensory and affective component of chronic pain**

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Pain is an essential protective mechanism meant to prevent tissue damages in organisms. However, inflammation or nerve injury can instigate a transition to chronic pain. Unlike acute pain, chronic pain lasts long after the initial injury or illness that caused it has healed. Chronic pain is therefore long lasting, provokes long-term disability for patients and its management represents a major public health problem. Understanding chronic pain molecular mechanisms is critical to develop innovative and efficient therapies.

Number of evidences have demonstrated a pivotal role of glutamate in nociceptive transmission. Glutamate receptors are then promising potential target for drug development. Glutamate is the most abundant excitatory neurotransmitter in the brain. Once released, glutamate acts through ionotropic and metabotropic glutamate receptors (iGluRs and mGluRs). iGluRs are ligand-gated ion channels triggering fast excitatory neurotransmission. mGluRs are G protein-coupled receptors modulating synaptic transmission.

Our work focuses on the role of mGlu4 in both sensory and affective components of pain. Using intra-amygdala delivery of both classical and photoswitchable ligands of mGlu4, we demonstrated that mGlu4 in the amygdala drives both sensory and affective component of inflammatory pain. In order to better understand the relationship between these two components, we used a model of neuropathic pain induced by the chronic constriction of the sciatic nerve. We first demonstrated that unilateral mGlu4 activation in the contralateral amygdala is sufficient to relieve neuropathic pain. Secondly, our results suggest that antidepressive effect elicited by mGlu4 activation is not subsequent to antinociceptive effect. Finally, we demonstrated that photocontrol of endogenous mGlu4 receptors in the amygdala via photoswitchable ligands dynamically attenuates neuropathic pain.

P3.068

### Sleep/wake activity in the Lewy bodies mouse model of Parkinson's disease

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Parkinson's disease (PD) is characterized by the loss of dopaminergic (DA) neurons of the substantia nigra pars compacta (SNc) and the presence of cytoplasmic inclusions named Lewy Bodies (LB) containing notably misfolded alpha-synuclein (a-syn). Although primarily a movement disorder, PD patients exhibit a myriad of non-motor symptoms. Sleep/wake alterations, such as rapid-eye movement (REM) sleep behavioral disorder (RBD), REM loss or increased day time sleepiness, may occur in the prodromal phase of PD. They are even considered as predictors of PD. While neurotoxin-based experimental models recapitulate both motor and non-motor symptoms, their poor face validity with regard to the neurodegenerative process make them unsuitable for investigating the likelihood of a relationship between progression of neurodegeneration, progression of the a-syn pathology and occurrence of sleep/wake issues.

We here take advantage of the recently developed LB mouse model of parkinsonian degeneration to investigate the potential occurrence of sleep/wake deficits as the pathology develops. Wild-type mice were injected with LB, containing pathological a-syn, extracted from the brain of PD patients leading to a progressive loss of DA neurons (LB mice). Control mice were injected with a fraction devoid of aggregated a-syn, extracted from the same patients (NoLB mice). Mice were implemented with a device recording both cortical neuronal activity (ElectroEncephaloGraphy, EEG) and neck muscles contractions (ElectroMyoGraphy, EMG) enabling the discrimination of sleep/wake cycle stages: wake, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. Recording sessions were performed once a month for 48h over a 4-month period. Alteration of the sleep/wake cycles are detailed in both LB and NoLB mice with an emphasis put upon the changes in power band frequencies.

Understanding if sleep disorders may serve experimentally as a surrogate marker of neurodegeneration or pathology progression could provide a way of early detection and lead to new therapeutic strategies to slow down its progression.

**P3.069 Impaired lysosome recycling and lipid clearance contribute to neurodegeneration**

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Heredity Spastic Paraplegias (HSP) are a group of genetic neurodegenerative diseases characterized by progressive spasticity and weakness of lower limbs. These symptoms are caused by the degeneration of motor neurons of the cortico spinal tract. The most frequent form of autosomal recessive HSP is due to mutations in *SPG11*, coding for spatacsin. Loss of spatacsin function impairs autophagic lysosomal reformation<sup>1</sup>, a mechanism that allows the recycling of membrane from autolysosomes after autophagy to promote the reformation of new lysosomes<sup>2</sup>. We observed that loss of spatacsin impaired the formation of tubules in lysosomes in basal conditions, indicating that spatacsin contributes to lysosomal membrane recycling. Moreover, the absence of spatacsin leads to accumulation of lipids in lysosomes in neurons and primary cultures of mouse fibroblasts<sup>3</sup>.

Our objective is to elucidate the link between the impairment of lysosomal membrane recycling and lipid accumulation in lysosomes.

We observed that cholesterol accumulated in lysosomes in absence of spatacsin. Live cell imaging with fluorescent cholesterol showed that the tubules emerging from lysosomes contained cholesterol. This was associated with a depletion of cholesterol in the plasma membrane, which impaired cytosolic calcium homeostasis. Interestingly, modulating cytosolic calcium levels restored tubulation and cholesterol levels in lysosomes. Together our results suggest that, in absence of spatacsin, alteration of cholesterol distribution and impairment of cytosolic calcium homeostasis are entangled. Similar results were obtained in neurons, suggesting that these alterations could contribute to neurodegeneration.

However, further investigations are required to clearly define the role of spatacsin in impaired calcium and cholesterol homeostasis.

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**P3.070 D-serine is involved in the  $\beta$ -amyloid-related pathophysiology in Alzheimer's disease**

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Activation of N-methyl-D-aspartate subtype of glutamate receptors (NMDAR), key regulators of functional brain plasticity and memory process, requires the binding of the co-agonist D-serine. The homeostasis of these receptors are affected by soluble oligomers of the beta-amyloid peptide (A $\beta$ o) in Alzheimer's disease (AD). The dysregulation of NMDA participates to the onset and development of neurodegenerative processes. However, the actual *in vivo* contribution of D-serine in the functional NMDAR-related deregulations mediated by A $\beta$ o is still unknown. In 3-4 month-old transgenic mice model of amyloidogenesis (5xFAD) showing marked increase in A $\beta$ o rates and apparent unaffected D-serine levels, extracellular electrophysiological recordings reveal impaired NMDAR-dependent long-term potentiation at CA1/CA3 hippocampal synapses, without significant changes in basal synaptic transmission. This deficit persists at 12 month of age when amyloid deposits are present with concomitant disabilities in cognitive functions. Importantly, these functional alterations and the long term behavioral impairment are prevented in 5xFAD mice in which the D-serine synthesis enzyme serine racemase has been invalidated, despite A $\beta$ o rates remain significantly elevated. These results therefore provide convincing evidence for a critical and transient involvement of D-serine in hippocampal network dysfunctions and related cognitive disabilities driven by increased amyloidogenesis.

**P3.071 Intracranial Zika virus injection for the treatment of recurrent high-grade glioma: preliminary case report**

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High-grade glioma is a primary malignant brain tumor for which there is no current curative treatment. It is characterized by a high rate of recurrence and a limited survival, thus encouraging development of novel therapies. Current standard treatment is based on maximal safe surgical resection followed by temozolomide and radiation therapy.

Additional treatments for the recurrence are limited and oncolytic viral treatments are under study in both, basic and clinical settings. Recently, it was shown that Zika virus (ZIKV) has an *in vitro* potential for selective destruction of glial cells with stem cell properties, but there have been no reports of this potential treatment approach in humans. Here, we report the effects of the intracerebral injection of ZIKV in a 66-year old female patient presenting with recurrence of a left fronto-parietal wild-type glioblastoma, previously submitted to standard treatment. The experimental treatment was proposed on a compassionate basis, overseen by the institutional ethics committee and for which consent was obtained from the patient and her family.

There were no serious adverse effects or complications following the procedure. The patient presented mild clinical signs of Zika in the 9<sup>th</sup>post-inoculation day (PID); viral copies were detected in both cerebrospinal fluid (CSF) and serum from the first to the 10<sup>th</sup>PID; NS1 protein was detected in the CSF from the third to the 14<sup>th</sup>PID and also detected in serum from the 8<sup>th</sup>to the 10<sup>th</sup>PID. Serum IgM antibodies were detected from the 11<sup>th</sup>PID and IgG in both CSF and serum from the 14<sup>th</sup>PID. There were clinical and radiological responses to the treatment during the first four weeks following inoculation, evidenced by decreased growth of the tumor and clinical improvement of the patient. Unfortunately, on the fifth week post-injection, the patient clinical status started deteriorating and she died 12 weeks after the inoculation. However, histological examination of the cerebral biopsies prior to the inoculation showed a change in tumor pattern, transforming from a glioblastoma to a gliosarcoma. The data presented here suggests that the use of ZIKV for the treatment of the recurrence of high-grade gliomas is both safe and feasible, thus warranting future investigation in human trials.

**P3.072 Neuron-glia interaction in stress-related behaviors: role of hippocampal glutamatergic tone**

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Contrary to the classical view, it is now firmly established that astrocytes can specifically regulate glutamatergic tone in various brain regions including the hippocampus. In particular, release of glutamate by astrocytes has been repeatedly demonstrated in response to glial activation. However, the mechanism and degree to which astrocytes modulate and control extracellular glutamate levels has been poorly studied. Moreover, the role of astroglial glutamate in the regulation of stress-related behaviors has yet to be solved. Because part of astrocytic glutamate is released by connexin 43 (Cx43), we sought to determine the effects of the constitutive or tissue specific downregulation of this protein on neurobehavior and extracellular glutamate levels in the hippocampus.

Our results demonstrated that the constitutive deletion of Cx43 in Cx43 Knock-down mice (KD), resulted in antidepressant-like behavior in the Forced Swim Test (FST); associated with a decrease in hippocampal extracellular glutamate concentrations. To better understand such relationship, we then inactivated Cx43 in WT mice by micro-injecting into the hippocampus a lentiviral vector containing a shRNA targeting this protein. Our results indicated that tissue specific silencing of Cx43 did not produce significant antidepressant-like behaviors in a large battery of tests. However, part of the neurobehavioral abnormalities detected in a mouse model of depression, were reversed by the inactivation of hippocampal Cx43 notably in the TST and the NSFT. Finally, our recent data argue in favor of a role of Cx43 hemichannels (HC) since we showed that the intra-hippocampal injection of Gap26 mimetic peptide, a specific Cx43 HC blocker, reduced immobility time in the FST in relation with its ability to prevent acute stress-induced increase in local extracellular glutamate levels.

Collectively, our data suggest that blocking specifically Cx43 HC in the hippocampus could be a new therapeutic strategy to attenuate stress-responses and promote antidepressant-like effects through a mechanism modifying neuron-glia interaction.

**P3.073 Hippocampal subfields alterations in terrorist attacks survivors with post-traumatic stress disorder**

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The November 2015 Paris attacks had dramatic consequences on the mental health of the trauma-exposed civilians with some developing a post-traumatic stress disorder (PTSD). Alterations of the hippocampus, whether pre-existing or sequels of the trauma, have been proposed to explain the aberrant processing of context during memory intrusion that further cascade into overgeneralization of fear in PTSD. This study aims to investigate structural alterations within hippocampal subfields and parahippocampal regions in adults with PTSD and to explore the links with re-experiencing symptoms.

92 individuals (18-60 years old) who were exposed to the November 2015 Paris attacks (53 with PTSD and 39 without PTSD) and 58 non-exposed controls underwent a high resolution ( $0.39 \times 0.39 \times 2\text{mm}^3$ ) T2-weighted MRI sequence between July 2016 and May 2017. The medial temporal lobe (MTL) regions were segmented using the semi-automatic method ASHS into: CA1, CA2-3/DG, subiculum, and entorhinal, perirhinal and parahippocampal cortices. First, we manually segmented the images of 22 subjects to create an atlas. Once ASHS was trained, it segmented automatically the remaining 128 images. Group comparisons were performed using an ANVOCO with hemisphere and MTL regions as within factors and age, sex, education level and intracranial volume as nuisance covariates, followed by post-hoc tests. Robust Spearman correlations were conducted with the Post-traumatic Check List intrusions subscore in the trauma-exposed group.

The results showed an interaction between group and MTL regions ( $F=3.13$ ,  $p<0.001$ ). This interaction was driven by a reduction of CA1 volume in the PTSD group compared to the non-PTSD trauma-exposed group and lower CA2-3/DG volume in the PTSD group compared to the two other groups. Volume reductions in CA1 ( $r=-0.32$ ,  $p<0.001$ ), and CA2-3/DG ( $r=-0.44$ ,  $p<0.001$ ) regions predicted an increase in intrusion score within exposed participants.

Re-experiencing symptoms are related to alterations of CA2-3/DG and CA1, known to be involved in pattern separation and completion processes. These results resonate with recent theories proposing that an increase in memory interference could contribute to the apparition of intrusions symptoms and promote overgeneralization of fear in safe contexts.

P3.074

**Glutamate dysfunction at extrasynaptic site in hippocampus of a mouse model of myotonic dystrophy type 1 (DM1)**

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Myotonic dystrophy type 1 (DM1) is an inherited type of muscular dystrophy that affects muscles and other body systems, due to an abnormal trinucleotide repeat expansion in the *DMPK* gene. The congenital form present at birth is the most severe form and includes intellectual and behavioral deficits, indicating dysfunctions of the central nervous system. To understand the cellular and molecular events leading to the central disease, DM1 was modeled in DMSXL transgenic mice carrying an expanded *DMPK* gene cloned from DM1 patients. Astrocytes from DMSXL mice failed to protect neurons against glutamate neurotoxicity and increased neurite collapse in co-culture. Like DM1 patients, brains of DMSXL mice show a reduced expression of the GLT1 glutamate transporter. GLT1 transfection in DMSXL astrocytes rescued neurite collapse to control levels, suggesting that DMSXL astrocytes are unable to protect neurons against glutamate excitotoxicity, pinpointing the altered expression of GLT1 as a potential therapeutic target. To determine the functional impact of glutamate homeostasis dysregulation, glutamate synaptic transmission and plasticity was studied in hippocampal slices of DMSXL and WT mice, using electrophysiological recordings. AMPA-mediated I/O curves, LTP and LTD were unchanged in the CA1 area and in the dentate gyrus (DG). However, the paired-pulse facilitation (PPF) ratio was increased in the CA1 area. Using whole-cell patch-clamp recordings, we found a significant increase in the amplitude of a tonic current mediated by the activation of extra-synaptic NMDA receptors by ambient glutamate, in both CA1 pyramidal cells and DG granule cells from DMSXL hippocampus. These results demonstrate a relative stability of synaptic-dependent mechanisms in the CA1 and DG areas of DMSXL mice, but a selective alteration of the extrasynaptic side of the glutamatergic synapse. Further experiments are necessary to understand the relationship between GLT1 reduced expression and the extrasynaptic disturbance. The treatment of DMSXL mice with Ceftriaxone to enhance GLT1 expression will be performed as a new therapeutic strategy.

**P3.075 The Amyloid Precursor Protein C-terminal domain alters CA1 neuron firing impairing spatial memory encoding**

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Alzheimer's disease (AD) is an incurable neurodegenerative disorder, with increasing prevalence in aging populations. Currently, there is a growing consensus that AD results from the failure of the homeostatic machinery, which underlies the firing stability of neural circuits. What are the culprits leading to neuron firing instability? The amyloid precursor protein (APP) is central to AD pathogenesis and we recently showed that its intracellular domain (AICD) could modify synaptic signal integration. Also, others demonstrated that AICD modulates intracellular calcium homeostasis. Together, these data strengthen the hypothesis that AICD could alter neuron firing homeostasis, thus contributing to the disruption of memory processes. We addressed AICD actions *per se*, on firing homeostasis and associated behavior, combining *in vivo* AICD expression or *ex vivo* AICD delivery with whole-cell electrophysiology, pharmacology or behaviour.

In CA1 hippocampal neurons, pathological AICD levels induced a weakening of firing homeostasis at the gamma-frequency range through a gene transcription-dependent mechanism. Briefly, when a neuron with increased AICD levels receives inputs to fire at gamma-frequency, alterations in L-Type  $\text{Ca}^{2+}$ -SK channels functional coupling causes an increased  $\text{Ca}^{2+}$ -sensitive AHP, lowering its firing frequency. A profile similar to what has been reported by others in CA1 neurons from aged rodents. Notably, we demonstrated that AICD impairs a spatial memory task known to require CA1 pyramidal neurons firing at gamma-frequency. The current findings highlight common features between physiological ageing and AD, thus suggesting that AICD might contribute to progressive neuron homeostatic failure, driving the shift from normal ageing to AD.

**P3.076 Significant low DNA methylation of *BDNF* gene in anorexia nervosa**

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**Introduction:** Anorexia nervosa (AN) is a psychiatric disorder characterized by an extreme behavior for weight loss. This is the most severe psychiatric illness in terms of morbidity with 1% death per year. AN is a disorder resulting of several factors including, genetic, biological, psychological and social events. Two subsets of the disease are diagnosed: the restrictive form (restrictive anorexia nervosa, RAN), where there is a gradual decrease in the amount of food ingested, and the purgative mixed form (binge/purging anorexia nervosa, BPAN), characterized by periods of purges (vomiting, diuretics, laxatives) and binge eating. Many studies involve the brain derived neurotrophic factor (BDNF) in AN. Thus, low circulating concentrations of BDNF and its genetic variant rs6265-Val66Met are associated with a higher risk of AN. The epigenetic regulations are also strongly suggested in AN. Thus, the DNA methylation level of *BDNF* gene could modify its expression.

**Aim:** Our work was to measure the level of the DNA methylation of CpG sites among *BDNF* gene in current AN patients, remitters and controls in the goal to identify a specific profile associate with AN or remission.

**Methods:** DNA was isolated from blood samples of a transversal cohort (ENDANO) of 24 current AN patients (12 RAN & 12 BPAN), 24 AN remitters (at least one year at a normal body mass index and no symptom of AN, previously 12 RAN & 12 BPAN), and 48 healthy controls. Methylation of DNA was measured for 73 CpGs encompassing *BDNF* gene by using the Infinium HumanMethylation450 BeadChip technology.

**Results:** Analysis showed a significant decrease of DNA methylation level in AN patients compared to controls ( $p < 0.01$ ). Among the 73 CpG sites, 10 sites located in the 3' region of *BDNF* gene, present a lower level of methylation in current patients compared to controls. Furthermore, remitters present an intermediate methylation profile between AN and controls, that are not significantly different to the controls.

**Conclusions:** We are currently assessing to replicate this observation in an independent cohort. We are measuring the circulating BDNF in subjects to confirm its implication in AN.

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P3.077

### Role of BIN1 in a development of late-onset Alzheimer's disease

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Genome wide association studies identified BIN1 (Bridging integrator 1, also known as amphiphysin2) as second, after apolipoprotein E (APOE), most important risk factor for late onset Alzheimer's disease (AD) (Lambert et al., 2013). BIN1 is widely expressed in human and mouse brains. BIN1 was shown to play a role in endocytosis, trafficking, calcium homeostasis, inflammation and apoptosis. Data suggest that BIN1 may increase AD risk by modulating tau pathology (Calafate et al., 2016). Recently, BIN1 was shown to be involved in beta-amyloid production (Miyagawa et al. 2016). Results obtained in our team indicates that mice overexpressing *BIN1* (hBIN1-Tg mice) show decreased synaptic plasticity in hippocampus, one of the first brain structure affected in AD, leading to cognitive deficits in novel object recognition test in these animals (Daudin, Marechal et al., 2018).

We have studied how *BIN1* overexpression affects onset and progress of AD pathology in mice with single humanized App knock-in carrying Swedish, Beyreuther/Iberian and Arctic mutation (APP-NL/G/F) (Saito et al., 2014). To this end, we studied kinetics of cognitive decline in APP-NL/G/F x hBIN-Tg mice using a pipeline of memory targeting tests, eg. novel object recognition, Morris watermaze and IntelliCage (TSE System) learning and memory tests. Very surprisingly, up to 15 months of age, we have not detected changes in cognition in APP-NL/G/F x hBIN-Tg mice. We are now investigating other biological markers of AD (eg. β amyloid plaques deposition, neuroinflammation) in these mutant animals.

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**P3.078 High frequency but not low frequency deep brain stimulation of the subthalamic nucleus reduces motivation for cocaine while increasing that for apple sauce in the monkey**

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There is currently no pharmacological treatment for cocaine addiction, therefore it is important to look for alternative treatment strategies. One possibility could be a surgical approach. Indeed, it has been shown in the rat that the inactivation of the subthalamic nucleus (STN), by either lesions or high frequency Deep Brain Stimulation (DBS), reduces motivation for cocaine while increasing motivation for food. It has thus been suggested that STN high frequency DBS could be a good strategy to treat cocaine addiction. Before testing in human addicts, the aim of the present study was to validate this hypothesis in non-human primates. We have trained two monkeys to work under various schedules of reinforcement (Fixed Ratio 15 (FR15) and Progressive Ratio (PR)) for either apple sauce or cocaine (intravenous 0.1 mg/kg/injection). After stabilisation of performance, electrodes have been implanted bilaterally in the STN, and high or low frequency chronic stimulation has been further applied (HF : 130 Hz, 2V or LF : 50 Hz, 3V respectively). All conditions (apple sauce-HF/LF stimulation ON, apple sauce-stimulation OFF, cocaine-HF/LF stimulation ON, cocaine-stimulation OFF) have been tested in alternance. Results have first shown that, after STN HF DBS, the motivation for apple sauce was significantly increased while that for cocaine was significantly decreased. Conversely, STN LF DBS failed to show such modulations. These results confirm the opposite effect of STN HF DBS on motivation, that has been previously demonstrated in rats, and allowed us to demonstrate the selectivity of the HF to elicit this effect. Since decreasing the motivation for the drug, without diminishing other forms of motivation is the goal for a possible treatment of cocaine addiction, STN HF DBS may thus be the appropriate strategy.

**P3.079 Symptomatic and biochemical assessment of an antidyskinetic compound in a L-DOPA induced dyskinesias rat model**

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Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in substantia nigra pars compacta (SNpc) and is associated to motor symptoms such as akinesia. Nowadays, L-DOPA remains the most effective therapy in the management of motor symptoms of PD. However, chronic treatment with L-DOPA is associated with the risk of development of motor fluctuations such as choreic and dystonic abnormal and involuntary movements affecting mainly the upper body, face and extremities. These disabling side effects are called abnormal involuntary movements (AIMs) or L-DOPA-induced dyskinesias (LIDs). Given that L-DOPA is still a necessity in the treatment of advanced PD, reducing or avoiding dyskinesias is a key therapeutic strategy in the management of PD motor symptoms. Intracerebral 6-OHDA injections in rodents allow the targeting of the SNpc and the generation of unilateral hemiparkinsonian models. Unilateral injections lead to asymmetric motor deficits (mostly akinesia) that can be quantified by behavioral tests such as the cylinder or the initiation time. Dyskinesias can be induced in this model by a chronic treatment with L-DOPA during several weeks. The aim of this project was to develop a suitable model of LID that can be quantified with a new rating scale of AIMs including duration and amplitude which increases the sensitivity of quantification of AIMS and in which a reference compound amantadine (weak NMDA antagonist) was able to reduce dyskinesias. Additionally to the symptomatic assessment, we studied the glutamatergic activity in our LID model using microdialysis in SNr and striatum performed in the same animal in awaken conditions. Results showed that the administration of amantadine reduced LID. Moreover, thanks to the microdialysis allowing the monitoring of the neurotransmitters activity in freely moving animals, our study showed that in Parkinsonian rats, the chronic L-DOPA treatment increased basal glutamate extracellular levels in the striatum and in the SNr. To conclude, the LID rat model is a suitable preclinical model to study antidyskinetic properties of a candidate compound on both symptoms (high sensitivity of a new rating scale) and dysfunctional neurotransmitters activity (using microdialysis).

**P3.080 Mitofusin alleles causing Charcot-Marie-Tooth neuropathy have opposite effects on mitochondrial fusion**

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Charcot-Marie-Tooth type 2A (CMT2A) is a dominant hereditary neuropathy caused by mutations in the GTPase Mitofusin (MFN). This mitochondrial outer membrane protein drives mitochondrial fusion a process by which two mitochondria fuse their membranes generating a single entity. To understand how mutations in MFN translate into neuronal dysfunction, we developed fly models of CMT2A by generating transgenics expressing four different MFN alleles frequently identified in patients. As for human, these alleles behave dominantly in flies and impair locomotion. Although all CMT2A alleles trigger mitochondrial synaptic depletion at neuromuscular junctions, and alter mitochondrial turnover in fly brains, we observed that they differently affect mitochondrial morphology and dynamics. Our data show that GTPase mutants aggregate mitochondria and inhibit their fusion, whereas, on the contrary, mutations affecting the HB1 domain of MFN enhance mitochondrial fusion activity in motor neurons. This work suggests for the first time that CMT2A could originate from excessive mitochondrial fusion in a significant fraction of patients, and highlights the importance of a tight balance between fusion and fission in neurons. We are now extending our studies to a larger number of pathogenic alleles to evaluate the extent of gain and loss of function and to shed light on structure-function relationships by mapping these mutations onto the 3D-structure of Mitofusin.

**P3.081 Early blockade of serotonin 5-HT6 receptor-dependent mTOR activation prevents onset of cognitive deficits in a developmental model of schizophrenia**

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Schizophrenia is a devastating mental disorder of neurodevelopmental origin, which affects ~1% of the population worldwide and represents a major socio-economic burden. It is characterized by a broad pattern of cognitive symptoms, including impaired memory, inaptitude to solve problems and alterations in social cognition. These deficits severely compromise the social and professional integration of patients and their quality of life. Cognitive symptoms are the earlier symptoms observed, are predictive of the risk of transition to schizophrenia and are poorly controlled by currently available antipsychotics. Although improving symptomatic treatments remains an important goal, progress in disease management will likely require shift to novel modes of intervention initiated at an early stage of the disease in high-risk patients. A critical time frame for such an early intervention aimed at altering the course of the disease is adolescence, when the brain is undergoing a major structural and functional reorganization, including sprouting and pruning of synapses, changes in neurotransmitter concentrations and in their receptor levels in brain areas essential for cognitive functions such as the prefrontal cortex (PFC). Among the targets currently under investigation to alleviate cognitive deficits of schizophrenia, the serotonin 5-HT6 receptor holds special promise. Highest receptor densities are found in brain regions involved in mnemonic functions and we previously demonstrated that a sustained non-physiological activation of mammalian Target Of Rapamycin (mTOR) elicited by 5-HT6 receptors in the PFC, mediates deficits in social cognition and episodic memory in two rodent developmental models of schizophrenia. Here, we propose a novel disease modifier strategy to prevent emergence of cognitive deficits at the adult stage, in the neonatal phencyclidine (PCP) model of schizophrenia. This strategy is based on early blockade of 5-HT6 receptor-operated mTOR signaling during adolescence. We show that early administration of a 5-HT6 receptor antagonist during adolescence abolishes the overactivation of prefrontal cortical mTOR at the adult stage, rescues the deficit in novel object discrimination and compensates the associated alteration of GABAergic transmission in PFC.

**P3.082 Therapeutic potential of autologous transplants of ecto-mesenchymal olfactory stem cells (EMs-OSCs) to repair hippocampal damage**

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This study evaluate autografts of ecto-mesenchymal olfactory stem cells (EM-OSCs) restore learning and memory abilities in a rats model of amnesia following global cerebral ischemia (GCI). The latter can occur following cardiac arrest (CA) and lead to deleterious neurological consequences such as cognitive and / or sensorimotor injuries.

Nowadays, intensive care following a GCI consists in slowing down the cerebral metabolism by inducing hypothermia while controlling and modulating different physiological variables (blood pressure, respiratory rate, notably). However, this management only limits the neurological damage and does not restore damaged brain areas.

Indeed, the brain displaying poor regenerative capacities and exogenous stem cell-based therapy has been proposed as an attractive strategy to regenerate cerebral tissue after acute injuries or neurodegenerative disorders. However, ethical and technical issues, associated with embryonic, fetal or adult neural stem cells, limit their use as an alternative source, we are interested in adult stem cells from peripheral nerve tissue in perpetual renewal: the EM-OSCs.

First, we validated a reliable and reproducible model of amnesia in the rat. We have selected a GCI-inducing CA model characterized by neuronal losses in the CA1 area of dorsal hippocampal lesions associated with learning and memory deficits.

Then, we evaluated the effect of EM-OSCs autografts on restoration of cognitive functions in these ischemic rats.. To start, we had developed a protocol to monitor the fate of EM-OSCs following autografts, without altering their endogenous properties. Then we demonstrated that these GFP<sup>+</sup> EM-OSCs autografts:

- i) restored learning and memory abilities,
- ii) stimulated neurogenesis, and
- iii) improved PLT in ischemic rats.

To conclude, these results indicated that the use of EM-OSCs can repair CNS damages. However, mechanisms, by which, this therapeutic potential has been seen need to be clearly indentified.

P3.083

### Neuronal activity-dependent changes in KRAS Rasopathy Model

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RASopathies are a group of diseases arising from autosomal dominant, germline mutations in one of the effector molecules of Ras/MAPK pathway. RASopathy patients present with overlapping disease phenotypes, consisting of mild to moderate cognitive impairments, facial dysmorphisms and cardiac abnormalities. Noonan Syndrome (NS) is a RASopathy resulting from mutations in either PTPN11, SOS1, RAF1, NRAS, SHOC2, CBL or KRAS genes, encoding different components of Ras/MAPK signalling cascade. Within these genes, KRAS encodes for KRAS GTPase that acts as a molecular switch for Ras/MAPK pathway by either promoting or limiting the downstream signalling cascade. Leading to impaired GTPase activity resulting in constitutive KRAS signalling, V14I substitution is a recurrent missense KRAS mutation seen in NS patients.

In order to evaluate neurological outcome(s) of the V14I mutation, we employ mice expressing the mutation specifically in excitatory or in inhibitory forebrain neurons. Forebrain lysates of mice expressing the mutation exclusively in excitatory neurons indicate impaired KRAS activity as well as increased phosphorylation of ERK1/2. Moreover, aberrant activity of AKT and JNK54 cascades could be also detected. Experiments in acute brain slices show changes in phosphorylation of ERK1/2 following chemical LTP induction but not after increasing neuronal activity via activation of synaptic NMDA receptors in both cortex and the hippocampus in an age-dependent manner. Mice carrying mutations in excitatory neurons also have deficits in spatial memory but show no behavioural impairments in fear-conditioning test.

The elucidation of neuronal phenotype in KRAS Rasopathy model not only help to develop early clinical interventions for cognitive deficits in Rasopathy patients but also provide new insights for activation of Ras/MAPK pathway that has key roles in signal transduction, GABAergic synaptogenesis and synaptic plasticity.

**P3.084 Persistent loss of depotentiation of the amygdala-insular pathway after withdrawal from chronic cocaine: involvement of muscarinic receptors**

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Chronic use of drugs is known to induce alterations in brain functioning leading to pathological behaviors. Identifying persistent dysregulations in neuronal networks involved in relapse is crucial to develop appropriate therapeutic approaches for addiction. In the last decade, several studies have highlighted a strong relationship between interoception, emotion, craving and risk of relapse. The basolateral amygdala (BLA) and insular cortex (IC) have been shown to play major roles in these processes.

The aim of this study was to examine cocaine-induced persistent changes in the activity of the BLA-IC pathway after long-term abstinence.

For this, we allowed male rats to self-administer cocaine for ten 6-h sessions. Control "yoked" rats received an injection of saline each time the paired "master" rat self-administered an injection of cocaine. After a month of forced abstinence, we used *in vivo* extracellular single-unit and evoked-local field potential recordings in anesthetized rats. Long-term potentiation (LTP) in the IC was induced by applying a theta burst stimulation (TBS) to the BLA, followed by a low-frequency stimulation (LFS) to reverse this LTP. Cocaine induced a persistent increase in the bursting activity and firing rate of BLA putative pyramidal neurons but no change in IC putative pyramidal ones. Moreover, we found no difference in the TBS-induced LTP in the BLA-IC pathway between cocaine and saline rats. However, whereas saline rats showed depotentiation in response to subsequent LFS to the BLA, the depotentiation was absent in cocaine rats. These data suggest that synaptic plasticity in the BLA-evoked activity in the IC is disrupted in cocaine abstinent rats. Interestingly, the muscarinic antagonist atropine (0.4mg/kg, i.v.), injected before LFS, was able to restore a depotentiation similar to control animals.

Therefore, self-administration of cocaine induces a long-lasting increase in the activity of the BLA, as well as a BLA-evoked LTP in the IC that is resistant to down-regulation. This adaptation to chronic cocaine can be reversed by blocking cholinergic neurotransmission. These results demonstrate that chronic cocaine alters BLA-IC information flow which may play a role in the persistence of drug-seeking behavior.

**P3.085 Impaired vocal communication, sleep-related discharges and transient alterations of slow-wave sleep and of brain microstructure in developing mice lacking the epilepsy and language related GluN2A subunit of NMDA receptors**

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Glutamate-gated NMDA receptors (NMDARs) are instrumental to brain development and functioning. Defects in the *GRIN2A* gene, encoding the GluN2A subunit of NMDARs, are the most frequent cause of the epilepsy-aphasia spectrum (EAS) - a group of age-dependent childhood disorders characterized by interictal discharges activated in slow-wave sleep (SWS) associated with infrequent seizures and with language, cognitive and behavioral deficits. The poorly understood developmental sequence of early EAS-related events, and the role of GluN2A-containing NMDARs in the development of SWS and associated EEG activity patterns, were studied in *Grin2a* KO mice. Using longitudinal diffusion tensor magnetic resonance imaging, we detected microstructural alterations in the neocortex, the *corpus callosum*, the hippocampus and the thalamus of *Grin2a* KO mice, mostly at one month of age but not earlier or later. Ultrasonic vocalizations recordings revealed altered vocal communication. *In vivo* extracellular local field potentials and chronic EEG recordings of neocortical activity detected a series of sleep-related anomalies in *Grin2a* KO mice. Increased occurrence of high voltage spindles was detected, and the pattern of slow-wave activity induced by low dose isoflurane was altered in the third postnatal week and at one month of age, with strong suppression of the delta oscillation power and an increase in the occurrence of spike-wave bursts. Moreover, proportion of SWS and sleep quality were reduced in *Grin2a* KO mice aged one month but recovered by the age of two months. *Grin2a* KO mice also displayed spontaneous spike-wave discharges, which occurred nearly exclusively during SWS at one and two months of age. The transient structural anomalies of the thalamus and neocortex, the impaired vocal communication, the spike-wave discharges seen almost exclusively in SWS, and the age-dependent alteration of SWS, matched the sleep-related and age-dependent manifestations of EAS disorders, hence validating the *Grin2a* KO as a reliable model of EAS. Our data also show that GluN2A-containing NMDARs are involved in early maturation of slow-wave activity. The period of postnatal brain development (P30) when several anomalies peaked might be critical for GluN2A-dependent, sleep-related processes.

P3.086

**Single-cell RNA-seq analysis of glioblastoma cell tumorigenic potential**

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Glioblastoma (GBM), the most devastating form of malignant brain tumors in adults, are highly heterogeneous. Each GBM includes multiple cancer cell populations in distinct functional states, with respect to stem-like properties, proliferation, migration capacity, drug resistance, etc.. This “functional heterogeneity” is thought to originate both from clonal selection of cells with varying mutational loads, and functional cell plasticity. Our previous studies uncovered factors driving reversible and irreversible phenotypic changes in GBM cell state, and showed them to be associated with relevant cell states in the patients' tumors. Here, we developed an original analytical strategy using published patients' GBM single cell datasets to group cells according to their functional state. Establishing links between each cell group transcriptomic profile and functional state showed an enrichment of defined metabolic pathways in cells with high tumorigenic potential. We validated our strategy using independent transcriptome datasets and experimental evaluation. Further development of our strategy should yield an integrated view of functional heterogeneity at the single cell level, and help to design efficient therapies.

**P3.087 *disrupted-in-schizophrenia-1 (disc1) regulates development of the hypothalamus and its related behaviours in zebrafish larvae***

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Affective disorders constitute a devastating disease spectrum characterised by social withdrawal and high suicide rates. Understanding how *Disrupted-in-schizophrenia-1*(*Disc1*) contributes to schizophrenia, bipolar disorder and major depression will help direct therapeutic efforts. Previous data from our lab demonstrated *disc1*mutant zebrafish larvae had alterations in hypothalamic development. Critically, behaviours relating to the hypothalamic-pituitary-interrenal (HPI) axis such as stress were also perturbed<sup>1</sup>. We have generated a *disc1* CRISPR/ Cas9 knock-out zebrafish line, closer to the human-equivalent mutation. After mutant validation, we set out to explore other cellular and behavioural phenotypes relating to hypothalamic functions. Results suggest mutants exhibit hypophagia relating to deficits in hunting behaviour, altered circadian rhythms as well as altered responses to stress. We are currently measuring whole-brain activity based on a recent study elucidating phenotypical commonalities of other risk-associated genes<sup>2</sup>. Preliminary data points to an increase in activity of hypothalamic regions.

<sup>1</sup>(Eachus *et al.*, 2017)

<sup>2</sup>(Thyme *et al.*, unpublished in BioRxiv)

**P3.088 Role of synaptic zinc in motor and non-motor deficits associated to Parkinson's disease: pharmacological & genetic studies in mice**

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Excessive glutamatergic transmission in the striatum is recognized as a key pathophysiological mechanism contributing to Parkinson's disease (PD). Subset of glutamatergic cortical-striatal projections uses ionic zinc ( $Zn^{2+}$ ) as a co-transmitter, but its role in PD remains unexplored. Here we used pharmacological and genetic tools in combination with neurotoxic murine models of PD to investigate the role of synaptic zinc in motor and non-motor deficits associated to PD. We first studied the effects of acute blockade of striatal synaptic zinc signalling on locomotor deficits induced by an extensive unilateral intrastriatal 6-OHDA lesion. Intrastriatal infusion of the extracellular zinc chelator CaEDTA (300 mM in 1  $\mu$ l) restored locomotor deficits induced by dopaminergic (DA) lesion, suggesting that synaptically released zinc in the striatum promotes expression of motor deficits. To explore the potential role of synaptic zinc in neurotoxicity, we performed partial unilateral intrastriatal 6-OHDA lesion in knockout mice (ZnT3 KO) lacking synaptic zinc. Lesioned wildtype mice displayed a locomotor impairment while significant improvement was detected in ZnT3 KO lesioned mice. By contrast, both genotypes showed a similar loss of striatal dopaminergic innervation (TH protein expression level), indicating that synaptic zinc mediates its deleterious action by altering striatal synaptic transmission. We next used partial bilateral striatal 6-OHDA lesion in ZnT3 KO mice to investigate the contribution of synaptic zinc to non-motor deficits (cognitive and emotional impairments) associated to PD. Unlike unilateral DA lesion, partial bilateral DA lesion does not induce motor asymmetry (circling behaviour) which makes it more suitable for studying the impact of striatal DA depletion on higher brain functions. Genetic depletion of synaptic zinc restored cognitive (recognition memory impairment) and emotional (enhanced anxiety/neophobia) deficits induced by the bilateral striatal DA lesion. Together, our findings suggest that striatal synaptic zinc may play a deleterious role in PD by promoting the expression of motor and non-motor symptoms.

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**P3.089 Syngeneic grafts of Olfactory Ecto-Mesenchymal Stem Cells restore breathing and locomotor functions in an acute rat model of high cervical contusion**

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The transplantation of Olfactory Ecto-Mesenchymal Stem Cells (OEMSCs) could be a helpful therapeutic strategy for spinal cord repair. Using an acute rat model of high cervical contusion that provokes a persistent hemi-diaphragmatic and foreleg paralysis, we evaluated the therapeutic effect of a delayed syngeneic transplantation (two days post-contusion) of OEMSCs within the injured spinal cord. Respiratory function was assessed using diaphragmatic electromyography and neuro-electrophysiological recordings of phrenic nerves (innervating the diaphragm). Locomotor function was evaluated using the ladder-walking locomotor test. Cellular reorganization in the injured area was also studied using immunohistochemical and microscopic techniques. We report a substantial improvement in breathing movements, in activities of the ipsilateral phrenic nerve and ipsilateral diaphragm and also in locomotor abilities four months post-transplantation with nasal OEMSCs. Moreover, in the grafted spinal cord, lesioned areas and inflammation were reduced. Some grafted stem cells adopted a neuronal phenotype and axogenesis was observed in the injury site. The therapeutic effect on the supraspinal command is presumably due to both neuronal replacements and beneficial paracrine effects on the injury area. Our study provides evidence that nasal OEMSCs could be a first step in clinical application, particularly in patients with reduced breathing/locomotor movements.

**P3.090 The microbiome gut-brain axis: are gut-microbiome the key to treating by probiotic of autism spectrum disorders?**

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The gut microbiome may influence brain development and behavior, mainly through the modulation of physiological metabolism and the immune system. Recent studies have determined that the microbiome has direct effects on behavior and may be dysregulated in neurodevelopmental conditions such as in the development of autism. Considering that at least 60% of the risk of autism is due to genetics, it is necessary to understand if genes associated with neurodevelopmental disorders, such as Shank3 and the deletion of Ch16p11.2, can influence the gut microbiome, and if probiotics can be a therapeutic tool. Our main objectives are to determine the dysregulation of the microbiome in people with the autism associated Ch16p11.2 deletion, as well as in mouse model. A second objective was to determine and to correlate the dysregulation of microbiome in the Shank3 mouse model in both models to neurotransmitter and immune dysregulation. We have determined the gut microbiome community and dysbiosis in both humans and mice models.

With regard to the Shank3 study, we have identified dysregulation of several genera and species of bacteria in both the gut and colon of mice, in addition to a sex-dependent dysregulation of neurotransmitter's receptor, oxytocin and the immune system. *L. reuteri*, a species with decreased relative abundance in the Shank3KO mice, positively correlated with the expression of GABA receptor subunits in the brain. Treatment of Shank3 KO mice with *L. reuteri* induced an attenuation of unsocial behavior and a decrease in repetitive behaviors, in males and just decrease in repetitive behaviors in females, without affecting anxiety. *L. reuteri* treatment also induced an increase in GABA receptor expression in multiple brain regions and affected serum immune system markers.

Ch16p11.2 deletions are strongly associated with development of autism. Some of the genes, including MAPK3, which are found on Ch16p11.2 are directly involved in the maintenance of the health of the gut and its microbiome community.

This study has confirmed that genetic differences associated with autism can induce changes in the microbiota profile and identifies bacterial species that are sensitive to an autism-related mutation, and further suggests a therapeutic potential for treatment.

**P3.091 Selective DBS of the subthalamic nucleus improved motor and non-motor deficits without affecting weight gain in a rat model of Parkinson's disease**

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is considered as a gold standard therapy for Parkinson's disease (PD). However, its effects on non-motor symptoms are still under debate. The present study aimed to investigate the effects of STN DBS on motor performance, anxiety, pain, food intake and weight gain. For this, we developed a new implantable stimulator, adapted for chronic stimulation in rodents and that mimics the conditions of DBS in patients. The stimulation device was well tolerated by the animals. STN-HFS (130 Hz frequency, 60 mA pulse width, 100-200 mA intensity) improved the motor deficits induced by 6-OHDA in rats in the open field as it significantly increased the number of spontaneous movements and the distance traveled by the animals compared to the values obtained without stimulation. Furthermore, it restored motor coordination by significantly increasing the time spent on the rotarod bar. STN HFS also improved anxiety in animals with bilateral lesion of dopamine neurons as it increased the number of entries and time spent in the open arms of the elevated maze. Furthermore, STN HFS improved pain by reversing mechanical allodynia measured by the Vonfrey test. Finally, STN HFS did not change food intake behavior and the evolution of body weight as compared with 6-OHDA animals without stimulation. Our data demonstrate that selective STN HFS dramatically improved motor deficits and majority of non-motor disorders related to PD without influencing food intake and body weight gain, in contrast to what is reported in some stimulated patients.

**P3.092 Impact of moderate chronic alcohol consumption and withdrawal on hippocampus and striatum-dependent learning and related synaptic plasticity**

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The hippocampus and striatum have dissociable roles in memory: while the first is necessary for spatial/declarative forms of learning, the former underlie cued/procedural learning. An emerging hypothesis suggest that drug addiction could lead to a functional cognitive imbalance, which would maintain addictive behaviour and support the risk of relapse by promoting habit learning while concurrently disrupting spatial memory. We examined, in C57BL/6J male mice, whether chronic ethanol consumption (5 months) or withdrawal might modulate the use of spatial memory vs cued memory, and related hippocampal and striatal functional synaptic plasticity. Mice were alcoholized for 5 month, and following chronic alcoholization, half of subjects were kept on an alcohol diet whereas the other half went through progressive withdrawal for 2 weeks. Memory performance of all mice was tested using a competition protocol in the Barnes maze assessing the respective use of hippocampus vs striatum-dependant learning strategies. Concurrently, we performed *in vivo* electrophysiological studies in freely-moving mice to assess learning-induced synaptic plasticity in the dorsal hippocampus (CA1) and dorsolateral striatum (DLS). Our results first show that withdrawn animals, but not animals which are still consuming alcohol, are severely impaired in the retention phase of the task. Moreover, alcohol withdrawal, and also to a lesser extent alcoholization, promote a shift from the use of spatial hippocampal-dependant strategy to an exclusive selection of non-flexible striatal-dependant cued strategies. Concurrently, we found that task-induced synaptic plasticity activity was reduced in the CA1 and increased in the DLS of withdrawn mice, and to a lesser extent, alcohol mice as compared with controls. Besides, the capacity to induce LTP was impaired in both withdrawn and alcoholized mice. We conclude that early alcohol withdrawal and, to a lesser extent, moderate chronic alcoholization, have disrupting effects on spatial memory processes and synaptic plasticity in the dorsal hippocampus, leading to the compensatory use of non-spatial, striatum-dependant learning strategies.

P3.093

**Loss-of-function mutations in *RAD51* and *NTN1* cause congenital mirror movements**

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Congenital mirror movements (CMM) is a rare genetic disorder with autosomal dominant inheritance and incomplete penetrance. CMM is characterized by early-onset involuntary movements of one side of the body that mirror intentional movements on the opposite side, persisting throughout life in the absence of other neurological symptoms. CMM usually involves abnormal decussation of the cortico-spinal tract. To date, the main culprit genes involved in CMM are *RAD51*, *DCC* and, recently discovered by our team, *NTN1*. Since *DCC* and Netrin-1 are a ligand/receptor couple well known for their role in axonal guidance, their involvement in CMM was not surprising. While the discovery of the involvement of *RAD51*, previously known for its key role in homologous recombinant DNA repair, revealed a totally unexpected role of this gene in the development of the motor system. In our cohort of CMM patients, a pathogenic or possibly pathogenic mutation in three known genes was identified in less than half of them. To assess the pathogenicity of the identified variants in the *NTN1* and *RAD51* genes, we study their impact on the biochemical and cellular properties of the encoded proteins. In this way, we hope to understand the pathophysiological mechanisms that lead to the occurrence of CMM. We previously found that the netrin-1 mutated proteins, expressed in stable cell lines, were almost exclusively detected in the intracellular compartment. Since netrin-1 is a diffusible extracellular cue, the pathophysiology likely involves loss-of-function. Similarly, we already showed that CMM patients with truncating mutation of *RAD51* (R254\*) had decreased mRNA levels likely due to the nonsense mediated mRNA decay. Recently, we observed by western blot a decrease in *RAD51* expression in lymphocytes of these CMM patients. This result strongly suggests that *RAD51* loss-of-function mutation by haploinsufficiency causes CMM in humans. The recent discovery of non-truncating *RAD51* mutations (such as R250Q) will allow us to analyze *in vitro* the biochemical properties of the mutated proteins and to investigate *RAD51* subcellular localization in mouse cortical neurons.

P3.094

**Memory dysfunctions in FUSΔNLS mice and associated epigenetic changes**

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The mislocalization and aggregation of the *FUS* protein is associated with frontotemporal dementia (FTD), a fatal neurodegenerative disease. FTD patients demonstrate cognitive deficits in executive functions, while spatial memory remains relatively stable. FUS is a DNA/RNA binding protein that induces epigenetic, alternative splicing and transcriptional changes. Yet, whether FUS can induce learning- and memory-associated epigenetic changes in the brain has never been studied.

We used a heterozygous knock-in FUSΔNLS mouse model, which recapitulates the partial delocalization of the FUS protein in the cytoplasm as observed in FTD patients. In this study, we performed a behavioral phenotyping and led transcriptomic and epigenetic analyses in brain regions involved in learning and memory (frontal cortex, hippocampus). FUSΔNLS mice presented a significant increase in global locomotor activity compared to WT, no evidence of anxiety (Light/Dark box) and no deficits in the novel object recognition test. However, in the spatial version of the Morris Water Maze, FUSΔNLS mice showed lower acquisition abilities, and less precision in retention performance when assessed at recent and remote time points. This suggests alterations in the hippocampal functions of FUSΔNLS mice. In addition, Western blot analyses performed on bulk chromatin in resting mice, revealed a clear increase of FUS-related hallmarks and some moderate epigenetic changes in the hippocampus of FUSΔNLS mice but not in the frontal cortex.

So far, we demonstrated that 4 month-old FUSΔNLS mice present memory alterations, likely due to hippocampal dysfunctions. Several histone epigenetic modifications (H3K36me3, H3K27ac, H3K4me3, H4K12ac) are currently being investigated at the genome level by chromatin Immunoprecipitation followed by deep sequencing (ChIP-seq) in NeuN+ FACS-sorted cells. These results will be integrated with RNA-sequencing studies in the frontal cortex and the hippocampus of resting and trained WT and FUSΔNLS mice. These studies will establish epigenomic/transcriptomic signatures associated with FUSopathies. In the long term, they may help to the design of new therapeutic interventions with epigenetic modulators.

P3.095

**The extent of dopamine cell loss induced in mice by stereotaxic injection of the glutamate transporter inhibitor L-trans-2,4-PDC is dependent on the type of anesthetic used for surgery**

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Some reports suggest that the loss of substantia nigra pars compacta (SNpc) dopamine neurons in Parkinson disease (PD) may result from a slow excitotoxic process mediated by an increased glutamatergic drive causing NMDA receptor overactivation. This process can be mimicked experimentally by blocking the transport of glutamate through stereotaxic infusion of the glutamate synthetic analog L-trans-2,4-PDC (PDC) (Assous et al, Neurobiol Dis, 2014). Our present objective was two-fold: (i) to adapt this lesion paradigm to C57BL6 mice for PD-related studies and (ii) to test the impact of two different anesthetic cocktails on the severity of the lesion.

Coherent with previous observations made by Assous and colleagues in rat, we found that a unilateral intranigral infusion of PDC in young adult C57BL6 (11-12 week old) mice caused a substantial loss of tyrosine hydroxylase (TH<sup>+</sup>) neurons on the injected side, 10 days after stereotaxic lesioning. Dopamine cell loss was dosage-dependent and optimal with 200 nmoles of PDC. At the same timepoint, contralateral SNpc TH<sup>+</sup> neurons remained unaffected. When the anesthetic Equitesin containing pentobarbital and chloral hydrate as main active components was replaced by a cocktail comprising ketamine and xylazine, the loss of TH<sup>+</sup> neurons induced by 200 nmoles of PDC was noticeably reduced. More precisely, TH<sup>+</sup> cell loss was estimated to 43% with Equitesin and to only 17% with ketamine/xylazine when expressed as percentage of the contralateral side. In agreement with these findings, the loss of TH<sup>+</sup> nerve fibers in the ipsilateral striatum was only significant in the group of mice anesthetized with Equitesin (-24%), indicating that the cocktail ketamine/xylazine provided neuroprotection to dopamine neurons. Also in line with these results, the neuroinflammatory reaction observed in response to PDC lesioning was much less prominent with the cocktail ketamine/xylazine.

Overall, our data suggest that modeling dopamine cell loss with PDC is achievable in mice but not with the usual anesthetic cocktail ketamine/xylazine. The most likely explanation is that ketamine impairs the effects of PDC via its capacity to block NMDA receptors.

**P3.096 Is cataplexy a dissociated state of paradoxical (REM) sleep? Role of the GABA/Glycinergic neurons of the ventromedial medulla in brainstem in a mouse model of narcolepsy type 1**

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Narcolepsy type 1 is a chronic neurology disorder due to degeneration of the hypocretin/orexin neurons of the lateral hypothalamus. It is characterized by excessive daytime sleepiness and episodes of cataplexy. Cataplexies are depicted by a bilateral loss of muscle tone during wakefulness that is triggered by a strong positive emotion, without loss of consciousness. Because of the many common points between paradoxical sleep (PS) muscle atonia phenotype and cataplexy, it has been classically proposed that the neuronal network recruited for the expression of muscle atonia during PS would also be involved during cataplexy. However, it has never been demonstrated.

The ventromedial medulla (VMM) in the brainstem, where are located GABAergic and glycinergic inhibitory pre-motoneurons responsible for muscle atonia during PS, contains neurons active during PS and also during cataplexy in narcoleptic dogs (Siegel et al, 1991). We thus hypothesize that these GABAergic/glycinergic pre-motoneurons would play a key role during cataplexy. To test this hypothesis, we abolished specifically and permanently the GABA/Glycinergic transmission in the VMM of narcoleptic Orex-KO mice (deficient in hypocretin/orexin), using short-hairpin RNA method (shRNA) directed against vGAT the vesicular transporter of GABA and Glycine. Mice were injected with the experimental (shVGAT) or a control (shCTRL) AAV, locally in the VMM, and implanted with electrodes for polysomnographic recordings. Vigilance states, loss of muscle atonia during PS and cataplexies are evaluated with polysomnographic and video recordings in baseline condition and in a protocol of cataplexy induction with chocolate at 1, 4, 6 and 8 weeks after viral injection. Our preliminary results indicate that blockage of the VMM GABA/Glycinergic transmission induced episodes of REM sleep without atonia in shVGAT mice as expected. Furthermore, cataplexy seemed to be reduced in its total amount or bouts number, in shVGAT mice compare to shCTRL, and this during baseline condition or after cataplexy-induced protocols. These preliminary data need to be conformed but suggest that GABA and Glycinergic pre-motoneurons of the VMM might be involved in cataplexy.

P3.097

### Neurometabolic sequelae following *Plasmodium Berghei* ANKA-induced cerebral malaria

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**Introduction:** Cerebral malaria (CM), the most lethal complication of *Plasmodium* infection, leads to an encephalopathy with seizures, coma, and death in 15-20 % of the cases. Survivors often have gross neurological deficits at discharge, and long-term cognitive deficits. The cerebral consequences of CM in survivors have received little attention. In this study, we explored brain sequelae in a non-lethal model of CM using magnetic resonance spectroscopy (<sup>1</sup>H-MRS).

**Subjects and methods:** C57BL6/J mice were injected with *Plasmodium Berghei* ANKA (PbA) (1). Chloroquine was administered from disease peak to d16. CM mice and healthy controls were explored at d7, and 1 and 3.5 months after CM induction on a Bruker AVANCE 500 WB spectrometer @11.75T under isoflurane anaesthesia. The protocol included axial 2D T<sub>2</sub>-weighted RARE sequence (RARE factor=8, TR =5000 ms, effective TE =36 ms, number of averages= 4, matrix 194x194, 31 slices, slice thickness 0.5 mm), field of view =15x15 mm<sup>2</sup>. <sup>1</sup>H-MRS of the thalamus: PRESS sequence, TR=1700 ms, TE=20 ms, voxel of 27 mm<sup>3</sup>, 512 averages with and without water saturation (VAPOR). MRS data were processed under CSIAPo (2). The metabolite basis set included 15 metabolites and 12 macromolecules. The signals of metabolites and macromolecules were normalized using the water signal intensity as an internal reference.

**Results:** After PbA injection, the animals were daily evaluated for clinical/neurological signs of CM and imaged at disease peak (d7). All the animals had a full-blown disease with brain oedema (1-2). The <sup>1</sup>H-MRS follow-up of CM mice unveiled significantly reduced levels of macromolecules mostly 1 month after the disease (MM\_4/H<sub>2</sub>O, MM\_12/H<sub>2</sub>O, MM\_19/H<sub>2</sub>O, 0.01< P< 0.05). At 3.5 months significant decreases in GABA/H<sub>2</sub>O and N-acetylaspartate/H<sub>2</sub>O were measured (P=0.0496 and P= 0.036/H<sub>2</sub>O respectively).

**Conclusion:** Our results show metabolic alterations several months after CM evocative of neuronal dysfunction, altered neurotransmission, and reduced macromolecule (proteins and lipids) production. These anomalies could be the substrates for persistent neurologic deficits.

#### References:

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**P3.099 Analysis of neuronal dysfunctions in a murine model of hereditary spastic paraplegia**  
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Hereditary Spastic Paraplegia is a group of Motor Neuron Disease characterized by progressive spasticity and paralysis of lower limbs mainly due to degeneration of cortico-spinal tract. In complex forms of the disease, motor issues are associated with cognitive deficits. Mutations in SPG11 gene coding for Spatacsin are a major cause of these complex forms. For a better understanding of SPG11-related HSP mechanisms, our team generated a Knock-Out mouse model (*spg11<sup>-/-</sup>*) mimicking the cognitive and motor deficits correlated with histological alterations. In Vivo EEG recordings of *spg11<sup>-/-</sup>* motor cortex highlighted the emergence of spike and wave-like discharges events (SWLD), concomitantly to a NeuN+ cells loss, suggesting a disturbance of excitability of cortical networks. No propagation to thalamus was found, but these SWLD seems to response in a dose dependant manner to pro and anti-Absence Epilepsy drugs (preliminary data). Ex vivo Electrophysiological recordings of adult *spg11<sup>-/-</sup>* hippocampi displayed reduced short and long-term potentiation, correlated with a loss of spatial and fear-related memories, suggesting an impairment in synaptic elements. This project aims to decipher the biological causes of those electrophysiological deficits. We hypothesized that alterations in motor cortex are due to a disturbance of excitation/inhibition balance and cerebral networks loss of efficiency is due to an issue in pre and/or post-synaptic elements. To check the validity of these hypotheses, we propose by using histology and electrophysiology to test the functioning and integration of cortical interneurons and motor neurons and study the pre and post-synaptic elements related to synaptic transmission function such as, neurotransmitters vesicles release and synaptic electrophysiological properties. Altogether, the results of these experiments will decipher the roles of Spatacsin in the pathogenesis of HSP and MNDs.

**P3.101 Different dentate granule cells are activated across time during paradoxical (REM) sleep and waking: a study using TRAP mice method**

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Paradoxical (REM) sleep (PS) is characterized by cortical EEG activation close to waking (W) paradoxically associated to muscle atonia. We and others previously identified subcortical structures generating W and PS such as the sublaterodorsal tegmental nucleus (SLD), lateral hypothalamic area (LHA) and supramammillary nucleus (SuM). Based on cFos expression as a marker for neuronal activation, we recently showed that only a few cortical structures such as the dentate gyrus (DG), claustrum (CLA), medial entorhinal (mENT) and retrosplenial (RSP) cortices are activated during PS in contrast to W during which most cortical structures are activated (Renouard et al., 2015). Our objective in the present study is to further determine whether the same or different neurons are activated during PS and W and during two successive W-W or PS-PS periods. To this aim, we used transgenic TRAP2 mice expressing tamoxifen-dependent CreER recombinase under cFos promoter. CreER can only undergo recombination when tamoxifen (or its active form, 4-OHT) is present, resulting in a permanent Cre-dependent reporter gene (DsRed) expression in cFos labeled neurons. Thus, neurons activated during the first condition under the 4-OHT treatment express DsRed. Neurons activated during the second condition taking place before perfusion express cFos. We examined 3 groups of mice: W-W group put 2h in an open field, PSR-PSR group with 2h PS recovery following 48h of selective PS deprivation and a W-PSR group. All mice were injected IP with 4-OHT 2h after the first condition and perfused 2h after the second condition.

In W-W group, a high percentage of DsRed neurons were Fos+ (double-labeled) in all regions examined excepting DG. In PSR-PSR group, many double-labeled neurons were observed in SLD, LHA and SuM but not in DG and CLA. In W-PSR group, only a few neurons were double-stained. These results first indicate that in structures generating PS or W, the same neurons are activated across time validating the TRAP method. They further indicate that W and PS are completely different states since different populations of neurons are activated during W or PS in many structures involved in cognition, learning and memory. These results open the avenue for the identification of their PS-related function.

**P3.102      Intracellular dynamics of CA3 pyramidal cells in awake head-fixed mice during large irregular activity**

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Wakefulness is comprised of distinct brain states, correlated with different behaviors and characterized by specific oscillatory patterns in the local field potential (LFP). While much work has characterized different brain states and their LFP signatures, the underlying cellular mechanisms are poorly characterized. It has been proposed that changes in single cell properties correlate with and possibly result in these changes in brain state.

Synchronized and coordinated activity among distributed neurons supports cognitive processes such as memory. The hippocampus is essential for spatial and episodic memory, and within the hippocampus, area CA3 is important for rapid encoding and consolidation of one-trial memory. CA3 is the site where information from the entorhinal cortex, dentate gyrus, and CA3 itself (via recurrent connections) is compared and integrated before output to CA1. During quiet wakefulness, the hippocampal LFP displays, among other oscillations, large irregular activity (LIA) punctuated by short oscillations known as sharp-wave ripples (SWR), which play a role in memory consolidation.

We explored the changes that occur in the intracellular dynamics of CA3 PCs during transition to LIA, by using whole-cell patch-clamp recordings from CA3 PCs in awake head-fixed mice. In order to characterize brain states, we combined those recordings with measurements of pupil diameter, treadmill running speed and LFP recordings of oscillatory activity. Our findings show that some CA3 PCs are prone to intracellular modulation during brain states, and that a subset of them tends to increase their membrane potential, subthreshold fluctuations and firing rate during LIA. These changes are independent of the initial membrane potential of the cell before transitioning to LIA, suggesting that the mechanism is not dependent on driving force of a particular ion. Future studies will demonstrate whether these effects are due to changes in synaptic and/or neuromodulatory inputs. These results are in line with what has been already reported in CA1 PCs and dentate gyrus. We propose that during LIA, principal cells of the hippocampus enter a more excitable state, which would allow generating and conducting SWR, essential for memory consolidation.

**P3.103 Effects of temporal features of a task and reward outcomes on the activity of the cholinergic TAN system in the monkey striatum**

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The striatum and its dopamine (DA) input from the midbrain have been implicated in reward-based learning and the representation of time. Given the importance of interactions between DA and acetylcholine in the modulation of striatal output, it is conceivable that the local cholinergic innervation of the striatum also contributes to the processing of temporal and reward information. To investigate this issue, we examined the activity of striatal tonically active neurons (TANs), thought to be cholinergic interneurons. Two macaque monkeys were trained to wait, after a visual stimulus (temporal cue), for a given time interval before initiating a movement leading to reward or passively expecting a reward. With this design, we asked whether temporal and reward information can be integrated in three task conditions with short and long intervals in the range of 1.0 to 2.3 s:

- (1) a duration estimation task (DET) in which a movement is triggered by an internal decision process based on the estimation of elapsed time from the cue onset;
- (2) a temporal prediction task (TPT) in which a movement is triggered by an external stimulus presented after a time interval following cue onset;
- (3) a Pavlovian conditioning task (PCT) in which a reward is automatically delivered after a time interval following cue onset.

These different conditions were presented to the monkeys in separate blocks of 30-40 trials with the two trial types (short and long intervals) varying randomly during each block. We then analyzed changes in activity as a function of the task condition, interval duration, and reward delivery, focusing on responses to the cue and the upcoming reward. Over 37 % of the TANs were responsive to the temporal cue, and these percentages did not vary significantly among the three conditions. On the other hand, we found a higher proportion of TANs responsive to reward in PCT (61%) than in TPT (30%) and DET (22%). In some instances, TAN response magnitude was differentially modulated by the interval duration. Our findings demonstrate that temporal features of task requirements interact with TAN signaling of the availability of reward, suggesting that the cholinergic TAN system might modulate its sensitivity to task events based on integration of temporal and reward information.

**P3.104 Dual control of sympathetic and parasympathetic regulation of cardiovascular activity by the respiratory oscillator**

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Heart rate and blood pressure fluctuate in phase with respiratory activity. This coupling between respiratory and cardiovascular activities optimises gas exchange and heart work. It is mostly controlled centrally, where brainstem neurons generating the respiratory command modulate the activity of pre-sympathetic and pre-parasympathetic cardiovascular neurons, however little is known about the precise circuitry involved. In juvenile and adult rats, using a combination of optogenetic inhibition and excitation *in vivo* and *in situ*, as well as neuronal tracing, we demonstrate that a group of respiratory neurons that is the kernel for respiratory rhythm generation (the preBötzinger Complex, preBötC) directly modulates both sympathetic and parasympathetic activities. Our data show that a subgroup of preBötC neurons provides a strong respiratory phasic and tonic inhibitory drive to cardiac preganglionic parasympathetic neurons, generating respiratory sinus arrhythmia (heart rate oscillations in phase with respiratory activity) and moderating bradycardia. Also, we show that a subgroup of preBötC neurons provides an excitatory drive to sympathetic vasomotor neurons, generating Traube-Hering waves (blood pressure oscillations in phase with respiratory activity) and increasing blood pressure. We confirm the primary role of the preBötC for respiratory rhythm generation, and we further show that it determines the duration of the different phases of the respiratory cycle. Overall, our data reveal the neuronal circuitry generating the respiratory entrainment of heart rate and blood pressure, showing that the preBötC is more than the kernel for respiratory rhythm generation, it serves as a cardiorespiratory oscillator. This is of primary physiological and pathological relevance, respiratory sinus arrhythmia being abolished and Traube-Hering waves exacerbated in major cardiovascular diseases such as hypertension and heart failure.

**P3.105 Impact of a maternal high fat high sugar diet on progeny's olfactory system in mice**  
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The influence of maternal diet on progeny's health has been thoroughly investigated regarding metabolic diseases, but the impact on sensory systems remains poorly documented. Olfaction is of great behavioral importance for avoiding hazards and for feeding behavior, including the establishment of food preferences. The olfactory system is made of sensory neurons that develop during the embryonic life, pursue their maturation after birth and are continuously regenerated over life. Olfactory neurons activity can be modulated by metabolic factors and patients with metabolic disorders are at risk of impaired olfactory abilities. Furthermore, it has been shown in rodents that adult exposure to an obesogenic or diabetogenic diet can trigger olfactory deficits. Our goal was to investigate the effect of a maternal high fat high sugar (HFHS) diet during preconception, gestation and lactation on the olfactory system of progeny. Female mice fed with the HFHS diet exhibited modified milk lipids composition compared to dams nourished with a standard diet (CTRL). The metabolic phenotype of pups born from HFHS diet fed dams was characterized by an increased body weight, along with higher amounts of epididymal fat and hyperleptinemia. Olfactory abilities were assessed in a buried food test and by measuring odor-induced sniffing behavior and were disrupted in the progeny of HFHS diet fed dams. However, gene expression of constituents of the olfactory transduction cascade in the main olfactory epithelium (MOE) was not affected by maternal HFHS diet. In line with this finding, electrophysiological measurements of MOE sensitivity revealed similar MOE responses for the tested odorants between HFHS and CTRL progenies. When investigating olfactory central processing, dendritic complexity of interneurons in the olfactory bulb was found to be affected by maternal HFHS diet. Meanwhile, neuronal activation in piriform cortex was not altered. These results show that maternal HFHS diet during pups' development alters olfactory perception in male progeny, without impairing odor detection by the MOE, but inducing neuronal modifications in olfactory central areas. Leptin is a metabolic hormone known to influence olfaction and neurons development which could have induced the olfactory defects.

P3.106

**Cav3.2 T-type calcium channels shape electrical firing in mouse Lamina II neurons**

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The T-type calcium channel, Cav3.2, is necessary for acute pain perception, as well as mechanical and cold allodynia in mice. Being found throughout sensory pathways, from excitatory primary afferent neurons up to pain matrix structures, it is a promising target for analgesics. In our study, Cav3.2 was detected in ~60% of the lamina II (LII) neurons of the spinal cord, a site for integration of sensory processing. It was co-expressed with Tlx3 and Pax2, markers of excitatory and inhibitory interneurons, as well as nNOS, calretinin, calbindin, PKC $\gamma$  and not parvalbumin. Non-selective T-type channel blockers slowed the inhibitory but not the excitatory transmission in LII neurons. Furthermore, T-type channel blockers modified the intrinsic properties of LII neurons, abolishing low-threshold activated currents, rebound depolarizations, and blunting excitability. The recording of Cav3.2-positive LII neurons, after intraspinal injection of AAV-DJ-Cav3.2-mcherry, showed that their intrinsic properties resembled those of the global population. However, Cav3.2 ablation in the dorsal horn of Cav3.2<sup>GFP-Flox</sup> KI mice after intraspinal injection of AAV-DJ-Cav3.2-Cre-IRES-mcherry, had drastic effects. Indeed, it

- 1) blunted the likelihood of transient firing patterns;
- 2) blunted the likelihood and the amplitude of rebound depolarizations,
- 3) eliminated action potential pairing, and
- 4) remodeled the kinetics of the action potentials.

In contrast, the properties of Cav3.2-positive neurons were only marginally modified in Cav3.1 knockout mice. Overall, in addition to their previously established roles in the superficial spinal cord and in primary afferent neurons, Cav3.2 channel appear to be necessary for specific, significant and multiple controls of LII neuron excitability.

**P3.107 Origin and diversification of vertebrate cerebral circadian clocks: insights from the lamprey *L. fluviatilis* and the catshark *S. canicula***

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Like all living organisms, vertebrates have developed endogenous cellular oscillators, which exhibit daily variations and allow them to anticipate daily environmental changes. These oscillators, referred to as circadian clocks, regulate metabolic, behavioural and endocrine processes and have been identified in a variety of tissues or organs. They have been extensively characterised in the brain, primarily focusing on the mouse and the zebrafish. Comparisons suggest that the organisation of cerebral clocks may substantially differ between these two species. In the former, analyses have highlighted major roles of bilateral hypothalamic nuclei, the suprachiasmatic nuclei, considered for long as the master circadian clock of mammals. In the latter, the hierarchical organisation of cerebral clocks may be more diffuse but recent analyses have reported an essential role of the pineal organ. In order to gain insight into the ancestral organisation and conservation of cerebral circadian clocks in vertebrates, we have analysed the cerebral expression of orthologues of two clock genes, *Period* and *Bmal*, in a cartilaginous fish, the catshark *Scyliorhinus canicula* and an agnathan, the lamprey *Lampetra fluviatilis*. We find that in both species, these genes exhibit highly specific, well-delimited expression territories located in the telencephalon, epithalamus, mesencephalon and hypothalamus of prolarvae (lamprey) and juveniles (catshark). On-going experiments aim at assessing whether these genes harbour cyclic expression variations during a day-night cycle. Taken together, these data should provide the first characterisation of putative cerebral circadian clocks in an agnathan and in a chondrichthyan, thus providing a foundation to further analyse their origin and diversifications across vertebrates.

**P3.108 Mechanotransduction of neurons contacting the cerebrospinal fluid: role of the kinocilium and interaction with the Reissner fiber**

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Spinal cerebrospinal fluid-contacting neurons (CSF-cNs) are sensory cells projecting in the central canal an apical extension, which bears numerous microvilli and a kinocilium which is in close vicinity with the Reissner fiber, a long thread resulting from the aggregation of the protein SCOspondin. We previously showed by combining *in vivo* and *in vitro* studies that CSF-cNs are mechanosensory neurons detecting tail bending via the transient receptor potential channel polycystic kidney disease 2-like 1 (Pkd2l1, or Trpp3) and whose activity at rest is correlated with the flow of CSF.

Here, we investigate the role of the kinocilium and the Reissner fiber in mechanoreception. By combining calcium imaging with patch clamp recordings, we highlighted CSF-cN properties and responses to mechanical inputs in mutants where either ciliary motility is affected, which we have previously shown leads as well to a disruption of the formation of the Reissner fiber, or when solely the fiber does not form. We find that defects in cilia motility where the fiber does not form affects the sensory response of CSF-cNs to passive tail bending and active muscle contraction without disrupting the Pkd2l1 channel activity. Interestingly, we show that mechanoreception in CSF-cNs *in vivo* is also impaired in *scospordin* mutants in which solely the Reissner fiber does not form but the kinocilium appear intact. Immunostaining reveals that the Reissner fiber and the apical extension and kinocilium of CSF-cNs are in close contact. Altogether, our results suggest that *in vivo* CSF-cN interact with the Reissner fiber to detect changes of CSF flow associated with mechanical bending of the spinal cord. A fine morphological analysis combined with a specific rescue of ciliary motility in CSF-cNs will decipher the contribution of their kinocilium in mechanoreception at the interface with the cerebrospinal fluid.

**P3.109 Membrane cholesterol depletion as a trigger of Nav1.9 channel-mediated inflammatory pain**

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Cholesterol is a major lipid component of the mammalian plasma membrane. While much is known about its metabolism, its transport, and its role in atherosclerotic vascular disease, less is known about its role in neuronal pathophysiology. This study reveals an unexpected function of cholesterol in controlling pain transmission. We show that inflammation lowers cholesterol content in skin tissue and sensory DRG culture. Pharmacological depletion of cellular cholesterol entails sensitization of nociceptive neurons and promotes mechanical and thermal hyperalgesia through the activation of voltage-gated Nav1.9 channels. Inflammatory mediators enhance the production of reactive oxygen species and induce partitioning of Nav1.9 channels from cholesterol-rich lipid rafts to cholesterol-poor non-raft regions of the membrane. Low-cholesterol environment enhances voltage-dependent activation of Nav1.9 channels leading to enhanced neuronal excitability, whereas cholesterol replenishment reverses these effects. Consistently, we show that transcutaneous delivery of cholesterol alleviates hypersensitivity in animal models of acute and chronic inflammatory pain. In conclusion, our data establish that membrane cholesterol is a modulator of pain transmission and shed a new light on the relationship between cholesterol homeostasis, inflammation, and pain.

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- P3.110 Predictive coding in the primary visual cortex? Synaptic contribution of the horizontal intrinsic connectivity to “filling-in”**
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Contextual long-range interactions involved in perceptual binding are generally thought to depend on cortico-cortical feedback and attention. In contrast, the contribution of lateral diffusion mechanisms intrinsic to V1 is less known. We explore here the role of the "horizontal" long-distance intra-cortical connections in the dynamic emergence of predictive responses in the primary visual cortex (V1) of the anesthetized cat.

A previous intracellular study of the spatiotemporal features of the subthreshold receptive field (RF) of V1 cells (Gerard-Mercier et al. 2016) showed that 1) synaptic responses to flashed 3-4° Gabor patches can be elicited from the far periphery and 2) that presentation of centripetal apparent motion (AM) of 2-stroke iso-oriented Gabor patches (GPs) at saccadic-like speeds (~200°/s) along the cell's preferred orientation axis induces a facilitatory synaptic modulation. We used here 6-stroke apparent motion (AM) concentric sequences of GPs to increase the gain efficiency and further characterize the spatio-temporal coherence requirements. The response to the RF center stimulation alone was compared to the one induced by the AM sequences, which were either centripetal or centrifugal, with GP collinear or cross-oriented to the motion path. Control conditions included randomized order of the GPs presentation and the change of the AM speeds. Sequences restricted to the silent periphery of the RF, thus omitting the RF center, were also tested to reveal possible "filling-in".

Our results show that the contextual sequence originating from the far periphery (up to 25°) has a strong boosting effect on the evoked discharge, resulting in a significant phase advance (5-20 ms) of the synaptic response. The supra-linear effect was specific to centripetal collinear AM at saccadic speeds and could not be induced by either the centrifugal AM or random sequences or at lower speed (50°/sec or less).

These results are consistent with our hypothesis that "Gestalt-like" interactions are triggered when the visual input carries a sufficient spatiotemporal coherence matching the properties of the underlying V1 connectivity. We propose that horizontal connectivity propagates some kind of "prediction" wave travelling through the V1 network.

**P3.111 Impact of cholinergic interneurons on corticostriatal transmission: an *in vivo* approach combining intracellular recordings and optogenetics in anesthetized mice**

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Basal ganglia (BG) are a set of subcortical interconnected nuclei that form, with the cerebral cortex and the thalamus, loop circuits involved in motor control and cognitive processes. The cerebral cortex massively innervates the striatum, the main BG entrance, where it targets the two populations of striatal projection neurons (called MSNs) forming the "direct" and "indirect" pathways linking the striatum to the BG output structures, as well as interneurons. Although in small numbers (< 2%), striatal cholinergic interneurons (CINs) show morphofunctional features, notably an extended neuritic arborization and a tonic firing (around 4 Hz *in vivo*), that place them as key players in the BG functioning, at the interface of striatal input systems and MSNs. However, the role of CINs in modulating corticostriatal transmission *in vivo* remains to be determined. Here we addressed this issue by examining the impact of optogenetic inhibition of CINs expressing halorhodopsin on basal and evoked corticostriatal transmission, using intracellular recording of MSNs *in vivo* in anaesthetized mice. Our results show that CIN photooinhibition for durations consistent with their pause observed *in vivo* in response to salient stimuli and conditioned stimuli in reward-related learning (500 ms and 1 sec) had no effect on MSN membrane potential fluctuations whereas 5 sec photooinhibition had a hyperpolarizing effect. However, this latter was unrelated to CINs inhibition as it was also observed in control mice that do not express halorhodopsin in CINs. Furthermore, CIN photooinhibition had no impact on cortically-evoked EPSPs or EPSPs paired-pulse ratio measured in MSNs. Altogether, these data surprisingly suggest that, in control situation, the tonic firing of CINs does not modulate corticostriatal transmission. Since we have previously shown that CIN photooinhibition alleviates motor symptoms in 6-OHDA hemi-parkinsonian mice, we are currently analyzing the impact of CIN photooinhibition on corticostriatal transmission in 6-OHDA mice.

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**P3.112 Complete and irreversible unilateral vestibular loss induces reactive neurogenesis in the vestibular nuclei in adult rat**

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Apart from two specific structures: the subgranular zone of the dentate gyrus of hippocampus and the subventricular zone of the lateral ventricles, the adult mammalian brain is considered non-neurogenic. Neurogenesis in other brain regions is limited under normal physiological conditions but could be induced after injury or pathological conditions. This is what happens after unilateral vestibular neurectomy (UVN) in adult cats: our work revealed for the first time the existence of adult reactive neurogenesis in deafferented vestibular nuclei located in the brain stem. We recently switched to the rodent model by replicating the same surgery (UVN) resulting in the same posturo-locomotor and oculomotor syndrome. The objectives of this study were to clarify the origin of the newly generated cells and to verify whether the reactive neurogenesis can also be evoked in the rodent after UVN. We used specific markers of cell proliferation (BrdU), stem cells (Sox2 and GFAP) and cell differentiation (GFAP: astrocytes, NEUN: neurons, GAD67: GABAergic neurons and IBA1: microglia). These markers reveal the presence of immunoreactive cells (Ir) to both Sox2 and GFAP in the medial vestibular nucleus of control animals with an absence of BrdU-Ir cells. UVN induces a significant increase in Sox2-Ir cells and Sox2/GFAP-Ir cells 3 days after the lesion. Significant cell proliferation restricted to the deafferented medial vestibular nucleus is observed 3 days after UVN. The presence of Sox2 and GFAP colocalization without cell proliferation reveals for the first time that quiescent neural stem cells are present in the medial vestibular nucleus complex in control animal. Most of the newly generated cells survived up to 1 month after UVN and differentiate into astrocytes and microglial cells but also into GABAergic neurons.

**P3.113 Olfacto-tactile interactions in mouse primary sensory areas**

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Perception is a multisensory phenomenon, however, the mechanisms allowing the integration of information coming from different senses remain poorly understood. A few recent multisensory studies in mice showed that multimodal interactions at the level of the primary sensory areas are ubiquitous. Yet, there is still no report precisely describing the impact of cross-modal interactions on the representations of combinations of stimuli occurring in a passive context or during associative learning.

In this study, we establish the existence of multimodal olfacto-tactile interactions in the mouse primary and secondary whisker cortical areas (wS1 and wS2). We performed 2-photon calcium imaging complemented with electrophysiological recordings in awake mice during the synchronized presentation of texture gratings and odors. Whiskers were tracked using high-speed videography and movements were precisely quantified.

We found that the average population and single cell activity was higher in the bimodal conditions than in the unimodal grating alone conditions. This modulation was not attributable to differences in whisking behavior. This result was confirmed with the high performance of linear classifiers in separating odor from odor free trials.

This result shows the existence of an olfactory modulation in the barrel cortex and secondary whisker area of awake mice in a passive stimulation context. It opens the way to the investigation of the functional pathways by which these prominent senses are integrated.

**P3.114 Two-photon imaging dramatically affects brain temperature, blood flow and oxygenation**

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Two-photon phosphorescence lifetime microscopy (2PLM) is the new emerging technique for high-resolution measurements of oxygen partial pressure ( $\text{PO}_2$ ) in vessels and tissue of brain and other organs. However, previous studies have disregarded that imaging through a cranial window lowers brain temperature, an effect known to change neuronal excitability and susceptible to affect cerebral blood flow, the properties of the oxygen sensors and thus brain  $\text{PO}_2$ . Here, we investigated the relationship between temperature, blood flow parameters and oxygenation in the olfactory bulb of anesthetized and awake mice. We show that in awake mice chronically implanted with a thermal sensor below the glass window, the postsurgical decrease of brain temperature recovers within few days. Imaging with a water immersion objective at room temperature decreases brain temperature by ~ 2-3 °C, causing resting capillary blood flow and  $\text{PO}_2$ , hemoglobin saturation and tissue  $\text{PO}_2$  to drop. These adverse effects are corrected by heating the immersion objective or avoided by imaging through a dry air objective, thus allowing the establishment of truly physiological values of brain oxygenation in awake mice.

**P3.115 Daily torpor and sleep in the non-human primate, the grey mouse lemur (*Microcebus murinus*)**

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Daily torpor is an energy-saving process which evolved as an extension of non-rapid eye movement (NREM) sleep mechanisms. In many heterothermic species, NREM sleep predominates whereas REM sleep is reduced or absent. Despite the presence of sleep during this period of hypothermia, torpor induces an accumulation of sleep debt which results in a rebound of sleep in mammals. We aimed to investigate the impact of torpor on sleep-wake rhythms in a non-human primate model, the grey mouse lemur (*Microcebus murinus*). Cortical activity was measured with telemetric electrocortical (ECoG) recordings in prefrontal cortex during torpor bout and the next 24h following hypothermia. Grey mouse lemurs were divided into two groups: the first submitted to normal temperatures (25°C) whereas the second were placed at lower temperatures (10°C). Contrary to normal temperatures, sleep-wake rhythms were maintained during torpor until Tb of the animals reached 21°C. Below this temperature, NREM and REM sleep strongly decreased or were absent whereas the EEG became isoelectric. The different states of sleep were positively correlated with Tb<sub>min</sub> during prior torpor in contrary to active phases. Our results showed that grey mouse lemurs efficiently sleep during torpor at 25°C but low temperatures were inconsistent with the recovery function of sleep. Heterothermy caused a sleep debt thus, there was a rebound of sleep at the beginning of euthermia to compensate the lack of sleep.

**P3.117 Sound-driven response in primary visual cortex of Shank3 $\Delta$ C mice model of autism spectrum disorder**

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Abnormal sensitivity to sensory information is a key feature of clinical presentation of autism spectrum disorders (ASD). Because sensory information processing drives adapted cognitive functions, our working hypothesis is that alterations in sensory responsiveness in ASD could be the basis of other autistic symptoms. To understand the integration processing alteration of sensory information in ASD we performed *in vivo* electrophysiological recordings in the primary visual cortex of Shank3 $\Delta$ C mice. The goal is to study cross-activation of (V1) by a non-dominant auditory modality. Previous studies have demonstrated that, in WT mice, activation of auditory cortex by a brief noise stimulus recruit inhibitory circuits in primary visual cortex (V1) originating from deep, infragranular layers of V1. This acoustic-driven inhibition reduces visual synaptic and spike responses in supragranular layers of V1. Consistently, we show here that *in vivo* recordings of LFP and multi-unit activities responses in V1, using laminar probe in WT mouse, showed evoked response potential (ERP) in different V1 layers after a visual stimulation. A concomitant sound burst is able to modulate these ERP. We hypothesize that a modification of the sound's threshold to modulate ERP in Shank3 $\Delta$ C mouse would be involved in abnormal sensory-based behaviors. In a classical fear-conditioning paradigm, pairing a visual stimulus with a mild electric foot-shock causes the emergence of a visually driven conditioned motor response, in both WT and Shank3 $\Delta$ C mice. Our data show that the noise burst degrade Shank3 $\Delta$ C mice (but not WT) behavioral response.

**P3.118 Vasoactive intestinal peptide deficiency elicits reversible cold and mechanical nociception in mice**

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The cross-functional vasoactive intestinal (neuro)peptide (VIP) is involved in nervous system development and regeneration. Several studies have also reported opposite effects of exogenous VIP on nociception depending on administration site. Our results show that compared to wild-type (WT) and heterozygous (Hz) adults, VIP null mice exhibited robust cold and tactile hyperalgesia whilst their sensitivity to heat remains unaffected, similar to human neuropathic symptoms. In VIP null mice, *in vivo* electrophysiology revealed that C fiber activation of spinal neurons was triggered by non-noxious mechanical and electrical stimulations compared to WT mice. Hyperalgesia can be restored to normal thresholds for more than 3 days by a single Intraperitoneal injection of VIP to deficient mice. This rescue was transduced by VIP receptor type 1 (VPAC1) that initiates rapid changes in early response genes. We then screened for changes in gene expression of numerous pain candidates and showed that only few specific thermo- and mechano-induced receptors as well as pain-related secreted factors were altered in VIP knock-out (KO) mice but were restored following VIP treatment. Intraperitoneal administration of SAHA, an HDAC inhibitor, abolished the analgesic effect of VIP, whilst the altered gene expression was associated with changes in DNA methylation. This strongly supports a link between chronic pain in VIP KO mice and epigenetic changes. It also highlights a novel role for VIP in nociceptive sensitivity in basal and pathological conditions.

**P3.119 Investigating new effects of anteroposterior GVS: EEG, eye motion and perception**

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The vestibular system is a bilateral sensory organ responsible for motion perception and balance, located in the inner ear. A good way to artificially stimulate the vestibular system is galvanic vestibular stimulation (GVS). An electric current is applied through the vestibular system using 2 to 4 electrodes (2 on the mastoids), inducing a polarity change of the vestibular apparatuses which results in their inhibition or activation. A discrepancy between the polarisation of the two vestibular systems results in lateral GVS, and no discrepancy in anteroposterior GVS (Severac Cauquil et al., 1998). As a matter of fact, lateral GVS consequences on body sway and eye movements are well known (eg.

Fitzpatrick et al., 1994 ; Severac Cauquil et al., 2003), but perceptive responses are not completely understood. The body sway obtained by using an anteroposterior GVS has also been described, however, both the perceptive and oculomotor responses are totally unknown. Here, we hypothesize that vergence movements will be observed. Furthermore, whereas the cortical processing of vestibular input has been studied using fMRI and GVS (Lopez et al., 2012), no study used EEG that enable the understanding of cortical areas dynamics. Therefore, the purpose of this study is to investigate perception, EEG, and ocular movements in response to anteroposterior GVS. Those three new components will participate to a better understanding of GVS as a major tool for vestibular investigation, and hence its optimal use, from basic research to clinics.

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P3.120

**A somatotopic organization of the secondary somatosensory cortex of the rat**

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Sensory cortices present topographical maps for a large range of sensory stimuli. For instance, the rat primary somatosensory cortex (S1) contains anatomically distinct structures called 'barrels' representing the whiskers. These neuronal groups are arranged in rows and arcs like the whiskers on the snout of the animal. In the secondary somatosensory cortex (S2), the anatomical organization of the map is less clear, being considered as a more diffuse integrative area due to the concurrent input from many whiskers to its neurons.

Here we show, by means of two different stimulation protocols, that there exists an anatomical functional map across several layers of S2. Our experiment consisted in applying a highly controlled multi-whisker stimulation to the 24 caudal whiskers (Jacob et al. 2010) of an isoflurane anesthetized animal while recording with an 8-shank 64-electrode silicon probe in S2.

The first protocol provided sparse deflections of single whiskers every 50ms. The second was a continuous dense stimulation of 24 whiskers, in which every whisker received a unique angular deflection drawn randomly from a Gaussian white noise distribution. To analyze the neuronal responses in the latter case, we used a recently developed 'Temporal Projection Method' (Goldin, Harrell et al. 2018). This method allows to find the likelihood of a neuron to respond to a family of relevant deflections for every whisker.

We measured the spiking activity of more than 1000 neurons and by grouping them by their recording shank and depth, we constructed a 1.4mm array map of functional activity across layers. The map shows a clear somatotopical organization in layer 4 and deep layers of S2.

In addition, we analyzed the single-neuron receptive field organization in S2 and compared it to S1 neurons. We therefore analyzed more than 1000 cells recorded using the same stimulation protocol in S1 and showed that S2 neurons have a broader whisker input. Both S2 and S1 areas present an anisotropic structure with more extended representation of whisker rows than whisker arcs.

Our results present the first topographical map of the granular and deeper layers of S2 of the rat and provide a detailed comparative characterization of the whisker inputs into the neurons of both S2 and S1.

**P3.121 Role of spinal dopamine D2 receptors**

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The spinal cord is the major relay station for sensory information generated at the periphery and transferred for processing to the brain. The gray matter of the spinal cord is organized into nuclei and laminae distributed along the dorsal and ventral horns. The dorsal horn is populated by a vast diversity of neurons that forms a complex network of excitatory and inhibitory circuits. Previous studies indicated that these neuronal ensembles could be modulated by the spinal dopaminergic system notably through the dopamine D2 receptors (D2R). However, the precise identity and role of spinal D2R cells remains largely unknown. To address this issue, we used D2R-Cre:Ribotag mice which express tagged (HA)-ribosomes selectively in D2R-containing cells. Three-dimensional imaging of clarified spinal cord using iDISCO revealed that D2R cells are preferentially distributed in the dorsal horn and all along the spinal segments. At the lumbar level, HA-labeled cells were detected throughout all the laminae being preferentially enriched in laminae II, III and IV. By combining immunofluorescence, *in situ* hybridization and targeted qRT-PCR analysis we found that D2R neurons correspond to both local excitatory/inhibitory interneurons and ascending projection neurons. To address the role of spinal D2R, partial deletion of D2R was achieved by injecting AAV-DJ-Cre in the lumbar spinal cord of Drd2-floxed mice. Somatosensory perception and motor coordination will be tested on male and female. This work will contribute to better understand the role of DA signaling in the spinal cord.

**P3.122 Radial glia synchronized activity events associated with motor behavior in the zebrafish larva**

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Astrocytes are essential for neural functions. Nowadays, there is an increasing interest in understanding the interaction between astrocytes and neurons and how this modules the sensory processing, plasticity, and motor behavior generation. Hence, it is necessary to be able to monitor the spontaneous and sensory-evoked activities of large neuro-glial networks in a living animal. In order to achieve these aims, the zebrafish larva offers the possibility to record the activity of several cells at the same time. On the other hand, Zebrafish larva express Radial Glial cell which is known to act as primary progenitor cells generating neurons and astrocytes in the vertebrate nervous system. Although, in mammals, radial glial cells are found just during the neurogenic phase and then degenerate after birth. In zebrafish, Radial Glial cells are maintained during adulthood. In addition, it has been reported that radial glial cells in zebrafish express GFAP and share some features with mammalian astrocytes such as structural association with neural processes and the expression of some proteins related to main astrocytes function. Together these findings suggest that radial glia may have further roles in zebrafish similar to astrocytes in mammals. Using GFAP: Gcamp transgenic fish and Two-Photon Microscopy, We have found that the calcium activation of the Radial Glial cells in zebrafish larva synchronizes just after the end of strong tail movements in the ventral region of the optic tectum. However, We showed that after blocking the muscle contraction, this phenomenon still remains, additionally, we realized that there is a high correlation of the Radial cell synchronization with a mild electric shock stimulus but a poor with the tail movement curvature. These findings suggest that tail movement could be a consequence of another unknown phenomenon that also induces the Radial cell synchronization, we think that could be related to arousal, alert response or pain. The biological relevance of this phenomenon and the underlying mechanisms are not yet understood. Therefore, we propose to assess the role of the Radial Glial cell population on the patterns of spontaneous and sensory-evoked neuronal network activities and its relation with motor behavior.

- P3.123 Characterizing patterns of dendritic activity in awake behaving mice with 3D arboreal scanning and real time movement correction**
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To understand brain function it is essential to identify how information is represented in neurons and how it is transformed as it flows through microcircuits. How sensorimotor information is represented and integrated in individual neurons is poorly understood because it is difficult to measure activity within morphologically complex structures such as dendrites with galvanometer-based two-photon microscopy. Deciphering when and where synaptic inputs are integrated across 3D dendritic trees requires recordings of patterns of activity across many dendritic branches of a single neuron. Acousto-optic lens (AOL) 3D microscopy enables this through fast focusing and selective imaging of regions of interest distributed within the imaging volume. We have recently extended this method to incorporate non-linear AOL functionality, which enables line-scan based imaging in any arbitrary x,y,z direction. Combining this with our real-time movement correction and semi-automated 3D dendritic tracing has enabled selective calcium imaging of a large fraction of the dendritic trees of layer II/III pyramidal cells expressing GCaMP6f in motor and visual cortices in awake behaving mice as they rest or run on a wheel and/or during presentation of classical visual stimuli. Our preliminary analysis suggests layer II/III cells exhibit mostly global, multi-branch  $\text{Ca}^{2+}$  events that are coupled to somatic events. Detectable local events reflect synaptic inputs, rather than local branch activation. We are investigating whether synaptic inputs are clustered on the dendritic tree and how dendritic activity in motor and visual cortex is affected by locomotion to explore the relationship between behavioural state and patterns of dendritic activity *in vivo*. Our findings will reveal how sensory and motor inputs activate single neurons in visual and motor cortex.

**P3.124 A link between dynamics and function in the anterior thalamus**

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The thalamus plays a central role in cognition by relaying sensory signals and supporting cortico-cortical communication. Thalamic function is generally understood through the structural organization of its nuclei, each showing different patterns of connectivity with cortical and subcortical structures. By simultaneously monitoring ensembles of neurons in the anterior thalamus and local field potentials in the hippocampus, we found that neurons show a large spectrum of spike train dynamics and modulation by hippocampal activity. On average, these firing characteristics are different across nuclei, yet each neuron has a unique relationship between its intrinsic dynamics and coupling to the hippocampus. While the description of the thalamus as distinct nuclei remains valid, our results suggest a more fundamental relationship between dynamics and function at the level of single thalamic neurons.

**P3.125 Anti-CASPR2 autoantibodies from patients with autoimmune encephalitis alter CASPR2 membrane distribution and Kv1.2 expression**

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Autoantibodies (autoAbs) against CASPR2 (contactin-associated protein-like 2) have been linked to autoimmune limbic encephalitis that manifests with memory disorders and temporal lobe epilepsy. According to the growing number of data supporting a role for CASPR2 in neuronal excitability, CASPR2 forms a functional complex with transient axonal glycoprotein-1 (TAG-1) and shaker-type voltage-gated potassium channels (Kv1.1 and Kv1.2). This so-called voltage-gated potassium channel (VGKC) complex can be found in compartments critical for neuronal activity, such as the axonal initial segment (AIS) and the Node of Ranvier (NOR). Notably, in CASPR2 KO mice Kv1 and TAG1 were no longer enriched at the NOR indicating that CASPR2 is required for proper Kv1 positioning. Whereas the perturbation of these functions could explain the symptoms observed in patients, the pathogenic role of anti-CASPR2 autoAbs has been poorly studied. In the present study, we show that introduction of CASPR2 into HEK cells induces a marked increase in Kv1.2 surface expression. Moreover, in cultures of hippocampal neurons Caspr2 positive inhibitory neurons appear to express high levels of Kv1.2. Importantly, anti-CASPR2 patient autoAbs increase Kv1.2 expression in both cellular models. In accordance with previous results, the level of CASPR2 at the cell surface did not change upon patient autoAbs addition. In this study however, we show for the first time that patient autoAbs cause a redistribution of CASPR2 at the neuronal membrane. This is a rather uncommon action mechanism of autoAbs, where internalization of the target is most frequently observed, and may lay at the basis of disturbed CASPR2 function. These results provide new insight into the pathogenic role of anti-CASPR2 autoAbs in autoimmune limbic encephalitis and thus pave the way for improved clinical treatment.

**P3.126 MT5-MMP may influence early stages of Alzheimer's disease through the control of neuroinflammation and amyloidogenesis**

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We first identified MT5-MMP (MT5) as a new pro-amyloidogenic factor, whose deficiency in the 5xFAD (Tg) mouse model of Alzheimer's disease (AD) strongly reduces Abeta, C99 and IL-1beta, all concomitant with reduced gliosis and the prevention of deficits in LTP and spatial learning. The possible connection between MT5, neuroinflammation and amyloidogenesis, likely leading to cognitive impairments in AD, is still not well understood. Making use of primary neuronal cultures exposed to inflammatory challenge, we sought to determine this possible link.

We used E16 primary mixed neuronal glial cultures from WT, Tg mice and their corresponding counterparts deficient for MT5, MT5<sup>-/-</sup> and TgMT5<sup>-/-</sup> mice, respectively. In order to assess the impact of MT5 deficiency on inflammation, IL-1beta was added to medium, at 11<sup>th</sup> and 21<sup>st</sup> day *in vitro*(DiV), for 24 h, in the presence or not of the gamma-secretase inhibitor DAPT. RT-qPCR, Western Blot, immunocytochemistry and whole cell patch clamp techniques were used.

Our data support the idea that MT5 deficiency attenuates IL-1beta-mediated neuroinflammation and APP metabolism at early stages of post-natal development in primary neuronal/astrocyte cultures from 5xFAD mice. Our data also indicate that such regulation is not necessarily interconnected and that MT5 modulation may affect neuroinflammation and/or APP/Abeta metabolism in an independent manner. Changes at the molecular level correlate to some extent with changes in spine loss/maturation and neuronal excitability.

Overall, this study reveals for the first time a functional interplay between MT5 and inflammation/amyloidogenesis that may contribute to early detrimental events in AD.

**P3.127 Neonatal maternal separation induces long-term alteration of pain responses and oxytocin analgesia**

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The neonatal period constitutes a critical time window during which the developing nervous system is particularly vulnerable to environmental influences. For instance, the function of the nociceptive system is clearly set around birth and especially during the first three postnatal weeks in rodents, when it is particularly vulnerable to early life adversity. Neonatal maternal separation is a well-established model known to induce long term neurophysiological/behavioral consequences in rodents, such as increased anxiety levels, depressive-like symptoms as well as chronic pain and visceral hypersensitivity. Since oxytocin has recently been suggested for being a critical determinant in neurodevelopmental disorders, we sought to evaluate here if neonatal maternal separation could affect somatic pain behavior and the function of the oxytocinergic descending control of pain.

We found that neonatal maternal separation induced long-term alterations of somatic sensitivity and oxytocin analgesia, which can be partially rescued with neonatal intraperitoneal oxytocin, allopregnanolone or SAHA.

In conclusion, impairment of oxytocin analgesia in adult rats having experienced a neonatal maternal separation seems to be a detrimental factor which could explain some of the other comorbidities associated with early life stress. The precise mechanisms of action leading to those sensory alterations are currently under investigation.

**P3.128 Brain mapping and functional characterization of the human MCHR2 in a "humanized" mouse model**

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Melanin-concentrating hormone (MCH) is a cyclic neuropeptide involved in a number of neuronal functions with major roles in the regulation of food intake and energy expenditure as well as stress control. MCH gene overexpression leads to obesity and insulin resistance whereas MCH gene null mice are hypophagic and lean and are resistant to ageing-associated increases in body weight and insulin resistance. Two MCH receptors, namely MCHR1 and MCHR2, have been found in human while only MCHR1 has been identified in rat and mouse. It can be predicted that a strategy aiming at blocking MCH action on MCH receptors could be a successful therapeutic approach in the treatment of obesity and/or mood disorders. However, it cannot be anticipated which MCH receptors and corresponding neuronal pathways would be the target of MCH antagonists in humans. Indeed, because of the lack of suitable animal models the biological functions of MCHR2 remained unknown up to date. To resolve the issue, a transgenic mouse has been generated carrying the human MCHR2 (hMCHR2) gene by a targeted knock-in approach, and designed thereafter hMCHR2<sup>Hprt/Hprt</sup> mouse. Neuronal expression of the transgene in hMCHR2<sup>Hprt/Hprt</sup> mice has been demonstrated by monitoring of the spatial and temporal expression of the transgene and direct *in situ* hybridization/RNA scope. In agreement with MCHR2 mRNA distribution in Primates, we found expression of the transgene in defined hypothalamic and cortical areas of the adult hMCHR2<sup>Hprt/Hprt</sup> mice. Since this experimental mouse model mimics MCHR2 expression in primate species, functional characterization of the hMCHR2 transgene was thereafter attempted. Strikingly, both feeding and weight were significantly altered in hMCHR2<sup>Hprt/Hprt</sup> mice (expressing both MCH receptors like in humans) when compared to wild type mice (expressing only MCHR1) treated with a high fat diet. This work established that expression of MCHR2 in mice may regulate obesity under high fat diet, a situation that could be related to the interaction found between the MCHR2 locus and Body Mass Index in general or depressive human populations.

**P3.130 Disclosing neuroendocrine mechanisms of seasonality, a step towards genetically modified models**

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Seasonal synchronization of reproductive activity is pivotal for offspring survival. Previous studies have highlighted the key role of melatonin for synchronizing reproductive activity with the seasons. Melatonin acts on the pituitary *pars tuberalis* to control thyroid stimulating hormone (TSH) production. TSH in turn acts on hypothalamic tanycytes to regulate the balance in deiodinase2/3 activities leading to higher hypothalamic concentration of T3 in long summer as compared to short winter day conditions. Although this melatonin-driven TSH/T3 signal has been demonstrated to be pivotal for synchronizing reproduction with the seasons, T3 cellular targets have not yet been established.

In hamsters, two hypothalamic peptides known to regulate GnRH neurons, kisspeptin and (Arg)(Phe)related peptide (RFRP), are inhibited by melatonin in short day adapted animals, but whether this regulation depends on a direct effect of T3 on kisspeptin or RFRP neurons is still unknown. Mechanistic studies in hamsters are hampered by the lack of genetically modified models, and seasonal studies in classic C57 mice are limited because they do not produce melatonin. Therefore, in this study we developed new murine models to help us disclosing the link between hypothalamic T3 and the regulation of kisspeptin/RFRP neurons.

First, we observed that both C57 mice supplemented with melatonin given in the drinking water at night, and melatonin-proficient CBA mice kept in long or short day conditions display the same melatonin-dependent inhibition of TSH, Dio2 and RFRP as observed in hamsters. . Next, we compared the effect of melatonin supplementation in wildtype or T3 receptor (TRalpha) mutated C57 mice, and we found that in mice lacking TRalpha, melatonin still reduce TSH and Dio2, but no longer inhibit RFRP expression. Altogether our data demonstrate that mice, like seasonal mammals, hold the molecular machinery to integrate the melatonin signal up to the hypothalamic RFRP and our first data indicate that the melatonin-driven inhibition of RFRP neurons depends on the effect of T3 on TR $\alpha$ .

**P3.131 TDP-43, the main constituent of FTLD/ALS neuronal protein aggregates, is a modulator of innate immune activation**

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Frontotemporal lobar degeneration (FTLD) is the most common cause of presenile degenerative dementia after Alzheimer's disease (AD). Degeneration of neurons in the frontal and temporal lobes causes behavioural, language and cognitive disorders and ultimately leads to the death of the patients. In FTLD, microglial activation correlates with the pattern of clinical impairment and occurs even before the appearance of marked brain atrophy [1]. In Neurodegenerative Diseases in general, more particularly upon chronic exposure to aberrant proteins, microglia mount a persistent sterile and proinflammatory immune response and neglect their physiological and beneficial functions. This chronic innate immune activation contributes to disease development and progression. Neuronal inclusions of TAR-DNA binding protein (TDP-43), a protein with cell-to-cell prion-like transmission properties [2] are observed in most FTLD cases (~60% of cases) as well as in other neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS, 95% of cases) and AD (20-30% of cases). Aberrant or misfolded proteins can directly act as DAMPs (danger associated molecular patterns), bind to PPRs (pattern recognition receptors) and initiate innate immune cascades in NDs [3]. The aim of our work is to uncover maladaptive innate immune signaling in FTLD, using cellular and animal models. We exposed wild type murine primary microglia to *in vitro* stimulation with human TDP-43. Cytokine release, phagocytosis, cell migration and survival and NLRP3 inflammasome activation were studied to understand how the modulation of innate immune activation by TDP-43 could participate in the disease.

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**P3.132 See-through the brain: 3Dimensional imaging of the neuroendocrine circuits controlling reproduction in mice**

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The proper functioning of the reproductive axis guarantees the survival of a species, and fertility in mammals is controlled by a population of gonadotropin-releasing hormone (GnRH) neurons located in the hypothalamus. These neurons integrate several signals from their interactors and release GnRH in the hypothalamo-pituitary portal circulation to stimulate gonadotropin secretion in the pituitary. In mice, GnRH neurons are born in the olfactory placodes around embryonic day 10.5 (E10.5), then migrate during the embryonic life from the nasal region towards the brain, using olfactory/vomeronasal nerve projections as guides. In the brain, the majority of the GnRH neurons migrate ventrally and settle in the hypothalamus, where they show little activity until puberty onset.

Most studies on GnRH neurons migration and their interactions in the brain were conducted on sections. Thus, there was a significant loss of information when trying to study the entire network involved in the control of fertility. Clearing and 3D-imaging techniques developed these last ten years are useful tools to allow easier visualisation and analysis of both physiological and pathological conditions at the network and organ scale. Here, using whole-mount immunolabelling combined with tissue clearing and light-sheet microscopy, we analysed the ontogenesis, migration, and axonal targeting of GnRH neurons in mice from embryonic development to adulthood. Moreover, using several transgenic mouse lines, we identified unexpected extrahypothalamic populations expressing GnRH, GnRH receptor, and the neuronal population expressing the most potent GnRH hormone stimulator, kisspeptin, in postnatal mouse brains. These data raise the intriguing hypothesis that GnRH could be implicated in the modulation of multiple brain functions.

**P3.134 Vasoactive peptide urotensin II in plasma is associated with cerebral vasospasm after aneurysmal subarachnoid hemorrhage and constitutes a potential therapeutic target**

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**Background:** Cerebral vasospasm (VS) is a severe complication of aneurysmal subarachnoid hemorrhage (SAH). Urotensin II (UII) is a potent vasoactive peptide activating the UT receptor, potentially involved in brain vascular pathologies. We hypothesized that UII may be associated with post-SAH VS. Objectives were to leverage an experimental model of SAH developing VS, to study the urotensinergic system antagonism on neurological outcome, and to show the association between plasma UII level and symptomatic VS after SAH in human.

**Methods:** To this aim, we used a double intracisternal blood injection SAH procedure in C57Bl/6 mice, which mimics the severity and complications occurring in SAH patients to study the impact of the UT receptor antagonist/biased ligand urantide on VS and neurological outcome. A clinical study in a neurosurgical intensive care unit was designed. UII levels were daily measured in plasma during 9 days and were compared with UII in plasma from healthy volunteers (HV).

**Results:** In the SAH mouse model, the expression of UT developed in the vasospasmed middle cerebral artery, within the hippocampus and in choroid plexus. Intracisternal administration of urantide prevented VS, fine motor coordination impairment and cognitive dysfunctions consecutive to SAH. In the human study, seventeen patients with SAH and external ventricular drainage were included. Median UII levels were 43 [14-80] pg/mL in plasma. No significant variation of plasma UII from D0 to D8 was observed. The mean level of plasma UII during the first days post-SAH was higher in patients with symptomatic VS compared with patients without VS (77 [33.5-111.5] pg/mL vs 37 [21-46] pg/mL, p<0.05). Concerning daily measures of plasma UII levels in VS, non-VS patients (27 [15-46] pg/mL, p<0.001) but no difference between VS patients and HV (44 [27-51] pg/mL) nor between non-VS patients and HV.

**Conclusion:** This study suggests that UT antagonism prevents VS and improves neurological outcome after SAH in mice and that higher plasma UII level seems to be associated with cerebral VS consecutive to SAH in humans. The causality link between circulating UII and VS after SAH remains to be established, but our data position UT as a potential therapeutic target in SAH.

**P3.135 Effect of radiofrequency electromagnetic fields exposure (4G, LTE, 900 MHz) on spatial memory persistence and transcriptome profile in the hippocampus and medial prefrontal cortex**

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The exponential development of information/communication technologies leads populations to be exposed to radiofrequency (RF) and the impact of new signals (4G, 5G) has been little explored. Clinical studies showed that acute RF exposure (2G, 3G) may or may not induce subtle cognitive changes, while animal studies show divergent results. We studied in rats the effects of RF exposure (4G) on the formation/persistence of a spatial memory and related-gene expression in 2 memory brain areas (dorsal hippocampus, dHip; medial prefrontal cortex, mPFC).

Six month-old Long-Evans male rats were exposed to RF (4G, LTE, 900 MHz, 61 V/m, SAR<sub>whole body</sub> ~ 0.33W/kg) in a reverberation chamber (4 h/day, 5 d/week) for 3 months (RF), not exposed to RF in the same chamber (Sham) or, placed outside of the chamber (Controls). At the end of the exposure, rats were subjected to a Morris water maze task to assess recent and remote spatial memory, as well as other parameters (body weight & temperature, actography, anxiety). Another group of rats was exposed to assess the transcriptomic profile (RNA seq, validation by RT-qPCR) in the dHip and the mPFC. Several post-exposure delays were studied: i) short-term (6 post-exposure days) in basal conditions or in rats given spatial training, and ii) long-term (33 post-exposure days) in basal conditions or in rats given spatial training (8 days).

Chronic RF exposure affected neither acquisition nor long-term retention of a recent or remote spatial memory (vs Sham exposure). Likewise, there was no effect of RF exposure on body weight & temperature, anxiety, diurnal/nocturnal activity. Transcriptomic analyses showed that RF induced some gene deregulations at both short-term and long-term delays in the dHip and mPFC. However, none of these deregulations could be confirmed by RT-qPCR, and other validations are currently being performed. Importantly, learning-induced neuronal activity evaluated by measurement of immediate early gene expression (*c-fos*, *erg-1*) was not altered by RF exposure in both structures.

In conclusion, chronic exposure to a mobile phone RF signal (4G) induced some gene expression changes both in the dHip and mPFC, but had no impact on spatial learning and memory (recent or remote).

**P3.136 Learning relative value in *Drosophila***

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Animals use memories of past experience to make appropriate decisions. We previously showed that flies can memorize information that correlates to the intensity of electric shock to make appropriate value-based decisions using specific mushroom body (MB) intrinsic circuits. Surprisingly, we found that during learning rewarding dopaminergic (DA) neurons are required to assign relative value (better or worse than) signals to odours associated with different intensities of electric-shock punishment. Using *in vivo* neuronal silencing during learning, we found specific subsets of rewarding and punishment DA neurons targeting the MB that are specifically required for relative aversive value coding. MB output neurons (MBONs) with dendrites within the MB zones targeted by the necessary DA neurons are also necessary for relative aversive value coding. *In vivo* calcium imaging during learning revealed that learning induces shock intensity-dependent persistent depression of the conditioned-odour drive to the relevant MBONs promoting appropriate avoidance behaviour. As anatomical connections exist between MBON and DA neurons targeting the MB, we therefore propose that memories of relative aversive value are written within the DA-MB-MBON network and compared *via* recurrent MBON-DA neuron recurrent circuits.

P3.137

### Involvement of glial connexin 43 in energy homeostasis

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The metabolic syndrome is a major public health issue due to a dysfunctional energy homeostasis leading to obesity and/or diabetes. Therefore, understanding energy homeostasis mechanisms is mandatory to provide new advances. This balance is regulated in the CNS, mainly by hypothalamus (HT) and dorsal vagal complex (DVC). Previous studies showed that glial cells based in HT and DVC take part in the fine tuning of energy metabolism and could interact with canonical neuronal populations. However, these inherent mechanisms have poorly been depicted until lately. Connexin 43 (Cx43), as being exclusively glial, is very important for astrocytic activity and might be a good mediator for neuron-glia interactions. It indeed belongs to a transmembrane protein family and can organize into hemichannels, which when bound to another one, lead to a gap junction between cells. These hemichannels can also be free at the membrane and allow uptake and release of small molecules. Here, we showed that Cx43 is strikingly expressed in HT and DVC and is mostly found in close apposition to synapses in these structures. Moreover, the GJA1 gene expression coding for Cx43 is modulated by modifications of metabolic status. Then, we observed that intracerebroventricular injection (ICVi) of TAT-Gap19, a peptide that specifically blocks Cx43 hemichannels activity, induced a strong decrease in food intake. This anorexigenic effect of TAT-Gap19 is associated with the activation of prototypic anorexigenic neurocircuitries. To go further, we generated a novel inducible and astrocyte specific Cx43 KO mice strain (Cx43fl/fl/GFAPCreERT2). After endoxifen induction, GFAP-promoted CreERT2 recombinase deletes the Cx43 coding DNA sequence. We administered endoxifen by ICVi to target specifically HT and/or DVC. The validity of this approach was first assayed using tdTomato reporter mice. Then, beta-galactosidase activity was used as positive reporter of deletion. The metabolic phenotype of astrocyte Cx43 KO mice is under investigation. Collectively, these results suggest a tonic delivery of orexigenic molecules via astrocytic Cx43 hemichannel and put forward the hypothesis that glial targeting may be a new therapeutic avenue for the treatment of obesity.

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**P3.138 A new behavioural paradigm in the study of action control in rats**

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Action control includes both the selection of the appropriate response and the inhibition of irrelevant responses. In humans, response selection is usually studied with the Simon task. In this task, stimuli are composed of two dimensions: one is task-relevant and must be discriminated in order to give a correct response; the other dimension, stimulus position, is task-irrelevant but induces the activation of the spatially congruent response. Action control in this task appears to operate following a dual route architecture. According to this model, task-relevant information is processed in a controlled way, whereas stimulus position is processed automatically. When controlled and automatic routes lead to the activation of different responses, action control must resolve this conflict through inhibition of the incorrect response. In the present study we developed an animal model to further investigate the neural substrates of the dual route architecture. To do so, we adapted the Simon task to rats. The animal is trained to give a response in a right or left nose poke depending on the light intensity: weak or strong (e.g. answer right to weak intensity and left to strong intensity). The stimuli are presented laterally (right or left). Two trial types can hence be distinguished: in congruent trials the stimulus's side and the response's side are the same (e.g. a weak stimulus on the right); in incongruent trials rats has to select the response opposite to the stimulus position (e.g. a weak stimulus on the left). As in humans, incongruent trials lead to longer reaction times and higher number of errors than congruent trials. Analysis of the dynamics of response activation and inhibition reveals both commonalities and differences with humans. The results of this study validate this adapted Simon task to rats. Therefore, in follow-up experiments, this model will be used to study neural mechanisms of the action control involved in the resolution of response conflict.

**P3.139 Automatic temporal order processing for subliminal asynchronies?**

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A perception of succession is not a succession of percepts. The aim of the present study was to check whether the temporal order of visual stimuli can be processed automatically on an unconscious level. Two nearby flashes were displayed, separated by a subliminal 17 ms asynchrony and followed by a square whose surface was colored with one of two greyscale values. Participants identified the greyscale value and gave a manual response. Throughout the experiments the order of the flashes was predictive of the following greyscale value. Error rates and response times (RT) were recorded and compared with two control conditions where either a single central flash (Neutral condition) or two simultaneous flashes presented at the same location as in the main condition (Simultaneous condition) were not predictive. Predicting the gray value on the basis of order information was expected to induce a decrease of both RTs and errors. In Experiment 1 one group was given information about the flashes' predictiveness of the upcoming greyscale value (without precision about the exact associations) at the beginning of the experiment, while the other group was given this information midway through the experiment. No effect of Group, Condition or interaction between the two factors was found in performance or RT. To check whether a conditioning process could influence the association between the order of the flashes and the greyscale values, in Experiment 2 one group underwent a conditioning phase and then was informed about the exact associations between the order of flashes and the greyscale values at the beginning of the experiment, while the other group underwent no conditioning and was only given limited information about the flashes' predictiveness (similar to the first group in Experiment 1). An effect of Condition was found on RT, with faster responses in the Asynchronous condition, but not on errors. We propose that the conditioning increases the salience of the asynchrony that functions as an alert signal after which participants respond faster. The lack of effect on errors suggests that subliminal order is not processed automatically.

**P3.140 Sensorimotor transformation in the zebrafish auditory system**

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Vertebrates can sense their environment through their sensory systems and integrate this information to produce behavior. How sensory information is converted into adequate motor patterns in the brain still remains an open question.

To address this question, we used two-photon and light-sheet calcium imaging in intact, behaving zebrafish larvae expressing GCaMP5. With this approach, we monitored neural activity elicited by auditory stimuli across the entire auditory system with single-cell resolution, while simultaneously recording tail movements with a high-speed camera.

We found a spatial organization of neural activity according to 4 different response profiles. Low frequencies (150-450 Hz) were locally processed in the hindbrain while higher ones (900-1000 Hz) were transferred to the midbrain, suggesting the existence of two channels for processing auditory information. We suggest that the local low-frequency channel is mainly used for the generation of an adequate motor behavior, while the second channel (low and high sound frequencies) may be involved in the modulation of alternative sensory modalities.

To study how sounds are processed into adequate motor patterns, we classified the neuronal responses according to their correlation with stimulus presentation and behavioral output. Interestingly, neither the number of neurons recruited nor their activity could explain the sensory motor transformations, but rather the duration of the activity patterns, suggesting that auditory perception in zebrafish is an integrative process of the neuronal sensory response.

Finally, we observed that ongoing spontaneous activity preceding the auditory stimulation can predict the generation of the motor behavior, suggesting that the probability of eliciting a motor behavior depends on the initial state of the neuronal circuit.

**P3.141 Somatostatin released by CSF-contacting neurons shapes exploration of zebrafish larva**

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Locomotion is critical for survival as it enables animals to navigate their environment in order to find optimal conditions for survival as well as to escape predators. The mechanism allowing internal sensory inputs to shape innate locomotion are not well understood. Our team investigates the role of interoceptive pathway relying on spinal sensory neurons called cerebrospinal fluid-contacting neurons (CSF-cNs). These cells constitute a sensorimotor loop in the spinal cord detecting mechanical flow and in return to modulate locomotion and posture via GABAergic projections. Recently, we showed that Somatostatin 1.1 (*sst1.1*) is selectively expressed in dorso-lateral CSF-cNs that are specifically recruited during lateral bending. Here we aim to understand the role for Somatostatin released by CSF-CNs on innate locomotion. We generated *sst1.1* mutants using CRISPR/Cas-mediated genome editing. We compare the kinematics of *sst1.1* mutant larvae to their control siblings during slow exploratory locomotion. Preliminary results indicate that *sst1.1* mutant larvae swim on average over longer distances and at higher speed, indicating that release of Somatostatin contributes to shape innate locomotion. Interestingly, we observe similar effects when Botulinum toxin light chain B (BotxLCB-GFP) is selectively expressed in CSF-cNs to silence vesicular release. Altogether, our results show that Somatostatin acts in concert with GABA in CSF-cNs to shape innate behavior. We show here that in the slow locomotor regime, release of this peptide and neurotransmitter contribute to slowing down and silencing locomotion. Further work will reveal the contribution of Somatostatin released by CSF-cNs in the fast locomotor regime, by investigating the kinematics of acoustic-induced escapes.

**P3.142 Mitochondria & Mood: can mitochondrial dysfunction and oxidative stress bridge emotional and metabolic disturbances?**

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Disturbances in energy metabolism involving mitochondria are frequently observed in patients and animal models of major depression (MD). Yet, the molecular mechanisms by which alterations in mitochondria connect psychological and physiological symptoms of MD are incompletely understood.

As individual variability in stress responsiveness affects the vulnerability to develop MD, a mouse model established by selective breeding for high (HR), intermediate (IR) or low (LR) stress reactivity was used to determine whether emotional and metabolic phenotypes are associated with changes in mitochondrial function in tissues with high metabolic demands (i.e., brain and liver).

Male mice of the stress reactivity lines were tested for depression-like behaviors in the open field and forced swim test. Body weight, food intake and body fat composition were also monitored. Oxygen consumption of isolated mitochondria from the liver and the hippocampus was measured using a Seahorse XFe96 Analyzer as a proxy for mitochondrial functional capacity. In addition, the integrity of the mitochondrial DNA (mtDNA) and profiles of mitochondria-focused gene expression were analyzed in the hippocampus using qRT-PCR.

We found that, compared to IR and LR mice, HR mice showed hyperactive locomotion and coping behaviors in the open field and forced swim test, respectively. HR mice also presented significantly lower body weight but higher relative food intake. When compared to IR mice, LR mice showed a trend for lower body fat accumulation. No major changes in mitochondrial biogenesis and functional capacity were observed between the lines. For instance, the oxygen consumption rate of isolated hippocampal and hepatic mitochondria was not significantly different between the three lines. Only slight changes in mRNA expression of some markers of oxidative stress and apoptosis were observed in the hippocampus of LR mice, yet they were not associated with changes in the lesion frequency at the mtDNA.

Overall, our results indicate that altered stress reactivity is not directly associated with major mitochondrial dysfunction under basal, non-stressed conditions. Yet, this does not preclude a role for mitochondria under more challenging conditions, e.g. in response to chronic stress or dietary challenges.

**P3.143 Brain activity during reciprocal social interaction investigated using conversational robots**

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We investigated neural activation during reciprocal interaction using language, with functional magnetic resonance imaging (fMRI). We compared human-human interaction (HHI) to human-robot interaction (HRI). We expected HHI to elicit more mentalizing and social motivation than HRI.

Data of 21 participants entered analysis. Alternating, participants in the scanner talked freely for 60 seconds about images with a confederate and robot outside. Interlocutors were connected via bidirectional audio and unidirectional video (from outside).

Functional MR images were acquired on a 3T scanner. Statistical analysis was performed with SPM12 for general linear model (GLM) and the connectivity toolbox for functional connectivity. (Results false-discovery rate-corrected for multiple comparisons)

Interaction including HHI and HRI: Activation was found in the occipital and lingual gyrus, cerebellum, superior temporal gyrus (STG) and sulcus (STS), pre- and postcentral gyri, the superior and left inferior frontal gyrus.

HHI (versus HRI): Activation was found in the STG, mid-temporal gyrus, temporal poles, temporo-parietal junction, cerebellum and subcortical structures. Functional connectivity revealed connections between the right and left paracingulate gyrus. The bilateral paracingulate gyrus and the anterior cingulate cortex were functionally connected to the left parietal operculum, and the posterior cingulate cortex to the mid-temporal gyrus.

HRI (versus HHI): Activation was found in the calcarine, lingual, and fusiform gyri, intraparietal sulcus, supramarginal gyrus and middle frontal gyrus. Functional connections were located in temporal areas.

We investigated natural interaction comparing HHI and HRI using fMRI. For HHI we found activation in brain areas associated with mentalizing and social motivation. Functional connectivity including the paracingulate gyrus support an adoption of an intentional stance in human interactions only. Activation for HRI revealed brain areas associated with perception and executive functions.

Conversational robots as control condition preserve reciprocal dynamics in interactions, presenting an advantage for social neuroscience.

**P3.144 Sensory and control limitations shape mouse behavioral strategies during sensory discrimination**

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Although we generally assume that adaptive behavior in an experimental setting is largely constrained by task contingencies, the actual pattern of behavior displayed by a normative agent should be the outcome of a trade-off between performance costs and control costs arising from differences between spontaneous tendencies and reinforced actions. We studied sensory discrimination of pure tones by head-fixed mice in a 2AFC setting. To reduce the performance-cost of impulsive responses, performance was calculated ignoring licks during a 'grace period' lasting 150ms after sound onset. Mice developed an asymmetric motor strategy to solve the task, licking to the spout associated to high-frequency tones by default, and only switching if necessary. Logistic regression models including non-sensory variables confirmed that this bias is present at the level of sensory predictors. Mice appear to adopt a 'detection' strategy (of low frequency tones) to cope with a more uncertain representation of higher frequencies. Lick-burstiness (revealed through lick autocorrelograms) represents a problem for this strategy, but this problem is offset by the existence of the grace period. Elimination of the grace period resulted in chance-level performance, suggesting that the cost of shaping the licking pattern is very high. However, mice shaped from the beginning to avoid inter-trial licking displayed symmetric discrimination behavior. A model with asymmetric representation of frequency and potentially asymmetric decoding could explain the behavior of biased and unbiased mice, and supports the interpretation that sensory and control limitations lead to treat the discrimination problem as a detection task. Finally, to test the generality of our findings, we also trained other batches of animals using a different set of frequencies or to discriminate the location of a tone. We found that indeed mice showed the same phenotype we described and seem to rely on the biased licking behavior to overcome sensory deficits. Taken together, our results reveal an asymmetry in the representation of sound frequency and highlight the importance of the interplay between spontaneous and reinforced actions in determining adaptive behavior.

**P3.145 Cannabinoid type-1 receptors on GABAergic neurons are necessary and sufficient for running motivation**

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The lack of intrinsic motivation to engage in, and adhere to, physical exercise has major health consequences. However, the neurobiological bases of exercise motivation are still unknown. Using wheel-running as an animal model of voluntary exercise, we have proposed that the latter is under tonic control by the endocannabinoid system (Dubreucq et al., Biol. Psychiatry 2013). However, because the analysis of wheel-running performance is by no means an index of motivation for running, we have developed an operant conditioning paradigm wherein mice have to nose poke to unlock temporarily a running wheel, doing so under fixed ratio (FR) and progressive ratio (PR) reinforcement schedules. Using pharmacological tools for the main cannabinoid receptor in the brain, namely the cannabinoid type-1 (CB1) receptor, we show that the acute blockade of CB1 receptors decreases running motivation, as assessed during PR sessions. This observation extended to mice bearing either a global deletion of CB1 receptors or a selective deletion of CB1 receptors from GABAergic neurons. Conversely, the inhibitory impacts of these deletions on PR performances were not associated with intrinsic wheel-running performances, as indicated by the ratio of the time spent running per rewarded running sequence. As opposed to the tonic role exerted by CB1 receptors on GABAergic neurons on running motivation, the deletion of CB1 receptors from cortical glutamatergic neurons proved inefficient on running motivation but increased the running duration per rewarded sequence. In keeping with the aforementioned evidence for CB1 receptors on GABAergic neurons playing a necessary role on running motivation, we next explored whether such a receptor subpopulation also plays a sufficient role. We thus used mutant mice in which CB1 receptors were silenced throughout and compared these animals to mice in which we specifically reexpressed these receptors in GABAergic neurons. The inhibitory impact of CB1 receptor silencing on running motivation was prevented by the reexpression of CB1 receptors in GABAergic neurons, hence indicating that this receptor population plays a necessary and sufficient role on running motivation (Muguruza et al., J. Clin. Invest. Insight, in press).

**P3.146 Phenotyping of tanycytes-like cells located in the brainstem, possible involvement in energy homeostasis**

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The homeostatic control of energy balance allows to equilibrate food intake and energy expenditure. Central structures, namely the hypothalamus and the brainstem, tightly regulate this energy balance. In these structures, nutritional, hormonal and neuronal information from the periphery are integrated and then relayed to reward circuits. Most research on the regulation of energy homeostasis has been focused on the involvement of neuronal signaling and the role of glial cells has been poorly explored. Nonetheless, emerging data suggest that glial cells could be sensors for circulating hormones, such as leptin or ghrelin. Tanycytes, a subpopulation of hypothalamic glial cells, were reported to transport circulating leptin into the 3<sup>rd</sup> ventricle. This route is altered in animals showing peripheral leptin resistance and its stimulation reverse a diet-induced obesity. Remarkably, a tanycytes-like cell population was identified in the dorsal vagal complex of adult rodents, at the interface between the area postrema (AP) and the nucleus of the solitary tract (NTS). To date, this cell population is poorly characterized. To deepen our knowledge, we isolated and cultured a zone comprised between the AP and the NTS from 10-days old rats. After passaging them 10 days later and letting them reach 80% confluence, we experimented and characterized them. Using RT-qPCR and immunocytochemistry, we identified different markers that were already reported to be expressed by hypothalamic tanycytes i.e. vimentin, DARPP32 and MECA32. On the other hand, GFAP (glial fibrillary acidic protein), a well-known astrocyte marker, not expressed by tanycytes, is here highly present. Moreover, BLBP (brain lipid binding protein) was identified as a specific marker of the tanycytes-like cells. Interestingly, the expression of GFAP is positively correlated with the expression of BLBP ( $r^2=0.84$ ). Using calcium imaging, we are currently testing the sensitivity of this cell population to metabolism-related hormones and peptides. These preliminary results indicate that we can obtain tanycytes-like cells enriched cultures from brainstem and suggest that these cells constitute a unique glial population.

P3.147

**Investigating the role of the striatum in motor learning and execution**

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Many of our daily motor behaviors are shaped through extensive repetition and trial-and-error adjustments, such as driving a car and brushing our teeth. The striatum, the main input structure of the basal ganglia, is assumed to contribute to trial-and-error motor learning. It is widely believed that the dorsomedial striatum (DMS) contributes to the early phase of motor learning whereas the dorsolateral striatum (DLS) is implicated in the execution of learned motor programs, however their exact roles still remain debated.

Here, we designed a time-estimation task wherein rats running on a powered treadmill learn, by trial-and-error, to maximize a reward/punishment ratio. All the animals progressively converge toward a common embodied strategy: they perform a stereotyped back-and-forth sequence on the treadmill whose duration matches the time they need to estimate. We examined the function of the DMS and DLS in learning and execution of this motor routine by performing striatal lesions of various size and location.

Interestingly, both DMS and DLS lesioned animals demonstrate similar results. They manage to learn and execute the task. However, lesions of the entire dorsal striatum hinder learning of the motor routine. Another common trait among lesioned animals is a prominent decrease in running speed. This effect on speed is correlated with the size of the lesion, but not its location. Altogether, these results provide new insights into the function of the striatum in motor learning and execution.

**P3.148 Executive functions and emotions in Alzheimer patients**

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A previous study demonstrated that most emotions in aging, even in a very old woman (104 years), are still presents, although not appropriated (1). Here, we report some preliminary results obtained with Alzheimer patients (AD), diagnosed in neurogeriatric service with a neuropsychological assessment and MRI, by using the same method to evaluate executive functions and emotions.

Executive functions were quantified by using Delayed Response Tasks (2) while emotions resulting from face expressions were captured by camera and coded by a software -Face Reader.

In comparison to adult or normal aging, executive functions were much more impaired in AD and emotions were not presents or not appropriate and differently expressed.

In Delayed Response Tasks, 3 successive tasks, Alternation, Non Alternation and Reversal tasks have to be discovered in a maximum of 80 trials. In adult, the solution to these problems were easily resolved. In very old subjects, Alternation and Non Alternation were found quite easily but they failed on reversal task. In AD patients from the start a subsequent deficit was seen and they were unable to perform correctly the first alternation task.

In emotions, considering AD patients, the arousal capacity was only slightly impaired but quite no emotions were elicited by the projection of the short movie. Consequently, neutral expression was dominant. This level of neutral expression was correlated with the number of trials accepted to perform by the AD patients on the first task. The result of this correlation seems to reveal the degree of cognitive impairment created by this neurodegenerative disease.

In conclusion, these preliminary results indicated that executive functions and emotions are deeply impaired in AD patients and could discriminate normal cognitive processes occurring during normal aging from the occurrence of AD.

(1) Sicard, G et al. (2018). Emotion Evaluation of Four Generations of Woman from a 104-Year Old Ancestress. World Journal of Neuroscience, 8(03), 350.

(2) Verin, M., et al. (1993). Delayed response tasks and prefrontal lesions in man—evidence for self generated patterns of behaviour with poor environmental modulation. *Neuropsychologia*, 31(12), 1379-1396.

**P3.149 A two-hit story: seizures and genetic mutation interaction sets phenotype severity in SCN1A epilepsies**

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SCN1A (NaV1.1 sodium channel) mutations cause Dravet syndrome (DS) and GEFS+ (which is in general milder), and are risk factors in other epilepsies. Phenotypic variability limits precision medicine in epilepsy, and it is important to identify factors that set phenotype severity and their mechanisms. It is not yet clear whether SCN1A mutations are necessary for the development of severe phenotypes or just for promoting seizures. A relevant example is the pleiotropic R1648H mutation that can cause either mild GEFS+ or severe DS. We used a R1648H knock-in mouse model (*Scn1aRH/+*) with mild/asymptomatic phenotype to dissociate the effects of seizures and of the mutation per se. The induction of short repeated seizures, at the age of disease onset for *Scn1a* mouse models (P21), had no effect in WT mice, but transformed the mild/asymptomatic phenotype of *Scn1aRH/+* mice into a severe DS-like phenotype, including frequent spontaneous seizures and cognitive/behavioral deficits. In these mice, we found no major modifications in cytoarchitecture or neuronal death, but increased excitability of hippocampal granule cells, consistent with a pathological remodeling. Therefore, we demonstrate for our model that an SCN1A mutation is a prerequisite for a long term deleterious effect of seizures on the brain, indicating a clear interaction between seizures and the mutation for the development of a severe phenotype generated by pathological remodeling. Applied to humans, this result suggests that genetic alterations, even if mild per se, may increase the risk of second hits to develop severe phenotypes.

**P3.150 Emotions can alter kinesthetic acuity**

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Kinesthesia allows us to perceive our own body movements and relies on the integration of proprioceptive information arising from muscle spindles. We recently showed that that emotion can alter the proprioceptive messages from such muscle afferents, making them more sensitive to muscle lengthening when participants were listening sad music.

Presently, we investigated whether these changes in proprioceptive feedback relating to emotional state may affect the perception of limb movements. Kinesthetic acuity was tested in 20 healthy, young adults by imposing very slow movements that consisted of either plantar flexion or dorsiflexion of the ankle, or no movement. Different emotional states were induced by listening to neutral, sad, or happy music, or they performed the task without music. The participants had to relax and focus on the music (or nothing), and then they had to shift their focus to the direction of an incoming movement. After each movement (or no movement), they were asked its direction. Muscle activity, heart rate, and electrodermal activity were recorded during each trial, and after each music condition the participants rated the emotion felt on a visual analog scale.

We showed that kinesthetic acuity was increased during the sad condition, as compared to the no music or neutral conditions. Furthermore, the rating of the emotional content of the music corroborated with changes in physiological measures.

We concluded that emotion can shape our perception of movements, since feeling sadness significantly increases our kinesthetic acuity. Functionally, this may be relevant for the preparation of appropriate behavioral responses.

**P3.151 Effects of ionizing radiation on learning and spatial memory after postnatal mouse brain exposure at low to moderate doses**

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Computed tomography scan is the most commonly used medical diagnostic procedure for head exploration in children. Long-term effects of brain exposure, at low to moderate doses ( $\leq 2$  Gy) of ionizing radiation on cognitive functions, such as learning and memory process, are not well established in humans and are an importance scientist issue. The relationship between dose and biological impact is not necessary linear contrary to observations made at higher doses ( $>2$  Gy). Doses range studies are essential for a better understanding of these low to moderate dose effects. Among brain structures, the hippocampus has a major role in memory processes. In the subgranular zone of the dentate gyrus of the hippocampus, new neurons are continuously generated during postnatal and adult life, and play an important role in several "hippocampal-dependent" forms of memory. The aim of our project is to study the impact of postnatal irradiation (doses range: 0.25, 0.5, 1 and 2 Gy) on learning and spatial memory, and the process of adult hippocampal neurogenesis. Two types of exposure were realized: whole-brain exposure and targeted exposure of the dorsal dentate gyrus. Irradiations were performed on ten-day-old mice. Spatial learning and memory abilities were assessed three months after exposure using a massed water-maze behavioral task. Results suggest that spatial learning is not altered by irradiation in both models of exposure and for each irradiation dose. However, some groups (for 2 Gy in both models and 0.25 Gy for whole brain exposure) seem to learn faster compare to the control group. Long term spatial memory is impacted only after 1 Gy exposure in the dorsal dentate gyrus. Thus, nonlinear dose effects on memory processes after targeted irradiation are observed. Currently, immunochemistry are performed to quantify the different cells type of the neurogenesis process, to try to explain the cognitive impairment observed after targeted irradiation at 1 Gy. This work will improve our understanding of how low-to-moderate doses of irradiation impact the brain and will bring scientific clues for the children's radioprotection program.

P3.152

**Comparing human and monkey neural circuits for processing social scenes**

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Recognizing agents, their actions, and their interactions is essential for understanding the world around us. In the monkey brain, these cognitive steps engage serially three distinct neural circuits: The face and body areas, the Mirror Neuron System (MNS) and finally the Exclusively Social Interaction Network (ESIN), a putative precursor of the Theory of Mind (ToM) network in monkeys (Sliwa and Freiwald, 2017). It has not been studied, however, whether these same brain regions are involved in humans who observe social scenes, or whether humans and rhesus monkeys use different neural strategies to analyze social scenes. To answer these questions, we scanned twenty-six human subjects (including eight women, age: 20-50 years, mean 32 years) for functional magnetic resonance imaging (fMRI) acquisition in two sessions, while they were presented with the same videos as the ones presented to monkeys, and additionally with videos of social scenes involving human actors. Whole-brain activity for watching blocks of human or monkey individuals, their actions and their interactions was compared to the activity for watching control videos of objects' still, moving and interacting, using Random Effects (RFX) Generalized Linear Model (GLM) group analysis. We show that similarly to monkeys, humans 1) engage face and body areas (mapped independently using a classic localizer) in all social video conditions, and 2) engage the MNS (mapped independently using a classic localizer) in a generic manner for watching agent-object, agent-agent and object-object interactions. Yet contrary to monkeys, humans spontaneously engage the ToM network (mapped independently using a classic localizer) when they look at agents that do not interact with each other or with objects or agents that perform actions directed to objects. These results identify which spontaneous neural activities are shared during the observation of social scenes and which neural activities could have adapted to the cognitive strategies of the species, and emphasize the human interest in understanding the actions of our peers directed to objects.

Sliwa J, Freiwald WA (2017) A dedicated network for social interaction processing in the primate brain. *Science*

P3.153

**Development of inhibitory control: an electromyographic study**

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Cognitive control refers to the goal-directed regulation of action. Inhibitory control, one of its core components, is studied in so-called “conflict tasks” in which a prepotent response must be suppressed in favor of the instruction-based response. Suppression failure leads to behavioral errors, whose proportion is taken as a measure of cognitive control efficiency. Behavioral errors, however, are only the tip of the iceberg: recording electromyographic (EMG) activity from muscles involved in response execution reveals that, on 15-20% of correct trials, a sub-threshold burst of activity of the muscle involved in the incorrect response is present. Such *partial errors* reflect automatic capture caused by irrelevant stimulus dimension; they have almost never been studied in children. In the present study, the combination of EMG recording and distribution analysis (advanced techniques to reveal the underlying dynamics), we aimed at clarifying the development of cognitive control from 6- to 14 years old.

In the study participated 123 children and 15 adults. The number of partial errors decreases with age. However, dynamic analysis reveals a comparable dynamics of incorrect response activation. In contrast, the dynamical analysis of interference on response time reveals larger interference effect for fast RTs which largely decreased for slower RTs. This decrease has been interpreted as irrelevant dimension suppression. This process, being moderate in small children, was at adults' level since 9 years old. These findings suggest that, in the Simon task, the susceptibility to incorrect response activation is age-independent, contrary to control of irrelevant dimension which develops gradually and is functional already in 9 years old children.

**P3.154 A mouse model for exploring the neurobiology of confirmation bias-like behaviour**

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Confirmation bias is a well-described cognitive behaviour whereby novel information from the environment is over-valued when it confirms and under-valued when it disconfirms previously consolidated cognitive content (e.g. knowledge, beliefs, learned associations, etc.). Described in various terms since antiquity, today the phenomenon is at least partly responsible for both scientific and societal dilemmas ranging from the reproducibility crisis to the proliferation of fake news.

Nevertheless, surprisingly little research has been dedicated to understanding the neural mechanisms or evolution underpinning this spontaneous and quasi-universal human cognitive response to novel information, less still to those mechanisms involved when an individual succeeds in suppressing or overcoming it.

Thus, we set out to design a mouse model for confirmation bias-like behaviour which would enable both exploration of and intervention into its neurobiological underpinnings, thereby also increasing our understanding of its evolution. Our model is based on the above cognitive level definition of the phenomenon - over-valuation of novel environmental elements which confirm and under-valuation of novel environmental elements which disconfirm a previously consolidated cognitive content. Our results to this point, using a two-task, two-context radial maze protocol, indicate that the core elements of this cognitive response to a novel, ambivalent (with respect to previous learning) environment have a long and shared evolutionary history.

**P3.155 *Crocus sativus* améliore la déficience de l'activité locomotrice et du système dopaminergique induite par le plomb contre la neurotoxicité du plomb chez la *Meriones shawi***

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Lead (Pb) is a metal element released into the atmosphere and a major source of environmental contamination. The accumulation and concentration of this metal in a food web may lead to the intoxication of the body, more precisely, the nervous system (NS). In addition, Pb-exposure can cause structural and functional disruption of the NS. Studies have shown that Pb-exposure could be a risk factor in the development of Parkinson's disease (PD). The latter is related to dopaminergic deficiency that may be triggered by genetic and environmental factors such as Pb intoxication. Our study will focus on the negative effects of oxidative stress on the brain of *meriones shawi*, since it is the organ most exposed to the oxidation due to the high phospholipid content of neuronal membranes and the link existing with the development of neurodegenerative pathologies such as PD. Also, we have evaluated, in one hand, the neurotoxic effect of Pb (25 mg / kg B.W i.p) for three consecutive days on dopaminergic system and locomotor performance in *Merione shawi*. In the other hand, the possible antioxidant effect and restorative potential of *C. sativus* (CS) (50 mg / kg BW) by oral gavage. The immunohistochemical approach has revealed that Pb-intoxicated *Meriones* show a significant increase of Tyrosine Hydroxylase (TH) levels within the Substantia Nigra compacta (SNC), Ventral Tegmental Area (VTA), Locus Coeruleus (LC), Dorsal Striatum (DS) and Medial Forebrain Bundle (MFB), unlike the control meriones, a group intoxicated and treated with *Crocus sativus* hydroethanolic extract (CSHEE) and treated group by CSHEE. Treatment with CSHEE, has shown a real potential to prevent all Pb-induced damages. In fact, restores the TH levels by 92%, 90%, 88%, 90% and 93% in SNC, VTA, LC, DS and MFB respectively, similarly, locomotor activity dysfunction in Pb-intoxicaed *meriones* was reinstated by 90%. In this study, we have revealed a new pharmacological potential of *Crocus sativus* that can be used as a neuroprotective product for neurodegenerative disorders, especially, which implying dopaminergic and noradrenergic injuries, like PD, triggered by heavy metals.

P3.156

**Role of sensory *stimuli* and palatability in oral-nicotine consumption in mice**

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Tobacco products are highly addictive and their abuse is a major public health problem. In humans, this addiction lies on the oral route with essential taste and odorant components. Nowadays, their role is further amplified with the increasing use of smokeless tobacco, especially e-cigarettes where nicotine is associated with additives including flavors and sugars. Thus, the impact of additives on smoking behavior must be evaluated. It has been shown that non-pharmacological visual stimuli become more salient when associated with nicotine, the addictive molecule of tobacco. Here we are interested in the putative secondary reinforcement of oro-olfactory stimuli by nicotine. Our hypothesis is that there is a bidirectional interaction where nicotine reinforces the values of associated orogustative cues while aromas enhance nicotine's palatability, increasing its consumption. First, we conducted an operant conditioning experiment in order to test the effects of aromas on the different stages of nicotine oral addiction. Oral nicotine (starting at 40 $\mu$ g/ml) was associated with a cue light and a flavor (alimentary vanilla flavor). Nicotine was not self-administered orally when associated with the cue light but no aroma, however, the association of nicotine and aroma allowed both acquisition and maintenance of self-administration in a fixed ratio training (FR3). Animals were sensitive to the quality and concentration of the reward in a dose-response manner. In addition, they are motivated to moderately increase their work for the reward (PR2). Mice relapsed to cue light presentation, to nicotine + aroma associated with the cue, but not to nicotine + aroma only, which showed the important role of visual stimuli but not the aroma in relapse. To deepen our focus, we are now setting up an hedonic reactivity test for studying nicotine solution palatability with or without aroma (modified sensory inputs), which will be followed by the study of the neural circuits recruited (c-fos brain mapping). Altogether, we expect to highlight an important role of additives on tobacco product's attractiveness and abusive consumption. Hence, dissection of these processes will make it possible the identification of the underlying brain circuitry involved.

**P3.157 Interlimb transfer of sensorimotor adaptation may not reflect interhemispheric transfer: New insights from patients with corpus callosum abnormalities**

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When humans adapt with one limb to a sensorimotor perturbation in a given workspace, this adaptation can generalize to a different workspace, or even to the opposite limb. Such generalization across limbs is known as interlimb transfer, and despite being well documented in the literature, there are still questions surrounding the underlying neural mechanisms (Ruddy & Carson 2013). For instance, several theoretical models highlight the corpus callosum as a potential key structure for mediating transfer (Taylor & Heilman 1980; Parlow 1989), however, certain research supports the involvement of ipsilateral projections (Criscimagna-Hemminger et al. 2003).

To investigate the role of the corpus callosum in interlimb transfer, we implemented a prismatic adaptation protocol to test for transfer from dominant to non-dominant arm and from non-dominant to dominant arm in a range of patients with corpus callosum insult. Based on models indicating the corpus callosum as a key brain structure mediating interlimb transfer, it would be hypothesized that such patients should not show interlimb transfer in either direction.

Results from two patients with recent naturally acquired lesions of the corpus callosum and one agenesis patient revealed clear sensorimotor adaptation of the arm exposed to the prismatic goggles. Our key finding was that the two patients with recently acquired corpus callosum lesions demonstrated significant interlimb transfer from the dominant to non-dominant arm. Further, the agenesis patient showed significant interlimb transfer from dominant to non-dominant arm but also from non-dominant to dominant arm. These results provide new insights into the theoretical models and mechanisms of interlimb transfer of sensorimotor adaptation: they show that interlimb transfer of sensorimotor adaptation can be observed despite lesions or even complete absence of the corpus callosum. Our findings thus suggest that interlimb transfer of sensorimotor adaptation may not reflect interhemispheric transfer, but perhaps relies on ipsilateral projections connecting the hemisphere and the arm, or subcortical structures such as the cerebellum.

**P3.158 Direct- and indirect-pathway striatal projection neurons and the control of locomotion**

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It is generally believed that the basal ganglia (BG) are critical for the control of well-learned action and locomotion. The dorsolateral striatum has been implicated in such function but its exact contribution is still debated. Striatal projection neurons (SPN) form two relatively separated pathways depending on their target. Direct pathway forming SPN (dSPN) project directly to the output nuclei of the BG while indirect-pathway forming SPN (iSPN) targets relay nuclei before modulated BG output. A classical pro/anti-kinetic models suggests that the activity ratio between dSPN and iSPN controls the amount of behavioral activity. In this model, prominent dSPN activity facilitates movements while prominent iSPN activity is associated with behavioral arrest. Recent studies showing co-activation of dSPN and iSPN during action initiation have challenged the kinetic model and suggested a role of both pathways in concurrent selection of adapted action and repression of unwanted motor programs.

To better understand the role of these two pathways in regard of these two functional models, we developed a task in which head-fixed mice, were trained to run continuously for a fixed distance to get a reward and then stay immobile for 4 seconds to start a new trial. We performed optogenetic-based manipulation of dSPN and iSPN using a close-loop paradigm, allowing to alter neuronal activity at different phases of the task, during running or immobility. Preliminary results are neither compatible with the pro/anti-kinetic nor the action selection models.

**P3.159 Neuronal control of parental nest building**

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Animal behavior is a dynamic process, which responds to physiological and environmental changes such as seasonal rhythms or reproductive fitness. Nest building is a well-documented behavior in mice that is essential for thermoregulation as well as shelter and reproduction. Interestingly, while adult mice spontaneously build simple nests, their structural complexity reliably increases during pregnancy in females. Here, we are seeking to elucidate the neuronal circuit controlling the switch towards parental nest building during pregnancy. We characterized the quality of nest building in cohorts of mice as a stable trait controlled by the time the animal spontaneously spends on the task over a day of unsupervised activity. We used unbiased brain-wide cellular mapping of neuronal activity by tissue clearing and light sheet microscopy to identify a neuronal network significantly more active during maternal nest-building centered on the Edinger-Westphal nucleus (EW) in the midbrain.

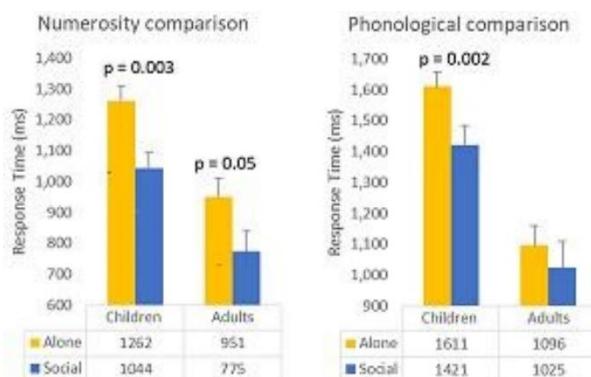
A subpopulation of EW neurons expresses neuropeptides such as urocortin1 (Ucn1), usually associated to stress, anxiety and feeding. However, the importance of those neurons in ethologically-relevant behaviors has been so far elusive. We show that the level of c-Fos expression in Urocortin (Ucn1) positive neurons in the EW correlates with the time spent building a nest in both virgin and pregnant female mice. Inhibiting the activity of the Ucn1+ EW neurons in pregnant females abolishes parental nest building by reducing the amount of time spent on the nest-building task. By combining behavioral tracking, whole brain activity mapping and 3D projection tracing, we characterized a network of brain regions modulated by the EW Ucn1+ neurons and propose that hormonal priming of the EW neurons could modulate the state of attention to foster parental nesting. This study suggests that pregnancy hormones could control complex behaviors such as nesting by modulating attention through the EW neurons.

**P3.160 Peer presence facilitates numerosity and phonological comparisons in 10-year-old children**

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The mere presence of others typically improves performance on easy or well-learned tasks, while it impairs performance on difficult or poorly learned tasks. These two phenomena are respectively referred to as social facilitation and impairment (SFI) effects. Highly studied in adults (and nonhuman animals), these effects remain poorly documented in children. Yet, peers are omnipresent in the school environment and SFI effects may play an important role in academic domains such as the acquisition of literacy and numeracy. To tackle this issue, we compared the performance of 10-year-old children on easy reading and number comparison tasks while testing them either alone or in presence of a classmate. In these tasks, either two arrays of dots (numerosity comparison) or two written words (phonological comparison) were presented. Subjects decided whether the first or second dot array comprised the largest number of dots (numerosity comparison), or whether the two words rhyme or not (phonological comparison). A total of 99 children were tested. Forty-seven young adults also performed the same tasks. Children tested in presence of a peer responded faster than children tested alone (as shown in the graph) while maintaining the same accuracy in terms of percent correct responses. Children were either as affected as adults by peer presence (numerosity comparison: effect size 0.61vs.0.59, respectively) or more affected than adults (phonological comparison: effect size 0.49vs.0.20). These results confirm that social facilitation is a life-long phenomenon and reveal that it may also affect academic performance in children. Further investigations of the effect of peer presence in school-age children could help optimize social context in education. Also, functional neuroimaging could shed light on the still-debated mechanism mediating peer influence on cognitive performance.



[Numerosity and phonological comparisons between children and adults on response time]

**P3.161 Contextual fear conditioning differentially activates extended amygdala circuits in male and female**

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The Bed Nucleus of the Stria Terminalis and the central nucleus of the amygdala contribute to fear learning and anxious behavior. The BNST and CE are reciprocally connected, sharing similar cell types and similar efferent targets, suggesting that they might coordinate their activity and/or function in parallel. Within the CE, different neuronal populations gate the expression of fear behavior and can be identified by the specific neuropeptides they express. For example, neurons within the CE that express the neuropeptide corticotropin-releasing factor (CRF) are active when an animal is in a fear-like or defensive state. Similar cell types exist in the BNST, but have not been characterized as fully. Most of these studies have been performed in male rodents whereas it is known that the BNST is a sexually dimorphic structure. We thus decided to test the contribution of the BNST and the CE to contextual fear in both males and females rats. Animals were tested for expression of context fear. Interestingly, context fear expression was associated with upregulation of the immediate-early genes ARC in the anterolateral portion of the BNST (BNST\_AL) in male rats but not in females. We further characterized these activated neurons by injecting the retrograde tracer FluoroGold (FG) into the CE of rats to label neurons in the BNST. Using standard immunocytochemical techniques, we determined whether FG-positive neurons within the BNST showed up-regulation of the immediate-early gene Arc, and thus whether contextual fear conditioning elicited neural activity in the BNST-CE pathway. We also determined whether Arc-positive and FG-positive neurons express CRF in males. The BNST\_AL-CE pathway being unspecific for the expression of context fear in females, we rather see increased neuronal activity in the central nucleus of the amygdala CE. However, non-specific extensive lesions of the BNST with ibotenic acid blocked expression of contextual fear expression in both sexes, suggesting that another portion of the BNST could be necessary for the expression of context fear in female rats. Accordingly, we have started investigation of targeted BNST\_AL-CE pathways in males and females that could unravel very specific sexually dimorphic mechanisms of contextual fear expression.

**P3.162 Can transcranial direct current stimulation over the frontal-midline areas modulate conflict-related ERPs?**

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Most studies investigating cognitive control with transcranial direct current stimulation (tDCS) aim to stimulate the dorsolateral prefrontal cortex. Despite the promising results of early studies, the effectiveness of a single-session stimulation over this area has been questioned recently. Alternatively, targeting the frontal-midline electroencephalographic (EEG) sites has been found to modulate oscillations related to control processes, as medial frontal areas are essential for effective cognitive control. Although event-related potentials (ERPs) are good signals of conflict-related processes, so far, no study has investigated whether this type of stimulation has an effect on ERPs. In the current study, we applied active or sham tDCS for 20 minutes over the frontal-midline sites of healthy individuals during the administration of a flanker task. Subsequently, EEG has been recorded during the task. Our aim was to reveal the effect of stimulation on latencies and amplitudes of ERPs at early (P100 and N170), as well as at later stages (N200, P300/Late Positive Component) of information processing. Moreover, we evaluated the effect of stimulation in the light of conflict adaptation processes. No effects of stimulation were found in terms of conflict, i. e. the difference between congruent and incongruent stimuli, at early stages of information processing. In contrast, conflict effect was present in the sham group as measured by P300 amplitudes over the parietal areas, while no such effect was found in the active stimulation group. This difference between the two groups was not observed after congruent elements. We conclude that frontal-midline stimulation might have subtle effects on control-related ERPs at later stages of information processing. It appears that stimulation effects also differ by the conflict adaptation processes. Our results might be helpful to develop effective methods to modulate cognitive control functions for research and clinical purposes as well.

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P3.163

### Memory formation in the absence of experience

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Memory is coded by patterns of neural activity in distinct circuits. Therefore, in principle, it should be possible to reverse engineer a memory by artificially creating these patterns of activity in the absence of any sensory experience. In olfactory conditioning, an odor conditioned stimulus (CS) is paired with an unconditioned stimulus (e.g., footshock; US), and the resulting CS-US association guides future behavior based on the olfactory memory trace. Here (*Vetere et al, Nature Neuroscience, in press*) we replace the CS with optogenetic stimulation of a specific olfactory glomerulus, and the US with optogenetic stimulation of distinct inputs into the ventral tegmental area that mediate either aversion or reward, and in doing so, **create a fully artificial memory in mice**. Similar to a natural memory, this artificial memory depended on CS-US contingency during training, and the conditioned response was specific to the CS and reflected the US valence. Moreover, both the real and implanted memories engaged overlapping brain circuits and depended on basolateral amygdala activity for expression.

P3.164

**Superior parietal lobule: a role in visual perception of multiple elements**

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A lesion of superior parietal lobule (SPL) leads to simultanagnosia, an inability to perceive simultaneously multiple elements. We have previously shown that a patient with bilateral lesion performs slower in visual search than controls but only for stimuli with separable features (Khan and al., 2015). Furthermore, if her visual field is experimentally reduced to a visibility window of 20° diameter, her performance does not change, as if she could not process visual items outside this window. This visuo attentional impairment may be a surface size reduction when processing separable features or a reduction of the number of elements that she can process simultaneously.

To distinguish between these 2 hypotheses, we tested five control subjects. We used stimuli with separable features (letters) or not (colors) and analyzed the number of saccades and the duration of fixation when the number of distractors increases.

We also explored visual processing in peripheral vision in this patient using a crowding task in which one element may be difficult to recognize in peripheral vision if it's surrounded by flankers below a critical spacing (corresponding in healthy controls to half of the target eccentricity: Bouma and al., 1970). This spacing increases linearly in peripheral vision in controls but in the patient with SPL lesion the identification of the central target remained at chance level even with large spacing. Different complementary conditions were explored to distinguish between a localization deficit or an inability to process multiple elements simultaneously. Our results show that the patient has a localization deficit with color patches and an impairment of simultaneous processing with letters.

We conclude that SPL can play a role in simultaneous processing of separable features, which may explain the associated visual search and reading deficits. These findings also provide insight into difficulties shown by visuo-attentional dyslexics, who have been shown to underactivate their SPL bilaterally (Peyrin et al. 2011) and to be slow in visual search for stimuli with separable features (Casco & Prunetti 1996).

**P3.165 Impact of cerebral radiofrequency exposures on oxidative stress and corticosterone in a rat model of Alzheimer's disease**

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Alzheimer's diseases (AD) is the most common type of neurodegenerative disease leading to dementia. The cause of AD remains unknown, however several studies suggested that mobile phone radiofrequency electromagnetic fields (RF-EMF) exposures interacted with AD memory deficits in rodent models. Here we aimed to test the hypothesis that RF-EMF exposure may modify memory through corticosterone and oxidative stress in a rat model of AD.

Long-Evans rats were healthy controls or AD models. AD rats received continuous intracerebroventricular infusion with ferrous sulphate, beta amyloid ( $\beta$ A) 1-42 peptide and buthionine-sufloxiimine (Lecanu, 2006). RF-EMF exposures were performed to the head for 1 month (5 days/week, 15 or 45 min/day in restraint) to mimic cell phone use. To look for hazard threshold, repeated exposures were set to reach high brain averaged specific absorption rates (BASAR): 1,5 W/Kg (15 min), 6 W/Kg (15 min) or 6 W/Kg (45 min). The sham group exposure was 0 W/kg (45 min). Endpoints were spatial memory in the radial maze, plasmatic corticosterone, heme oxygenase 1 (HO1) and neurofibrillary **tangles**. Results indicated that AD rats had increased thioflavine and HO1 staining, reduced memory performances and similar corticosterone level compared to healthy rats. In AD rats, reduced corticosterone and increased hippocampal HO1 staining were observed after the 6 W/kg 45 min exposure. There was no RF-EMF effect on memory and cortical HO1. In healthy rats, increased cortical HO1 staining was observed after the 6 W/kg 45 min exposure. There was no RF-EMF effect on memory, hippocampal HO1 staining or corticosterone.

According to our data, neither AD nor healthy rats showed modified memory after RF-EMF exposures. Unlike healthy rats, AD rats showed higher hippocampal oxidative stress and reduced corticosterone after our highest BASAR exposures. This data may support the hypothesis of a specific fragility related to neurodegenerative disease towards RF-EMF exposures. Further studies should be performed to replicate this data.

**P3.166 Neural dynamics in human frontal cortex during performance monitoring and decisions to check**

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In human beings, information seeking is one major behavioral activity which encompass in particular the verification of one's own performance. Verification or checking potentially increase efficiency of decisions and reduce uncertainty about outcomes. Decisions to check influence our behavior, and their neurobiological bases rely in part on the frontal cortex which might have a role in controlling and regulating the impulse to check.

The present study addresses the question of the neural bases of decisions to check for information, and in particular the neural dynamics that relate to these decisions. We performed EEG recordings in young and healthy human subjects in an experimental task that challenges the verification process using positive and negative reinforcements. In each trial subjects can freely decide either to perform a visual categorization task to win points, or to check how close (based on a visual gauge that evolves with proximity to the bonus) and, in one of two conditions, whether they can get a bonus number of points. In the second condition, the subject have to check to avoid losing the equivalent amount of points. The protocol leaves freedom to subjects to create their own strategy to solve the task.

Preliminary behavioral and electrophysiological analyses with 20 subjects will be presented. The behavioral analyses reveal that subjects mostly resort to two different strategies to complete the task, which imply or not, two reasons for carrying out the verification process: getting information about the task (speed of the gauge), or information about the result (bonus delivery, avoidance of loss). In addition, the ERP and time/frequency analyses show modulations in frontal theta and alpha oscillations depending on the information obtained through the verification process, at different levels of task progress and for both conditions of the test. The analysis also revealed the different levels of frontal alpha oscillation before decisions to check compared to decisions to do the main task

This work provide important data on the potential identification of electrophysiological markers of verification.

**P3.167 Respective roles of the distinct populations of Medium Spiny Neurons of the nucleus accumbens in reward processing**

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The nucleus accumbens (NAc) is a major structure that plays a key role in action selection and execution as well as reward processing and reward-dependent learning. It is largely composed of GABAergic Medium Spiny Neurons (MSN) that are divided into two distinct subpopulations, those expressing the dopamine D1 receptor (D1R; dMSNs), and those expressing the D2 receptor (D2R; iMSNs). Based on the model of the dorsal striatum, it has been proposed that dMSNs and iMSNs of the NAc play antagonistic effects on reward processing, but their respective roles are still largely debated (Carvalho Poyraz et al. 2016; Soares-Cunha et al. 2016). Herein, we aimed at deeper exploring the implication of these two populations of MSNs of the NAc core on various components of reward processing. Using operant conditioning tasks and pharmacogenetic approaches we show that activation of iMSNs decreases motivation to obtain a food reward but increases food consumption, while inhibition had the opposite effect, with no impact on hedonic reactivity. Interestingly, *in vivo* electrophysiology experiments in anesthetized animals revealed that the increased iMSN excitability boosts the activity of dopaminergic VTA neurons. Surprisingly, we observed that both inhibition and activation of dMSNs led to a decrease in performance in motivational tasks, likely related to a strong modulation of consummatory processes. Our data shed light on the complex function of dMSNs and iMSNs of the NAc core in reward processing and highlight differential effects on consummatory vs. motivational processes.

**P3.168 Assessing model-based inferences in decision making with single-trial response time decomposition**

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Decision-making models based on evidence accumulation processes (e.g. the drift diffusion model, or DDM) are widely used to draw inferences about psychological processes from chronometric data and single cell spike recordings. Ideally, the validity of such inferences should be tested beyond data-fitting criteria using external evidence. The broad question of model validity has seldom been explored in this way. We used an electromyographic (EMG) decomposition of each response time into two components, pre-motor (PMT) and motor times (MT), to provide measures external to standard chronometric data. Mapping these measures to model parameters allowed to explicitly test the validity of some of the core assumptions and inferences made from the DDM. In two perceptual decision tasks, we manipulated stimulus strength and speed-accuracy trade-off instructions to assess their effects on response time, PMT and MT. The results of both experiments showed that

- 1) the decision context can affect MT,
- 2) while PMT and MT are stochastically independent under mild time pressure, they become negatively correlated under stronger time pressure, suggesting that time pressure modifies the core information processing architecture.

Concerning modeling, the DDM accurately predicted the recorded MT with the corresponding parameter and was able to correctly recover the locus of some experimental effects but misallocated or misestimated some others. Furthermore, despite the violation of the core independence assumption under speed constraints, the DDM could still satisfactorily account for the data, questioning the mapping between the model's supposed cognitive architecture and how the decisions are actually made.

**P3.169 Effects of a counter measure to prevent the deconditioning induced by 5 days of simulated microgravity (dry immersion): impact on the processes involved in facial expression recognition and on cerebral activity**

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The space environment and microgravity cause changes that may affect the performance of astronauts. Prolonged exposure to weightlessness can lead to significant loss of bone, muscle mass, strength, cardiovascular and sensory-motor deconditioning, immune, hormonal and metabolic changes. However, the influence of microgravity on cognitive processes involved in social interactions, such as facial expression recognition, has received almost no attention despite the crucial role of these processes in collaborative team work and interactions between astronauts. Recognition of these social stimuli relies on mental transformations and in particular on egocentric mental rotations that have been shown to be disrupted in microgravity. Hence, investigation of mental states mediated by facial expressions have almost exclusively focused on basic emotions while most facial expressions in social interactions are non-emotional forms of expressions. Mostly static pictures were used, whereas the dynamic test material including cognitive and emotional expressions used in the present study enabled a more ecological approach. At MEDES, Institute for Space Medicine and Physiology, 20 volunteers experienced for 5 days simulated weightlessness by dry immersion, a model that reproduces most of the effects of microgravity: physical inactivity, thoracocephalic fluid shift and support unloading. We tested the impact of microgravity on recognition of facial expressions (3 primary emotions and 3 complex emotions rotated in 8 different orientations) and its compound processes on such as mental rotation (a digit or a letter presented in different orientations), working memory, inhibition and attention, according a within-subject design (base line; immersion day 1, day 3, day 5; post-immersion) and between-subject design. Half of the participants were tested with a counter measure (wearing a thigh cuff for 12h a day). They should display smaller or insignificant effects on performance as the consequences of microgravity on cerebral blood flow would be prevented. Recognition performance was further explored by concurrent eye-tracking and near-infrared spectroscopy recordings. The results may also shed light on clinical disorders such as vestibular system disorders or social cognition disorders.

**P3.170 Model of the 'place' cell in the retrosplenial cortex and the path integration based on head direction cells**

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The development of Computational modelling and biological neurosciences promote each other in many ways. Inspired by the experiments done by Dun Mao and D.Nitz, we simulate square maze and treadmill experiments to test the performance of a new model where the Path Integration (PI) is modelled by the activation of Head Direction (HD) cells and the velocity of the agent using a classical conditioning mechanism. The activity of the 'place' cell in the retrosplenial cortex (RSC) is simulated by a 2D Kohonen map projected from a one dimension PI field. During the square maze simulation, we test the model with different decay rates(time constant) and different sizes of the HD cell bump. A one-step delay mechanism is added in the simulation of the treadmill experiment to realize the reset of the PI when the agent is fixed running on a linear treadmill rewarded once per lap, the projection on the Kohonen map shows similarity with the activity of the RSC 'place' cell in the biological experiment. A correlation between the performance of PI and the size of the HD cell bump is represented. The size of the bump should be more than half of the turning angle to ensure the precision of the PI. We hypothesize that the rodent will be disoriented under too fast rotation (e.g. turn more than 90 degrees within 0.5 seconds). With these results, we present that the integration of a one dimension HD cell field is capable to build the PI in RSC where the 'place' cell activation can be achieved by the discretization of PI using Kohonen map.

**P3.171 MiRAMINT: modelling RNA-seq time-series data through variable selection and shape analysis narrows miRNA regulation in Huntington's disease mice**

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MicroRNA (miRNA) regulation is believed to play a significant role in modulating Huntington's disease (HD) pathogenesis as supported by studies of individual miRNAs and system level studies of RNA-seq time series data in the allelic series of HD knock-in mice (Hdh mice). Here, we revisited this question by using miRAMINT, a pipeline that combines network, tree-based and shape-matching analyzes for precisely modelling the dynamics of miRNA regulation across multiple conditions. miRAMINT retained a small number of CAG-length- and time-dependent miRNA-mRNA pairs in striatum, including miRNAs and mRNAs previously associated with neuronal development and maintenance and with HD pathogenesis. Data prioritization emphasizes striatal miRNAs of particular interest, e.g. those paired with high-amplitude change of target mRNA levels. No CAG-length-dependent pairs were retained in cortex. The miRNA-mRNA pairs highlighted by miRAMINT differ from those reported in previous bioinformatic analyzes of miRNA regulation in the mouse or human HD brain. These findings strongly suggest that miRNA regulation may have a limited global role in regulating the dynamics of gene expression in the brain of HD mice. These findings provide a precisely-built resource, *i.e.* shape-matched explanatory miRNA-mRNA relationships implicated in neuronal integrity, neurotransmission and cell survival, for investigating how the mouse striatum may dynamically use miRNAs to compute responses to HD.

**P3.172 Virtual experimentation as a testbed to study the relational and informational organization in orbital and medial prefrontal cortex**

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The literature related to the Orbito Frontal Cortex (OFC) is growing rapidly, implicating OFC in numerous cognitive functions (response inhibition, valuation, credit assignment etc.,) and neuronal disorders. Better understanding these functions is crucial in many domains studying human cognition including Neuroscience and Artificial Intelligence. However, a number of ideas that explain OFC function and the data sets used to explain these ideas have been questioned (Stalnaker et al., 2015). This diversity in the proposed OFC functions and the attempts to invalidate them, simultaneously highlight the necessity and importance of designing experiments that allow to challenge the validity of these ideas. Moreover these ideas might have to be studied alongside each other, rather than individually, demonstrating their role in the emerging behavior. We propose a framework to study a variety of such functions in the form of the behavior of an artificial agent in a virtual experimentation environment, the video game Minecraft. This environment has been exploited before to create scenarios in the domain of Artificial Intelligence (Strannegård et al., 2018) and we develop an adaption of it to help test functional hypotheses in the field of neuroscience. Precisely, we attempt to model certain functions of the lateral and the medial OFC (IOFC, mOFC) that have been widely studied and reported (Noonan et al., 2012). We refer to the implications of IOFC in pavlovian responses in the context of multiple stimuli and those of mOFC in making a decision from a reduced number of choices filtered by IOFC. To observe how these roles of OFC fit in the context of emergent behavior, the framework also utilizes functional description grounded in the understanding of the roles of other regions of PFC like Anterior Cingulate Cortex (ACC) and those which form the primitive sensori-motor loops with the basal ganglia. Numerous testable predictions can be made from such a framework that help study each of these regions in detail. The framework is expected to be generic with same learning and decision-making mechanisms operating at different functional levels. Studying such frameworks of cognition also enables a constructive approach to a class of problems related to Artificial Intelligence.

### P3.17 Extracellular action potentials simulation of neuronal populations

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Neural signals are recorded on various spatial and temporal scales. At the cell level, microelectrodes record a mixture of high-frequency components reflecting action potentials (APs) activity and low frequency patterns, mainly attributed to the synaptic currents. Simulating realistic extracellular recordings is a challenge because state of the art [1] methods are based on neuron models having multiple active and passive compartments making the simulation time-consuming.

In [2], we presented a new method to reproduce extracellular signatures of APs based on a geometrical filtering and requiring only once the computation of the neuron dynamics. Here, we propose to evaluate our model to simulate extracellular APs signatures of neural populations. Following [3], 5,000 neurons were simulated and microelectrodes were placed inside the populations. A 10s-simulation takes only 70 seconds on a regular computer.

The enclosed figure illustrates that an action potential signature changes with the electrode position and the axonal propagation delay can be visible. The proposed method could be a useful tool to simulate efficiently neural signals to benchmark spike sorting algorithms or to investigate the variation of the APs waveforms.

[1] Einevoll, G. T. et al. (2013). **Modelling and analysis of local field potentials for studying the function of cortical circuits.** *Nature Reviews Neuroscience*, 14(11), 770.

[2] H.Tran et al, **Simulating extracellular signatures of actions potentials using single compartments neurons and geometrical filtering.** In the 27<sup>th</sup> Computational Neuroscience, Seattle, USA, 2018

[3] Mazzoni, A. et al. (2015). **Computing the local field potential (LFP) from integrate-and-fire network models.** *PLoS computational biology*, 11(12), e1004584.

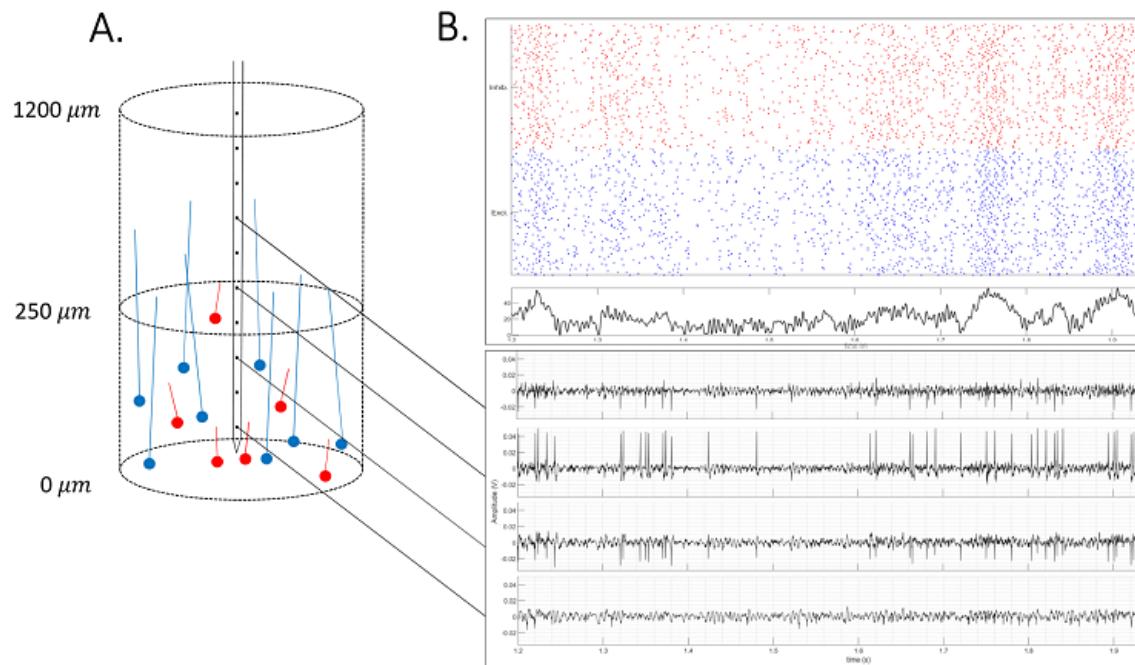


Figure A. Sketch of the 3D network made of two stacked cylinders with 250μm radius and 250μm height.

Figure B. Top. Raster plot of the spiking activity of the populations with the firing rate (black signal).

Bottom. Recordings simulated from four microelectrodes inside the populations.

[Simulation environment, raster plot and simulated signals]

**P3.17 On a toy network of neurons interacting through nonlinear dendritic compartment**

4 Veltz R. (Sophia Antipolis, France)<sup>1</sup>, Fournier N. (Paris, France)<sup>2</sup>, Tanré E. (Sophia Antipolis, France)<sup>3</sup>

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The dendrites of many neurons are endowed with active mechanisms which enable the genesis of local dendritic spikes (DS). The case of the linear dendrite has been intensively studied in the literature [2]. The case of a nonlinear dendrite is much less known especially for its implication of the network dynamics.

In this work, we consider the propagation of DS in a dendrite composed of a single branch. Because the dendrite morphology is modeled after a segment, DS propagate in both directions. Two DS propagating in opposite directions cancel out when they collide because of some ion channels become inactivated after a spike.

We focus on an abstract description of this nonlinear behavior which is more amenable to analysis. This mathematical structure has been supported in [2].

We then consider a network of  $n$  neurons with random connectivity.

When a neuron spikes, it produces two DS on the postsynaptic neurons.

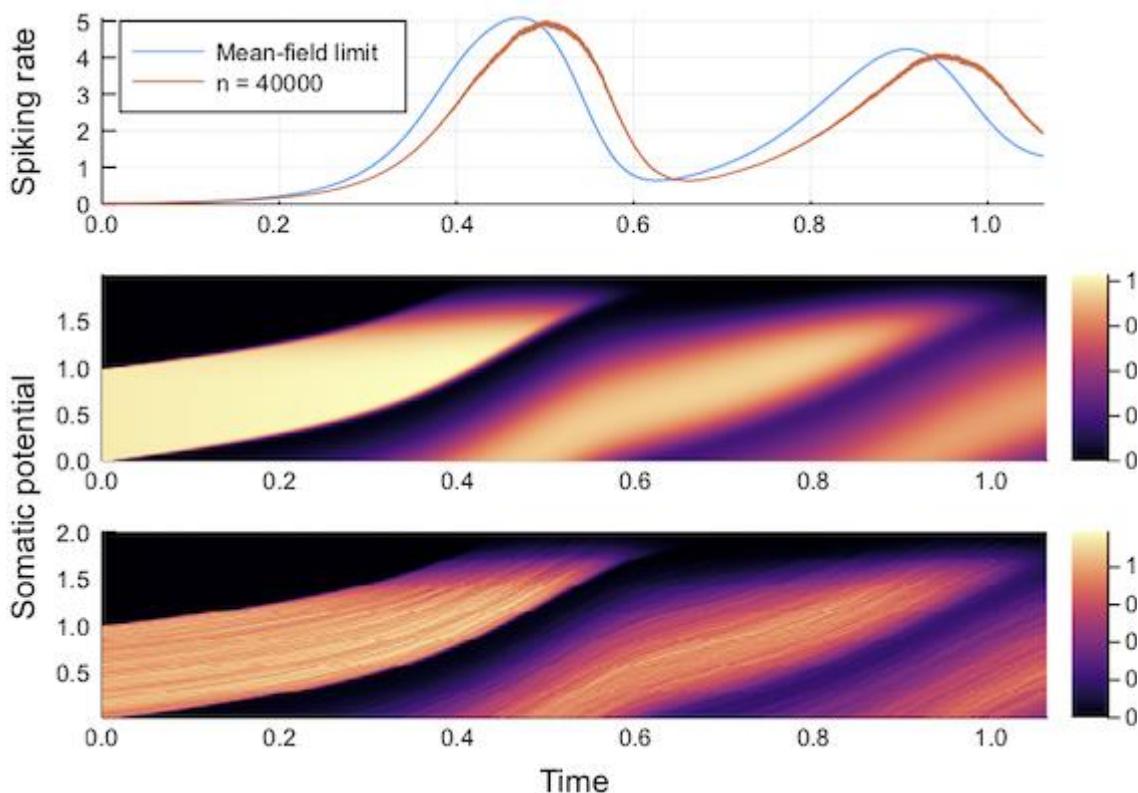
When a DS hits the soma, its potential is increased by a small value  $w_n$ .

The soma dynamics follows a leaky integrate and fire mechanism.

We prove the existence and uniqueness of a heuristically derived mean-field limit of the system when  $n, N \rightarrow \infty$  with  $w_n \sim N^{-1/2}$  unlike the classical  $N^{-1}$  that one sees in usual mean field models.

Numerical simulations are shown in the figure: we show the firing rate for the finite size network and the mean-field prediction.

We also show the distribution of membrane potentials for the mean field model (2nd figure) and for  $n=40000$  neurons.



[net4e4]

This is one of the first work on mean field limits of networks of spiking neurons with a dendritic branch.

**References:**

[1] Bressloff, Coombes. "Synchrony in an Array of Integrate-and-Fire Neurons with Dendritic Structure." PRL 1997

[2] T. Górski, R. Veltz et al "Dendritic sodium spikes endow neurons with inverse firing rate response to correlated synaptic activity" JCN, 2018

**P3.175 Model-based analysis of neural recordings of auditory and prefrontal cortex of mice and hindbrain of zebrafish**

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The availability of large-scale neural optical recordings or multi-electrode make now possible the modelling of the simultaneous activities of tens to thousands of neurons. One promising approach relies on the inference of detailed functional connectivity between the recorded cells, that is, of an effective coupling network reproducing the correlation structure of the spiking events. Another one is based on the inference of restricted Boltzmann machines, a class of graphical model known to learn a compositional representation of the data.

Here we report some recent applications we made of those approaches to

- (i) auditory and
- (ii) prefrontal cortex of mice and
- (iii) rhombencephalon of zebrafish.

i) We follow the changes of effective connectivity in the primary auditory cortex obtained from 2 photon calcium imaging recordings of mice during the learning of an associative behavior.

ii) We extract cell assemblies in the prefrontal cortex from electrophysiological recordings during sleep and follow their coupling modifications before and after a task.

iii) We fit a line attractor model on the calcium recordings of a neural-oscillator located in the rhombocephalon of zebrafish.

In the end, we illustrate how functional coupling networks and restricted Boltzmann machines may be useful to decode complex brain representations, and reveal important feature of neural recordings while building probabilistic models.