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Résumés des présentations orales

PL01 Conférence Paul Broca / Paul Broca Conference

Contact social et représentation sociale dans le cerveau antérieur des rongeurs

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Responses in sensory cortices to simple stimuli have been well characterized, but we are ignorant about how cortical neurons represent the complex sensory patterns evoked by social interactions. We addressed this question in barrel cortex by recording from neurons in rats engaging in social facial touch. A large fraction of barrel cortex neurons responds to facial touch. Whisker trimming abolishes responses. Intact and trimmed stimulus animals, which differ in shape, evoked similar responses, whereas stuffed animals (similar in shape but behaviorally aversive stimuli compared to intact rats) evoked strongly inhibitory responses. Neural activity was sexually dimorphic and mirrored interaction preferences. Males interacted to the same extent with both sexes and male neurons responded similarly and strongly to both sexes. Females interacted preferentially with males. Female neurons responded less than male cells and with an excitation bias to males and an inhibition bias to females. Response patterns could not be predicted by whisker motion parameters. A synopsis of our data suggests that barrel cortex responses represent the behavioral meaning rather than the mechanics of social stimuli. If time permits I will also discuss social representations in other parts of the rodent forebrain.

PL02 Conférence plénière / Plenary lecture

Homéostasie des réservoirs de cellules souches neurales adultes dans le télencéphale du zebrafish

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Neural progenitor cells are maintained life-long in defined germinal zones of the central nervous system of vertebrates, and participate in the generation of neurons and glia during adulthood. Germinal zones host neural stem cells (NSCs), self-renewing and multipotent progenitors situated at the top of the neurogenesis hierarchy. The success of NSC maintenance and mobilization in the adult brain varies widely among species, brain territories, pathological conditions and individual environment, with impact on brain physiology and health.
We aim to gain insight into the molecular and cellular processes controlling the formation and equilibrium of adult NSC pools. We use as a model the dorsal telencephalon (pallium) of the adult zebrafish, which is ideal to reveal novel mechanisms of NSC pools´ homeostasis: it hosts a large ventricular germinal zone directly accessible to experimental manipulations and to live imaging, and is enriched in quiescent but highly activable NSCs. I will discuss (i) the progenitor hierarchies that sustain homeostasis in this NSC pool, (ii) the molecular cascades and cellular interactions that underlie NSC activation, and (iii) the impact of NSC “history” on quiescence and activation properties. We recently identified Notch signaling as a key component controlling homeostasis of the pallial germinal zone, and I will largely focus on this pathway. Our most recent findings combining pharmacological and genetic manipulations support a model where different Notch receptors control the successive steps of NSC recruitment, and implicate Notch3 at the top of this hierarchy to gate

NSC activation and amplification. This molecular mechanism is shared with the activation of muscle satellite SCs and the physiological maintenance of the satellite SC pool size, and we propose that it more generally protects the homeostasis of adult SC reservoirs under physiological conditions. These results will also be presented in the frame of current knowledge on NSC pools´ homeostasis in the adult mammalian brain.

PL03 Conférence plénière / Plenary lecture

Recherche translationnelle pour les dyskinésies dopa-induites dans la maladie de Parkinson

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The objective is to discuss recent achievements in elucidating the molecular mechanisms of L-DOPA-induced dyskinesia (LID) and in targeting these mechanisms for LID management. LID is a side effect of L-DOPA therapy in Parkinson´s disease (PD), manifesting itself as abnormal involuntary movements. Anti-LID therapy has been largely unsuccessful, as it proved difficult to reduce LID and retain antiparkinsonian effect of L-DOPA. Several recent studies proposed different mechanism-based approaches to ameliorate LID. Our group found that in the dyskinetic brain D1 receptor persists on the plasma membrane, instead of being internalized after L-DOPA administration, which increases cAMP production. We will present a series of experiments supporting this claim and experimental demonstrations that removing D1 from the plasma membrane alleviates LID. Targets of interest to be presented include the D3 dopamine receptor, the G protein-coupled receptor kinase 6 (GRK6) and the weak D1 interactor that is postsynaptic density protein 95 (PSD-95) also known as SAP-90 (synapse-associated protein 90). Thus, the seminar concentrates on the mechanisms of the D1 receptor supersensitivity, how this supersensitivity is propagated along the signalling pathways in the striatal neurons, and on the correction of signalling aberrations as novel anti-LID therapy.

PL04 Conférence plénière / Plenary lecture

Des réseaux neuronaux de fréquences distinctes pour l´intégration descendante et ascendante des signaux dans le cerveau

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Visual cortical areas are thought to form a hierarchy and to subserve cognitive functions by interacting in both bottom-up and top-down directions. While this has long been predicted by cognitive psychology, and while the corresponding circuits have been shown by anatomy, the respective inter-areal neurophysiological mechanisms remain largely elusive. I will present electrocorticographic (ECoG) data recorded simultaneously from 252 sites distributed across large parts of one hemisphere in two macaques, spanning from primary visual cortex to prefrontal cortex. Analyses of Granger-causal influences between pairs of areas demonstrate that bottom-up influences are carried by gamma-band (50-90 Hz) synchronization and top-down influences by beta-band (14-18 Hz) synchronization. These beta-gamma influence asymmetries correlate significantly with anatomically defined asymmetries across 20 pairs of areas. We have used this to build a visual cortical hierarchy solely from beta-gamma asymmetries, i.e. from functional rather than anatomical data. This functionally derived hierarchy is very close to anatomically derived hierarchies, yet it might in principle change with cognitive context, and it might be observable in the living human brain. Further analysis of topographical patterns of inter-areal synchronization across the entire hemisphere reveals that a given brain area can participate simultaneously in spatially distinct gamma and beta synchronization networks. These networks are at the same time widespread across the hemisphere and spatially fine grained. Finally, I will show that both, top-down beta-band influences and bottom-up gamma-band influences are enhanced when subserving inter-areal communication that is behaviorally relevant, confirming their functional relevance for effective inter-areal communication.

PL05 Conférence plénière / Plenary lecture

Dynamique de la synapse

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Shank3 is a major post-synaptic scaffolding protein that is mutated in mental retardation and autism spectrum disorders. Expression of this protein is required for formation and maintenance of dendritic spines in cultured hippocampal neurons. Chemically induced long-term potentiation (cLTP) in cultured hippocampal neurons was characterized by an increase in spine size and density, as well as enhanced cell surface targeting of the AMPA receptor GluR1 subunit. These modifications were potentiated by over-expression of Shank3 and RIch2, a new RhoGAP specific of Rac1 that binds to Shank3. Consistent with these results, quantitative single cell BRET microscopy indicated that Shank3-Rich2 complex formation increased during cLTP, in dendritic spines. Conversely, these effects were antagonized by knock-down of Shank3 and/or Rich2 with siRNA, as well as by disruption of the Shank3-Rich2 interaction with a mimetic interfering peptide. These results identify Shank3-Rich2 as a new complex involved in synaptic plasticity.

PL06 Lecture Alfred Fessard / Alfred Fessard Conference

Les singularités d´un système de neurotransmission diffus

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Serotonin (5-HT) neurotransmission is implicated in a large number of physiological functions from the most elemental such as feeding, sleep, to more elaborate such as mood, and learning. As a result, 5-HT dysfunction is implicated in a number of psychiatric disorders such as depression, anxiety, and autism. Developmental mechanisms have major bearings to these neuropsychiatric disorders. The developmental role of 5-HT neurotransmission is one of the clearest example pointing to the fact that genetic or pharmacological manipulations of 5-HT systems during critical periods of development affects neural circuit development, with lasting consequences on behaviour.
In a first part of the talk, we will summarize previous work of the team demonstrating the role of 5-HT in building precise sensory circuits in the somatosensory cortex and the visual system {Gaspar et al. 2003). The underlying molecular mechanisms that were revealed, in particular the role of synaptic versus non-synaptic acitivity for the refinement of brain maps will be discussed. These findings will be placed in the context of human genetic variants of genes that control 5-HT homeostasis (MAOA or SERT).
In a second part of the talk we will present ongoing work of the team on the development of the 5-HTergic raphe neurons with a focus on the individualisation of different anatomo-fucntional subsystems in the raphe. Evidence from our and other laboratories indicates that several different anatomical/physiological subsets of serotoninergic neurons exist in the brain (Gaspar and Lillesaar 2012). Different 5-HT neurons form different neural circuits and are involvved in different functions, for instance in their response to stress. Ongoing studies on the individualisation of different raphe subnuclei, using a combination of anatomical, physiological and behavioural approaches will be presented.
Parsing the 5-HT subsystems is a crucial step in better understanding their developmental roles and the possible side effects of antidepressants in the developing brain (Homberg et al. 2011). This should also help specify the implication of different 5-HT subsystems in anxiety disorders (Fernandez and Gaspar 2012).

PL07 Conférence plénière / Plenary lecture

Les mécanismes neuraux du risque social des maladies psychiatriques

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Mental health and social life are intimately inter-related, as demonstrated by the frequent social deficits of psychiatric patients and the increased rate of psychiatric disorders in people exposed to social environmental adversity. In this lecture, we review emerging evidence that combines epidemiology, social psychology and neuroscience to bring neural mechanisms of social risk factors for mental illness into focus (Meyer-Lindenberg and Tost, Nat Neurosci 2011). In doing so, we discuss existing evidence on the effects of common genetic risk factors in social neural pathways and outline the need for integrative approaches to identify the converging mechanisms of social environmental and genetic risk in brain. Even for highly heritable disorders such as schizophrenia, environmental risk factors are relevant and often have higher associated risk than common genetic variants. Specifically, we discuss neuroimaging work that has begun to define neural mechanisms that might mediate environmental risk factors for schizophrenia, such as unstable social status (Zink et al., 2008), migration, or urbanicity (Lederbogen et al., Nature 2011). Interestingly, the results of this work converge with imaging genetics studies that have characterized risk variants that by themselves show a degree of gene environment interaction or correlation, such as 5-HTTLPR (Pezawas et al., Nat Neurosci 2005) or MAO-A (Meyer-Lindenberg et al., PNAS 2006). This convergence on a systems-level suggests neural mechanisms by which environmental adversity might be reflected in an inability to process negative emotions in the context of the processing of the social environment. This systems-level definition also aids in constraining new approaches to ameliorate environmental risk, either through environmental interventions (Lederbogen et al., Nature 2011) or through molecular approaches such as prosocial neuropeptides (Meyer-Lindenberg et al., Nat Rev Neurosci 2011).

PL08 Conférence plénière / Plenary lecture

Hippocampe et navigation spatiale: que nous disent les cellules de lieu?

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Spatial navigation involves a widespread neural network, which includes head direction and entorhinal grid cell systems, as well as brain structures important for the emergence of goal-directed behaviour, such as prefrontal cortex and striatum. At the core of this network lies the hippocampus and its place cells, discovered more than 40 years ago. When recording from a rat performing spatial navigation, these cells have remarkable functional properties that I will summarize. The stability of place fields is an essential feature of place cells. Nevertheless, place cell discharge can also be extremely variable, a property deemed necessary for ensuring the network flexibility required for efficient coding of spatial information. Furthermore, the discharge of place cells can be time-locked to particular phases of the navigation task (e.g., at goal locations). The firing properties of place cells during goal-directed spatial behaviours help understand the fundamental role of the hippocampus in spatial navigation.

PL09 Conférence plénière / Plenary lecture

Comprendre les relations entre gènes et comportement chez les oiseaux chanteurs : parallèles avec la parole et le langage chez l´homme

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The evolution of human language has been discussed for centuries from different perspectives. Linguistic theory has proposed grammar as a core part of human language, and equivalents to human grammar have not been described in non-human animals. However, other components of language also exist in animals. For instance, spoken language and birdsong share a number of striking parallels. I will summarize the biologically tractable cognitive abilities necessary for spoken language and for birdsong and argue that the similarities are not limited to sensorimotor processes - but may extend to

the conceptual and computational systems. I will review evidence for the relevance of the *FoxP2* gene and its associated molecular network for language, its role in the acquisition and production of birdsong, as well as for particular behaviors in mice, bats and fruit flies. Many questions regarding the similarities between spoken language and birdsong remain unanswered, but increasing evidence suggests that human and non-human communication systems may rely on conserved molecular toolkits that act as genetic modules. These may specify the neural circuits subserving these particular behaviors, and organize their function. Elucidating these genetic modules in different animal models promises insights into the evolution of language and other complex traits. The emerging data can help us understand how complex cognitive traits can ´descend with modification´.

PL10 Conférence plénière / Plenary lecture

L´amygdale et la reconsolidation des mémoires de la peur et des drogues d´abus

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Consolidated memories can, under some circumstances, become labile - or destabilised - at retrieval and must undergo a restabilisation process to persist in the brain. This restabilization process has become known as reconsolidation, a disruption of which leads to amnesia. I will discuss experiments using psychologically well-characterised behavioural procedures, which have demonstrated a requirement for a specific protein, ZIF268, (the protein product of the immediate-early gene *zif268*) in the amygdala in the reconsolidation of cued fear and drug memories. For example, infusion of Zif268 antisense oligodeoxynucleotides into the basolateral amygdala, prior to the conditioned stimulus (CS) presentation-evoked reactivation of a fear memory results in the loss of fear following subsequent presentation of the fear CS. Knockdown of the same gene at the reactivation of a CS-cocaine memory results in the loss subsequently of the acquired conditioned reinforcing and other properties of the drug-associated CS and a reduction in drug seeking, thereby preventing relapse. Antagonism of glutamate transmission at NMDA receptors or adrenergic transmission at ß-adrenoceptors also prevents the reconsolidation of CS-fear and CS-drug memories and, in the case of NMDA receptor blockade, this is associated with reduced expression of *zif268* in the amygdala, suggesting a link between neurotransmission events and intracellular signaling that are engaged at memory retrieval and result in restabilisation of the memory. These experimental data suggest the possible utility of targeting reconsolidation in the treatment of neuropsychiatric disorders that are characterized by maladaptive and intrusive memories. These include prost-traumatic stress disorder as well as drug addiction in which drug-associated stimuli evoke memories of prior drug use, craving and relapse to drug use.

Symposia

S01 Rôle des connexines gliales dans la signalisation et la pathologie du système nerveux central. / Impact of glial connexins in brain signalling and pathology.

S01.1
Approches génétiques pour étudier les fonctions biologiques des connexines gliales

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Most astrocytes express Connexin(Cx)43 and Cx30, whereas oligodendrocytes express Cx47 and Cx32. Intercellular coupling between astrocytes and oligodendrocytes depends on heterotypic gap junctional channels which are composed of two different connexin proteins, i.e. a distinct Cx isoform in each connexin hemichannel (connexon). Using double Cx30/Cx47 deficient mouse mutants we have previously reported that these glial connexin proteins are required for the maintenance of myelin in the central nervous system (Tress et al., J. Neurosci. 32, 7499 - 7518 (2012)).
Recently we have discovered a new mechanism by which the expression of oligodendrocytic Cx47 in mouse brain is dependent on the expression of Cx43 in astrocytes. Gap junction channel - inactive Cx43 protein can also execute this effect. Our results illuminate the complexity of the functional panglial gap junctional network and indicate that the conclusions drawn from earlier studies using astrocytic Cx43 deficient mice need to be reconsidered.

S01.2
Réseaux et interactions neurone-glie dans les glomérules olfactifs

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While the role played by astrocytes in synaptic transmission has now largely been documented, their contribution to network activities only starts to be appreciated. A typical feature of astrocytes is their high rate of connexin expression (Cx43 and Cx30), the molecular basis for gap junctional communication and hemichannel (HC) formation. Even though connexin-formed HCs have been shown to be permeable to several neuroactive compounds, their role in physiological conditions has largely been unexplored. We thus question whether the function of Cx-based HCs in astrocytes has an impact on neuronal network behaviors in the mouse olfactory bulb (OB).
In OB acute slices, we observed that the membrane potential of mitral cells (MCs) alternates between a DOWN (hyperpolarized, silent) and an UP (depolarized, spiking) state at a slow frequency (~0.2Hz), resembling slow oscillations observed in cortical neurons during slow-wave sleep. Such alternations were inhibited by a pharmalogical blockage of glutamatergic transmission and correlated with the local field potential monitored within the corresponding glomerulus, highlighting a network effect.
Interestingly, this spontaneous neuronal activity induced the opening of Cx HCs in astrocytes as shown by ethidium bromide uptake assays. We then asked whether such astroglial HC activity can in turn impact on the slow network activity, using knock-out (KO) mice for astroglial Cxs. In absence of Cx43, but not Cx30, MCs showed significant decrease in UP state amplitude compared to control. This alteration was mimicked by a blockage of Cx43 HCs, pointing out the role played by Cx43 HC function in the modulation of MC UP and DOWN states. Importantly, we found that this effect requires the activation of adenosine A1 receptors, likely *via* ATP release by astrocytes through Cx43 HCs. These results suggest that Cx43 HC function in astrocytes is promoted by neuronal activity, and in turn modulates neuronal network activity. Such bidirectional neuroglial interactions could play an important role in olfactory information processing.
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S01.3

Potassium extracellulaire, signalisation astrocytaire et canaux formés par les connexines et les pannexines

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To achieve long distance intercellular communication, astrocytes utilize two major pathways: direct gap junction mediated signal transmission and the release of ATP through pannexin1 channels. Elevated extracellular potassium of the magnitude occurring during periods of high neuronal activity affects both gap junction and pannexin1 channels. The action on Cx43 gap junctions is to increase intercellular coupling for a period that long outlasts the stimulus. Pannexin1 can be activated by elevations in extracellular potassium through a mechanism that involves alteration in activation voltage, thereby allowing channel opening at resting potentials. The impact of enhanced activity of both these channel types by elevations in extracellular potassium will be discussed, particularly the role of Panx1-mediated paracrine signaling to seizures.

S01.4

Rôle central des jonctions communicantes dans l´épileptogénèse

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Glial cells are now recognized as active communication partners in the CNS, and this new perspective has rekindled the question of their role in pathology. We observe unusual immunohistochemical and functional phenotypes of glial cells surviving in the sclerotic hippocampus (HS) of patients with temporal lobe epilepsy (TLE), including a complete loss of gap junction coupling. It is, however, unclear whether these changes reflect the cause, effect or adaptive response in the progression of epilepsy. To investigate temporal aspects of glial dysfunction during epileptogenesis we established a mouse model of epilepsy (intracortical kainate injections) which reflects many key aspects of human TLE. Changes in interastrocytic coupling were assessed by tracer diffusion studies in acute slices at different time points post status epilepticus. These studies revealed a pronounced reduction of coupling before onset of neuronal death and hyperactivity and a complete loss of coupling during the chronic phase, providing strong evidence that this dysfunction is a crucial factor in epileptogenesis. Mechanistically, pro-inflammatory molecules appeared to cause the uncoupling, since no seizure-induced reduction of coupling could be found in toll-like receptor 4 knockout mice. Moreover, induction of inflammation by LPS injection as well as incubation of acute slices with inflammatory cytokines resulted in a comparable inhibition of astrocytic communication. Fate mapping studies revealed that astrocytes in HS do not transdifferentiate into another cell type but rather acquire another functional phenotype. These data challenge the common view of epileptogenesis according to which changes in neurons are considered the prime cause of this condition.
Supported by Deutsche Forschungsgemeinschaft (SFB/TR3) and the European Commission (FP7-202167 N*eu*roGLIA).

S01.5

Les réseaux astrocytaires sont affectés par des changements dans le cycle veille-sommeil

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Astrocytes are important modulators of neuronal activity through a variety of mechanisms such as neurotransmitter uptake, 'gliotransmitters' release, potassium buffering and metabolic supply. Astrocytes have been show to play a role in the modulation of sleep. Besides mechanisms at the cellular level, we are interested in the action of astrocytes in sleep-wake cycle at the network level. Astrocytes form networks of communicating cells via gap junction channels, which are constituted by connexins (Cxs). To investigate whether astroglial networks are involved in the regulation of sleep-wake cycle, we use pharmacological treatment and sleep deprivation to manipulate sleep-wake status

and examine if astroglial networks would change in response. The networks were revealed and measured by loading of a patch-clamped astrocyte with a fluorescent dye and monitoring intercellular diffusion of the dye into neighboring astrocytes through gap junctions. Also, Cxs expression was measured as a parameter of the level of connections among astrocytes. The results are as follows. First, I.P. injection of modafinil, a potent wakefulness-promoting drug, increased both mRNA and protein expression of Cx30 in the mouse cortex. Superfusion of modafinil also enhanced dye coupling among astrocytes in acute coronal slices of the mouse somatosensory cortex. This effect was abolished by TTX treatment, which implicates involvement of neuronal activity. In contrast, γ-Hydroxybutyric acid (GHB), a sleep-promoting agent, propofol and ketamine, two general anesthetics, decreased astroglial coupling in cortical slices. Next, we used a gentle sleep deprivation model to deprive mice of sleep for 6 hours. As a result, mRNA of Cx30 but not Cx43 was increased in both cortex and the hippocampus. Dye coupling of astrocytes in cortical slices was enhanced as well in mice after sleep deprivation compared to mice after normal sleep. This increase in dye coupling, however, was not observed in Cx30 knockout mice after the same sleep deprivation treatment. The results above implicate that astroglial networks are bidirectionally regulated by pertubations in sleep-wake cycle and that Cx30 is the major Cx sensitive to such changes.
Supported by the ANR-12-BSV4-0013-01

S02 Mécanismes présynaptiques impliqués dans les synaptopathies. / Update on presynaptic contributions to synaptopathies.

S02.1

Régulation des processus pathologiques par le transporteur vésiculaire de glutamate atypique, VGLUT3

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Glutamate is the major excitatory neurotransmitter in the brain. Before its exocytotic release, glutamate is accumulated into synaptic vesicles by proton-driven transporters named VGLUT1-3. VGLUT1 and VGLUT2 are expressed by cortical and subcortical (respectively) glutamatergic neurons. VGLUT1 and VGLUT2 are functional and anatomical markers of canonical glutamatergic neurons. In contrast, VGLUT3 is found in discrete populations of neurons releasing other transmitters than glutamate such as: cholinergic interneurons from the dorsal and ventral striatum, subpopulations of GABAergic basket cells from the hippocampus or the cortex and serotoninergic neurons from raphe nuclei. We have recently established that VGLUT3 and the vesicular acetylcholine transporter (VAChT) are present on the same synaptic vesicles. As a consequence, VGLUT3 accelerates vesicular filling and release of acetylcholine in striatal cholinergic interneurons. Through this new presynaptic regulatory mechanism (named: vesicular synergy), glutamate accelerates striatal cholinergic vesicular accumulation. Consequently, mice lacking VGLUT3 (VGLUT3-KO) show a decreased cholinergic transmission. We also observed that VGLUT3 regulates locomotor activity and sensitivity to substance of abuse such as cocaine. Moreover, VGLUT3 colocalizes with 5-HT and VMAT2 (the vesicular monoamine transporter type 2) in subpopulations of 5-HT terminals from the hippocampus and the limbic cortex. As reported in cholinergic interneurons, glutamate and VGLUT3 stimulates 5-HT accumulation in hippocampal and cortical synaptic vesicles. The loss of VGLUT3 results in a marked decrease of 5-HT outflow in the hippocampus. VGLUT3-KO do not avoid social interactions neither do they show aggressive behavior. However, VGLUT3 deletion markedly increase anxiety-related behaviors. These results unravel the existence of subclasses of VGLUT3-positive 5-HT terminals in limbic areas that play a crucial role in anxiety-like behaviors. Thus, glutamate, through VGLUT3 modulate 5-HT and ACh transmission as well as related behaviors. Thus VGLUT3 could impact on normal and pathological processes such as locomotor activity, reward/addiction, anxiety and mood regulation.

S02.2

Analyse fonctionnelle du rôle de VGLUT2 dans les neurones dopaminergiques du système central de récompense

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The mesostriatal dopamine (DA) system contributes to several aspects of responses to rewarding substances and is thus heavily implicated in conditions such as substance dependence [1]. Subpopulations of midbrain DA neurons express *Vglut2* and have been implicated in reward-related behavior [2]. We recently addressed the functional significance of the glutamate/DA cophenotype by analyzing mice lacking VGLUT2 in DA neurons in an operant self-administration paradigm for cocaine [3]. Operant response to high- and low-sucrose food was also analyzed, as were biochemical parameters of striatal DA function using by DA-selective *in vivo* chronoamperometry and DA receptor autoradiography. Mice in which *Vglut2* expression in DA neurons had been abrogated displayed a strongly increased operant self-administration of both high-sucrose food and intravenous cocaine, yet their consumption of low-sucrose food was unaltered. Cocaine-seeking maintained by cocaine-paired cues was strongly increased, indicating an effect on reward-dependent plasticity. This study showed that targeted loss of *Vglut2* expression leads to alteration in reward consumption and reward-associated memory formation, features of relevance for substance dependence [3]. To further pinpoint the role of VGLUT2-mediated signaling from neurons on the VTA, we are currently analyzing neural activity and neurotransmitter release in response to various kinds of stimulation in different paradigms of reward-associated behaviour.

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S02.3

Régulation de la balance excitation/inhibition par MeCP2

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Rett syndrome (RTT) is a progressive childhood neurodevelopmental disorder and shows features of impaired social interactions, but also neurological symptoms associated to dysbalanced excitation-inhibition balance in neural circuits. RTT is caused by mutations in the transcriptional regulator MeCP2. We use MeCP2 deficient murine neurons in culture to study the primary deficits of MeCP2 loss on synaptic function and -connectivity, and how this affect the synaptic interaction of glutamatergic and GABAergic neurons.

S02.4

Dysfonctionnements synaptiques et maladies psychiatriques

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Psychiatric disorders are among the most frequent and devastating disorders. According to the World Health Organisation, they represent the second leading cause of disability in the world and risk to reach the first place by 2020. Although twin and adoption studies suggest a strong influence of genetic factors to the vulnerability to psychiatric disorders, only few couples of genes have been reported to be altered in patients with mental illnesses yet. Recent genetic data suggest dysfunction of synaptic mechanisms in vulnerability to many psychiatric disorders. However, no evidence of specificity has been found yet between genes and one of the major psychiatric disorders, suggesting the existence of shared genetic vulnerability pattern for most of them. Here, we will use singular examples to show how a single gene can be considered as a good candidate for vulnerability to various psychiatric disorders. We will describe the genetic exploration of common and rare variations in candidate genes in patients and control subjects as well as how cellular and animal models can shed light on the pathophysiology of mental illnesses.

S02.5
Déficits des fonctions pré-synaptiques dans les retards mentaux d´origine génétique

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Although mutations in more than 80 human X-linked genes are associated with intellectual disabilities (ID), a condition characterized by deficits in learning and memory, little is known about the role of most ID-genes in synaptic function and plasticity. Here, we show that mice deficient for X-linked ID-genes oligophrenin1 (*ophn1*), ribosomal S6 kinase 2 (*rsk2*) and interleukin-1 receptor accessory protein-like 1 (*il1rapl1*) exhibit a selective deficit in presynaptic, but not postsynaptic, long-term potentiation (LTP) in the lateral amygdala. In all three models, the deficit in presynaptic LTP was caused by the selective uncoupling of evoked, but not spontaneous, glutamate release from cAMP signaling, one of the major regulatory signaling pathways in presynaptic function. Our data identify a deficit of presynaptic LTP as a key physiological signature in a subset of X-linked ID models. The talk will also describe how multi-scale strategies can help in the understanding of pathophysiology of ID.

S03 Cellules et circuits pour le codage des cartes spatiales. / Cells and circuits for the coding of spatial maps.

S03.1
Intégration de l´information contextuelle par les cellules de lieu et les cellules de grille

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Place cells are hippocampal neurons that are selectively active when an animal visits a particular location in the environment: however, their activity is context-sensitive, being modulated by environmental features such as colour and odour. This modulation has two cardinal features it is *heterogeneous* (different cells respond differently) and it is *configural* (the cells respond to unique combinations of contextual features), indicating convergence of this featural information upstream of the place cells themselves.
Our interest is in how the place cells piece together the information that allows this contextually modulated responding. Place cells receive information from grid cells, in the dorsomedial entorhinal cortex, which show activity that forms a spatially regular array, in a hexagonal close-packed

arrangement known as a grid. Unlike place cells, grid cells are active in every environment, although a grid can shift and/or rotate when the environment is changed. We investigated whether place cells might inherit their heterogeneous and configural response properties from grid cells, by recording in boxes that could be changed in visual appearance between black and white, and changed in odour between lemon and vanilla. We found that grid cell responding was also configural, but was homogeneous (when one grid cell shifted its firing, other simultaneously recorded cells did so too). Furthermore, place cells showed considerably more sensitivity to visual changes than did grid cells. These two observations imply that place cells "know" things about the environment that grid cells do not, suggesting that there may be a convergent contextual input onto place cells independent of the grid cells. We are currently employing immediate-early gene imaging to try and determine the source of this input, in order to clarify how place and grid cells collectively process the sensory information that allows unique identification both of a spatial context and of the animal´s position within it.

S03.2

Caractéristiques de l´activité intracellulaire des cellules de lieu dans un nouvel environnement

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The hippocampus is critically involved in coding and storing spatial informations. During spatial exploration, hippocampal principal cells fire action potentials only when an animal visit a particular location in its environment and are hence called place cells. Only ~1/3 of hippocampal cells are place cells in a given environment while the majority of them remain silent in the entire environment (the silent cells). Thus information about a given environment is not only represented by the place selective firing of place cells but also by which cell is active versus silent in that environment. Despite 40 years of research, the intracellular factors leading to the selective activation of a subgroup of place cells in a given environment are still unknown. To address this question, we performed whole-cell patch-clamp recordings of hippocampal neurons in rats freely exploring a new environment using the head anchoring technique (Lee et al., 2006; 2009). We report a dichotomy in the membrane potential (Vm) behavior between place and silent cells. While the Vm of place cells showed a unique sustained depolarisation in the place field, the Vm of silent cells remained flat and far away from threshold in every location of the environment. Furthermore, in place but not silent cells, we recorded a high incidence of specific intracellular events such as spikelets and plateau potentials which strongly contributed to their place selective firing. Place and silent cells also differed in several intrinsic properties such as the firing threshold, firing burst propensity and baseline Vm. Altogether, these results suggest the involvement of intrinsic conductances, in addition to synaptic inputs, in the selective activation of place versus silent cells. Surprisingly, some intrinsic differences between place and silent cells could be detected even before the new exploration began. Therefore, based on their intrinsic properties, a subset of hippocampal cells could be pre-selected to map and potentially memorize the next explored environment.

S03.3

Dynamiques oscillatoires dans les circuits entorhino-hippocampiques

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Population representation of spatial memories in hippocampus exhibits complex spatio-temporal dynamics. It is likely that understanding mechanistic origin of this dynamics and link to animal behaviour is the key to understanding the code. To this end we investigate the role of gamma synchronization dynamics across entorhino-hippocampal system and ongoing exploratory behaviour of the rat as dynamics contributors to the population coding in hippocampus. We show how dynamic changes in gamma synchronization and exploratory behaviour affect hippocampal activity.

S03.4

Rôle des interneurones hippocampiques dans l´apprentissage spatial

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In the hippocampus, the cognitive map of place cells can help animals to solve spatial learning tasks though preferentially encoding goal locations. Interneuron circuits are thought to shape the firing field of place cells and they may be instrumental in new map formation. We performed a spatial learning task in a cheeseboard maze, which led to the formation of new place maps incorporating the location of the new reward locations. We found that some CA1 interneurons developed associations with the newly-formed maps through selectively increasing or decreasing their activity when the new pyramidal maps were present. Moreover, in using cross-correlation analysis, we have identified monosynaptically connected pyramidal interneuron pairs and measured spike transmission probability to estimate their connection strength. This analysis suggested a dynamic reconfiguration of interneuron circuits: changes in the connection weight between interneurons and pyramidal cells were detected, which mirrored the firing associations of interneurons to the pyramidal assemblies. Our results suggest that spatial learning is associated with inhibitory circuit modifications in the hippocampus that might assist in the segregation of competing pyramidal cell assembly patterns in space and time.

S03.5

Les troubles cognitifs dans l´épilepsie: implication des oscillations et de la synchronie neuronale

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Multiple epilepsy syndromes, including migration disorders and channelopathies are associated with GABAergic neuron abnormalities. In addition to the seizures resulting from loss of inhibition, these syndromes are also characterized by pronounced cognitive and behavioral impairments. Dravet syndrome is a severe childhood epilepsy disorder with profound cognitive deficits. It is associated with a mutation of the voltage gated sodium channel $Na_v1.1$ and results in a selective impairment of fast spiking GABAergic neurons in-vitro. Although seizures per se have a negative impact on cognitive function, the degree of impairment is not always correlated with the frequency and severity of the seizures, suggesting that other factors may be involved.
To understand the mechanisms responsible for cognitive dysfunction in Dravet syndrome, we developed an RNA interference approach allowing us to specifically down-regulate Nav1.1 in a single brain structure and therefore avoid seizures, ataxia and premature death, which are common in transgenic models of this syndrome. Via lentivirus delivery, we were able to decrease Nav1.1 expression in the medial septum, a structure at the origin of theta rhythm (5-12Hz) in the hippocampus. Single unit and EEG recordings were simultaneously recorded as rats performed a spatial and object recognition tasks. This down-regulation was associated with a specific alteration of fast spiking firing in the medial septum, a decrease of hippocampal theta frequency and a specific impairment in the spatial but not the object recognition task. No seizure was observed in continuous 48h EEG monitoring.
These results suggest that cognitive deficits in Dravet syndrome are in part due to oscillatory activity alterations caused by GABAergic neuron impairments.

S04 Approche transnosographique de la relation impulsivité / compulsivité dans les pathologies neuropsychiatriques / Transnosological approach of impulsive / compulsive relationships in neuropsychiatric disorders.

S04.1

Effets secondaires non-moteurs des traitements dopaminergiques dans les modèles expérimentaux de maladie de Parkinson

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Symptomatic treatment of Parkinson's disease (PD) with chronic dopamine replacement therapy (DRT) has important limits such as motor and non-motor side-effects. The latter include the dopamine dysregulation syndrome, impulse control disorders and dopamine agonist withdrawal syndrome.

Available evidence indicates an interaction between DRT and an underlying individual susceptibility, together with a potential facilitative role of the degenerative process of PD. However, the exact mechanisms and the respective contributions of the DRT, the disease process and individual susceptibility are unknown.
To address some of these issues, we assessed the reinforcing and motivational properties of DRT in experimental models of PD. Sham and bilaterally 6-OHDA lesioned rats were allowed to self-administer the dopamine agonist pramipexole (PPX). While lesioned rats were slower than sham rats in acquiring self-administration behavior, they later reached the same level of intake. PPX heightened deltaFosB expression in the striatum with a involvement of different striatal subregions between groups The reinforcing value of PPX was moderate in both groups but a subset of animals displayed a high number of responses and appeared to be particularly sensitive to this drug.
The rewarding properties of levodopa were tested using conditioned place preference (CPP) in a bilateral alpha-synuclein rat model of PD. Though L-Dopa had no effects in sham rats a significant CPP was observed exclusively in lesioned animals, indicating that dopaminergic loss is mandatory for the expression of the rewarding properties of this drug. In addition, L-Dopa decreased the animals' interest in other nondrug reward (saccharin) only in lesioned rats without affecting their appetency for sweet taste or discrimination capacities.
These results show that drug-naïve rats self-administer PPX and that the dopaminergic lesion doesn't affect its reinforcing effects. Conversely, the acquisition of “psychostimulant-like” properties of L-Dopa requires a dopaminergic lesion. The existence of high responders to PPX calls for further investigating the differential individual vulnerability, as it appears to be an important contribution to the non-motor side-effects of DRT.

S04.2

Le spectre impulsif-compulsif dans la maladie de Parkinson : impact de la médication et de la neurostimulation

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective therapy for treating motor fluctuations and dyskinesias in advanced Parkinson's disease. DBS is thought to reduce the excessive glutamatergic drive of the STN to the output nuclei of the basal ganglia (internal globus pallidus and substantia nigra and to release these structures from abnormal information flow. Succesful STN-DBS can mimic the best motor ON-state induced by levodopa. Because stimulation acts synergistically with medication, dopaminergic drugs are markedly reduced in most patients after surgery.
Neuropsychiatric symptoms are not uncommon in the postoperative period. Depression, anhedonia, compulsive behavior or apathy have been reported in up to 20% of the patients and are often linked to excessive withdrawal of dopaminergic drugs. Hypomania or mania may be present in 3-5% of the patients. The STN is part of a limbic and frontal-associative loop, which run in parallel with the motor loop. Unintended current spread into the limbic areas of the STN may be responsible for some of the disinhibitory psychic effects of DBS.
This lecture summarizes the clinical and experimental data on neuropsychiatric adverse effects of STN-DBS and discusses the complex interaction between medication and stimulation in their origin. The concept of a “U-shape” dose-response relationship for medication and stimulation is introduced, which for the limbic system results in typical “hypo-“ or “hyperdopaminergic” behaviors, if not optimally tuned.

S04.3

Locus neurobiologique de la dénervation dopaminergique dans un modèle rat de la maladie de Parkinson: un nouvel endophénotype de vulnérabilité aux déficits de la motivation

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Parkinson´s Disease (PD) involves the degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) that is thought to cause the classical motor symptoms of this disease. However, motivational and affective impairments are also often observed in PD patients. These are usually attributed to a psychological reaction to the general motor impairment or to a loss of some of

the neurons within the ventral tegmental area (VTA). We induced selective lesions of the VTA and SNc DA neurons in rats that did not provoke motor deficits, and showed that bilateral dopamine loss within the SNc, but not within the VTA, was predictive of motivational deficits and affective impairments that mimicked the symptoms of PD patients. Importantly, these deficits were reversed by DA pharmacological treatments commonly used in PD, pointing toward a crucial therapeutical role of D2/D3 receptors. Thus, motivational and affective deficits are a core impairment of PD, as they stem from the loss of the major group of neurons that degenerates in this disease (DA SNc neurons) and are independent of motor deficits. This new insight into the pathophysiological mechanisms of mood and motivational dysfunctions in PD will facilitate the design of new treatments.

S04.4

Nouveaux bio-marqueurs associés à l´impulsivité chez le rat: implication pour le TADA et l´addiction

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Pathological forms of impulsivity are manifest in a number of psychiatric disorders listed in DSM-IV, including attention-deficit hyperactivity disorder and addiction. However, the molecular and cellular substrates of impulsivity are poorly understood. Prior research indicates that highly impulsive rats on a five-choice serial reaction time task are prone to escalate intravenous cocaine self-administration, following repeated intermittent access, and more readily develop compulsive patterns of cocaine seeking than low impulsive rats. The neurotransmitter dopamine is strongly implicated in such behaviour. However, recent research indicates that whilst dopamine D2/D3 receptors in the ventral striatum, including the nucleus accumbens, inversely predict impulsive responding, the role of dopamine in this region is unlikely to account for the full complexity of this particular form of impulsive behaviour. Evidence will be presented demonstrating the existence of structural and neuronal markers in the core sub-region of the nucleus accumbens that strongly implicate GABA-ergic mechanisms in the expression of impulsivity on the 5-choice task. In addition, the results of recent neurophysiological investigations and a genome-wide association study will be presented, which collectively demonstrate that trait-like impulsivity on the 5-choice task is heritable and underpinned by a complex array of dopaminergic and non-dopaminergic biomarkers that may prove tractable for the development of new therapies for clinical disorders of impulse control.

S04.5

Approche transnosographique des relations impulsivité / compulsivité dans les désordres neuropsychiatriques: apport des études précliniques

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The factors contributing the the development and the severity of compulsive spectrum disorders, such as Obsessive Compulsive Disorder, Tourette's syndrome, Pathological Gambling, addictions or dopamine dysregulation syndrome in Parkinson Disease, remain poorly understood, thereby limiting the development of therapeutic and preventive strategies. Recent evidence suggests that impulse control deficits may contribute to the severity of compulsivity in various of these compulsive disorders. This suggests that impulsivity may be an trans-nosological endophenotype of vulnerability to compulsivity. If this has been demonstrated to be the case in the field of drug addiction, impulsivity and compulsivity are multifaceted constructs and, to date, the nature of their relationships in other, anxiety-related, compulsive disorders remains unknown. We therefore provide an update of the recent advances in the understanding of the dynamic interactions between impulsivity and various behavioural expressions of compulsivity in preclinical and clinical models. The presented experimental work provides insights into the reciprocal influence of impulsivity and compulsivity in compulsive disorders but they may also account for the apparent lack of dimensional relationship between impulsivity and compulsivity in clinical studies.
This work is supported by the INSERM, the University of Poitiers, the FRM, the Fyssen Foundation, the ANR and the IREB.

S05 Nouveaux mécanismes dans la régulation centrale du métabolisme. / Novel brain mechanisms in metabolic regulation.

S05.1
Pas de résumé

S05.2
Systèmes intracellulaires senseurs d´énergie et régulation de la balance énergétique

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Similar to individual cells, hypothalamic neural circuits profit from intracellular pathways known to work as fuel sensors to maintain energy balance.
The mammalian target of rapamycin complex 1(mTORC1) signaling cascade is among the latest intracellular fuel-sensing pathways to be implicated in the hypothalamic regulation of energy balance. mTORC1 activity is found in both NPY/AgRP- and POMC-producing neurons of the arcuate nucleus. Activation of mTORC1 and phosphorylation of its downstream targets are critical intracellular steps mediating the anorectic actions of both nutrients, such as amino acids, and hormonal signals like leptin. Interestingly, mTORC1 activity in the mediobasal hypothalamus varies as a function of the cell type and of the particular stimulus employed, as opposed to responding in a uniform manner to nutritional and hormonal changes. Furthermore, a link exists between intracellular fatty acid metabolism and mTORC1 and recent studies have shown that high-fat feeding and diet-induced obesity are conditions leading to the impairment of mTORC1 activity in the hypothalamus.
Here we will give an overview of the known functions of this pathway in the context of energy balance regulation and we will further present downstream mechanisms that we have recently identified to be engaged by mTORC1 for the control of food intake and body weight.
Taken together, these findings lead to conclude that mTORC1 is a highly conserved fuel sensor, which integrates signals from both stored and immediately available fuels and whose activity in the hypothalamus triggers adaptive feeding responses.

S05.3
Autophagie, hypothalamus et obésité

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One of the brain´s core functions is to help the body maintain homeostasis. The hypothalamus plays an essential role in this function by ensuring that physiological responses remain in tune with environmental demands. Accordingly, the regulation of hypothalamic circuits is influenced by signals that carry information about nutritional and metabolic states. However, the exact nature of metabolic-sensing pathways that are involved in in this process remains largely unknown. This talk will provide an overview of recent evidence concerning the role autophagy, an central metabolic sensor involved in the degradation of misfolded proteins and organelles, in influencing the development and activity of various hypothalamic circuits that regulate feeding behavior and energy balance.

S05.4
Rôle des tanycytes dans le contrôle de l´accès des molécules périphériques au cerveau métabolique

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The delivery of blood-borne molecules conveying metabolic information to neural networks that regulate energy homeostasis is restricted by brain barriers. The fenestrated endothelium of median eminence microvessels and tight junctions between tanycytes together compose one of these. Here, we show that the decrease in blood glucose levels during fasting alters the structural organization of this blood-hypothalamus barrier, resulting in the improved access of metabolic substrates to the arcuate nucleus. These changes are mimicked by 2-deoxyglucose-induced glucoprivation and

reversed by raising blood glucose levels after fasting. Furthermore, we show that VEGF-A expression in tanycytes modulates these barrier properties. The neutralization of VEGF signaling blocks fasting-induced barrier remodeling and significantly impairs the physiological response to refeeding. These results implicate glucose in the control of blood-hypothalamus exchanges through a VEGF-dependent mechanism, and demonstrate a hitherto unappreciated role for tanycytes and the permeable microvessels associated with them in the adaptive metabolic response to fasting.

S05.5
Implication du système serotoninergique dans les troubles du comportement alimentaire

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Feeding anomalies are often attributed to deficits of the homeostasic regulation, but much less to a deficit in decision-making to eat. However, in a stressful context, pathologic decision may, trigger the brain to persistently inhibit feeding despite mounting energy requirements. Little is known about the neuronal mechanisms associated with decision-making, except that choice depends on the hyperactivity of dorsal raphé nucleus (DRN) serotonergic neurons induced by the medial prefrontal cortex (mPFC). Here, we show that the serotonin 4 receptors (5-HTR_4) in the mPFC are required to cause hypophagia following stress. We previously found that the 5-HTR_4 knock - out (KO) abnormally persist to eat in response to stress, which is associated with an impaired activity of DRN 5-HT system. Here, siRNA-mediated 5-HTR_4 knock - down in the mPFC mimicked the behavioral and neuronal KO phenotype. The viral 5-HTR_4 knock - up in the mPFC of 5-HTR_4 KO has restored the feeding and DRN 5-HT responses to stress in the KO. Using a large spectrum of techniques, we conclude that stress triggers the stimulation of cortical 5-HTR_4, reduces the density of DRN 5-HT transporter, which promotes an increased level of DRN 5-HT in the synaptic cleft. The DRN 5-HT next stimulates 5-HTR_{1A} and avoids that hypophagia becomes anorexia after stress. Collectively, our findings support that the neuronal network of decision-making to eat after stress involved a 5-HTR_4 control in the mPFC of the DRN 5-HTR_{1A} neuronal activity.

S06 Observer des assemblées de neurones en action par des enregistrements de haute densité. / Observing neuronal assemblies in action through massively parallel recordings.

S06.1
Représentation de la structure spatio-temporelle de l´activité neuronale (unitaire et potentiels de champ) du cortex moteur au cours des mouvements de saisie et de manipulation

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Grasping an object involves shaping the hand and fingers in relation to the object´s physical properties. Following object contact, it also requires a fine adjustment of grasp forces for secure manipulation. Earlier studies suggest that the control of hand shaping and grasp force involve partially segregated motor cortical networks. However, it is still unclear how information originating from these networks is processed and integrated. We addressed this issue by analyzing massively parallel signals from population measures (local field potentials, LFPs) and single neuron spiking activities recorded simultaneously during a delayed reach-to-grasp task, by using a 100 electrode Utah array chronically implanted in monkey motor cortex. Motor cortical LFPs exhibit a large multi-component movement-related potential (MRP) around movement onset. Here, we show that the peak amplitude of

each MRP component and its latency with respect to movement onset vary along the cortical surface covered by the array. Using a comparative mapping approach, we suggest that the spatio-temporal structure of the MRP reflects the complex physical properties of the reach-to-grasp movement. In addition, we explored how the spatio-temporal structure of the MRP relates to two other measures of neuronal activity: the temporal profile of single neuron spiking activity at each electrode site and the somatosensory receptive field properties of single neuron activities. We observe that the spatial representations of LFP and spiking activities overlap extensively and relate to the spatial distribution of proximal and distal representations of the upper limb. Altogether, these data show that, in motor cortex, a precise spatio-temporal pattern of activation is involved for the control of reach-to-grasp movements and provide some new insight about the functional organization of motor cortex during reaching and object manipulation.
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S06.2
Echelles spatio-temporelles des interactions neuronales

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The developments in electrophysiological recording techniques nowadays enable the simultaneous observation of a large number of individual neurons. However, a meaningful interpretation of the resulting high-dimensional data presents a serious challenge. We follow the hypothesis that cortical processing is organized in cell assemblies, i.e. groups of neurons that interact by coordination of their spiking activities. In order to detect such interactions between neurons and thus the activities of neuronal groups, the simultaneous spike trains need to be analyzed for significant spike correlation. For doing that we developed the Unitary Events (UE) analysis method (Grün et al, 1999; 2002a,b) and found dynamically occuring excess synchrony that was clearly related to the behavior of the animals (Riehle et al, 1997; 2001; 2003) and their state of practice of the task (Kilavik et al, 2009). These results were retrieved from mostly pairwise analyses of a few simultaneously recorded neurons. A straightforward extension of the UE method to massively parallel spike train (MPST) recordings, however, is due to the combinatorial explosion not possible. Therefore we developed new methods that are applicable to MPST and which enable to infer higher-order correlations (HOC) between the neuronal activities, which are interpreted as expressions of active assemblies. In this presentation I will briefly introduce such methods (Grün et al, 2008; Schrader et al, 2008; Louis et at, 2010a; Staude et al, 2010a,b; Gerstein et al, 2012). In particular I will discuss a newly developed method based on frequent itemset mining (Picado-Muino et al, subm) that includes a surrogate data approach for the evaluation of the significance of spike patterns (Grün, 2009; Louis et al, 2010b). The application to experimental MPST data will be illustrated.

S06.3
Différentiation entre neurones excitateurs et inhibiteurs et leur relation avec le potentiel de champ dans les enregistrements multi-électrodes chez l´homme

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Intracranial recordings are routinely used in epilepsy surgeries. Recent technological advances have enabled us to simultanesously record from large ensemble of neurons. With 96 electrode Neuroport arrays (otherwise, known as Utah electrodes), we were able to record from unit activity of ~90neurons and 96 local field potentials (LFPs) of a 4x4 mm patch of neocortex in human epileptic patients. We were able to successfully separate two classes of cells, FS (fast-spiking, putative inhibitory) and RS (regular spiking, putative excitatory), based on their distinctive morpho-functional characteristics. Dynamics of cell-cell interactions during different states of sleep showed that the correlation of excitatory cells follows an exponential decay with a time-dependent decrease in its amplitude. In

contrast, inhibitory cells showed a distant-independent correlation. In deep SWS (slow-wave sleep), delta-waves dominated the activity of cortex and neuron firings were tuned to the Up and Down states. Both RS and FS showed marked decrease of firing during Down-states, while their tuning to LFP oscillatory activity was different from each other. The spatio-temporal correlation of LFPs and cells were larger during SWS (slow wave sleep). The spectral transfer function (LFP-unit) of REM, light SWS and deep SWS, each showed a distinct signature representing a change in tuning of unit activity to the underlying oscillatory mechanisms. We also compared the balance of the two interacting inhibitory and excitatory group of cells at multiple time-scales. Our results showed that an overall excitation-inhibition balance is preserved during sleep, while across multiple scales, a highly rich dynamics evolves around this interaction.These findings show clues of functional architecture of excitatory-inhibitory mechanisms in neocortex of man and are in parallel to the known features of other mammals, specifically cats and rats.

S06.4

Observation, détection et interprétation des décharges neuronales simultanées dans le cortex auditif

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One of the most common definitions for neural assemblies is “a group of neurons [that are] at least transiently working together as indicated by correlation of unit activity” (Gerstein and Kirkland 2001). The use of multielectrode recordings is an exciting challenge for analyzing and understanding neural assemblies but it emphasized some unresolved issues. In particular, it remains impossible to observe the full assembly and properties of neural networks must be inferred from a very limited sample of neural activity recorded.
What we can learn from those recordings is not insignificant though. I will illustrate a few questions that can arise from observing multisite local field potential and unitary activity from the auditory cortex of mammals and humans. For instance, anatomical maps of neural activation can be correctly inferred from blind clustering of multielectrode signals. I will also show that local field potential and unitary activity do not lead to similar spatial activations both during spontaneous and evoked neural activity. On this occasion, I will introduce a few methods for detecting and analyzing the patterns of neural activation. The search for a neural code, among which the famous rate or temporal codes for instance, heavily depends on the ability and the way to detect neural correlations.
Finally, I will introduce some recent data showing a way to compute information carried by multisite activity. Short segments of 5 vowels were selected with durations of 2, 4, 8, 16, 32, 64 or 128ms. We wanted to investigate whether the coding abilities of ACx neurons would be robust even in situations where potentially less spikes are emitted as well as fuzzier stimulus spectrum are available. These stimuli were first used for a psychophysical experiment with human listeners. Performance increased with duration from above chance level (8-ms) to almost perfect (128ms). Then, we recorded ACx neurons in anaesthetized guinea pigs to the same set of vowels. Mutual information was applied to confusion matrices to quantify the ability of neurons or populations to discriminate the vowels. Actually, it was possible to approach performance from psychoacoustics based on the activity of populations of neural responses but never from that of a single cortical site.

S06.5

La boussole cérébrale : organisation des assemblées neuronales du thalamus antérieur codant pour la direction de la tête

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Navigation capabilities rely upon a large network of cortical and subcortical structures whose neurons show spatial dependent activity. Neurons in the antero-dorsal nucleus (ADN) of the thalamus fire in a specific direction of the animal´s head in the horizontal plane and have thus been called head-direction (HD) cells. They provide the building block for the spatial navigation system located in downstream areas where HD information, among others, give rise to cognitive maps described by grid and place cells. The behavioral properties of HD cells have been the subject of numerous studies, yet the organization of their activity at the population level is still largely unknown.
Here we report unprecedented recordings in behaving mice of large population of HD cells in the ADN. We first showed that the structure of pairwise interaction between HD cells is preserved across brain

states and that this circuit is somehow hard-wired despite the lack of direct connections between these thalamic neurons. During wake, overlapping or orthogonal head-direction fields of two cells were associated with positive or negative correlation of their spike trains, respectively. During sleep, the ADN showed sustained activity and neuronal pairwise correlations were virtually the same during wake, slow-wave sleep (SWS) and rapid eye movement (REM) sleep. Similarly, when the animals explored new environments, HD cell ensembles were coherently realigned to the new reference frame. On the contrary, the temporal scale of HD information encoding was dramatically different in the various brain states. Reconstruction of the internal head direction during sleep (based on a Bayesian decoder trained on wake data) revealed two important features: first, the internal representation was continuous and was not subject to abrupt ´jumps´ between virtual head directions; second, during SWS the angular head velocity was in average 10 to 20 times faster than during wake, and 50% slower during REM compared to wake . It remains to be answered what the origin and the function are of such a spontaneous activity during sleep.

S07 Mécanismes moléculaires des interactions microglie/neurones en situation normale ou pathologique: au delà du bien et du mal. / Molecular mechanisms of neuron/microglia interactions in health and disease: beyond good and evil.

S07.1
Contrôle des fonctions synaptiques par la microglie

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The discovery of astrocytes as major of synaptic transmission revealed the fact that the regulation of neuronal activity is not a neuron-autonomous mechanism. Microglial cells are closely associated with astrocytes and react rapidly to the modifications of their environment. They are able to sense neuronal activity and/or to communicate with astrocytes. Therefore, microglia display functional features of synaptic partners, but their involvement in the regulation of synaptic transmission barely been addressed. We have investigated the ability of microglia to regulate excitatory and inhibitory synapses. We first showed that stimulation of microglia by application of lipopolysaccharides (LPS) onto acute mouse hippocampal slices results in a rapid enhancement of the frequency of the spontaneous excitatory post-synaptic currents (EPSCs). We characterized the mechanism of this regulation and showed that stimulation of microglia induces a rapid production of ATP. Microglial ATP then recruits astrocytes that release glutamate. The astrocytic glutamate then increase the EPSC frequency through neuronal metabotropic glutamate receptors. In another set of experiments, we explored the regulation of inhibitory synapses by microglia. We showed that in spinal cord, microglia differentially control the accumulation and dynamic stabilization of glycine and $GABA_A$ receptors at synapses. These results on both excitatory and inhibitory synapses reveal microglia as a genuine regulator of neurotransmission.

S07.2
Rôle de la microglie dans la maturation fonctionnelle des synapses thalamo-corticales du cortex somato-sensoriel

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Microglial cells, the resident macrophages of the central nervous system, have been mostly studied for their roles in pathologies but accumulative evidence indicates that they also influence the normal development of brain synapses. Yet, the mechanisms by which these immune cells target maturating synapses and influence their functional development at early postnatal stages remain unknown. Using the whisker-related barrel field of the mouse somatosensory cortex as a model of cortical map formation, we analyzed the role of CX3CR1, a microglial receptor activated by the neuronal chemokine CX3CL1 (or fractalkine) which controls key functions of microglial cells. We show that the

microglial recruitment into the barrel centers where maturating thalamo-cortical synapses are concentrated occurs only after postnatal day 5 and is controlled by the fractalkine/CX3CR1 neuron-to-microglia signaling pathway. Indeed, at this developmental stage CX3CL1 is over-expressed in the barrels and CX3CR1deficiency delays the recruitment of microglial cells within the barrels and the expression of a specific microglia phenotype associated with this recruitment.
We then used acute thalamo-cortical slices to study the effect of CX3CR1 deficiency on the functional maturation of thalamo-cortical synapses. Our results indicate that the developmental pattern of AMPA and NMDA postsynaptic glutamate receptors which normally occurs between the first and the second postnatal weeks at thalamo-cortical synapses is severely affected in CX3CR1 knockout mice.
This study demonstrates that neuron-to-microglia signaling pathways control the initial distribution of microglia in the neocortex and that disruption of the microglial receptor CX3CR1 not only impairs microglia recruitment at sites of synaptic maturation but also results in modifications of the functional maturation of thalamo-cortical synapses.

S07.3

Signaux neuronaux, expression microgliale des récepteurs P2X et douleur neuropathique

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Up-regulation of P2X4 receptors in spinal cord microglia is crucial for tactile allodynia, an untreatable pathological pain reaction occurring after peripheral nerve injury. How nerve injury in the periphery leads to this microglia reaction in the dorsal horn of the spinal cord is not yet understood. It is shown here that CCL21 was rapidly expressed in injured small-sized primary sensory neurons and transported to their central terminals in the dorsal horn. Intrathecal administration of a CCL21-blocking antibody diminished tactile allodynia development in wild type animals. Mice deficient for CCL21 did not develop any signs of tactile allodynia and failed to upregulate microglial P2X4 receptor expression. Microglia P2X4 expression was enhanced by CCL21 application *in vitro* and *in vivo*. A single intrathecal injection of CCL21 to nerve-injured CCL21-deficient mice induced long-lasting allodynia that was undistinguishable from the wild type response. This effect of CCL21 injection was strictly dependent on P2X4 receptor function. Since neuronal CCL21 is the earliest yet identified factor in the cascade leading to tactile allodynia, these findings may lead to a preventive therapy in neuropathic pain.

S07.4

Implication croisée des récepteurs P2X4 neuronaux et microgliaux dans le remodelage hippocampique induit par un status epilepticus

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Within the CNS, ATP-gated channel P2X4 (P2X4R) are expressed in subset of neurons and in activated microglia. P2X4R functions in brain are still poorly understood, yet their activation in both neurons and microglia coincides with high or pathological neuronal activities. As such neuronal P2X4R contribute to long-term potentiation in the hippocampus, and in the spinal cord microglial receptors trigger gabaergic dishinibition and local network hyperexcitability. Activity-dependence of P2X4R activation suggest that these receptors might be involved in excitotoxic process associated with different pathologies. We thus investigated the potential involvement of P2X4R in a model of kainate (KA)-induced *status epilepticus*, in which both neurons and microglia activities contribute to excitotoxicity. We found that induction of *status epilepticus* was associated with a progressive and lasting P2X4R upregulation in the hippocampus, mostly localized in activated microglial cells but also present in pyramidal neurons. Shortly after induction of *status epilepticus*, a transient, but complete, decrease of the expression of the neuronal potassium chloride transporter KCC2 was observed in wild-type mice, but not in P2X4R-deficient mice. Because the down regulation of KCC2 was observed prior the induction of P2X4 expression, these results suggest the involvement of P2X4R expressed in pyramidal neurons. 48 hours after induction of the *status epilepticus*, several features of microglial activation, such as cell recruitment, upregulation of voltage-dependent potassium channels and

transcriptional regulation of different pro-inflammatory genes, were impaired in P2X4R-deficient mice. Consistent with the role of P2X4R in activity-dependent degenerative processes, CA1 area was partially protected from neuronal death in P2X4R-deficient mice compared to wild-type animals. These observations demonstrate that both neuronal and microglial P2X4R contribute to excitotoxic damages associated with *status epilepticus*. They also suggest the existence of a cross-talk between neuronal and microglial P2X4R in hippocampal remodeling associated with *status epilepticus*.

S07.5
Les cellules myéloïdes du cerveau

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The diseased brain hosts a heterogeneous population of myeloid cells, including parenchymal microglia, perivascular cells, meningeal macrophages and blood-borne monocytes. To date, the different types of brain myeloid cells have been discriminated solely on the basis of their localization, morphology and surface epitope expression. However, recent data suggest that resident microglia may be functionally distinct from bone marrow- or blood-derived phagocytes, which invade the CNS under pathological conditions. During the last few years, research on brain myeloid cells has been markedly changed by the advent of new tools in imaging, genetics and immunology. These methodologies have yielded unexpected results, which challenge the traditional view of brain macrophages. On the basis of these new studies brain myeloid subtypes can be differentiated with regard to their origin, function and fate in the brain.

S08 Prise de décision et traitement des récompenses chez l'homme: combinaison des approches neurocomputationnelles et de neuroimagerie. / Advances in understanding human decision making and reward processing by combining neurocomputational and neuroimaging approaches.

S08.1
De la décision perceptuelle à la décision basée sur les valeurs: apports de l´approche combinée IRMf et modélisation

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Neuroimaging and neurocomputational approaches have begun to elucidate the neuronal mechanisms underlying reward processing and decision making in humans. In particular, model-based fMRI allows us to characterize how a particular computational signal is implemented in the brain. This symposium will discuss some of the recent advancements that have led to the current understanding of how the human brain processes reward information and makes decisions. To characterize the neural coding of computational factors affecting value-based decision making, we have recently investigated how the brain respond to parameters such as reward/punishment types, magnitude, probability, delay, effort and uncertainty using either fMRI in healthy humans or intra-cranial recordings in patients with epilepsy. We decomposed brain signals modulated by these computational factors, showing that prediction error, salient prediction error (being excited both by aversive events and by rewards) and uncertainty signals are computed in partially overlapping brain circuits and that both transient and sustained uncertainty signals co-exist in the brain (Metereau et al., 2012; Dreher, 2013; Li et al., in prep). Moreover, we have demonstrated that there is not a single valuation system in the brain but that separate valuation systems are engaged for delay and effort costs when deciding between options (Prevost et al., 2010). We also have extended sequential sampling models of perceptual decision-making to value-based decision making (Domenech et al., 2010). Finally, although social decision making is ubiquitous and central to human society, its underlying neural mechanisms remain poorly understood. There is a need for understanding the fundamental computational principles underlying social decision processes. In particular, the fact that social decision making relies on the intentions and cooperativeness of other individuals has been underappreciated. We have therefore, used extended models of inequity aversion and reinforcement learning models to explain how the brain learns social hierarchies, predicts whether the other is cooperative or competitive and

respond to social norm violations in different group decision making situations (Ligneul et al., see poster; Girard et al., see poster).

S08.2

Prise de décision par le cerveau humain: de la prise décision perceptive à la décision basée sur des valeurs

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Perceptual decision making is the act of choosing one option or course of action from a set of alternatives based on the available sensory evidence. Thus, when we make decisions, sensory information must be interpreted and translated into behavior. Decision-making research has resulted in mathematical models of the assumed underlying cognitive processes and sequential sampling models are particularly successful in explaining response time data and accuracy in two-choice reaction time tasks. Recent studies in monkeys and humans have begun to model not only psychophysical but also neurophysiological data as a diffusion-to-barrier process providing a quantitative link between behavior (decision outcome) and neural activity (decision processing). I will discuss how we can use this framework to better understand the neurocognition of human decision making. Importantly, the neurophysiological mechanism previously established for perceptual decision-making - that is, the difference-based accumulation of evidence - can also play a key role in value-based decisions. This emerging link between research on perceptual decision-making and value-based (or economic) decision-making is an important step towards the goal of developing a common framework for these different flavors of decision-making**.**

S08.3

Comment le cerveau humain décide de faire un effort

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No pain no gain: cost-benefit trade-off has been formalized in classical decision theory to account for how we choose whether to engage effort. Yet how the brain decides when to have breaks in the course of effort production remains poorly understood. We propose that decisions to cease and resume work are triggered online by a cost-evidence accumulation signal reaching upper and lower bounds, respectively. We recently developed a task in which participants are free to exert a physical effort, knowing that their payoff would be proportional to their effort duration. Functional MRI and MEG recordings conjointly revealed that the theoretical cost-evidence accumulation signal was expressed in proprioceptive regions (bilateral posterior insula). Furthermore, the slopes and bounds of the accumulation process were adapted to the difficulty of the task and the money at stake. Cost evidence accumulation might therefore provide a dynamical mechanistic account of how the human brain maximizes benefits while avoiding exhaustion.
In this talk, I will first present the combined fMRI-MEG study that identified cost accumulation signal in the human brain and its modulation by incentive motivation (Meyniel et al. PNAS 2013). Then I will address two follow-up questions: 1) are the accumulation parameters (slopes and bounds) adjusted online or set up in advance with respect to incentive and difficulty levels? 2) what is the neural mechanism that translates higher incentives into shorter breaks?

S08.4

Troubles de l´impulsivité dans la prise de décision basée sur les valeurs: dévaluation des récompenses chez les joueurs pathologiques

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Decision-making often involves a trade-off between short-term and long-term outcomes. Typically, humans de-value rewards as the time to their delivery increases, a phenomenon termed temporal discounting. In my talk I will introduce this concept and outline the neural systems that support such so-called inter-temporal decisions. Impulsive choices of temporally proximal but inferior options are

abundant in many disorders of reward and motivation such as substance abuse and pathological gambling. I will focus on excessive reward discounting in gamblers and outline potential neural mechanisms underlying this phenomenon (e.g. elevated striatal-amygdala coupling, altered neural valuation signals in the ventral striatum and ventro-medial prefrontal cortex). I will then show data that suggest that gambling related cues can further increase impulsivity in pathological gamblers via an attenuation of neural valuation signals in the ventral striatum and ventromedial prefrontal cortex. Finally, I will discuss how processes such a time perception and episodic future thinking may modulate inter-temporal choice in controls and pathological gamblers.

S08.5

Raisonnement, apprentissage et créativité dans la prise de décision humaine

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The prefrontal cortex subserves executive control and decision-making, i.e. the coordination and selection of goal-directed actions. We recently proposed a computational theory describing the network of ventromedial, dorsomedial, lateral and polar prefrontal regions as a unified executive system arbitrating between
(1) perseverating with the ongoing behavioral strategy for allowing it to learn external contingencies;
(2) switching to behavioral strategies stored in long-term memory;
(3) exploring and possibly creating new strategies for adapting to uncertain, changing and open-ended environments (Collins & Koechlin, 2012, PloS Biology).
In this talk, I will present recent functional resonance magnetic data from our laboratory supporting this theory: As predicted, we found that the ventromedial prefrontal regions monitor the reliability (i.e. the ability to predict action outcomes) of the ongoing strategy driving action selection and learning; the polar prefrontal region monitor the reliability of up to two alternative strategies stored in long-term memory that may be subsequently used according to their reliability; the dorsomedial and lateral prefrontal implement switching in and out exploration periods when on the basis of strategy reliability, arbitrating between strategy retrieval and creation occur . Thus, the proposed computational model explains how the ventromedial, dorsomedial, lateral and polar prefrontal regions form the core of an unifying executive system underlying human reasoning, learning and creative abilities in the service of decision-making and adaptive behavior.

S09 Le cytosquelette neuronal en conditions normales et pathologiques. / Neuronal cytoskeleton in normal and pathologic conditions.

S09.1

Renouvellement des protéines synaptiques et plasticité synaptique: rôle du transport microtubule-dépendant

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Intracellular transport regulates protein turnover including endocytosis. Because of the spatial segregation of F-actin and microtubules, internalized cargo vesicles need to employ myosin and dynein motors to traverse both cytoskeletal compartments. Factors specifying cargo delivery across both tracks remain unknown. We identified muskelin to interconnect retrograde F-actin- and microtubule-dependent GABA-A receptor (GABA-AR) trafficking. GABA-ARs regulate synaptic transmission, plasticity, and network oscillations. GABAAR alpha 1 and muskelin interact directly, undergo neuronal cotransport, and associate with myosin VI or dynein motor complexes in subsequent steps of GABA-AR endocytosis. Inhibition of either transport route selectively interferes with receptor internalization or degradation. Newly generated muskelin KO mice display depletion of both transport steps and a high-frequency ripple oscillation phenotype. A diluted coat color of muskelin KOs further suggests muskelin transport functions beyond neurons. Our data suggest the concept that specific trafficking factors help cargoes to traverse both F-actin and microtubule compartments, thereby regulating their fate.

S09.2
Polarité et plasticité neuronale: microtubules et cargos

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In neurons, the distinct molecular composition of axons and dendrites is established through polarized targeting mechanisms, but it is currently unclear how non-polarized cargoes become uniformly distributed. In both axons and dendrites, the majority of vesicle movements are microtubule-based and characterized by alternating outward (or anterograde) and inward (or retrograde) transport, interspersed with periods of stationary docking. Such bidirectional transport suggests that cargos interact with both families of microtubule-based motors, kinesins and dynein, which drive transport towards the microtubule plus-end and minus-end, respectively. These opposing motors are also involved in polarized transport and sorting of cargo between axons and dendrites. In several model systems, it has been demonstrated that kinesin motors specifically target the axon and drive synaptic vesicle transport, whereas the dynein/dynactin motor complex sorts postsynaptic receptors and Golgi outposts to dendrites. While two different transport mechanisms exist to control polarized transport in neurons, it is unclear which machinery is used to uniformly distribute non-polarized neuronal cargos, such as mitochondria.
Here we will discuss how mammalian TRAK family adaptor proteins, TRAK1 and TRAK2, which link mitochondria to microtubule-based motors, are required for axonal and dendritic mitochondrial mobility and utilize different transport machineries to steer mitochondria into axons and dendrites. TRAK1 binds to both kinesin-1 and dynein/dynactin, is prominently localized in axons and needed for normal axon outgrowth, whereas TRAK2 predominantly interacts with dynein/dynactin, is more abundantly present in dendrites and required for dendritic development. These functional differences follow from their distinct conformations: TRAK2 preferentially adopts a folded state by a head-to-tail interaction, which interferes with the kinesin-1 binding and axonal transport. Our study demonstrates how the molecular interplay between bidirectional adaptor proteins and specific microtubule-based motors drives polarized mitochondrial transport in neurons.

S09.3
Modifications post traductionelles des microtubules et neuro-dégénération

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The microtubule cytoskeleton of neurons is highly differentiated, and fulfils a variety of key functions in developing and mature neurons. Posttranslational modifications of tubulin, in particular enzymatic detyrosination and polyglutamylation, have been shown to accompany neuronal development and differentiation, but also regeneration after injury. Recently, our team has demonstrated that deregulation of polyglutamylation leads to neuronal degeneration in a mouse model for Purkinje cell degeneration (pcd). We are now studying the cellular mechanisms that are regulated by these two modifications, and how this is controlled on a molecular level. In parallel, we will use the KO mice we have raced to study the impact of different neuronal enzymes involved in the modification of tubulin on the organism level. Our goal is to understand how polyglutamylation is regulated on a subcellular level, and how pathological changes in these regulatory events can lead to neurodegeneration.

S09.4
Deux enseignements des souris déficientes pour MAP6/STOP: MAP6 est cruciale pour la mise en place de tracts axonaux et les microtubules sont des cibles pertinentes pour le développement de nouveaux antipsychotiques

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Cytoskeletal elements including actin filaments and microtubules play major roles in neuronal function. During neurodevelopment, microtubules contribute to axonal growth and spines formation and in adult brain, they are involved in synaptic plasticity events. Dynamic properties of microtubules are regulated by MAPs (Microtubule-Associated Proteins) such as MAP6 which functions will be detailed here. MAP6 deletion in mice has dramatic effects on integrated brain functions: MAP6 null mice display severe behavioral disorders associated with dopaminergic, glutamatergic and serotonergic neurotransmission abnormalities and impaired synaptic plasticity. We have shown that underlying neuronal circuits are disorganised and specific action of MAP6/STOP proteins during axonal tract formation via semaphorine3E signaling will be discussed.
Several biological and behavioral disorders of MAP6/STOP null mice are reminiscent of symptoms observed in schizophrenia. Accordingly, both typical and atypical antipsychotics treatment have been shown to alleviate synaptic and behavioral deficits in these mice. The ability of microtubular-related drugs (Epothilone D or Davunetide) to replicate the reduction of cognitive symptoms in MAP6/STOP null mice will be presented.

S09.5

Coupures des filaments d´actine médiées par le complexe ADF/cofilin: rôle dans la formation des neurites pendant le neurodéveloppement

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Axons do not regenerate after spinal cord injury because the axons are growth incompetent, and inhibitory factors in the CNS myelin and the scar prevent the axons from regrowing. Microtubule dynamics regulate key processes during scarring, including cell proliferation, migration and differentiation. Moderate microtubule stabilization using the FDA approved drug Taxol prevents axonal retraction and swelling of the axon tip after CNS injury, and stimulates axon growth of cultured neurons enabling them to overcome the growth inhibitory effect of CNS myelin. Moreover, we found that moderate microtubule stabilization decreased scar formation after spinal cord injury in rodents via various cellular mechanisms, including dampening of TGF-β signalling. It prevented the accumulation of chondroitin sulfate proteoglycans (CSPGs) and rendered the lesion site permissive for axon regeneration of growth competent sensory neurons. Additionally, microtubule stabilization promoted growth of CNS axons of the Raphe-spinal tract and led to functional improvement. Thus, microtubule stabilization reduces fibrotic scarring and enhances the capacity of axons to grow. Manipulation of microtubules may offer the basis for a multi-targeted therapy after spinal cord injury.

S10 Dynamique neurale de la navigation spatiale: données électrophysiologiques et modèles computationnels. / Neural dynamics of spatial navigation: electrophysiological data and computational models.

S10.1

Réconciliation des enregistrements électrophysiologiques et des modèles du rôle du réseau hippocampo-préfronto-striatal dans la navigation et les changements de stratégie

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While representations of spatial context have been intensively studied in the hippocampus, little is known about how these signals are exploited by brain areas more closely associated with controlling navigation decisions. Thus we have recorded simultaneously in hippocampus (Hpc) and prefrontal

cortex (Pfc) or Hpc and ventral striatum (VS), and compared our results with biologically inspired computational models. The VS is linked with goal-directed behavior which has been modeled by temporal difference (TD) learning. However in recordings in the hippocampal afferent zone of VS of rats performing in a plus maze with different rewards in the respective arms, those responses that anticipated rewards had temporal properties incompatible with existing models. This discrepancy was reconciled by making the (in retrospect, intuitive) assumption that each neuron does not receive complete state information about the environment and implementing this. Thus the electrophysiological data inspired development of a more adequate model. Another project developed models of the rat´s behavioral choices in a multi-rule Y maze task which presented multiple and partial conflicting cues. Bayesian models permit estimates of hidden internal states and the model was employed to indicate the current strategy best corresponding to the animal´s behavior. This then gives an objective estimate of that trial when the rats first acquired a new rule (and also when it subsequently abandoned it for another). This is then reconciled with simultaneous recordings of Hpc and Pfc in rats learning and shifting between different strategies. The first trial where a new strategy appeared is compared with the first trial manifesting changes in network electrophysiological properties such as significant increases in Hpc-Pfc coherence and the activation of Pfc cell assemblies at the maze decision point. In this way the relation between this electrophysiological activity and navigational decision behavior can be assessed. (Supported by EC IPs ICEA and BACS, and ANR Neurobot)

S10.2

Apprentissage dynamique de séquences spatio-temporelles (présentation conjointe avec le modélisateur Dr. Benoît Girard du CNRS UMR 7222)

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Spatio-temporal sequence learning requires distinguishing between different locations visited at different time points and associating to each location a particular action. It particularly relies on the ability to maintain a representation of the order in which locations have been experienced over time. Such complex behavior involves interaction between different memory systems to encode spatial as well as temporal information and motor behavior. We have shown that such learning requires the hippocampus, in mice as well as in humans. Our aim is to model spatio-temporal sequence learning in mice at two levels: biological, to identify the structures underlying such learning, and computational, to understand the learning processes.
Our task consists in learning a 2-turn route in a multiple Y-maze, with no environmental cues. Here, the spatial component does not refer to an allocentric representation of space but to the representation of the order in which the intersections have been visited.
We first identify the structures underlying spatio-temporal sequence learning by Fos imaging following the behavioural study. We are investigating the different learning stages: initial exploration and over-training with an automation of the sequence.
Conjointly, we explore which computational models of the learning could explain the observed learning dynamics. We show that both model-based and model-free reinforcement learning algorithms may fit the data, as long as the model-free one has a memory of the last actions performed. Interestingly, the performance of the model-free system is more variable than the model-based one, which seems to be closer to the animal behavior. The analysis of the parameterizations of the models which allow good fits, gives us insights about the learning and exploration rates of the animals in this task. This approach also suggests what are the putative computational roles of the networks of structures identified by correlation analyses of Fos imaging.

S10.3

Enregistrements unitaires dans le striatum pendant l´adaptation comportementale

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Several studies on instrumental conditioning suggest the existence of two independent decision-making processes, one inflexible and dependent upon dorsolateral striatal (DLS) activity, the other based on flexible goal-oriented responses and mediated by the dorsomedial striatum (DMS). However, very few studies have investigated whether a similar dissociation exists in more complex behaviors, such as spatial learning. The present study examined the role of the two structures in this behavior 1) by analyzing the effects of excitotoxic DMS and DLS lesions and 2) by comparing DMS and DLS neuronal activity, during the acquisition and extinction of a spatial alternation behavior in a continuous alternation T-maze task.
We first demonstrated that DMS and DLS lesions have opposite effects, the first impairing and the second improving rats performance during learning and extinction. Secondly, neurons from the two brain areas displayed different task-related responses. In particular, DMS provides a signal necessary to dissociate different spatial trajectories, whereas the DLS preferentially activates for egocentric movements and reward delivery, irrespective of left/right goal position. Moreover, preliminary analysis seem to indicate that DMS but not DLS neuronal activity rapidly adapts to changes in reward contingency in the T-maze task.
Taken together, these results indicate that the DMS and DLS may support in different ways the acquisition and performance of a spatial goal-directed behaviour, and suggest that DMS- and DLS-mediated learning strategies develop in parallel and compete for the control of the behavioral response during learning.

S10.4
Psychophysique de la reconnaissance des lieux

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The recognition of places is a basic element of spatial behaviour and spatial memory combining context from other places (map and route knowledge, O´Keefe & Nadel´s 1978 taxon system) with sensory cues available at the target place (local position information, O´Keefe & Nadel´s locale system). It can be argued that the latter part, place recognition from current sensory cues, is the more basic one, as it has less memory requirement.
What are the sensory cues used in place recognition? In insects, the concept of a snapshot has been developed which is a panoramic view of the environment, as seen from the target position. The snapshot can be raw, i.e. an array of light intensities taken at the receptor level, or processed to various degrees, for example snapshots based on intensity edges (Cartwright & Collett Nature, 1983), distances to surrounding walls (c.f. Stürzl et al., JEP:ABP 2008), or skyline elevation (e.g., Basten & Mallot, Biol. Cybern. 2010). Humans are able to recognize places from relatively raw snapshots if no other cues are available (Gillner et al., Cognition 2008). In addition to snapshot-like place codes, landmark objects and configurations of landmark objects have been shown to be used in place recognition (e.g., Morris, Learning and Motivation 1981; Hort et al. PNAS 2007). Recently, ´spatial layout´ has been suggested as a third type of cognitive place codes (Epstein, Trends in Cognitive Sciences 2008). Multisensory integration in a `spatial image´, i.e. a working memory of the current place or environment has been suggested by Loomis et al. (in Lacey & Lawton, eds, Multisensory imagery, Springer 2012).
In the talk, I will review the evidence on perceptual codes for place recognition and place approach. Recent experiments into the role of depth- and object information in place recognition will be discussed.

S10.5
Un modèle intégratif neurorobotique du réseau hippocampo-préfronto-striatal pendant la navigation

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We present a neural network model where the spatial and temporal components of a task are merged and learned in the hippocampus as chains of associations between sensory events. One key element is that CA1 neurons do not encode static place cells as classically hypothesized but "**transition cells**" predicting also the future place or state of the animal. The prefrontal cortex integrates this information

to build a cognitive map representing the environment. The cognitive map can be used after latent learning to select optimal actions to fulfill the goals of the animal. A simulation of the architecture is made and applied to learning and solving tasks that involve both spatial and temporal knowledge. We show how this model can be used to solve the continuous place navigation task, where a rat has to navigate to an unmarked goal and wait for 2 seconds without moving to receive a reward. The results emphasize the role of the hippocampus for both spatial and timing prediction, and the prefrontal cortex in the learning of goals related to the task. Moreover, this model allows a very simple connection with the nucleus accumbens for action selection. The complete model has been tested on a mobile robot using mainly visual information to reproduce different neurobiological experiments. The interest of going back and forth between robotics experiments and modelling and neurobiological experiments will be discussed.
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This work is supported by the ANR project NEUROBOT and the DIGITEO project AUTOEVAL.

S11 Assemblage de circuits neuronaux au cours du développement cortical / Assembling neuronal circuitries during cortical development.

S11.1

De nouveaux facteurs de régulation de la neurogenèse des cellules gliales radiales avec des rôles clés dans la régulation de la taille du cerveau

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Organ size is regulated by balancing stem cell self-renewal versus the generation of differentiated progeny or transit-amplifying progenitors to enlarge the progeny number. This is of particular relevance in brain development as the evolution of the mammalian brain encompassed a remarkable increase in size of specific brain regions, such as the cerebral cortex. This process encompasses expansion in the tangential (larger brain area) and radial (higher number of neurons per brain area) dimension. However the mechanisms underlying these key features are still largely unknown. Here, I describe a novel type of radial glial cells involved in radial extension and a novel molecular factor regulating these radial glial cells. The novel DNA associated protein Trnp1, which is highly conserved only in mammals, acts a regulator of neural stem cell self-renewal and mammalian cerebral cortex expansion. Its dynamic regulation during brain development together with gain and loss of function experiments in the mouse cerebral cortex *in vivo* demonstrate that higher Trnp1 levels promote neural stem cell self-renewal and tangential expansion. In contrast, lower levels promote radial expansion with a potent increase of the number of subapical radial glia, intermediate progenitors and basal radial glial cells leading to folding of the otherwise smooth murine cerebral cortex. Remarkably, *TRNP1* expression levels exhibit regional differences in the cerebral cortex of human fetuses anticipating radial or tangential expansion. Thus, the dynamic regulation of *Trnp1* is critical to regulate tangential expansion by promoting neural stem cell self-renewal while its reduction results in rapid amplification of transient progenitor lineages causing a fast increase in neuron numbers and their appropriate guiding structures.

S11.2

Connecter le cerveau antérieur: rôles et mécanismes de la migration cellulaire

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Forebrain functioning relies on complex circuits that begin to be established in the embryo by intrinsic developmental programs. Such programs coordinate the assembly of millions of neurons via an integrated choreography of neuronal migration and axonal navigation, which remains largely to be explored. In addition, intrinsic programs can be modulated by maternal environment, as illustrated by the fact that prenatal inflammation is a major risk factor for schizophrenia and autism spectrum disorders. Understanding how embryonic programs and maternal signals control forebrain wiring is

essential not only to progress in our comprehension of cerebral morphogenesis but also to provide a framework for assessing the etiology of neuropsychiatric disorders. We recently showed that neuronal migration, in addition to its role in cell distribution, acts as a dynamic system to display guidance cues essential for the formation of major axonal tracts. Indeed, migrating corridor neurons within the basal ganglia are required for the formation and organization of thalamo-cortical projections, a main connection of the neocortex. Thus small neuronal populations can act, by their specific positioning and cell properties, as orchestrators of neocortical wiring.
Here we will present novel evidence that it is also the case for a subpopulation of immune cells, microglia. Microglia are brain resident macrophages and, in addition to their immune functions, they have been recently involved in postnatal remodeling of circuits notably via elimination of synapses. We found that microglia regulate forebrain wiring by modulating the progression and positioning of specific axonal populations and migrating neurons, as well as act as deleterious mediators of prenatal inflammation. These findings reveal a novel and remarkable interplay between the development of the neural and immune systems during normal and pathological forebrain morphogenesis.

S11.3

Contrôle moléculaire de la navigation axonale cortico-corticale

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The neocortex, designated as the seat of our highest cognitive abilities, relies largely on the appropriate connections of cortical neurons with other brain regions, including the neocortex itself. One of the major axonal tracks that interconnect the two cerebral hemispheres is the corpus callosum. Malformations of the corpus callosum in humans occur in over 50 congenital syndromes that are associated with a wide spectrum of deficits. Callosal projection neurons are critical for bilateral transfer and integration of cortical information and have been implicated in autism spectrum disorders. Absence or surgical disruption of corpus callosum in humans is also associated with deficits in abstract reasoning and problem solving. Recently we identified Satb2, Sip1 and NeuroD transcription factors as major players in corpus callosum development. Molecular pathways controlling cortico-cortical axon navigation downstream of these factors will be discussed.

S11.4

Coordination entre prolifération et migration radiale dans la spécification des aires corticales pendant la corticogénèse

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The cytoarchitecture of the cerebral cortex is determined by variation of the number, density and morphology of neurons in individual layers. Therefore, cortical cytoarchitecture requires the fine spatiotemporal control of neuron production in the germinal zones and its coordination with radially directed migration. These two processes orchestrate the emergence of cortical layers and ultimately cortical circuitry.
We have explored the dynamics of both precursor proliferation and radial migration by means of real-time imaging on organotypic slices of primate embryonic cortex. Our data show that the developmental regulation of both
(i) precursor pool dynamics and
(ii) cell-cycle parameters differ strikingly from what has been previously described in rodents.
We show that the different area-specific radial migration kinetics in presumptive areas 17 and 18, is tightly correlated to differences in area-specific proliferation rates (high rates of proliferation and migration in area 17; low rates of proliferation and migration in area 18). The radial migration kinetics are stage-specific and are selectively observed in OSVZ generated neuroblasts destined for the supragranular layers. In contrast, infragranular neurons, generated by VZ precursors, exhibit identical radial migration kinetics in presumptive areas 17 and area 18. Congruent variations in the expression level of cytoplasmic p27 and radial migration velocities were observed.
Supported by EU FP7-2007-ICT-216593 (SECO), LabEx CORTEX, LabEx DEVweCAN.

S11.5

Mise en place des aires cérébrales et spécification neuronale dans le cerveau des mammifères en développement

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Corticogenesis involves the formation of six distinct layers and of functionally specialized areas characterized by specific sets of pyramidal neurons with distinctive morphologies, connectivity, and developmental programs of gene expression (reviewed in *1*). We have previously shown that the transcriptional regulator COUP-TFI is required in balancing the neocortex into motor and sensory areas (*2*) by regulating a genetic program leading to the correct differentiation of deep layer projection neurons (*3*). Here, we demonstrate that COUP-TFI controls areal subdivision and cell-type specification at the post-mitotic level by regulating a series of transcription factors involved in sub-type specification and areal subdivision. We found that the transcriptional code specific for each cortical sub-population is altered in the absence of COUP-TFI function, leading to abnormal neuronal activity and corticofugal connectivity. In particular, we found a novel mechanism at the basis of the Ctip2 inhibition by Satb2, which interferes with the formation of the NURD complex, and leads to the increase of a non-yet well characterized projection neuron sub-population. Together, our studies emphasize the fundamental role of COUP-TFI in subdividing the neocortex into distinct functional areas and in controlling discrete sub-populations of neocortical projection neurons by regulating expression levels of cell-type specific determinant genes at post-mitotic levels.

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S12 Codage neuronal rare et dense dans les systèmes sensoriels. / Sparse and dense neural coding in sensory systems.

S12.1

Variation de la densité de codage des odeurs dépendantes de la concentration dans le bulbe olfactif de la souris

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In mammals, odorant molecules are sensed by a large family of receptors expressed by sensory neurons projecting their axons in a receptor specific manner onto olfactory bulb (OB) glomeruli. Each odorant is thought to activate only a few glomeruli and thereby a limited number of output neurons in the bulb, which has led to the hypothesis that odor coding in the OB is sparse. However, the studies that support this model used anesthetized animals or monomolecular odorants at a limited concentration range. In this study, we evaluated natural odor coding in awake mice using natural stimuli. Using optical imaging and tetrode recordings in awake mice, we show that natural odorants at their native concentration activate a large fraction of the glomeruli and that OB output neurons are more broadly tuned than previously thought. By decreasing the odorant concentration, we observe a sparsening of the patterns of activated glomeruli and we report that OB output neurons become more narrowly tuned. We conclude that the sparseness of the odor code can strongly vary with the strength of sensory stimuli.

S12.2
Densité et dynamique de codage suivant les populations corticales

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Sensory signals are processed through the combined activity of large neuronal populations. Different neuronal classes use different strategies to encode information. This talk will focus on the coding strategies used by different neuronal populations of sensory cortex. While pyramidal neurons of superficial layers use a sparse code, deep layer pyramidal cells and interneurons of all layers employ dense codes. More generally, the structure of population activity within a neural class is strongly constrained by the dynamics of a simple quantity, the “population rate,” defined as the instantaneous firing probability averaged over all neurons in the class. Population rate dynamics varies between both neuronal classes and brain states, constraining possible patterns of pairwise correlations and multi-neuron firing patterns.

S12.3
Etude multi-échelle de la densité et de la fiabilité des dynamiques corticales durant le traitement de scènes visuelles naturelles

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Irregular ongoing activity and large response variance during sensory activation are considered to impede the efficiency of sensory processing in cortical networks. In order to search for a possible dependency of the temporal precision and reliability of the neural code on input statistics, we have performed a multi-scale study of the trial to trial reliability of visually evoked dynamical states in the primary visual cortex of anesthetized cat. The visual responses were recorded at the single cell level with intracellular sharp electrodes and at a more mesoscopic level with multi-electrode (local field potentials (LFP) and multi-units). In addition the dynamics of excitatory and inhibitory conductances were estimated with intracellular recordings and correlated with the spiking reliability. Different types of visual stimuli of increasing complexity, and controlled spatial and temporal statistics, were presented either in full field, central or surround-only configurations: optimal drifting grating, optimal grating and natural image animated by a simulated eye-movement sequence and dense binary white noise. In order to compare the different signals, the same frequency-time wavelet analysis was applied to all these types of recordings. This decomposition allows the extraction of several time-frequency dependent measures: signal power, noise power and signal-to-noise ratio power and to compare directly the temporal evolution of information contents at different scales of integration. Furthermore, we explored the potential of large scale simultaneous recordings to provide views of neural dynamics. We found that natural scene animation evoked temporally precise sparse spike responses and highly reproducible and irregular dynamics in the subthreshold membrane potential. At more mesoscopic level, the dynamic and the reliability of the local field potentials changes radically during the various stimulations. These studies in cat primary visual cortex shown that the noise, the temporal reliability and the correlation of cortical responses depend on the visual input statistics and adaptation.
Work done with the support of CNRS, ANR: Natstats and V1-Complex and EC grants BrainScales (FP7-2010-IST-FETPI 269921) and Brain-i-nets (FP7-2009-ICT-FET 243914).

S12.4
Dynamique synaptique et densité de codage dans le cortex en tonneaux de la souris éveillée

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Rodents use their whiskers to actively collect information about their surrounding environment. Sensory information collected by the whiskers are processed and encoded in primary somatosensory cortex (barrel cortex) after being relayed through the brainstem and the thalamus. Sensory inputs enter the barrel cortex mainly in layers 4 and 5, and then propagate to superficial layer 2/3. Layer 2/3

pyramidal neurons are sitting in a key position to integrate sensory information, receiving synaptic inputs from different sensory pathways and cortical areas, and sending output mainly to other cortical areas. On average, layer 2/3 pyramidal neurons discharge at very low firing rates during both quiet wakefulness and active whisker movements, despite high amplitude membrane potential fluctuations. Similarly, passive whisker stimulation evokes a depolarizing post-synaptic potential of several mV but only few action potentials. During active sensing, each contact between an object and the whisker invariably evokes a depolarizing response but little or no action potential in most cells. However very few layer 2/3 pyramidal neurons fire reliably in response to active contacts, indicating sparse coding representation of sensory information in supragranular layers of the barrel cortex. A major determinant of the firing probability of pyramidal cells is the apparent reversal potential of the sensory evoked response: as the cell depolarizes the depolarizing response progressively decreases in amplitude, is abolished at reversal potential and becomes hyperpolarizing at more depolarized levels. This apparent reversal potential is cell specific and hyperpolarized relative to firing threshold for most neurons. Successive contacts progressively depolarize and clamp the cells membrane potential around this specific reversal potential. The hyperpolarized value of the reversal potential and higher firing rate of local GABAergic interneurons, suggest that inhibition is playing a key role in gating the discharge of layer 2/3 pyramidal cells during active sensing in the barrel cortex.

S12.5

Différence de traitement des entrées sensorielles par des cellules pyramidales voisines dans la couche 2 du cortex en tonneaux révélée par l´expression des gènes précoces

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Neocortical pyramidal neurons display considerable heterogeneity in spontaneous and sensory evoked firing rates. The underlying circuit and synaptic mechanisms that leads to sensory response diversity have not been determined, in part because of the lack of molecular markers for pyramidal neuron subpopulations. Recently, we used expression of the activity-dependent immediate-early gene c-fos to identify a more active subnetwork of layer 2 pyramidal neurons in whisker primary somatosensory cortex using a fosGFP transgenic mouse. Here we investigate the spontaneous activity and sensory response properties of fosGFP+ve and fosGFP-ve layer 2 pyramidal neurons using in vivo dual two-photon targeted whole-cell recordings in the urethane anaesthetized mouse. We show that fosGFP+ve neurons receive larger amplitude depolarising synaptic input as compared to neighboring fosGFP-ve neurons both during spontaneous upstates and airpuff triggered sensory responses. Surprisingly, analysis of the subthreshold sensory response shows that fosGFP+ve neurons also respond with a significantly shorter latency. Further investigation has demonstrated that fosGFP+ve neurons have a larger receptive field integrating sensory input from wider range of input within the barrel filed. The postero-medial nucleus of the thalamus (POm) is known to be activated by multiwhisker stimulation and his projection target the entire barrel cortex field. We used optogenetic stimulation to activate specifically POm and found that fosGFP+ve neurons receive a stronger and shorter latency input. Thus, a subpopulation of more active layer 2 pyramidal neurons expresses the immediate early gene c-fos and integrate sensory input from a wider receptive field.

S13 Comportements et stress : dissection des mécanismes développementaux, cellulaires et moléculaires. / Stressed-out behaviours: developmental, cellular and molecular mechanisms.

S13.1

Programmé pour gagner ou perdre ?

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Stress is encountered throughout life and the organism adapts its physiology and behaviour accordingly. While stress *per* se is not harmful, certain stressors can lead to maladptations, depending on when they occur during the life course. This lecture will review some of the neural processes and mechanisms that determine healthy or unhealthy adaptations, with a particular focus on cognitive and affective behaviours.
Supported by EU-funded FP6 (Crescendo) and FP7 (SwitchBox) Collaborative Projects.

S13.2
Stress et prise de décision

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Prolonged exposure to stress and the associated hypersecretion of glucocorticoids cause psychopathologies ranging from hyper-emotional states and mood dysfunction to cognitive impairments. More recently, research in both humans and animal models has begun to identify the impact of stress on corticostriatal networks that rule decision-making processes. Briefly, the structural changes triggered by stress were associated with a bias in decision-making strategies, as behaviors in stressed rats rapidly shifted from goal-directed actions to habits. This automatization of recurring decision processes into stereotypic behaviors or habits caused by exposure to stress can be viewed as “advantageous”, as it increases behavioral efficiency by releasing cognitive resources for more demanding tasks. However, to adapt to ever changing life conditions, the ability to select the appropriate actions to obtain specific outcomes based on their consequences is of utmost importance. In fact, the capacity to shift between habit-based and goal-directed actions is a condition for appropriate decision-making that seems to be affected in several neuropsychiatric conditions for which stress is a known trigger factor.

S13.3
Stress et comportements sociaux

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In addition to its well-known impact on cognitive function, stress has prominent effects in social behaviors. Our recent work in rodents shows that exposure to high and/or sustained stress alters the nature of social interactions, individuals' sociability, social dominance and aggression levels. Furthermore, these alterations in social behaviors are also programmed by exposure to early life stress and can be transmitted to the next generation in the absence of social learning. I will discuss some of the neural mechanisms altered by stress and linked to the deficits in social behaviors. Among others, mechanisms include changes in brain regional activity and interactions, as well as in the expression of synaptic cell adhesion molecules and genes of the serotonin family. These findings will be discussed within a broader context reflecting on the societal implications of stress.

S13.4
Neurogenèse et contrôle de l´axe du stress

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Hippocampal neurogenesis seems the mandatory mechanism by which antidepressant drugs (AD) achieve remission. However, it is still unclear how newborn neurons that are expressed in the dentate gyrus of the hippocampus can enable the recovery of the deficit of the large cerebral network underlying depression. One possible explanation is related to the hypothalamic-pituitary-adrenal (HPA) axis. It is well known from the literature that the HPA axis is disrupted in depression, and that the restoration of this dysfunction is necessary to observe ADs effects. Further, it is known that the hippocampus participates to the negative feedback over the HPA axis. We thus hypothesized that one of the functions of neurogenesis in the AD's effects may concern its ability to restore this feedback when it has been disrupted. We demonstrate that Unpredictable Chronic Mild Stress (UCMS), a protocol known to induce depression-like behavior in mice, reduces the number of new hippocampal neurons and decreases the negative feedback on the hypothalamo-pituitary-adrenal (HPA) axis measured by the dexamethasone suppression test. This involves the hippocampus, as injection of dexamethasone induces an increased fos in the dentate gyrus and as intra-hippocampal dexamethasone also elicits corticosterone suppression. This suppression is absent after UCMS, an

effects that is reversed by fluoxetine. This is achieved via a pathway going from the hippocampus to the paraventricular nucleus of the hypothalamus, via a relay in the bed nucleus of stria terminalis (BNST), as intra-hippocampal dexamethasone induces an activation of the BNST, that is reduced by UCMS and counteracted by fluoxetine. While ablation of hippocampal neurogenesis has no effect on its own in the intra-hippocampal dexamethasone test, UCMS elicits a deficit in corticosterone suppression. This deficit is reversed by fluoxetine in non irradiated mice, but not in mice having abolition of hippocampal neurogenesis. These results suggest ADs act through neurogenesis to re-establish hippocampal regulation of the HPA axis. This model generates several predictions, that were all tested experimentally.

S13.5
Rôle du récepteur des glucocorticoïdes dans l´aversion sociale

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When exceeding coping resources, stress increases the morbidity for psychiatric disorders. Repeated traumatic events induce long-lasting behavioral changes that are key to organism adaptation and that affect cognitive, emotional, and social behaviors. Rodents subjected to repeated instances of aggression develop enduring social aversion and increased anxiety. Such repeated aggressions trigger a stress response, resulting in glucocorticoid release and a persistent boost of mesolimbic dopamine (DA) transmission. We bred mice with selective inactivation of the gene encoding the glucocorticoid receptor (GR) along the DA pathway, and exposed them to repeated aggressions. GR in dopaminoceptive but not DA-releasing neurons specifically promoted social aversion as well as enhanced DA release within the nucleus accumbens and increased VTA DA neuron activity. In contrast, anxiety and fear memories remained unaffected. Acute inhibition of the activity of DA-releasing neurons fully restored social interaction in socially defeated wild-type mice indicating that increased DA neuron activity is a prerequisite for social aversion. Our data suggest a GR-dependent neuronal dichotomy for the regulation of emotional and social behaviors, and clearly implicate GR as a link between stress resiliency and dopaminergic tone.

S14 Sommeil, rêve et cognition. / Sleep, dream and cognition.

S14.1
Sommeil, mémoire épisodique et cerveau

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Sleep favours consolidation of recently acquired information into long-term memory. For episodic memories, this complex mechanism occurs by means of a dialogue between the hippocampus and neocortical areas where memories will be stored for the long term[1]. Over the least two decades, several methodological approaches have been used and combined to specify the cerebral substrates of the beneficial effect of sleep on memory. For instance, using positron emission tomography, Peigneux et al.[2] showed that the hippocampus, activated during a spatial learning task, was reactivated during post-learning slow-wave sleep. Interestingly, the amount of hippocampal activity during sleep was positively correlated with the overnight improvement of performance confirming, as previously reported in rodents, that these reactivations play an important role in memory consolidation. Other data showed that increasing the amount of slow oscillations during post-learning sleep with transcranial direct current improves retention on an episodic memory task[3]. Thalamo-cortical sleep spindles may also play an important role in this process[4]. Combining sleep deprivation and fMRI data acquisition, Gais et al.[5] revealed differences in the pattern of reorganization of episodic memory traces within neural networks in sleep compared to sleep deprived young adults and highlighted the role of the medial prefrontal cortex in the retrieval of consolidated memories. Finally, using a directed forgetting paradigm consisting in presenting “to be remembered” and “to be forgotten” information, thus allowing to selectively increase or decrease the strength of individual memory traces according to the instruction provided at learning, we showed that hippocampal activity at learning specifically triggers sleep-dependent memory consolidation[6].

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S14.2

Quel est le rôle du sommeil dans la consolidation de la mémoire émotionnelle, étude en IRMf

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Recent brain imaging studies in humans provide evidence for a role of sleep in emotion brain functions, including the consolidation of emotional memories. Moreover, sleep restriction modify response of emotion, mood disorders are related to sleep pathology, brain regions involved in the processing of emotions are highly activated during REM sleep, and emotions in dream reports are more intense and negative than emotions experienced during daytime. The observations may reflect emotion regulation processes occurring during sleep. However, the relationship between the processing of emotions during sleep and brain responses to emotions during wakefulness is still highly speculative. First, we used fMRI to characterize the influence of sleep on the consolidation of emotional memories. We presented cues, previously associated to emotional and neutral pictures, during subsequent phasic REM sleep or during other sleep stages. We observed that reactivating memories during phasic REM sleep by exposure to cues induces a reorganization of memories, detectable during retrieval, suggesting that REM sleep provides favourable conditions to system-level brain plasticity. Second, we demonstrated that sleep, as compared to wakefulness, impacts on the discrimination of morphed emotional faces. The sleep-dependent effects on perception boost the identification of emotionally-significant faces, particularly in relatively ambiguous situations. Third, we tested whether emotions experienced in dreams correlate with brain responses to emotional stimuli at wake. We show that individuals who report more emotional dreams also activate the amygdala more strongly in response to aversive stimuli. This result supports a link between emotional processes occurring during sleep and emotional brain functions during wakefulness.

S14.3

Comportements moteurs pendant le sommeil: une fenêtre ouverte sur le rêve

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Sleepwalking and REM sleep behavior disorder (RBD) are overt, often violent behaviors exhibited by asleep subjects. They include complex verbal, motor and emotional behaviors that can be monitored by video and polysomnography. Several recent evidences demonstrate that these behaviors correspond to dream enactment, even in sleepwalking (Oudiette, Sleep 2008). This isomorphism between the mental content of the sleeper and his overt behavior can be used as a tool to test several hypotheses about dreaming, without the recall bias.
The dream enactments provide an overt insight into how our brains process information. We observed that complex sleeptalking and learned behaviors occurred during RBD, suggesting that a motor and temporal cortices source, as during wakefulness (Oudiette, Neurology 2008). The RBD model allowed us to show that REMs during REM sleep are coded in the same direction as the arm and hand movements, as if the dreamer were imitating the scanning of the dream images (Leclair-Visonneau, Brain 2010). In another set of experiments, sleepwalkers and RBD patients implicitly learned a motor sequence (a hand choreography) in the evening, which was improved after sleep. One sleepwalker partially replayed the motor sequence during a sleepwalking episode, representing the first direct and unambiguous demonstration of overt behavioral replay of a recently learned skill during human sleep (Oudiette, Plos One 2011). Eventually, we found that amputated patients had a complete body in dreams, while paraplegics (veen with congenital paraplegia) walked and danced in their dreams, suggesting a complete mental imaging of the motor process, possibly via mirror neurons. (Saurat, Con Cog 2011).

S14.4

Quelle activité cérébrale différencie des sujets avec grande et faible fréquence de souvenir de rêve ? Etudes en potentiels évoqués et en PET

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Dreaming is still a mystery of human cognition. The paucity of experimental results about the cerebral correlates of dreaming is due to the difficulty in knowing when dreaming occurs in the subjects sleep cycle. Indeed, the REM sleep hypothesis of dreaming has been challenged and it is now generally considered that dreaming can occur in any sleep stage (Nir & Tononi 2010; Ruby 2011). It is thus currently not possible to scan the dreaming brain versus the non dreaming brain.
To bypass this methodological difficulty, we proposed a new approach : to compare healthy subjects with high and low dream recall frequency (High recallers, HR versus Low recallers, LR), using various neuroimaging techniques. By comparing these two groups during sleep and wakefulness we can investigate the cerebral organization promoting the dreaming process or the memorization of the dream content . We used event-related potentials (ERPs) and positron emission tomography (PET) during wakefulness and sleep, to measure brain activity in high and low recallers (more than 3 dream reports per week versus less than 2 dream reports per month). During EPRs data acquisition, participants (18 HR vs 18 LR) passively listened to sounds while they were either watching a silent movie or sleeping at night. PET data were acquired in the afternoon while participants (21 HR vs 20 LR) were resting (wakefulness) or sleeping (N2, N3 and REM sleep). ERPs results revealed that the primary steps of auditory processing (N1 and MMN) match in HR and LR. However, latter responses, reflecting higher cognitive processing, dramatically differ in the two groups during pre-sleep wakefulness and during sleep (Eichenlaub et al. 2013). In the PET study, HR vs LR contrast showed rCBF increases in TPJ during REM sleep, N3, and wakefulness, and in MPFC during REM sleep and wakefulness (Eichenlaub et al. under review). This study reveals for the first time functional neuroanatomical correlates of the ability to recall dreams in healthy subjects and argue in favor of the forebrain "dream-on" hypothesis (Solms 2000). Results of the two studies support the hypothesis that high/low dream recall frequency is associated with particular cerebral functional organisation independent of the state of vigilance.

S14.5

Sommeil, rêve et conscience

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Sleep is characterized by varying levels of conscious awareness, being lowest in deep nonREM sleep and reaching levels close to wakefulness during REM sleep. Altered cerebral activity and neural networking during sleep may cause these phenomenological changes. We will present simultaneous EEG/fMRI data derived from all sleep stages which characterize waxing and waning of consciousness during sleep, and compare these results to pharmacologically induced loss of consciousness. Exploiting lucid dreaming, we will show how normal REM sleep dreaming and lucid dreaming differ in terms of cerebral activity, which may help to explain higher-order consciousness as observed in this particular dream state.

S15 Rôle et signalisation du VEGF dans le cerveau: son action sur la plasticité. / VEGF signaling and function in the brain: insight into brain plasticity.

S15.1

Interaction entre les signalisations VEGFR et Plexin dans la mise en place des connexions neuronales

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Vascular and axon guidance both share morphological and molecular similarities. For example, axon guidance cues are used in the guiding of developing blood vessels and, reciprocally, vascular endothelial growth factor (VEGF) signaling direct axon growth in the developing nervous system. Here we present evidence for crosstalk between axonal and vascular guidance cues during circuit formation in the nervous system. First, we show that some function of the Semaphorin (Sema) receptor PlexinD1 is mediated by transactivation of the vascular endothelial growth factor receptor 2 (VEGFR-2), which is selectively expressed by a subset of axonal tracts. Notably, activation of the VEGFR-2 signal transduction pathway by the PlexinD1 ligand Sema3E is required for proper development of the postcommissural fornix in mice. Recent data indicate that disruption of this signaling pathway could contribute to the defective fornix observed in the STOP null mouse model of schizophrenia. Finally, we will discuss new data on the role of Synectin, an important regulator of arterial differentiation, downstream of PlexinD1 receptor during the formation and fasciculation of brain commissures.

S15.2

Rôle de l´interaction entre les récepteurs au VEGF et NMDA dans le guidage neuronal et la transmission synaptique

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Emerging evidence indicates that the prototypic angiogenic factor VEGF regulates various neuronal processes via direct effects on VEGF receptors (VEGFRs) in neurons, yet little is known via which molecular mechanisms VEGF signals in neurons. We recently provided genetic evidence for a direct chemo-attractive effect of VEGF on neurons in vivo. We reported that VEGF, upon activation of the signaling VEGF receptor VEGFR2, chemo-attracts cerebellar granule cells (GCs) in the developing cerebellum. We further established that VEGF stimulates GC migration by enhancing NMDA receptor (NMDAR)-mediated currents and Ca2+ influx in immature GCs before synapse formation. Stimulation of VEGFR2 by VEGF activates Src-family kinases in GCs, which increases tyrosine phosphorylation of GluN2B expressing NMDAR and amplifies their NMDAR-mediated currents and Ca2+ influx. These findings reveal that VEGF is a modulator of NMDARs before synapse formation. We further hypothesized that this VEGF/NMDAR cross-talk could also be operational in hippocampal neurons in synaptic transmission and plasticity. Electrophysiological experiments demonstrated that VEGF potentiates NMDAR mediated synaptic transmission in CA1 and CA3 hippocampal regions, through a postsynaptic modulation of GluN2B expressing NMDAR. Our findings also showed a VEGF-dependent mechanism for regulating NMDAR localization at hippocampal synapses. Altogether, our results provide further evidence for the importance of this identified VEGF/NMDAR link in hippocampal dependent synaptic processes that may be critical for long-term synaptic plasticity, learning and memory.

S15.3

Les voies de signalisation des récepteurs au VEGF dans la neurogenèse adulte

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During development, the neural and vascular networks are closely associated and share common signaling molecules. Recent evidence has suggested that the receptors for vascular endothelial growth factors (VEGFs) are expressed by neural cells and provide trophic support to neural progenitor cells, as in endothelial cells.
Work from our lab has demonstrated that VEGFR3, the main receptor for VEGF-C, is expressed by neural stem cells (NSCs) in the adult brain and that signaling through this receptor regulates stem cell function. Using inducible *Glast-CreERT2* and *Cdh5-CreERT2* mice, we are able to specifically delete

VEGFR3 in the astroglial cells and endothelial cells (ECs), respectively. We then analyze the morphologic and genetic changes of NSCs and ECs in brain and retina. Our focus has also been drawn to the Notch pathway, which has been previously linked to VEGFR2/3 signaling in ECs. In addition, we are trying to elucidate the role of VEGFs/VEGFR3 in the embryonic brain where VEGFs are well expressed while cerebral ECs and certain types of radial glial cells also express VEGFR3. Through these various approaches, we expect to determine the role of VEGFRs in brain neurovascular interactions. Examination and further characterization of this signaling pathway will reveal downstream targets of potential therapeutic interest and their relation to other signaling pathways already implicated in regulation of neurogenesis.

S15.4
VEGF et niche neurogénique

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Increasing evidence, primarily based on physical proximity, suggests that the vasculature is an important component of stem cell niches. Neural stem cells (NSCs) of both the SVZ and hippocampus are indeed found to be intimately associated with blood vessels. Yet, in-vivo evidence for the effect of blood vessels on hippocampal NSCs activity is currently missing. To address this, we are analyzing hippocampal neurogenesis following experimental expansion of the niche vasculature. To manipulate the vasculature, conditional transgenic systems designed for a reversible VEGF gain of function in the hippocampus are being used. Neurogenesis is determined following switching-off transgenic VEGF after it has induced durable vessels in the dentate gyrus (DG), to uncouple already established direct effects of VEGF on NSCs and their descendents from effects of the vasculature per-se. We show that mere expansion of the DG vasculature is sufficient to maintain an elevated basal rate of neurogenesis. Enhancement of neurogenesis is proportional to the increase in microvascular density and does not come on the expanse of accelerated depletion of the exhaustible reservoir of hippocampal NSCs. Experiments of ´rejuvenating´ the niche vasculature in older mice support an exciting prospect of attenuating the natural process of age-dependent neurogenic decay via manipulating the niche vasculature.

S15.5
Le système VEGF interfère avec deux causes de lésions cérébrales néonatales: l´excitotoxicité et l´exposition à l´alcool

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In human neonates, brain lesions affect 2 to 2.5 children per 1000 births. Even if risk factors are several (preterm birth, exposure to toxins, hemorrhage…), the immaturity of the vascular system is suspected to play a key role in the etiology of these lesions. The aim of the present study was to determine if the VEGF system interfered with two toxic stresses frequently observed in neonates *i.e*. the excitotoxicity and the prenatal alcohol exposure. Regarding excitotoxicity, previous results from the laboratory showed that in $^{\delta/\delta}VEGF_A$ transgenic mice, glutamate-induced brain lesions were exacerbated suggesting that VEGF could play a protective action. Consistent with this hypothesis, we found, using a model of cultured cortical slices from mice neonates, that VEGF abolished the glutamate-induced necrosis observed in the cortical layers VI.[1] L-NAME, a pan inhibitor of NOS, abrogated the protective effect of VEGF while it favoured the excitotoxic action of glutamate. *In vivo* repression of nNOS by siRNA exacerbated excitotoxicity and mimicked the effects of NOS inhibitors. Finally, glutamate and VEGF modulated S-nitrosylation and phosphorylation of GluN1 and GluN2A subunits. Regarding prenatal exposure to alcohol, using *in vitro* and *in vivo* approaches in mice, we found that prenatal alcohol exposure induced a reduction of cortical vascular density, a loss of the radial orientation of microvessels, and altered expression of VEGFR1 and VEGFR2. Moreover, time-

lapse experiments performed on brain slices revealed that ethanol inhibited glutamate-induced calcium mobilization in endothelial cells and promoted death of microvessels. These effects were prevented by VEGF. Finally, in FAS human fetuses, we evidenced a stage dependent alteration of the vascular network in the cortex. In particular, the radial organization of microvessels was clearly altered from gestational week 30 to GW38. In conclusion, because alcohol possesses glutamate antagonist properties, all these data suggest that glutamatergic and VEGF systems interact during neuronal and vascular development in the immature brain.
Supported by FEDER, INSERM, IRIB, University of Rouen Région Haute-Normandie and La Fondation Motrice. *[1]ElGhazi et al., Neurobiol Dis, 2012; [2]Jegou et al., Ann Neurol 2012.*

S16 Développement d'oscillations gamma. / Development of gamma oscillations.

S16.1

Des oscillations gamma précoces lient le thalamus et le cortex en développement dans le système somatosensoriel de rats nouveau-nés

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During development, formation of topographic maps in sensory cortex requires precise temporal binding in thalamocortical networks. However, the physiological substrate for such synchronization is unknown. We report that critical period of somatosensory maps formation coincides with the expression of unique oscillatory activity in gamma frequency range - Early Gamma Oscillations (EGOs). Analysis of EGOs revealed their thalamic origin and a developmental recruitment of the intracortical mechanisms of gamma-synchronization (cortical inhibition). It was also shown that EGOs provide conditions for the plasticity in thalamocortical synapses through precise syncronization of thalamic and cortical neuronal activity and multiple replay of the sensory input during EGOs. Multiple replay of sensory input in the thalamocortical synapses during early gamma oscillation (“repetitio est mater studiorum”) may allow thalamic and cortical neurons to be woven into vertical topographic functional units prior to the development of “adult” gamma oscillations in mature brain.

S16.2

Différentiation postnatale de la signalisation des interneurones corticaux

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Gamma frequency (30-100 Hz) oscillations in the mature cortex underlie higher cognitive functions. Fast signaling of GABAergic inhibitory interneuron networks plays a key role in the generation of these network activity patterns. During development of the rodent brain, however, gamma activity appears at the end of the first postnatal week, and frequency and synchrony reach adult levels only by the fourth week. What are the network mechanisms underlying the maturation of gamma activity? Here I aim to summarize our current knowledge on the cellular and synaptic alternations of hippocampal fast-spiking perisoma-inhibiting basket cells (BCs) during the course of differentiation between postnatal day 6 (P6) and P25. I will provide evidence that during the maturation process, action potential duration, spike propagation time, duration of the GABA release period, and the decay time constant of unitary IPSCs decreases by 30-60%. Furthermore, the nature of $GABA_A$ receptor-mediated BC output signaling in the hippocampal dentate gyrus alters from depolarizing in the first to shunting in the second postnatal week. Thus, postnatal development converts BCs from slow into fast signaling devices. Computational analysis reveals that BC networks with young intrinsic and synaptic properties as well as reduced connectivity generate oscillations with moderate coherence in the lower gamma frequency range. In contrast, BC networks with mature properties and increased connectivity generate highly coherent activity in the upper gamma frequency band. Thus, late postnatal maturation of BCs enhances coherence in neuronal networks and will thereby contribute to the development of cognitive brain functions.

S16.3

Oscillations gamma dans les réseaux hippocampo-préfrontaux au cours du développement en conditions physiologique et pathologique

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Binding of neuronal assemblies by synchronizing their activity patterns in gamma-band oscillatory rhythms enables selective attention and mnemonic processing. The ability to generate such fast oscillatory rhythms is not a hallmark of the adult brain, but is present already during early development. While early gamma oscillations in the primary sensory cortices have been recently identified as organizers of topographic maps, their function and underlying mechanisms in neuronal networks involved in cognitive processing remain largely unknown. Combining *in vivo* extra- and intracellular electrophysiology with pharmacology and immunohistochemistry, we characterized for the first time the discontinuous patterns of oscillatory activity in the developing rat and mouse prefrontal cortex (PFC) and unraveled their mechanisms of generation within a prefrontal-hippocampal circuit. Low (16-40 Hz) and high (> 150 Hz) gamma oscillations are superimposed on theta bursts in the neonatal PFC, and time the firing of neurons in layer II/III. They result from the entrainment of local prefrontal networks that is driven by hippocampal theta bursts via direct synaptic projections. Neonatal gamma oscillations are strongly modulated by cholinergic afferents from the basal forebrain acting on muscarinic receptors. With ongoing maturation gamma oscillations are less confined to specific layers, and are broadly synchronized across the entire PFC. This coincides with the switch of prefrontal-hippocampal communication from uni- to bidirectional. Early gamma oscillations are particularly sensitive to insults during neonatal development (e.g. hypoxic-ischemic episode). Thus, they may not only contribute to the correct refinement of prefrontal-hippocampal circuitry under physiological conditions, but also to disease-related miswiring that has been associated with mnemonic and executive deficits.
Supported by the Emmy Noether-Program and SFB 936 of the DFG and German Ministry of Education and Research.

S16.4

Développement de la synchronisation neuronale au cours de la maturation du cerveau humain

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Recent evidence suggests that the adolescent brain is associated with profound modifications of anatomical and physiological properties of cortical networks. However, little is known about the course of synchronous oscillatory during the late brain maturation.
In the first study, development of neural synchrony was investigated during perceptual integration in participants (N=68) between 6-21 years. Perceptual integration was assessed with Mooney faces. EEG-recordings were analysed for spectral power as well as for phase-synchronisation of induced oscillations. In the second study, the development of visuo-spatial working memory (WM) was tested with MEG in a sample of n = 100 adolescent and adult participants (age range: 12-24 years). MEG-data were analysed for spectral power and a beamforming-technique was employed to locate the sources of oscillatory activity.
Study I: Improved detection rates and reaction times were accompanied by pronounced increases in spectral power and phase-synchrony in the theta-, beta- and gamma-band with increasing age. This development occurred in two distinct phases the transition being characterized by a marked reorganization of network topology and reduction of neural synchrony during adolescence.
Study II: During development, there was an increase in working memory capacity and improved inhibition of distractor elements. Spectral power of alpha- and gamma-band oscillations was significantly reduced in early adolescent participants (12-15 years) relative to adult participants during the encoding and delay period, suggesting a late maturation of neural oscillations in a fronto-parietal network.
These data suggest close relations between the increase of neural synchrony and the maturation of functional networks during the transition from adolescence to adulthood. In addition to the relevance for the understanding of normal brain development, the late maturation of neural synchrony may also be of importance for the emergence of neuropsychiatric disorders, such as schizophrenia, that correlate with impaired neural synchrony and a characteristic onset during late adolescence.

S16.5

Dissection des circuits de genèse des oscillations gamma et de la synchronisation à longue distance dans le bulbe olfactif chez l´animal éveillé

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Gamma oscillations were first reported in the olfactory bulb, however, the mechanism by which they are generated in the awake animal remains unknown. Using a selective pharmaco-genetic approach, we show that in the awake mouse olfactory bulb, gamma oscillations result from the synaptic interplay between excitatory output neurons and inhibitory interneurons, but not from gap junctions or from intrinsic interneuron-interneuron connections. The loss of output neurons abolishes gamma oscillations while their optogenetic activation amplifies gamma rhythms and reveals their resonant properties. Gamma oscillations are subdivided into high (70-100Hz) and low (40-70Hz) bands and we show that the excitatory-inhibitory balance of output neurons sets the gamma frequency. Furthermore, paired single-unit recordings demonstrate that low gamma reflects long-range synchronization of output neurons mediated by slow inhibitory kinetics. Thus, the frequency of gamma oscillations generated by output neurons reflects the relative recruitment of distant inhibitory synapses and the spatial scale of olfactory processing.

S17 Neurobiologie de la perception et de l'apprentissage chez l'insecte. / Neurobiology of insect perception and learning.

S17.1

Bases neurobiologiques de la mémoire et de l´apprentissage olfactifs chez l´abeille

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Honeybees contradict the notion that insect behaviour tends to be relatively inflexible and stereotypical: they live in colonies and exhibit complex social, navigational and communication behaviours as well as a relatively rich cognitive repertoire. Because these relatively complex behaviours are controlled by a brain consisting of only 1 million or so neurons, honeybees offer an opportunity to study the relationship between behaviour and cognition in neural networks that are limited size and complexity. I shall report electro- and optophysiological studies aiming to characterize memory traces at the single neuron and network level. The key structure will be the mushroom body, a high order integration centre of the insect brain. At its input sites the memory trace appears to be coded in the combinatorics of multiple sensory inputs, and at its output sites in multiple processing categories that represent the acquired values. This framework offers a structure for experimental and modeling approaches and prevents us from believing that the properties of the memory trace can be captured by just assuming flexible and experience dependent sensory-interneuron-motor connections. Rather we have to search for the coding/recoding, evaluating and predicting processes involved in storing the contents of memory, the engram. I conclude that the memory engram will not be found in single of neurons. Rather it results from distributed network properties that add their respective contents when memory is formed, processed (consolidated), and retrieved.

S17.2

Oscillations des neurones dopaminergiques et apprentissage olfactif chez la drosophile

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Drosophila flies can undergo distinct forms of associative learning. For example, they can memorize association between odorants and electric shocks. Short-term memory is formed after a single cycle conditioning. Multiple presentations of an odorant with electric shocks with rest intervals (spaced training) induce the formation of long-term memory (LTM), a consolidated memory phase that depends on *de novo* protein synthesis.
A fundamental duty of any efficient memory system is to prevent long-lasting storage of poorly relevant information. We studied dopaminergic neurons that innervate the mushroom body, the olfactory learning and memory center in Drosophila, and identified two pairs of neurons that play an

essential role in the regulation of memory consolidation. By *in vivo* imaging experiments using the calcium reporter, we evidenced a phenomenon of slow synchronized calcium oscillations (~0.1 Hz) in these neurons. The occurrence and magnitude of these oscillations were enhanced after spaced training, when LTM is formed. Interestingly, blocking those oscillating dopaminergic neurons specifically during the inter-trial intervals of a spaced training precluded LTM formation (Plaçais et al. 2012). We thus identified a mechanism of LTM gating that takes place at an early stage of memory consolidation, during spaced training.
Furthemore, we showed that upon starvation these oscillations were abolished to block LTM formation (Plaçais an Preat 2013), thus saving energy for the fly survival.

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S17.3

Traitement parallèle dans les centres supérieurs de la voie olfactive de l´abeille

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Honeybees display a rich diversity of odor-guided behaviors and possess an elaborated olfactory system. Axons from olfactory receptor neurons (ORNs) on the antennae project to the glomeruli in the antennal lobe (AL), and two segregated uniglomerular projection-neuron (PN) output tracts, the medial and the lateral antennal-lobe protocerebral tracts (m- and l-APT), project to higher integration centers in the mushroom bodies (MB) and lateral horn. This dual olfactory pathway is a unique feature in Hymenoptera (Rössler and Zube 2011, Arthropod Struct Dev 40:349; Galizia and Rössler, 2010 Ann Rev Entomol 55:399). We asked whether this system serves parallel processing of olfactory information using simultaneous multi-unit recordings from PNs of both tracts. The results show that PNs of both tracts are activated by widely overlapping response profiles, which is a requirement for parallel processing. Whereas lateral-tract neurons responded faster and had broad response profiles suggesting generalized odor coding properties, medial-tract neurons responded slower and with high odor-specificity (Brill et al., J Neurosci, in press). In analogy to the “what-” and “where-” subsystems in the vertebrate visual pathway the two parallel subsystems in the honeybee olfactory pathway may provide “what-” (quality) and “when” (temporal) olfactory information. Temporal response characteristics further suggest that the dual olfactory pathway supports parallel odor processing and, potentially, coincidence coding at the level of MB intrinsic neurons (Kenyon cells, KCs). Ultrastructural investigations at the level of PN-KC synapses in the olfactory subregions of the MB calyx revealed an enormous space for long-term synaptic plasticity in these higher-order olfactory centers (Groh et al. 2012, J Comp Neurol 520:3509). The results of these studies suggest that parallel processing and coincidence coding of different features from similar odors via a dual olfactory pathway is likely to enhance the odor coding and memory capacities in the brain of this highly olfactory insect. Supported by DFG SPP 1392 (RO 1177/5-1).

S17.4

Représentation nerveuse des odeurs dans le cerveau de l´abeille : comportement et imagerie cérébrale

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Through different processing steps, olfactory systems create evolving internal representations that differently represent odors' chemical characteristics and/or biological value. In addition, experience may modify how odors are represented in the olfactory system. Honeybees are a traditional experimental model for addressing these questions, and the study of olfactory perception, learning and memory can be addressed using a range of behavioural protocols associated with neurophysiological and neuroanatomical techniques. In honeybees, odors are detected by sensory neurons on the antennae, which project to a primary processing centre, the antennal lobe (AL). Then two main tracts of projection neurons convey odor information to higher brain centers, the mushroom bodies (MB) and the lateral horn (LH). The honeybee olfactory system arbors two mostly non-

overlapping subsystems, from the AL to the MB and LH, corresponding to the lateral- and medial-tracts of projection neurons. Previous work has almost exclusively studied the representation of odors in one subpart of the AL (corresponding to the lateral tract) and in the MB, but odor representations in the medial part of the AL and in the LH have remained mostly unaddressed. Using in vivo calcium imaging, we studied odor representation in these two neglected regions of the honeybee brain. Using a panel of aliphatic odorants, we find that the two AL subsystems differentially code odors' functional group and chain length information, suggesting that both subsystems contribute for shaping honeybees' behavioural responses to these odorants. In addition, we found a clear segregation of the two subsystems for coding different pheromone types. While queen-emitted pheromones are processed by the lateral system, brood pheromone is processed by the medial system. Our recordings at the next processing level, in the LH, show that it contains odor-specific maps in which different pheromone types are clearly segregated. We will discuss the implications of these findings for understanding how the insect brain classifies odorants with different biological meanings.

S17.5
Plasticité de l´olfaction chez le papillon de nuit mâle: neurones, hormones et comportement

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Moths, as many other animals, use olfactory cues to communicate and to orient towards different types of resources. The most well known example is sex pheromone communication, where females emit tiny amounts of a species-specific blend of compounds, which are detected by males over large distances. Male moths have a specialized, highly sensitive olfactory sub-system dedicated to sex pheromone detection and processing, leading ultimately to an oriented flight towards the conspecific pheromone signal. In male moths, these volatiles are detected by specialized olfactory receptor neurons on the antennae. Their axons project via the antennal nerve into a specific part of the primary olfactory centre, the antennal lobe (AL), the macroglomerular complex. There they make synaptic contact with intrinsic AL neurons, the local interneurons, and with AL output neurons, the projection neurons, which transfer information to higher brain centres, such as the mushroom bodies and the lateral protocerebrum. After protocerebral processing, the information ultimately induces specific sex pheromone-oriented behaviour. This behaviour has long been thought to be innate and the associated sensory system to be hard-wired. There is now, however, increasing evidence for plasticity within the sex pheromone system of male moths. In noctuid moths we have shown that the physiological state, such as the hormonal or mating state, have a strong impact on sex pheromone responses. When searching for the physiological origins, we identified hormones and biogenic amines as important modulators of olfactory-guided behaviour. Juvenile hormone, ecdysteroids and biogenic amines seem to regulate pheromone-guided behaviour during adult maturation via modulation of the olfactory network within the brain over periods of a few days, whereas the peripheral olfactory system does not change its sensitivity. Rapid mating-induced inhibition of pheromone attraction, on the other hand, appears to be independent of hormonal modulation, and the inhibition of sex pheromone responses within the AL, must originate from fast neural modulation. These mechanisms might help insects to adapt to internal and environmental conditions in order to optimize reproduction success without a waste of energy.

S18 Intégration multisensorielle. / Multisensory integration.

S18.1
Le rôle des oscillations grande-échelle dans l´intégration multisensorielle

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Picture yourself on a crowded sideway with people milling around. The acoustic and visual signals generated by the people provide you with complementary information about their location and motion. Thus far, it is not well understood how such inputs from different sensory channels are integrated. Here, I will suggest that coherence of neural signals may be an essential mechanism supporting multisensory perception. Data from recent studies will be discussed which indicate that coupled oscillatory activity, in particular at frequencies in the beta- and gamma-band, may serve to link neural signals across uni- and multisensory regions and to express the degree of crossmodal matching of

stimulus-related information. These results argue for a new view on multisensory processing, which considers the dynamic interplay of neural populations as a key to crossmodal integration.

S18.2
Dynamique de l´intégration multisensorielle

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The temporal coincidence of auditory and visual events is a necessary condition for multisensory integration. Crucially however, temporal coincidence is defined by the brain, not by veridical simultaneity. For instance, AV speech perception tolerates as much as 200-300 milliseconds of asynchrony between auditory and visual speech inputs; consistent with perception, a temporal window of integration can readily be observed neurophysiologically and considered a marker for predictive coding in the context of AV speech. Beyond temporal coincidence, is temporal coherence across sensory modalities sufficient to enable the construction of a supramodal object in the brain? To address this question, complex AV dynamic patterns were presented to participants while they were recorded with magnetoencephalography (MEG). Participants were trained in a difficult visual coherence discrimination task with or without sounds. We show that temporally coherent AV stimulation drove a supramodal processing mode of cortex and importantly, that an AV learning history selectively affects downstream plasticity in areas classically considered to be unisensory (here, visual cortices). These results suggest that in natural environments, the brain exploits temporal correlations for building internal representations irrespective of the sensory modality of inputs. Finally, (multisensory) integration also implies the loss of temporal information yet our awareness of time and temporal order across sensory modalities can be surprisingly precise. A major question thus emerges: how can integration and segregation occur simultaneously in the brain, for the same informational content? It is here proposed that the encoding and the structuring of events in time capitalize on the natural dynamics of brain processes at an early stage of sensory processing. Specifically, the phase of neural oscillations is proposed to serve an automatic temporal flagging mechanism across sensory modalities while preserving the integrative properties of the system.

S18.3
Voir ce que l´on entend - les bases neurales de l´intégration audiovisuelle

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Integrating information across the senses is critical for effective interactions with the environment. Over the past decade, evidence has accumulated that multisensory integration is not deferred to later processing in association cortices but starts already in primary, putatively unisensory, areas. Given this multitude of multisensory integration sites, characterizing their functional similarities and differences is of critical importance.
Combining psychophysics, functional imaging and effective connectivity analyses, our research demonstrates that multisensory integration emerges in a functional hierarchy with temporal coincidence detection in primary sensory, informational integration in association and decisional interactions in prefrontal areas. Audiovisual interactions in low level sensory areas are mediated via multiple mechanisms including feedforward thalamocortical, direct connections between sensory areas and top down influences from higher order association areas.
In addition to identifying where in the brain sensory information is integrated, we also aimed to provide insights into the underlying computational operations using multivariate analyses at the macroscopic level of the BOLD response. In line with Bayesian principles our results suggest that audiovisual neural representations are formed by integrating sensory signals weighted according their relative reliability and task-relevance.

S18.4
Mécanismes prédictifs dans l´intégration audiovisuelle du langage parlé

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That feed forward and top-down propagation of sensory input use separate frequency channels is an appealing assumption for which evidence remains scarce. I will present several studies using MEG and intracranial depth recordings, which provide evidence that the brain uses frequency multiplexing to propagate ascending and descending speech-related information.

S18.5
Les mains comme outils pour façonner les représentations du corps et de l´espace pour l´action

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The binding of visual information available outside the body with tactile information arising, by definition, on the body, allows for the representation of the space lying in between, which is often the theatre of our interactions with objects. The definition of what has become known as “peripersonal space”, originates from single-unit electrophysiological studies in monkeys, based on a class of multisensory, predominantly visual-tactile neurons. Such neurons, identified in several parietal and premotor regions of the monkey brain, respond both to visual and tactile stimuli, their visually evoked responses being stronger when objects are closer to the tactile receptive field. These functional properties allow for the coding of visual information in advance to the contact with the body (e.g., with hands), in a body-part centred reference frame. Here, we will first review the behavioural and functional neuroimaging evidence that suggested the existence of a similar representation of the peripersonal space in humans, which is similarly based upon a network of posterior parietal and premotor areas. We´ll present results indicating that, similar to non-human primates, the peri-hand space in humans is represented in hand-centred coordinates. Our focus will be the following question: what is the function of such multisensory systems? We will provide behavioural and electrophysiological evidence for their implication in the planning and execution of both defensive (avoidance) and appetitive (reach-to-grasp) actions on nearby objects. This evidence demonstrates how multi-sensory-motor systems may process hand-related visual inputs within just 70 ms following a sudden event, and before the execution of a grasping action. Overall, previous and on-going work in our laboratory indicate that performing actions induce a fast remapping of the multisensory peripersonal space, as a function of on-line sensorimotor requirements, thus supporting the hypothesis of a role for peripersonal space in the generation and control of rapid hand-centred avoidance and acquisitive actions.

SP01 Symposium ITMO Neurosciences, Sciences cognitives, Neurologie, Psychiatrie / ITMO Neuroscience, Cognitive Sciences, Neurology, Psychiatry Symposium

SP01.1
Pas de résumé

SP01.2
Imagerie bi-photonique de l´inflammation après lésion de moelle épinière

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Macrophages from the peripheral circulation and those derived from resident microglia are among the main effectors of the inflammatory response in central nervous system pathologies, yet their precise roles remain controversial. We will present a quantitative assessment of their recruitment and

redistribution dynamics as well as the study of their real-time interactions with lesioned neurons in mice with spinal cord injury or with EAE.
We used Thy1-CFP//LysM-GFP//CD11c-YFP triple transgenic mice to track the distributions and interactions of infiltrating LysM(+) macrophages and resident CD11c(+) macrophages of microglial origin relative to injured Thy1(+) dorsal column axons. To this end, we developed a method for implanting windows over the exposed spinal cords for repeated two-photon fluorescent imaging. With this approach we can achieve simultaneous four-color fluorescence imaging, perform time-lapse of individual cells over several hours or acquire images with sub-cellular resolution, for up to 30 imaging sessions on the same animal over the period of one year post-implantation. We then performed quantitative correlative analyses of the fluorescence images.
We will show that for both pathologies, CD11c(+) and LysM(+) cells have differential recruitment dynamics to lesioned sites over time. After spinal cord injury, LysM(+) cells are rapidly recruited and peaked within 2-5days. They redistributed mostly caudally towards retracting axon terminals by 7-8days. By contrast, CD11c(+) cells peaked at the injury site between 18-22d, and were preferentially distributed rostrally towards degenerating axon terminals. At early post-injury times, axon retraction and deterioration are independent of interactions with LysM(+) and CD11c(+) cells whereas 4-6 days after injury LysM(+) cells may 'trigger' collapse of axon terminals but never retraction despite strong in vitro evidence showing that activated macrophages actively promote the retraction of dystrophic axons. Following EAE induction, we found that earlyclinical signs associate with a large and rapid recruitment of LysM(+) cells concentrated near blood vessels. Conversely, as EAE symptoms progressed the number of LysM(+) cells decreased towards baseline whereas the number of CD11c(+) cells continued to increase. Altogether our results support a differential role in disease progression between different mononuclear phagocyte sub-populations.

SP01.3
Génétique du trouble bipolaire et système limbique

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SNAP25 is a presynaptic protein, part of the SNARE complex implicated in the synaptic vesicle membrane docking and fusion. We previously identified a functional SNAP25 risk variant for early-onset bipolar disorder. Here, we show that this variant is associated with decreased left hippocampus volume, a neuroanatomical feature of early-onset bipolar disorder. We also found associations of this risk variant with brain anatomical and functional connectivity, assessed with DTI and resting state fMRI in healthy controls and patients with bipolar disorder. We discuss the interpretation of our findings in the context of neurobiology of mood disorders and synapses.

SP02 Symposium Fédération pour la Recherche sur le Cerveau - Société des Neurosciences / Fédération pour la Recherche sur le Cerveau - Société des Neurosciences Symposium

SP02.1
Robustesse de l´excitabilité neuronale: rôle des co-régulations de canaux ioniques

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As most complex biological systems, the nervous system of higher organisms is astonishingly robust to external and internal perturbations, as exemplified by the cognitive recovery that follows major injuries or the long preclinical asymptomatic phase of Parkinson's disease. Ultimately, this robustness relies on the ability of neurons and neuronal networks to maintain stable patterns of activity. Over the past twenty years, a number of studies have demonstrated that neuronal intrinsic and synaptic ion channel properties and expression are dynamically regulated in response to activity perturbations in order to maintain a stable level of activity in neuronal networks. Our studies suggest that, rather than simple up- and down-regulation of ion channel expression, complex co-regulation of the expression and/or properties of functionally-overlapping ion channels underlies the robustness of neuronal activity. Co-regulation of ion channels would in fact provide robustness not only against external

perturbations but also against the variability in the expression and properties of ion channels. Therefore, our findings suggest that the co-variability of ion channel properties observed in different invertebrate and vertebrate neurons is both a source and an expression of the robustness of neuronal activity.

SP02.2

Neurones transitoires migrateurs: rôle d'organisateurs dans le développement du cortex cérébral

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The neocortex represents the brain structure that has been subjected to a major expansion in its relative size during the course of mammalian evolution. An exquisite coordination of appropriate growth of competent territories along multiple axes and their spatial patterning is required for regionalization of the cortical primordium and the formation of functional areas.
During development, progenitors expressing the Dbx1 homeodomain transcription factor are strategically positioned at boundaries between compartments, including the pallial-subpallial borders in mice, and their location is coinciding with signaling centers. Using genetic tracing and ablation in mice we have shown that at the earliest stages of cerebral cortex development $Dbx1^+$ progenitors give rise to subsequent waves of glutamatergic neurons which have the unique characteristics to migrate tangentially at long distance from their generation site and to be transiently present during development. Cortical patterning and the fine tuning of neuronal numbers leading to the formation of functional areas depends on the migration of Dbx1-derived transient neurons. By signaling to cortical progenitors in the mitotic compartment these neurons serve as organizers during development, therefore acting as “mobile signaling units”.
Our work points towards a novel general strategy for long-range patterning in large structures whereby morphogens at signaling centers induce the generation of migrating cells which by producing themselves morphogens deliver them at distant locations.
We will discuss the molecular mechanisms mediating transient neuron function in cortical development and how the acquisition of new progenitor domain(s) at patterning centers and of migrating transient signaling neurons in mammals might represent one of the evolutionary steps leading to increase vertebrate brain complexity.

SP02.3

Etude de la communication GABAergique entre interneurones et précurseurs d´oligodendrocytes dans le cortex somatosensoriel au cours du développement

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Myelination is required to speed neuronal transmission. Major developmental brain disorders induce irreversible myelination defects. One possibility to overcome myelination impairment is to stimulate the production of oligodendrocytes from endogenous oligodendrocyte precursor cells (OPCs; also named NG2 cells). To reach this aim, it is necessary to understand first the cellular signals that control OPC activity, proliferation and differentiation. Interestingly, OPCs are contacted by *bona fide* neuronal glutamatergic and GABAergic synapses that might influence OPC development. We initially studied the GABAergic synaptic communication of OPCs during myelination of the somatosensory cortex. We demonstrated that spontaneous GABAergic synaptic activity in OPCs is higher during the production of pre-oligodendrocytes (PN7-PN14); functional synaptic contacts disappear after. However, a mode of extrasynaptic communication that involves a form of GABA spillover is established after the loss of synapses. In neurons, synaptic and extrasynaptic $GABA_A$ receptors ($GABA_A$Rs) differ in their subunit composition. Therefore, the postnatal switch of GABAergic transmission in OPCs might be accompanied by changes in $GABA_A$R subunit expression. Single cell RT-PCR and pharmacological experiments showed that γ2, a crucial subunit for the clustering of $GABA_A$Rs at postsynaptic sites, is down-regulated in OPCs prior to the loss of synapses. In keeping with the synaptic nature of γ2 in neurons, the expression loss of this subunit is an important molecular determinant that impacts the change of GABAergic transmission modes. More recently, we performed paired recordings between interneurons and OPCs during their active phase of differentiation (PN7-PN14). Our results

demonstrated that OPCs are synaptically contacted by fast-spiking (FSI) and non-fast-spiking (NFSI) interneurons. However, a predominant input was received by FSI, a class of interneuron that constitutes a minor population at this stage. Altogether, our results provide a framework for further research aiming at deciphering the role of GABAergic synapses in OPCs and open new perspectives to understand the signaling mechanisms between interneurons and OPCs in the healthy and pathological brain.
Support: FRC, ANR blanche, ARSEP.

SP02.4
Mouvements miroirs congénitaux: du gène à la fonction

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The ability to perform independent movements with our two hands is an important aspect of our daily activities, such as opening a jar, holding a cup while filling it with coffee, controlling a steering wheel while moving the gear lever, typing, and playing a musical instrument. However, the neurodevelopmental basis and the functionnal network underpinning the lateralization of the motor control are poorly known. Congenital mirror movement is a unique paradigm to adress these issues. Mirror movements are involuntary movements of one side of the body that accompany and mirror intentional movements on the opposite side. They mainly involve the distal upper limbs and reflect various morphological and functional abnormalities of the motor network. Congenital mirror movement is a rare movement disorder that can be familial with an autosomal dominant inheritance. Mirror movements results in an inability to perform tasks requiring skilled bimanual coordination or purely unimanual movements. The patients have also pain in the upper limbs during sustained manual activities. Using the combination of conventional linkage analysis and whole exome analysis, we demonstrated the heterogeneity of the disorder and identify a culprit gene for mirror movements, *RAD51*. *RAD51* is a well-known gene, identified for a completely different function: it encodes a key protein of the DNA repair system.
We are currently investigating the morphological and functional disturbances linking *RAD51* haploinsufficiency to alterations of motor control lateralization. We will comprehensively characterize the expression pattern of RAD51 during mouse brain development with specific focus on corticospinal tract and transcallosal fibers. We will then generate conditional KO mice and a haploinsufficient mouse for the *RAD51* gene and analyze their motor phenotype and the morphology of their motor network. In human, we will investigate the pathophysiological mecanisms of mirror movements using neuroimaging and neurophysiology. Results of preliminary experiments wil be shown during the presentation.

SP02.5
Recherche des facteurs de susceptibilité génétiques de la Maladie d´Alzheimer par analyses génomiques à haut-débit

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Alzheimer´s disease (AD) is the prime cause of dementia and presents a strong genetic predisposition (60 to 80% of the attributable risk). Beyond *APOE* -a major recognized genetic determinant of AD- and despite strong research efforts, there was until recently an absence of consensus on the genetic determinants of AD. This frustrating observation was mainly driven by major methodological issues. However, as for other multifactorial diseases, the study of AD genetics benefited from the use of very high-throughput genotyping analyses. These approaches (genome-wide association study or GWAS) involve case-control studies including thousands of individuals and hundreds of thousands (or even millions) of genetic polymorphisms. In addition to APOE, these GWASs allowed us to characterize 9 new AD genetic determinants from 2009 to 2011.
However, a large part of the genetic risk for this disease remains unknown. We thus conducted a large two-stage study based upon GWAS on individuals of European ancestry. In stage 1, we used genotyped and imputed data (7,055,881 single nucleotide polymorphisms (SNPs)) to meta-analyse four previously published GWAS datasets consisting of 17,008 Alzheimer´s disease (AD) cases and

37,154 controls. In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 AD cases and 11,312 controls. In addition to the apolipoprotein E locus, 19 loci reached genome-wide significance ($P< 5x10^{-8}$) in the combined stage 1 and stage 2 data of which 11 are new associations with AD.
The characterization of these new AD genetic determinants is likely going to strongly modify our perception of the pathophysiological process involved in AD.

SP03 Handicap et plasticité - Session organisée par l'ARC2 "Qualité de Vie et Vieillissement" / Handicap and plasticity - Session organized by the Academic Research Community " Quality of life and ageing " (ARC 2)

SP03.1

Présentation de la session et des recherches sur le thème “Neurosciences et Handicap” au sein de l'ARC2 de la Région Rhône-Alpes

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The Rhône-Alpes region Academic Research Community 2 (ARC2) is devoted to “Quality of life and Aging”. It groups research centres from the Rhône-Alpes region focussing on issues related to Quality of life and Aging, with an economic and societal aim. Its ambition is:
- To structure networks of research actors, around major societal challenges, which federate several research fields and which represent a strong potential for socio-economic, sanitary or cultural development for the Rhône-Alpes region.
- To reinforce connections with companies and industry, by contributing to regional economic development and by fostering the creation of new companies and start-ups, that will benefit from the strong research and knowledge basis of the ARC2 cluster.
- To facilitate interactions between companies and research laboratories.
- To provide for knowledge transfer from research centres to socio-economic and political actors who may be unaware of real needs and specific issues.
- To amplify and structure these regional actions by promoting international complementary partnership, in order to achieve European visibility, at least.
Within these main goals, the ARC2 axis “Handicap and Plasticity” includes research projects aiming at improving quality of life, by unveiling physiological mechanisms, the impairment of which may induce sensory or cognitive handicaps. This special session on Handicap and Plasticity will start with an introductory framing talk, followed by the presentation of the research results of the 2013 “Handicap and Plasticity axis” award winners.

SP03.2

L'expérience sensori-motrice modifie la manière dont le cerveau traite les informations auditives et visuelles

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How does sensorymotor experience shape how the brain processes sensory signals and binds them into a coherent percept?
First, we will explore how the brain adapts when deprived of visual inputs since early childhood. Visual deprivation may induce plastic changes not only in the visual system, but also in the remaining intact sensory-motor system, secondary to altered experience using the spared modalities. Our results demonstrate that occipital, usually visual, areas are reorganized and recruited by auditory processing primarily via cortico-cortical connectivity. This functional incorporation into other sensory systems preserves the structural integrity of visual association areas, while early visual areas are more susceptible to disuse atrophy.
Second, we will investigate how sensorymotor experience such as music training tunes how the brain temporally binds signals from multiple senses. Behaviourally, musicians exhibited a narrower temporal

integration window than nonmusicians for music but not for speech. At the neural level, musicians showed increased audiovisual asynchrony responses and effective connectivity selectively for music in a superior temporal sulcus-premotor-cerebellar circuitry. Our findings show intimate links between action production and audiovisual synchrony perception. Our sensorymotor experience determines whether and how we integrate auditory and visual inputs into a unified percept.

SP03.3

Liage audiovisuel et perception de la parole en conditions adverses

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Seeing the face of one´s interlocutor not only helps to better UNDERSTAND through "lip reading", but also to better HEAR. Actually, we have recently developed a new experimental paradigm showing that the identification level in audiovisual speech perception is preceded by a binding level able to control and modulate fusion. The principle is to precede the target stimulus by a contextual audiovisual stimulus in which sound and image are incoherent. This contextual inconsistency modulates the audiovisual perception due to a binding/unbinding effect, according to which subjects consider that, since the sound and picture are incoherent, they should not be merged and then untie the two sensory modalities. Unbinding effects seem to be fast: one to two seconds are enough to produce the effect. Rebinding is then achieved by presenting a new coherent sequence after the incoherent context and before the target. The various experiments done in this audiovisual binding effect will be presented, together with the research program envisioned in the next two years to better understand how binding proceeds and what are its implications in the processing of speech in noise and adverse conditions in subjects with normal hearing, through a combination of behavioral and neurophysiological approaches, and also to determine, by comparison, how these mechanisms work in patients with hearing deficits.

SP03.4

Un modèle de simulation des processus de récupération de l'équilibre chez les populations âgées et handicapées

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Fall is a major problem for elderly and people with balance troubles, increasing fear of falling and reducing mobility. Recently, Aftab (2012) proposed a numerical model that predicts the appropriate actions of balance recovery (BR) from a given situation. The BR simulation tool is made of a mechanical model: an inverted pendulum-plus-foot, supplemented by a flywheel representing upper-body angular inertial effects (UBI). This model is close-looped with a predictive controller which selects the adequate control actions that minimize a cost function (Aftab et al,2012), to maintain the mechanical model's balance.This model has only been validated on young adult behaviors, but gives considerable perspectives for other populations. So, our further objective is to represent elderly and disabled populations' behavior under unbalanced conditions.In adapting few model parameters, like reaction time or physical limitation such as maximal trunk rotation, we obtained close-to-experimental results, in a one-step BR scenario from a lean angle perturbation, for an elderly subjects' configuration.

[Figure 1]

Figure shows experimental step length from Hsiao & Robinovitch (2007) (white bars) compared to predicted step length from our model, with a set of adjusted parameters (black bars) from an initial balance perturbation (tether-release method). As we can see, predictions are very accurate. However, a lack in this model concerns sensori-motor integration of the perturbation. Future work has the ambition to model and integrate to the model the balance sensors (visual, vestibular and proprioceptive). Indeed, better understand how these systems are linked to biomechanical actions could advance knowledge on elderly and disabled people's ability to recover balance.

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SP03.5

Les fuseaux de sommeil n´inhibent pas la réponse corticale à la douleur: étude par enregistrements de scalp et intracérébraux

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Sleep spindles, generated by the thalamic reticular nucleus, are transmitted into the thalamocortical network. Given their inhibitory nature, they are seen as a sleep protection mechanism. Therefore they may represent one of the factors preventing systematic sleep disruption by nociceptive stimuli.
The aim of this study was to test this inhibitory effect of sleep spindles on cortical responses evoked by laser thermo-nociceptive stimulations. The stimulation intensity was kept stable during the whole night, slightly above individual pain threshold, during electrophysiological recordings for nine healthy subjects and eleven patients with intracerebral recording electrodes. For scalp or intracerebral recordings, laser potentials were analyzed in sleep stage 2, according to whether the stimulations were delivered during or outside a sleep spindle. Sleep spindle detection was done on fronto-parietal electrodes for scalp recordings and in the thalamus for intracerebral recordings. Scalp results showed the presence of N2-P2 component, whether stimulations were delivered inside or outside sleep spindles. Intracerebral results showed the persistence of the evoked response in the posterior insula, a structure known to systematically respond to nociceptive stimulations, and with larger amplitude when the stimulations were delivered during rather than outside sleep spindles in the thalamus.
Our data suggest that the hypothesis of an inhibitory effect of spindles does not apply to nociceptive information processing. Within a sleep stage globally inhibitive, sleep spindles could represent a micro-state where cortical inhibition could be transiently lifted, facilitating nociceptive information processing.

SP03.6

Rôle du microenvironnement cellulaire dans la cicatrisation cutanée

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Cell adhesion to the extracellular matrix stimulates signal transduction cascades known to impinge on cell behaviour. Although integrins are the major cell surface receptors for the extracellular matrix, other adhesive systems including matrix and membrane-bound glycosaminoglycans molecules such as syndecans, have recently drawn the attention as an important class of adhesion receptors working in concert with integrins. Like integrins, syndecans lack intrinsic enzymatic activities and transmit intracellular signals by interacting, through adhesion complexes, with various effector proteins, including both structural and signalling molecules and thus regulate cell shape and motility. Basal keratinocytes of the epidermis adhere to their underlying basement membrane through a specific interaction with laminin 332, which is composed by the association of α3, β3 and γ2 chains. Increasing interest in its biological function has emerged from the understanding that distinct biological cellular events are assigned to laminin 332 depending on the level of processing of its α3 and g2 subunits. For instance, laminin 332 lacking its carboxyl-terminal globular domains 4 and 5 (LG45) induces the stable adhesion of keratinocytes, while the precursor laminin 332 (including the LG45 domain) is found in migratory situations such as wound repair. Recent findings have even suggested that the α3 chain C-terminal domains LG45 may have a role to play during the epithelialization phase in wound repair. Integrins are primarily involved in these processes, however recent findings have reported that the LG45 domain may influence the cellular behaviour through binding of the heparan sulphate proteoglycan syndecan-1. Participation of syndecan-1 in cytoskeleton dynamic and cell movement after cell adhesion to laminin 332 is a challenging hypothesis that opens up new avenues of research but also promising clinical perspectives for the development of innovative skin repair strategies.

SP04 Fondation IPSEN - Prix Plasticité Neuronale 2013 / Fondation IPSEN - Neuronal Plasticity Prize 2013

SP04.1
De la synapse au réseau: un voyage Hebbien

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For the last four decades LTP has been the dominant model for studying Hebbian learning rules and how they contribute to information storage in the mammalian brain. In the process much has been learnt about the physiology and molecular biology of synaptic plasticity, but the exact relationship between LTP and learning remains elusive. I will discuss the historical background leading up to the discovery of LTP, go on to consider recent evidence which challenges the view that LTP is primarily expressed as a postsynaptic change, and conclude by discussing the experimental approaches that are being adopted to settle the still incompletely resolved issue of whether LTP provides the neural substrate for memory.

SP04.2
Encodage de la mémoire et sa persistance: des récepteurs NMDA aux schémas

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The mechanisms responsible for the making, keeping and losing of memories is one of the grand challenges of contemporary neuroscience, and a problem with translational potential with respect to education, neurodevelopmental disorders in children and age-associated memory disorders.
Following the discovery of long-term potentiation (LTP) by Bliss and Lömo, a key issue was whether activity-dependent synaptic potentiation plays a causal role in memory encoding. Studies from my laboratory using the watermaze (Morris et al, 1982) and with selective antagonists of the NMDA receptor (AP5) established that blocking LTP impaired learning but had no effect on memory retrieval (Morris et al, 1986). Later work by Tonegawa and others using molecular-genetic approaches extended these findings, while we also established boundary conditions on the contribution of NMDA receptors to learning. New paradigms looking specifically at 'episodic-like' encoding of memory in both watermaze and event-arena tasks established that NMDA receptor-dependent mechanisms are absolutely necessary for memory encoding but not for retrieval.
The issue of 'keeping' memories has been addressed in laboratories looking at memory consolidation, including that of Dudai, leading to the distinction between cellular and systems aspects of consolidation. New work in Edinburgh has reconsidered the systems aspect from the perspective of whether the subjects do or do not have prior knowledge, revealing that prior experience has a major impact on ease of new learning such that gradually learned frameworks or 'schemas' accelerate the rate at which new paired-associate information can be 'assimilated' (consolidated) into schemas stored in the neocortex (Tse et al, 2007). Learning is again dependent on hippocampal NMDA receptors, but systems consolidation now involves a rapid, on-line interaction between the hippocampus and medial prefrontal cortex. Up-regulation of plasticity-related genes (zif268, Arc) occurs in the neocortex when new information being processed in hippocampus is consistent with a relevant activated schema, but is lower for novel paired-associate information that cannot be assimilated (Tse et al, 2011). Further research on the neurobiology of neocortical schemas is an exciting challenge.

SP04.3
Consolidation de la mémoire: d´un début concluant à une fin incertaine

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Memory consolidation is the hypothetical process in which a memory item is transformed from a short- into a longer-term form. The process is conventionally described at two levels of analysis: "synaptic",

referring to stabilization of cellular information at local nodes in the neuronal circuits that encode the memory; and "systems", referring to reorganization of internal representations over distributed brain circuits. Synaptic consolidation probably serves as a subroutine in systems consolidation. The beginning of consolidation is assumed to be reflected in established or candidate molecular and physiological signatures starting immediately after encoding of the memorandum.
The end of consolidation is, however, more of an enigma. First, ample evidence indicates that consolidation can linger for long and at times reboot, both at the synaptic and at the systems level, once long-term memory is reactivated. Second, systems consolidation of the memory of unique events (i.e. episodic memory) transforms the quality of the stored information from a contextually-rich to a lean, semantic form, generating dynamic palimpsests of knowledge in which the distinctiveness of the original items is blurred. This again questions the notion that the consolidation of distinct memory items ever ends. Interestingly, the semantication of episodic information is reflected in decreased activation of retrieval circuits in the brain on the one hand, but enhanced correlation of the activity with correct retrieval on the other. It is tempting to propose that the minimization of energy expenditure resulting from the transformation of the engram into a distilled form that still allows the retrieval of the gist of past events while requiring only parsimonious brain activity, might have been an adaptive pressure that had promoted the evolution of systems consolidation in the first place.
All in all, understanding memory consolidation at different levels of brain and cognition illuminates the mechanisms and function of memory systems, and contributes to the understanding of memory phenomena of great impact in real life, such as the resilience of traumatic memories and the widespread occurrence of false recollection.

SP05 Bioimagerie à haut contenu des cerveaux d'organismes modèles : challenges et perspectives / High-content bioimaging of model organism brains: challenges and perspectives

SP05.1
Pas de résumé

SP05.2
Neurogenesis and transcriptome-wide analysis of transcriptional regulators in the zebrafish

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Teleosts have an enormous capacity to regenerate neural tissue. New neurons are born in the adult teleost brain during the entire life of the animal. We previously showed that the neurogenic niche of the zebrafish telencephalon is remarkably similar to that of mammals. Moreover injury of the telencephalon is rapidly repaired without glial scar formation.
As a prerequisite to investigate the regulatory gene hierarchies in the adult telencephalon, we characterised the expression pattern of more than 1100 transcriptional regulator (TR) genes in the adult zebrafish telencephalon in a genome-wide, whole mount in situ screen.
Comparison of the transcriptomes of injured versus uninjured telencephali followed by in situ hybridization revealed 14 factors that are expressed in the ventricular stem cell domain and whose expression is specifically up-regulated in response to injury.
A crucial process is the balance of quiescence and proliferation of stem cells. We identified *id1*, a negative regulator of basic helix loop helix transcription factors among the TRs that are up regulated in the stem cell niche of the injured telencephalon.
I will present data, which suggest that *id1* is part of a negative feedback mechanism that assures the maintenance of quiescent type 1 cells.

SP05.3
Microscopie multiphoton avancée: de l´illumination en feuille de lumière à l´imagerie multicouleurs

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High-content imaging of biological processes tremendously benefits from recent advances in fluorescence microscopy. While standard two-photon excited fluorescence microscopy excels in achieving high imaging depth in scattering tissues, its acquisition speed is limited and it remains challenging to obtain efficient multicolor excitation. On the other hand, one-photon light sheet microscopy (SPIM, DSLM, etc) has gained widespread recognition in recent years, due to its distinct advantages for imaging live organisms with high acquisition speed and low phototoxicity. However, its imaging depth remains a limitation. In this context, we report on two recent advances in multiphoton microscopy (i) to improve imaging speed [1] and (ii) to perform efficient multicolor imaging [2]. (i) First, we present the implementation and application of two-photon light-sheet microscopy, combining two-photon excited fluorescence with orthogonal illumination. Using live imaging of fly and zebrafish embryos, we demonstrate the performance of multiphoton light-sheet microscopy in maintaining good signal and high spatial resolution deep inside biological tissues, as well as high acquisition speed and low phototoxicity. (ii) Then, we present a new strategy based on wavelength mixing to perform optimal and simultaneous two-photon excitation of three chromophores with distinct absorption spectra. To illustrate its application, we show multicolor multiphoton imaging of Brainbow-labeled tissues.

References:

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SP05.4

La plateforme Vibe-Z

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A central requirement to make microscopic volumetric data sets like 3D gene expression patterns comparable between different individuals, different experiments or even different labs worldwide is their precise alignment to a standard reference. Established registration techniques from the medical community often fail in microscopic applications due to the inhomogeneous data quality, severe deformations from different treatments and random orientation in automated high content experiments. In the talk I will present the Virtual Brain Explorer for Zebrafish "ViBE-Z", that allows to overcome these shortcomings. The framework contains (1) a two-view fusion with attenuation correction to record thick objects (here 400µm) with a standard confocal microscope, (2) a trainable landmark detection, and (3) a fast landmark initialized elastic registration. Up to now the ViBE-Z database contains spatially aligned high-resolution expression patterns of 85 individual three days old larvae, representing expression of fourteen different genes, transgenes, or antigens. We show the flexibility of the whole approach by applying it to two, three and four days old larvae, by using different reference stains: nuclear stain and a labelling of the axonal scaffold by antiacetylated tubulin antibodies; and by different preparation treatments: a mild treatment by immunofluorescence stain and a harsher whole mount in situ hybridization. The ViBE-Z database and atlas are freely available, and the software is provided to end-users via a web interface at http://vibez.informatik.uni-freiburg.de/

SP05.5

Petits cerveaux, grosses données. La génération de la collection Gal4 de Janelia Farm / Small brains, big datas. Generation of the Janelia Farm Gal4 collection

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Over the last four years we generated ~7000 Gal4 lines, using methods described in Pfeiffer et al. (2008), and imaged the brain and ventral nerve cord (VNC) from adults of each line. Our objective was to facilitate Drosophila neurobiology by generating an annotation database that can easily be queried for Gal4 lines with expression patterns in any region of interest in the brain of D. melanogaster. Because this approach is based on the names of anatomic regions in the fly brain the first step was to develop a complete map of the Drosophila brain (Standard-atlas, Ito et al. in press), which was used as the ontology and anatomic framework for our work.
While the adaptability of human perception is a strong benefit in manual annotation it is also a reason for error and inconsistency when annotating thousands of specimens. Therefore we developed a set of algorithms that help to analyze the distribution of the Gal4 expression patterns. This approach was enabled through the extensive application of the brainaligner (Peng et al. 2011). After thorough proofreading, the initial set of manual annotations was used to train the MAA. This renders the results of the MAA human-like with the benefit of speed and consistency. However, due to a number of potential error sources in the process of the MAA, we believe it is still necessary for a human specialist to proofread the results prior to publication. We have developed computation tools to assist in this proofreading.
Our current goal is the generation of stable fly lines with small, morphologically homogenous or at least well defined cell populations expressing Gal4 in the central complex using the Rubin line collection as raw material.
The abundance of different expression patterns in the Rubin line collection together with first successes using enhanced reagents for intersectional strategies (splitGal4, Gal4/LexA-combinations) gives us the confidence that we will be able to isolate the majority of homogeneous cell populations in the central complex and by this make them available to further experimental probing in other fields. Assuming that the morphologic resemblance of neurons of a given population reflects their functional union/similarity, this approach aims to promote the investigation and assignment of functions of the central complex to small, well-defined populations as functional units.