10e Colloque de la Société des Neurosciences
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Résumés des présentations orales

Conférences plénières / plenary lectures

PL01.1
Mécanismes de réparation du cerveau après traumatisme

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Large spinal cord or brain injuries lead to life-long, often major functional deficits. In contrast, small lesions of the CNS often have a good prognosis with extensive functional recovery; the underlying mechanisms are not well understood, however. In adult rats, spinal cord injury transecting the hindlimb corticospinal (CST) axons induces spontaneous sprouting of the lesioned fibers in the upper spinal cord and to new connections of former hindlimb CST neurons and cortex to the forelimb. Forelimb sensory connections now expand to the former hindlimb motor cortex. A similar re-wiring and map shift was observed after focal cortical strokes destroying the forelimb cortex. In all these cases, however, extent and length of fiber growth was limited to about 0.2 - 2 mm.
20 years ago, our group has discovered the presence of specific neurite growth inhibitiory factors in myelin of the CNS, among which the membrane protein Nogo-A, currently the most potent known neurite growth inhibitor. Function blocking antibodies against Nogo-A have been generated and applied to rats and macaque monkeys with spinal cord injuries as well as animals with strokes in the sensory-motor cortex. Biochemical readouts showed an up-regulation of growth specific proteins. On the anatomical level, injured fibers showed enhanced regenerative sproutingas well as long-distance regeneration with formation of large terminal arbors. Simultaneously, spared fiber tracts showed enhanced compensatory sprouting, often covering relatively long distances. In animals with cortical strokes, fibers from the intact corticobulbar or corticospinal system crossed the midline, supplying innervation to the denervated brain stem or spinal cord under the influence of anti- Nogo-A antibodies. Behavioural experiments for locomotion, grid and beam walk, swimming, as well as skilled forelimb reaching showed marked improvements of functional recovery in the Nogo-A antibody treated injured animals. In collaboration with Novartis, a human anti-human Nogo-A antibody was generated. The antibody enhances regeneration of corticospinal fibers and recovery of precision movements of the paralysed hand after high cervical hemisections in adult monkeys. A clinical trial in acutely spinal cord injured patients is currently ongoing.

PL02.1
Neural computation as probabilistic inference

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A wide range of behaviors can be formalized as instances of probabilistic inferences. This includes odor recognition in insects, navigation in rodents, motor control, decision making in primates, simple arithmetic in children and monkeys, and causal reasoning in humans, to name just a few. In all cases, the probabilistic inferences involve products of probability distributions and another type of inference known as marginalization. We will show that, given the variability reported in neural responses, products of probability distributions can be implemented through linear operations over firing rates, while marginalization over Gaussian random variables requires a particular nonlinearity known as quadratic divisive normalization. Both operations are conspicuous in many neural circuits raising the

possibility that seemingly unrelated behaviors, such as causal reasoning in humans or olfactory processing in rodents, could in fact rely on very similar neural mechanisms.

PL03.1

"La Nature" ne jette pas les dés, elle joue au Lego et au billard: création de gènes chimères et évolution du cerveau humain

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Among the traits that distinguish humans from other mammals are the relative size, organization and functions of the brain. The physiological substrates underlying the unique features of the human behavior have been extensively studied while our knowledge of the genetic changes associated with their emergence remained elusive for decades. The first publication of the almost complete human genomes in 2001, followed by the chimp genome in 2004 opened the era of genome-wide comparisons with a powerful resolution. The search for primate-specific genes and genomic-features linked to human brain evolution provides insights into three main directions I propose to follow during my talk:
1) the speed of divergence of brain-expressed gene sequences in the human lineage;
2) changes in gene expression among primates, and the sequences of regulatory elements, that could play a major role in adaptive evolution;
3) emergence or deletion of genes that have contributed to the evolution of the human brain structure and function.
In this context, we provided the first evidence for the emergence of two chimaeric genes in Hominids. These genes were named *PMCHL1* and *PMCHL2* based on partial homology with the *PMCH* gene encoding the melanin-concentrating hormone (MCH), a neuropeptide involved in energy homeostasis. Phylogenetic analyses showed that the *PMCHL1* gene was created about 32 million years ago (Mya) by a complex “lego-like” mechanism involving MCH antisense mRNA retrotransposition while *PMCHL2* arose 5-10 Mya through segmental duplication. These chimaeric genes have been submitted to strong regulatory constraints during primate evolution. Indeed, emergence of new exons and new cis-regulatory sequences resulted in different expression patterns of PMCHL1 sense and antisense RNAs in the primate brain. Most of these transcripts are non-coding RNAs and could target either *PMCH* itself or genes that could alter MCH signaling, offering multiple players for a fascinating “billiard game”. Strikingly, the creation of novel genes during human evolution is not a rare event. Many primate-specific genes have been found often located in chromosomal domains called “gene nurseries” and they provide further raw material for gene innovation that potentially underlied human brain evolution.

PL04.1

Apprentissage associatif et mini cerveau: ce que nous apprennent les abeilles

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Equipped with a mini brain smaller than one cubic millimeter and containing only 950000 neurons, honeybees could be indeed considered as having rather limited cognitive abilities. However, bees display a rich and interesting behavioral repertoire, in which learning and memory play a fundamental role in the framework of foraging activities. We focus on the question of whether adaptive behavior in honeybees exceeds simple forms of learning and whether the neural mechanisms of complex learning can be unraveled by studying the honeybee brain. Besides elemental forms of learning, in which bees learn specific and univocal links between events in their environment, bees also master different forms of non-elemental learning, including categorization, contextual learning and rule abstraction, both in the visual and in the olfactory domain. Different protocols allow accessing the neural substrates of some of these learning forms and understanding how complex problem solving can be achieved by a relatively simple neural architecture. These results underline the enormous richness of experience-dependent behavior in honeybees, its high flexibility, and the fact that it is possible to formalize and characterize in controlled laboratory protocols basic and higher-order cognitive processing using an insect as a model.

PL05.1
Développement et fonctions des commissures cérébrales

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Coordination of the left and right sides of the body requires the action of neurons whose axons cross the nervous system midline. The precise contributions of "commissural" neurons to sensory and motor functions remain poorly understood. To probe these crossing circuits, we took advantage of the recent finding that the Robo3 axon guidance receptor is required for midline crossing by axons at most axial levels. A Robo3 conditional knockout mouse line was generated, allowing Robo3 to be deleted in selective neuronal populations. This led to disruption of specific commissures in the sensory, motor, sensorimotor and respiratory systems, and resulted in severe but specific functional deficits. Surprisingly, although rerouted axons do not cross the midline, they still project to their appropriate neuronal targets, suggesting that midline crossing is not required to complete the axonal guidance program of those neurons. We further showed that the ipsilateral rewiring of the projections from the brainstem which convey sensory information to the thalamus, has profound effect on the development of the barrel field. These mouse lines represent good models for human syndromes, including horizontal gaze palsy with progressive scoliosis (HGPPS), which is characterized by deficits in coordinated eye movements. This study links defects in commissural axon guidance with specific and dramatic behavioral phenotypes. We have also generated mice that lack all Robo receptors or all Slit ligands which are being used to interfere with axon guidance and neuronal migration but also to study the function of these molecules in the adult brain.

PL06.1
Les récepteurs métabotropiques synaptiques: subtils objets de communication et d´adaptation

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I started my PhD work at the Collège de France in 1968 and I remember well Alfred Fessard . At that time I never had a chance to speak with him for two obvious reasons, one was that I was just a young and shy student the second was that I was doing my PhD with F.More on vasopressin receptors receptors in kidney... Receptors were just a concept and nobody had physically detected receptors. I prepared highly radioactive vasopressin at Saclay and started “binding” experiments succeeding in 1970 almost at the same time that J.P Changeux with nicotinic receptor and M.Rodbell with glucagon. Following M.Rodbell, I demonstrated that vasopressin receptors were coupled to G proteins and stimulated cAMP production. G-protein coupled receptors (GPCRs) were in hand. Being at Northwestern University important papers came out. SH Snyder discovered opiate receptors using binding experiments and P.Greengard demonstrated that dopamine receptors in striatum were coupled to adenylyl cyclase (AC). Neurotransmitter GPCRs could be studied in brain. Coming back, I contacted J.Glowinski ´s team and we started to track brain GPCRs. We discovered rapidly D1 receptors in the frontal cortex and substantia nigra, adenosine A2 in striatum, 5-HT receptors coupled to AC and with H Gerschenfeld their control of K+channel . In 1982 I decided to create a new laboratory in Montpellier. The first goal was to discover new GPCRs and their signalling pathways in neuronal cultures. Noting that acetylcholine was acting on both ionotropic (nicotinic) and GPCRs (muscarinic) receptors we look for the possibility that glutamate was also acting on GPCRs .We published in 1985 the first paper clearly demonstrating the existence of metabotropic glutamate receptors (mGluRs). mGluRs remained central for our laboratory, to synaptic plasticity field (LTD in particular) and are targets for psychiatric (X fragile mental retardation, schizophrenia, anxiety) and neurological diseases (Parkinson, pain). We discovered 5-HT4 receptors coupled to AC implicated in learning and memory, feeding behaviour and likely depression. Our more recent activity is using of proteomics to discover the nature and functions of GIPs (GPCR interacting proteins) implicated in fine tuning GPCR functions at synaptic level.

PL07.1
Mécanismes synaptiques de la perception sensorielle

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A key goal of modern neuroscience is to understand the neural circuits and the synaptic mechanisms underlying sensory perception. Here, I will discuss our efforts to characterise sensory processing in the mouse barrel cortex, a brain region known to process tactile information relating to the whiskers on the snout. Each whisker is individually represented in the primary somatosensory neocortex by an anatomical unit termed a 'barrel'. The barrels are arranged in a stereotypical map, which allows recordings and manipulations to be targeted with remarkable precision. In this cortical region it may therefore be feasible to gain a quantitative understanding of neocortical function. We have begun experiments towards this goal using whole-cell recordings, voltage-sensitive dye imaging, viral manipulations, optogenetics and two-photon microscopy. Through combining these techniques with behavioral training, our experiments provide new insight into sensory perception at the level of individual neurons and their synaptic connections.

PL08.1
L´optogénétique: développement et applications

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The technology of optogenetics has allowed millisecond-precision optical control over activity in defined cell types within freely moving mammals. The approach introduced by the Deisseroth laboratory in August of 2005 has now been adopted by thousands of scientists around the world. In 2010 optogenetics was named Method-of-the-Year across all fields of science and engineering by Nature Methods, and headlined the Breakthroughs-of-the-Decade piece in Science. Beyond initial tool discovery, Deisseroth's team has also developed the enabling in vivo methods (molecular targeting, fibreoptics and solid-state optics), and led the application of optogenetics to obtain insights into neural circuit dynamics in health and disease states such as anxiety and Parkinsonism. Deisseroth's talk will briefly review this history and also focus in detail on new optogenetic technologies which have enabled the first optogenetic loss-of-function behavioral results in freely-moving mammals (complementing their earlier gain-of-function work). This recent set of papers has resulted in identifying a causal role for nucleus accumbens cholinergic neurons in cocaine conditioning (Science 330:1677-81, 2010), and allowed Deisseroth's team to map out a specific amygdala projection causally involved in anxiety (Nature, in press 2011), the most common of the psychiatric diseases. Deisseroth's development of optogenetics in his bioengineering laboratory has allowed millisecond-precision optical control over activity in defined cell types within freely moving mammals. He has received numerous prestigious and international awards for this work, including the Lawrence C. Katz Prize from Duke University, the Schuetze Prize from Columbia University, the Society for Neuroscience YIA Award, the Koetser Prize, and the Nakasone Prize from the international HFSP, all for optogenetics.
www.stanford.edu/group/dlab/papers/breakthroughscience2010.pdf
www.stanford.edu/group/dlab/papers/deisserothnature2010.pdf
www.stanford.edu/group/dlab/optogenetics/sciam.html

PL09.1
Définition des circuits neuronaux de la peur

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We use an interdisciplinary approach to address the question how amygdala microcircuits mediate the acquisition and extinction of conditioned fear responses. In my talk, I will describe how switches in the activity between distinct types of amygdala neurons mediate context-dependent expression and extinction of fear memories. Moreover, I will present recent data demonstrating that functionally distinct types of amygdala neurons are specifically embedded and precisely connected both within the local circuitry and within larger-scale neuronal networks. Thus, in contrast to previous models

suggesting that amygdala neurons are active during states of high fear and inactive during states of low fear, our findings indicate that activity in specific neuronal circuits within the amygdala cause opposite behavioral outcomes and provide a new framework for understanding context-dependent expression and extinction of fear behavior.

PL10.1

La question de l'amélioration cognitive comme exemple de notre programme de travail en neuroéthique

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Neurosciences not only open new avenues to alleviate neurological and psychiatric disorders - and some day to repair our nervous system - but also present targeted ways to control and enhance vegetative (being awake, sleep, appetite, sexuality, etc.) as well as mood and cognitive behaviors (memory to ideation), already triggering a strong adhesion and a huge market. On the one hand we may consider this as a new life style, a general trend to obtain improved memory and comprehension capacities through so-called “smart pills”, rewards from technical progress. Physicians or regulatory governmental agencies should only be required to check for safety and efficiency of “treatments”. Considered as a basic need, people should only be concerned about equal access to enhancement drugs and devices. If we take this view, cognitive enhancement is just considered as any technical element in the market field, consumer needs and satisfaction being the only goals to fulfill. On the other hand, currently available drugs will not only change some quantitative aspects of neural activities, whose improvement implies no problem, but also the global internal economy of cognition. This is where come neuroethics, a portion of bioethics which is the consideration of consequences in medical practice and biological research. Available “smart-pills” are controlling childrens' behaviors but they are also increasing immediate, pre-learned skill-based and short-term rewarded strategies. Such treatment may be detrimental to long-term goals and social interactions, and consequently challenge our philosophy of human rights. Cognitive enhancers do not only change the amplitude of a given brain capacity, *i.e*. memory, but also the balance between emotional and rational networks, and will thus change our relationship to others, essential to the building of our thought and social life. Furthermore we are at risk at becoming addicted to our own brain enhancement, thus succumbing to leading to renouncing our free-will, provided it exists. These fundamental changes should encourage us to understand the driving forces of our “neurotechnological gourmandize” and wonder if cognitive enhancement is not a mystification that covers up social pressure for enhanced productivity and behavior control.

Symposia

S01 Périodes critiques et plasticité synaptique. / Critical period in synaptic plasticity.

S01.1

Les microcircuits GABAergiques contrôlent la spike-timing dependent plasticity (STDP)

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Spike-timing-dependent plasticity (STDP), a Hebbian synaptic learning rule considered a first law of synaptic plasticity, occurs from invertebrates to mammals. During STDP, the synaptic strength between neurons is modified by their activity and the timing of neuronal firing on either side of the synapse. Synaptic inhibition mediated by GABAergic interneurons controls neuronal excitability and therefore the spike timing. GABAergic signaling through ionotropic $GABA_A$ receptors ($GABA_A$Rs) is divided into synaptic (phasic) and extrasynaptic (tonic) components. Although involvement of GABAergic circuits has been evidenced in experience-dependent plasticity, whether GABAergic circuits rule the STDP remains unknown. Here, using dual patch-clamp recordings together with a biophysical synapse model, we show that GABAergic circuits govern the corticostriatal STDP polarity. The corticostriatal pathway, the main entrance of basal ganglia, processes inputs from the cerebral cortex. The corticostriatal long-term plasticity provides a fundamental mechanism for the function of the basal ganglia in procedural learning. We demonstrate that GABA acts as a Hebbian/anti-hebbian switch. Indeed, we observed both *in vitro* and *in silico* that GABA is able to reverse the temporal order of STDP potentiation and depression. Our biophysical model indicates that such effect relies on L-type-VSCC activation, induced by a depolarizing effect of GABA in the MSN distal dendrites. Blockade of $GABA_A$Rs by biccuculline, picrotoxine or gabazine, reversed the temporal order of STDP potentiation and depression. Both tonic and phasic GABAergic signaling are differently implicated in controlling STDP. Furthermore, we show that the GABAergic control of STDP evolves along development, due to the late maturation of GABAergic circuits. These findings establish a central role for GABAergic circuits in shaping STDP. It suggests that central disorders (schizophrenia, dystonia, Tourette syndrome or obsessive compulsive disorders) affecting inhibitory circuits may change the polarity of plasticity and therefore impair a proper learning and memory. Thus, subtle manipulations of GABAergic dynamic could be used to restore proper learning and memory.

S01.2

Les neurones GABAergiques pionniers orchestrent la maturation des circuits neuronaux de l´hippocampe en développement

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The developing hippocampus displays a functional connectivity organization particularly effective in supporting network synchronization as it includes superconnected “hub neurons”. If a subpopulation of GABAergic interneurons displaying a dense and widespread axonal arborisation was shown experimentally to carry such “hub” network function, it remains unknown whether these hub cells are only transiently expressed or later develop into distinctive subclasses of interneurons. This is a difficult issue given the complexity of the GABAergic neuron population and the poor expression of most conventional interneuron markers at early developmental stages. We have circumvented this limitation using “genetic fate mapping” approaches allowing selective labelling of interneuron subtypes according to their spatio-temporal embryonic origin. Following theoretical predictions, we tested the hypothesis that pioneer cells could develop into hub neurons. To this aim, we have performed a thorough neuroanatomical analysis of early migrating hippocampal GABAergic neurons and assessed their network power by combining single-cell electrophysiological recordings with multineuron calcium imaging in transgenic mouse slices. To specifically label early migrating interneurons, a $Dlx1/2^{CreERTM}$ driver line was transiently activated by tamoxifen administration at the earliest stages of interneuron

migration. We show that, early migrating GABAergic cells form a subpopulation of hub neurons in the developing hippocampus, which in adulthood, acquires classical markers for long-range projecting GABAergic neurons.

S01.3
Assemblage sequentiel de microcircuits dans l´hippocampe

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The extent to which individual neurons are interconnected selectively within brain circuits is an unresolved problem in neuroscience. Neurons can be organized into preferentially interconnected microcircuits, but whether this reflects genetically defined subpopulations has remained unclear. Here we show that the principal neurons within the major hippocampal subdivisions consist of distinct subpopulations that are generated during distinct time windows, and interconnect selectively across subdivisions. In two *Thy1* mouse lines, transgene expression visualized distinct principal neuron subpopulations that exhibited unique and matched patterns of gene expression, shared distinct neurogenesis and synaptogenesis time windows, and exhibited selective connectivity at dentate gyrus-to-CA3 and at CA3-to-CA1 synapses. Matched subpopulation marker genes and neuronal subtype markers mapped near olfactory receptor gene clusters. The non-overlapping matched timings of synaptogenesis accounted for the selective connectivities in CA3. Therefore, the hippocampus involves parallel connectivity channels assembled from distinct principal neuron subpopulations through matched schedules of synaptogenesis.

S01.4
Role de la matrice extracellulaire dans les périodes critiques de la plasticité synaptique

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The extracellular matrix (ECM) is a meshwork of proteins present in the extracellular space which role extends far beyond structural scaffolding. ECM proteins are important contributors to embryonic development and finely tune synaptic transmission and experience-dependent plasticity in the postnatal and adult brain. The secreted ECM glycoprotein reelin illustrates this duality: reelin is crucial for the correct development of laminated structures and modulates neuronal network plasticity in the postnatal brain. Restricted temporal windows called critical periods characterize the postnatal development of the mammalian brain. Critical periods are short time windows during which experience and environment imprint neuronal circuits and impact on both physiology and behavior. In this context, we will discuss recent advances in the understanding of reelin functions during critical periods of development of network plasticity.

S01.5
n/a

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Experience-dependent plasticity in the brain requires balanced excitation-inhibition. The late onset of ocular dominance plasticity in mouse visual cortex is triggered by a specific transfer of Otx2 homeoprotein into GABAergic interneurons expressing parvalbumin (PV). We identified a 15 amino-acid sequence within Otx2 with prototypic traits of a glycosaminoglycan (GAG) binding domain, which mediates localization to PV-cells. A mimicking peptide *in vivo* reduced Otx2 and PV expression, while transiently reopening visual cortical plasticity (loss of acuity and cortical responsiveness to an eye deprived of vision) in adult mice. These results, analogous to peri-neuronal net (PNN) removal by chondroitinase treatment, demonstrate that the persistent accumulation of Otx2 by mature PV-cells requires PNNs and is responsible for maintaining critical period closure. Unlike the typical progressive loss of pyramidal-cell ocular dominance upon deprivation, direct intracellular recording from fast-spiking cells *in vivo* revealed a paradoxical, initial shift towards the occluded eye followed by a late preference for the open eye. Together, these results suggest that the bidirectional plasticity of normally binocular GABA circuits may contribute to experience-dependent plasticity in the developing

visual cortex. The Otx2 GAG-binding domain may further serve as a potential target for recovery from critical period disorders in adulthood.

S02 De la perception à l'action chez le primate non-humain: études en électrophysiologie et neuroimagerie. / From perception to action in non-human primates: insights from electrophysiology and neuroimaging.

S02.1

Traitement cortical de l´espace visuel chez le macaque: de la cellule unique à l´IRMf

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In primates, the intraparietal cortex is involved in the control of visually guided actions, like reach-to-grasp movements, which require extracting the 3D shape and position of objects from 2D retinal images. Using fMRI in behaving monkeys (JB Durand et al., 2007), we have investigated the role of the intraparietal cortex in processing stereoscopic information for recovering the depth structure and the position in depth of objects. We found that while several areas (CIP, LIP, and AIP on the lateral bank; PIP and MIP on the medial bank) are activated by stereoscopic stimuli, AIP and an adjoining portion of LIP are sensitive only to depth structure. Furthermore, only these two anterior regions are sensitive to both the depth structure and the 2D shape of small objects, indicating that they are more specifically engaged in extracting the 3D shape of objects. Electrophysiological recordings with similar stereoscopic stimuli (Srivastava et al., 2009) have further confirmed the involvement of AIP in 3D shape processing, and they have clarified the underlying neuronal coding. By replicating the fMRI experiments in human subjects (JB Durand et al., 2009), we have been able to identify 2 regions in human anterior parietal cortex, DIPSA and DIPSM, showing functional properties reminiscent to those previously evidenced in AIP and anterior LIP. Besides clarifying the role of the anterior intraparietal cortex in 3D shape processing, these studies illustrate the potential of fMRI techniques in behaving monkeys for guiding electrophysiological recordings toward regions of interest and identifying their functional homologues in humans with similar functional imaging approaches.

S02.2

n/a

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A fundamental task of vision is to group the image elements that belong to one object and to segregate them from other objects and the background. I will discuss a conceptual framework that explains how perceptual grouping is implemented in the visual cortex. According to this framework, two mechanisms are responsible for perceptual grouping: base-grouping and incremental grouping. Base-groupings are coded by single neurons tuned to multiple features, like the combination of a color and an orientation. They are computed rapidly because they reflect the selectivity of feedforward connections that propagate information from lower to higher areas of the visual cortex. However, not all conceivable feature combinations are coded by dedicated neurons. Therefore, a second, flexible form of grouping is required that is called incremental grouping.
Incremental grouping takes more time than base-grouping because it relies also on horizontal connections between neurons in the same area and feedback connections that propagate information from higher to lower areas. These connections spread an enhanced response to all the neurons that code image elements that belong to the same perceptual object. This response enhancement acts as a label that tags those neurons that respond to image elements to be bound in perception. The enhancement of neuronal activity during incremental grouping has a correlate in psychology because attention is directed to precisely those features that are labeled by the enhanced neuronal response.
I will also show data indicating that feedforward and feedback processing rely on different receptors for glutamate. Feedforward processing mainly relies on AMPA receptors that drive the neurons whereas feedback processing involves a larger contribution of NMDA receptors that are modulatory.

S02.3

Contributions du réseau pariéto-frontal au control attentionnel et à la décision perceptive: ces régions sont-elles fonctionnellement distinctes ?

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Brain lesion and brain imaging studies in humans have demonstrated the involvement of the parietal and frontal cortices in visual attention and perception. However, little is know about how these two functions are implemented and whether they can actually be dissociated at the neuronal level. Indirect evidence suggests that the frontal eye field (FEF) may have a top-down biasing effect on lower visual areas, including the lateral intraparietal area (LIP) (Buschman and Miller, 2007; Ekstrom et al. 2008), however, the nature of this biasing signal is unknown. Furthermore, most studies addressing the functional role of these areas are limited by the fact that they do not allow for a differentiation between attention control, which is mainly top-down or goal driven, and perceptual decision, which is a distinct process more closely associated with visual awareness.
I will present simultaneous recordings from the FEF and LIP while two monkeys were engaged in a modified rapid serial visual presentation cued target-detection task which permitted a temporal and a spatial dissociation between attention orientation and target selection processes. I will show that while a high proportion of cue related neurons encode a physical attribute of the cue (its position with respect to the receptive field or its identity), a significant proportion of cells encode the spatial abstract instruction held by the cue. I will show that these higher order signals arise early on in the FEF suggesting that it plays a crucial role in mapping abstract instructions onto a spatial priority map to covertly guide spatial attention. I will compare these FEF neuronal responses to the cue-related responses observed in LIP.
In a second step, I will focus on the target-related responses
1) as a function of the physical presence or absence of the target and
2) as a function of the animal's trial by trial detection performance.
I will show that both areas simultaneously represent the physical presence of the target and the corresponding perception of the animal, although the computations at work in each area attest for distinctive contributions to this cognitive process.

S02.4

n/a

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When grasping an object, human and non human primates naturally shape their hand and fingers in relation to the object´s physical properties. Following object contact, grasp forces are finely adjusted for secure holding and manipulation. Earlier studies suggest that the control of hand shaping and grasp force involve partially segregated cortical networks in which MI plays a central role. However, it is still unclear how information originating from these networks is integrated within MI. We addressed this issue by analyzing the activity of MI neurons in macaque monkeys performing a reach to grasp task. Following an imperative GO signal, the monkey had to use one of two grip positions (precision grip or side grip) to grasp and pull an object that could be either heavy or light. One second before the GO, a precue provided advance information about either hand grip or object weight and the GO provided the complementary information. We recorded simultaneously from a large population of neurons (more than 100) using a high-density multi-electrode "Utah" array chronically implanted in MI. Single unit activity for the 4 movement types (2 grips x 2 weights) was analyzed during movement planning and execution. Before and during movement, a larger proportion of neurons responded to differences in hand grip than to differences in object weight. Grip-related activity was limited to the most lateral and posterior part of the array, towards the central sulcus. This spatial distribution was compared with the distribution of somatosensory receptive fields across the array. A close matching was observed between the distribution of distal receptive fields on the hand and fingers and the distribution of grip-related activity. These data provides some new insight about the functional organization of MI for the control of hand grip and contact forces during object grasp and manipulation.
project funded by a RIKEN/CNRS collaborative research agreement

S02.5

Indices électrophysiologiques de la récupération fonctionnelle suite à une lésion unilatérale de l´aire motrice primaire

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The ability of primates to perform fine movements of the hand and digits relies mainly on the primary motor cortex (M1) and the integrity of its direct connections to the motoneurones controlling the hand muscles via the corticospinal tract (CST). Other premotor cortical areas, such as the rostral part of the ventral premotor cortex (PMv) are strongly interconnected with M1 and also project to the cervical cord via the CST. Repetitive intracortical microstimulation (ICMS) applied at low intensity in the motor cortex elicits electromyographic activity (EMG) in the hand muscles and therefore is a valuable tool to measure the excitability of limited motor cortical areas.
In this context, we studied in macaque monkeys the electrophysiological consequences of a transient inactivation of the M1 region responsible for finger movements on EMG activity of hand muscles elicited by ICMS. Twenty to fifty minutes after the micro-infusion of a GABA agonist, we observed a complete disappearance of the EMG activity resulting from ICMS in M1 and simultaneously a pronounced decrease of EMG activity in the same muscles from ICMS in PMv rostral, whereas the EMG activity elicited by direct stimulation of the CST at pyramidal level was not reduced in a comparable range.
We can compare the obtained results with observations made in an animal suffering from a slowly developing cortical malformation. The examination post-mortem of the brain of this macaque monkey showed an increased number of microgyri in the frontoparietal regions, with a local disruption of the layered cortical organisation in both hemispheres. The behavioral assessment of manual dexterity in a bimanual task did not show any impairment, except a longer reaction time, whereas other time intervals measured in this complex task were not significantly different. In addition, single joint movements of the hand could be evoqued by ICMS at comparable intensities. This emphasizes a pronounced difference in the dynamic of compensatory mechanisms involved in the recovery of manual dexterity.
An intermediary step will be to quantify the effects of a permanent lesion of the hand area of the M1 on its excitability and on the excitability of other motor areas participating directly in manual dexterity such as PMv rostral.

S03 Les sémaphorines dans le cerveau embryonnaire et postnatal. / Semaphorins in the developing and postnatal brain.

S03.1

Les sémaphorines de la classe 6 jouent le rôle de récepteur au cours de la formation de circuits neuronaux

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Semaphorins form a large family of axon guidance molecules. In contrast to the well studied secreted class-3 Semaphorins, much less is known about the role of transmembrane class-6 Semaphorins. Because of their spatial and temporal expression patterns, we tested for a role of class 6 Semaphorins in neural circuit formation. Semaphorin6A was expressed exclusively in boundary cap cells, a transient population of cells which cluster at the transition zones between the CNS and the PNS. In the absence of Semaphorin6A migrating cells appear to miss the stop signal and thus fail to cluster at the boundary between CNS and PNS. Boundary cap cell clusters act as gatekeepers between the CNS and the PNS to allow transition of axons but not cell bodies during neural development.
Semaphorin6B was found to be expressed in dorsolateral commissural neurons of the developing spinal cord during the time when their axons have crossed the midline and are ready to turn into the longitudinal axis.
In the absence of Semaphorin6B, commissural axons often stalled at the floor-plate exit site and lacked an instructive signal directing them rostrally along the contralateral floor-plate border. Thus, post-crossing commissural axons chose randomly to grow either rostrally or caudally. The expression pattern of PlexinAs, the binding partners of class-6 Semaphorins, suggested an interaction between Semaphorin6B on commissural axons and PlexinA1 and A2 expressed by floor-plate cells. Indeed

downregulation of these two Plexins in floor-plate cells resulted in stalling of commissural axons at the midline. Thus, Semaphorin6B acts as a receptor in commissural neurons that mediates a guidance effect of midline-derived PlexinAs on post-crossing commissural axons.
Taken together our results suggest a receptor role for both Semaphorin6A and Semaphorin6B in neural circuit formation.

S03.2

Les sémaphorines et les Wnts coopèrent pour permettre l'établissement des réseaux neuronaux à sérotonine et à dopamine

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Dopaminergic neurons in the mesodiencephalon (mdDA neurons) make precise synaptic connections with targets in the forebrain. Due to the functional importance of these remarkably complex ascending axon pathways and their implication in human disease, the mechanisms underlying the development of these connections are of considerable interest. Despite extensive *in vitro* studies, the molecular determinants that ensure the perfect formation of these pathways *in vivo* remain largely unknown. In recent studies, we have determined the embryonic origin and ontogeny of the mouse mesoprefrontal pathway and have employed these data to reveal an unexpected requirement for
1) semaphorin 3F (Sema3F) and its receptor neuropilin-2 (Npn-2), and
2) Wnt proteins and their planar cell polarity (PCP) receptors during mdDA pathway development.
We show that Sema3F is a bifunctional guidance cue for mdDA axons, some of which have the remarkable ability to regulate their responsiveness to Sema3F as they develop. Intriguingly, chemoattraction mediated by Sema3F and Npn-2 is required to orient mdDA axon projections in the cortical plate of the medial prefrontal cortex. This finding for the first time demonstrates that regulation of axon orientation in the target field occurs by chemoattractive mechanisms. Furthermore, we find that mdDA axons express the core planar cell polarity components Frizzled3, Celsr3 and Vangl2 and that *Frizzled3*, *Celsr3* and *Vangl2* mutant mice display anterior-posterior (A-P) axon guidance defects in the brainstem. The only known ligands for PCP signaling are Wnt proteins. In culture, Wnt5a repels mdDA axons and Wnt7b attracts mdDA axons. However, mdDA axons from *Frizzled3* mutant mice are unresponsive to Wnt5a and Wnt7b. Both Wnts are expressed in gradients along the A-P axis, consistent with their role as directional cues. Finally, *Wnt5a* mutants show transient A-P guidance defects in mdDA projections. These results support a role for PCP-Wnt signaling in determining the A-P organization of mdDA pathways. In all, these studies provide a framework for further dissection of the molecular basis of mdDA pathway development and disease.

S03.3

Signalisation des sémaphorines et orientation de la migration des neurones à GnRH: établissement des circuits neuronaux contrôlant la reproduction

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Reproduction in mammals is dependent on migration of specific neurons secreting the neuropeptide gonadotropin hormone-releasing hormone (GnRH). These cells originate during embryonic development in the olfactory placode and migrate into the forebrain, where they become integral members of the hypothalamic-pituitary-gonadal axis. This migratory process is regulated by a wide range of guidance cues, which allow GnRH cells to travel over long distances to reach their appropriate destinations. Alterations of the migratory process result in delayed or absent pubertal maturation and infertility.
Semaphorins constitute one of the largest protein families of phylogenetically conserved guidance cues and have been shown to play a significant role in the control of several migratory systems. Using genetic mouse models as well as *in vitro* manipulations, we recently showed that the class-4 semaphorin, Sema4D, promotes directional migration in GnRH cells by coupling its PlexinB1 receptor

with activation of the Met tyrosine kinase (Hepatocyte Growth Factor receptor) and identify PlexinB1-Met receptor complex as a fundamental asset for GnRH neuronal cell migration and guidance.
In addition, we also present novel data which provide direct evidence of a role for the GPI-anchored semaphorin, Sema7A, in this neuronal migration. We show that Sema7A is essential for the development of the GnRH neuron system: loss of Sema7A signaling alters the migration of GnRH neurons but not the patterning of the olfactory/vomeronasal axons. As a consequence of the GnRH migratory defect, Sema7A deficient mice exhibit a reduction in this GnRH cells in adult brain and reduced gonadal size. Finally we provide evidence that Sema7A signals mainly through its receptor, beta1-integrin, to regulate GnRH cell motility by favoring directional persistence of these neuroendocrine cells.
Our results demonstrate an important role of both Sema4D and Sema7A in the establishment of the GnRH system and raise the possibility that disruption of semaphorins´ signaling pathways may result into reproductive disorders.

S03.4

La voie de signalisation Semaphorine 3A contrôle la plasticité des axones à GnRH dans l'hypothalamus au cours du cycle ovarien

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The median eminence of the hypothalamus provides an excellent model in which to investigate the complex relationship between neurosecretion, function-related morphological plasticity involving neuronal-glial-endothelial interactions, and the expression of key physiological functions. Over the past decade, it has been established that fluctuating physiological conditions during the ovarian cycle do indeed have the power to reversibly alter structural relationships among the various cell types of the median eminence that specifically interact with axon terminals containing gonadotropin releasing hormone (GnRH), the neuropeptide that controls gonadotropin secretion and reproduction. During the ovarian cycle, under conditions of low gonadotropin output, GnRH-secreting axon terminals are completely surrounded or engulfed by specialized glial cells named tanycytes, which prevent direct access to the vascular wall and thus create a diffusion barrier impeding GnRH entry into the pituitary portal circulation. During the preovulatory surge, a structural remodeling of tanycytes occurs, resulting in the release of the engulfed axons, their sprouting towards the pericapillary space and the establishment of direct neurovascular contacts between GnRH neurons and the endothelial Wall. Here we will explore the cellular mechanisms and signaling pathways underlying these function-related structural changes in the GnRH system and show that semaphorin 3A (Sema3A), the ligand of Neuropilin-1 (Npn-1), is expressed by adult vascular endothelial cells in response to the ovarian cycle and promotes the sprouting of axons containing GnRH at the neurovascular junction. These data identify a previously unknown function for Sema3A/Npn-1 signalling in inducing adult central nervous system axon growth, and raise the possibility that endothelial cells may actively participate in synaptic plasticity in specific functional domains of the adult brain.

S03.5

Rôle des sémaphorines dans le cerveau postnatal

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The semaphorins are secreted and membrane-bound proteins that have key roles in various neuronal developmental processes. Sema6A is a membrane-bound molecule that was initially characterized as a chemorepellent for sympathetic axons. In the central nervous system, we and others have shown that Sema6A regulates the formation of lamina-specific axon projections in the hippocampus, the development of the corticospinal tract, and that it controls the migration of cerebellar granule cells. Sema6A has two known receptors, Plexin-A2 and A4, which belong to the Plexin family.
We have recently studied two different roles of sema6A: the control of lamina-specific neuronal stratification in the retina and the migration of granule cells in the cerebellum.
Parallel processing of neuronal signals is an essential aspect of all sensory systems in vertebrates. In the retina, the different neurons have to set up precise synaptic connections in defined layers in order to process visual information and for accurate visual perception. Retinal ganglion cells, bipolar cells

and amacrine cells establish stereotypic neurite arborization patterns to constitute functional neural circuits in the inner plexiform layer (IPL), a laminar region that is divided into an ON and OFF sublayer. The ON and OFF synaptic pathways are totally separated and involved in the processing of increments and decrements in luminance of visual stimulation. The IPL is further conventionally divided into five major parallel sublaminae. We showed that the transmembrane semaphorin, Sema6A signals through its receptor PlexinA4 to control lamina-specific neuronal stratification in the mouse retina. Finally, we demonstrated that Sema6A and PlexinA4 also interact genetically *in vivo* for the regulation of dopaminergic amacrine cell laminar targeting. In the cerebellum, we have used a variety of neuronal culture assays together with *in utero* and post-natal electroporation combined to time-lapse video-microscopy. We showed that in the postnatal cerebellum, the plexin-A2 receptor and its ligand Sema6A control the migration of granule cells through a modulation of centrosome-nucleus coupling.

S04 Neuropeptides hypothalamiques et sommeil: des modèles animaux aux pathologies humaines. / Hypothalamic neuropeptides and sleep: from animal models to human diseases.

S04.1
Neurones à hypocrétines-implications fonctionnelles

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Hypocretin/orexin (hcrt/orx) neurons are located in the perifornical area and lateral hypothalamus from where they send widespread projections throughout the brain. Their importance relates to the evidence that their lesion, associated with a decrease of hcrt/orx secretion, results in the sleep/wake disorder narcolepsy characterized in particular by daytime sleepiness and cataplectic attacks.
The ways by which hcrt/orx neurons exert their action is still debated. Here, based on in vitro studies, the properties of these neurons, their modulation in different conditions as well as the actions exerted by the peptides they secrete will be reviewed.

S04.2
Neurones à histamine et à hypocrétines: complémentarité et synergie dans le contrôle des états de vigilance

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We have previously shown that mice lacking histamine (HA) synthesis are characterized by an EEG/behavioral somnolence. Indeed, they show a deficit of wakefulness (W) when high vigilance is required, i.e., lights-off or a new environment; whereas orexin (Ox) knockout (KO) mice are distinguished by a W deficit faced with motor challenge. We then suggested that HA and Ox exert a distinct but complementary control on W. To access the synergies of the two hypothalamic waking systems, we have studied the sleep-wake phenotypes of KO mice lacking HA and Ox.
The double KO mice were obtained by crossing KO mice lacking HA-synthesis and those lacking prepro-orexin. The mouse model was validated by PCR and immunohistochemistry showing the deletion of the HA- and Ox-synthesizing genes and loss of HA and Ox cells. EEG and sleep-wake recordings were performed in adult mice under baseline conditions and after behavioural and pharmacological tests.
The double KO mice were characterized by a somnolent phenotype severer than that seen with KO mice lacking HA alone, i.e., 1) significant decrease in W and sleep latencies after behavioural tests; 2) unable to stay awake faced with a new environment. This somnolence was abolished by modafinil but not by H3-receptor inverse agonists indicating functional loss of HA. On the other hand, these mice showed phenotypes characteristic of Ox KO mice, i.e., direct REM sleep onset (DREMs) and W deficit faced with a motor challenge, both being rescued by central Ox-A dosing. Finally, these double KO mice displayed aggravated sleep fragmentation, obesity and also phenotypes never seen with the single KO mice, such as EEG hypersynchronisation and cataplexy, defined as sudden loss of muscle tone during W and characteristic of human narcolepsy.

Our data suggest that HA- and Ox-neurons exert a distinct but complementary and synergistic control on W, the amine being mainly responsible for EEG arousal and cognitive activities and the neuropeptide being more involved in the behavioural activities. They could be co-responsible for narcolepsy: Ox deficiency is likely the direct cause of DREMs and cataplexy, whereas a decreased HA neurotransmission could account for the excessive somnolence seen in this disease and other sleep disorders.

S04.3

Les neurones à hypocrétines: au croisement entre la régulation des états de vigilance et de l´humeur

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Impaired sleep is a symptom that often associates with affective disorders including depression and anxiety. Conversely, sleep disorders may impact mood as recently shown in narcoleptic patients which frequently develop a depressive syndrome. However, the mechanisms underlying both mood and sleep regulation and their link remain unclear. Here, we propose that hypocretin (orexin) neurons may act as integrators to modulate both sleep and emotional behaviour in tight relation with the serotonergic system. To investigate the functional role of hypocretin-serotonin interactions, a special attention was devoted to animal models with impaired serotonergic or hypocretinergic neurotransmissions under depressogenic and/or stressful experimental conditions.
Mutant mice that do not express the 5-HT transporter (5-HTT-/-) display a marked increase in extracellular 5-HT levels, a depression-like syndrome with a rapid eye movement (REM) sleep increase, enhanced helplessness and an altered response to stress. Thus, in contrast to wild-type mice, 5-HTT-/- mice fail to exhibit the delayed increase in REM sleep after restraint stress (RS). This impairment appeared to be causally related to an enhanced hypocretinergic neurotransmission, since, by blocking the hypocretin type 1 receptor, the sleep response to stress in 5-HTT-/- mutant mice could be normalized. These results emphasize the role of hypocretin neurons in the disrupted stress response consecutive to 5-HTT deficiency in mice. Conversely, mutant mice that do not express the hypocretin precursor preprohypocretin (ppHcrt-/-) display a narcoleptic-like phenotype which includes sleep fragmentation and cataplectic-like attacks. Interestingly, these mice exhibit a depressive-like behaviour in the forced-swimming test and an impaired response to stress. Such alterations might be accounted for, at least in part, by decreased serotonergic neurotransmission as suggested by a decrease in brain serotonin turn-over in ppHcrt-/-mice.
Taken together, these data strengthen the hypothesis that hypocretin neurons and the interactions between hypocretin and serotonin systems modulate in a convergent manner sleep homeostasis and emotional related-behaviour.

S04.4

n/a

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We recently discovered, using Fos immunostaining, that the tuberal and mammillary hypothalamus contain a massive population of neurons specifically activated during paradoxical sleep (PS) hypersomnia (Verret et al., 2003, 2006). We further showed that some of the activated neurons of the tuberal hypothalamus express the melanin concentrating hormone (MCH) neuropeptide and that icv injection of MCH induces a strong increase in PS quantity (Verret et al, 2003). However, the chemical nature of the majority of the neurons activated during PS was not characterized. To determine whether these neurons are GABAergic, we combined *in situ* hybridization of GAD_{67} mRNA with immunohistochemical detection of Fos in control, PS deprived and PS hypersomniac rats. We found that 74% of the very large population of Fos-labeled neurons located in the tuberal hypothalamus after PS hypersomnia were GAD-positive. Combining MCH immunohistochemistry and GAD_{67} *in situ* hybridization we further demonstrated that 85% of the MCH neurons were also GAD-positive. Finally,

based on the number of Fos-ir/GAD$^+$, Fos-ir/MCH$^+$, and GAD$^+$/MCH$^+$ double-labeled neurons counted from three sets of double-staining, we uncovered that around 80% of the large number of the Fos-ir/GAD$^+$ neurons located in the tuberal hypothalamus after PS hypersomnia do not contain MCH. Based on these and previous results, we propose that the non-MCH Fos/GABAergic neuronal population could be involved in PS induction and maintenance while the Fos/MCH/GABAergic neurons could be involved in the homeostatic regulation of PS.
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Verret L, Fort P, Gervasoni D, Leger L, Luppi PH (2006) Localization of the neurons active during paradoxical (REM) sleep and projecting to the locus coeruleus noradrenergic neurons in the rat. J Comp Neurol 495:573-586.

S04.5
Actualités sur la narcolepsie: hypothèse autoimmune et nouvelle approche thérapeutique

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La narcolepsie est une maladie rare et sporadique du sujet jeune. Elle est caractérisée par des accès de sommeil irrésistibles et des cataplexies (pertes soudaines du tonus musculaire à déclenchement émotionnel). Les autres signes, inconstants, sont des hallucinations hypnagogiques, des paralysies du sommeil, un mauvais sommeil de nuit, des comportements oniriques et une prise de poids.
Le diagnostic clinique nécessite un enregistrement polysomnographique: il met en évidence une latence moyenne d'endormissement en moins de huit minutes et au moins deux endormissements directs en sommeil paradoxal. L'association au génotype HLA DQB1*0602 est très sensible (97%) mais peu spécifique. Depuis la découverte récente d'une mutation du récepteur 2 de l'hypocrétine chez le chien narcoleptique et de l'absence d'hypocrétine 1 dans le liquide céphalorachidien de plus de 90 % des patients narcoleptiques avec cataplexie, un taux d'hypocrétine 1 inférieur à 110 pg/ml dans le liquide céphalorachidien est spécifique de ce diagnostic. La perte des neurones à hypocrétine dans l'hypothalamus pourrait être d'origine auto-immune. Le traitement comprend des stimulants de la veille (modafinil, méthylphénidate), des anticataplectiques (antidépresseurs) et du sodium oxybate. Les pistes thérapeutiques actuelles sont les agonistes de l'hypocrétine, les antagonistes des récepteurs H3 de l'histamine (un système d'éveil) et les immunosuppresseurs.

S05 Nouveaux outils expérimentaux et nouvelles thérapies pour la maladie de Parkinson. / New experimental tools and therapies for Parkinson's disease.

S05.1
Modifier le cours évolutif de la maladie de Parkinson: point de vue clinique

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Les médicaments antiparkinsoniens améliorent les symptômes de la maladie mais n'empêchent pas le handicap de s'aggraver. Ce phénomène résulte de la progression de la dégénérescence neuronale sous-jacente, responsable de symptômes moteurs et non moteurs de plus en plus marqués et de plus en plus réfractaires. Après 10 à 15 ans d'évolution, la qualité et l'espérance de vie des malades sont significativement compromises.
Depuis des décennies, la recherche fondamentale tente d'expliquer les mécanismes de la mort neuronale pour identifier des cibles thérapeutiques permettant de développer des médicaments « neuroprotecteurs », susceptibles de freiner, voire de bloquer, le cours évolutif de la maladie.
Le développement de ces médicaments se heurte à de nombreux obstacles, en raison de la complexité des phénomènes cellulaires et moléculaires et à la mauvaise prédictibilité des modèles expérimentaux. Un autre obstacle réside dans les difficultés méthodologiques que soulèvent les essais cliniques dans le domaine : choix des malades, choix des critères de jugements cliniques pertinents, absence de biomarqueurs faisant office de critère de substitution, lenteur d'évolution de la maladie, facteur confondant induit par l'efficacité symptomatique des traitements disponibles… Pour tenter de contourner ces difficultés, divers critères de jugement ont été proposés (aggravation d'un

score de handicap, survenue d'un évènement marquant, marqueur de neuro-imagerie) et divers plans expérimentaux ont été utilisés (non comparatif de type analyse de futilité ou comparatif de type wash-out, delayed -start ou pragmatique)…
En dépit d'un riche « pipe-line », les résultats de la plupart des essais visant à évaluer la capacité d'un médicament à ralentir le cours évolutif de la maladie de Parkinson restent à ce jour « négatifs » ou ambigus. Des données récentes provenant d'essais cliniques de type delayed-start avec la rasagiline (étude ADAGIO) montrent qu'on peut pourtant différentier cliniquement un effet « symptomatique » d'un effet « disease-modifying » dans une cohorte de malades au début de leur maladie. L' l'importance clinique de ces résultats demande désormais à être mieux évaluée à long-terme.

S05.2

Le venin d'abeille dans le traitement de la maladie de Parkinson

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Background: The project was based on a clinical observation that bee venom may possess both symptomatic and protective effects in an advanced Parkinson disease (PD) patient. More, specifically, preclinical data suggest that one of the components of bee venom, a polypeptide named apamin which may protect primary dopaminergic neurons from death.
Methods: We used the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)/probenecid mouse model of PD: bee venom and apamin dosages were chosen by extrapolating from those used in our PD patient. Tissue analysis was conducted after two different dosages of bee venom (low = 0.3 µg/injection; high = 3.0 µg/injection) and apamin (low = 0.5 mg/kg/BW; high = 1.0 mg/kg/BW), respectively. 70 animals (62 survivors) were treated this way.
Results: Tyrosine hydroxylase (TH) cell counts in the substantia nigra pars compacta showed that both apamin and bee venom protected nigral DA neurons against MPTP/probenecid treatment. This effect was significant only in the “high” groups and the magnitude of this effect was comparable for apamin and bee venom. Striatal dopamine (DA) concentrations determined by high pressure liquid chromatography reflected this protection on the nigral cellular level: both apamin and bee venom protected nigral dopaminergic neurons against MPTP/probenecid treatment, and this effect also appeared dose-dependent; significance, however, was only reached in the bee venom “high” group. Striatal homovanillic acid/DA ratios reflected protection on the nigral cellular level by apamin and bee venom against MPTP/probenecid, as well as the decrease of striatal DA levels in control animals treated with apamin, with significant differences in all MPTP-treated groups except for bee venom “high” group.
Conclusions: Repeated (x10), high bee venom concentrations have protective effects on the nigral and striatal level in the MPTP/probenecid model of PD. Moreover, apamin is not the only neuroprotective compound present in bee venom, although the TH+ cell counts in MPTP/probenecid-treated mice suggest that it plays a major role. The mechanism by these effects are mediated (decrease in neuroinflammation, free radicals, mitochondrial dysfunction and/or protein misfolding) remain to be elucidated.

S05.3

Modulating α-synuclein phosphorylation as a therapeutic strategy for the treatment of Parkinson 's disease

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Increasing evidence suggests that phosphorylation plays an important role in the oligomerization, fibrillization, Lewy body (LB) formation, and neurotoxicity of a-synuclein in Parkinson's disease (PD) and related synucleinopathies. However, whether phosphorylation promotes or inhibits a-syn aggregation and neurotoxicity *in vivo* remains unknown. This understanding is critical for elucidating the role of a-synuclein in the pathogenesis of PD and for development of therapeutic strategies for the treatment of PD. I will present recent studies from our laboratory aimed at i) elucidating the role of a-synuclein phosphorylation at S87 and S129 on modulating the structure, aggregation, membrane binding, subcellular localization and neurotoxicity of α-synuclein; and ii) validating the Polo Like Kinases, PLK2 and PLK3, as therapeutic targets for the treatment of Parkinson's disease.

S05.4
Progrès et perspectives des biothérapies dans la maladie de Parkinson

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Oral dopaminergic treatments have remained the primary standard of care for Parkinson´s disease (PD) for the last 40 years. Although highly efficacious in the early stages of disease they are associated with debilitating long term side effects that impact on the quality of life and restrict the longevity of such treatment. The severity of PD, lack of a cure and the limited long term effectiveness of current therapies allow for the consideration of novel therapeutic approaches based on cell and gene therapies. The purpose of the presentation is to describe the current statut of different therapeutic approaches aiming at restoring local and continuous release of dopamine or delivering neurotrophic factors to restore and protect dopaminergic neurons from degeneration.

S05.5
Les récepteurs métabotropiques du glutamate du groupe III: des nouvelles cibles pour le traitement de la maladie de Parkinson

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The loss of substantia nigra dopaminergic neurons in Parkinson´s disease (PD) leads to impairment of the excitation/inhibition balance within basal ganglia (BG) synaptic pathways and hyperactivity of BG output to the thalamus. Dopamine-mimetic treatments are effective in restoring this balance and alleviating PD motor symptoms. However, in the long-term they lose efficacy and induce debilitating side-effects. Surgical procedures such as deep brain stimulation provide remarkable motor improvement in patients but, on the other hand, they are associated with psychological/behavioural side-effects, and their cost and applicability present significant limitations. For these reasons, new pharmacological targets bypassing dopamine system are currently under investigation.
Group III metabotropic glutamate (mGlu) receptors are located at key BG synapses becoming hyperactive in PD, i.e., cortico-striatal, striato-pallidal and subthalamo-nigral pathway. We have previously demonstrated the efficacy of mGlu4 receptor orthosteric agonists in alleviating PD symptoms when injected in the striatum or the globus pallidus, where they inhibit synaptic transmission (1, 2).
Current interests in our laboratory are in determining whether these findings can be replicated by an mGlu4 receptor positive allosteric modulator (PAM) which crosses the blood-brain barrier (BBB). *In vitro* electrophysiological recordings showing dose-dependent reduction of cortico-striatal and striato-pallidal synaptic transmission, and enhancement of the inhibitory effect of an orthosteric mGlu4 receptor agonist (2) are ongoing. In addition, behavioral studies on hemiparkinsonian rats (6-OHDA injection in the substantia nigra pars compacta) are currently performed to explore the hypothesis that a combined mGlu4 PAM + L-DOPA treatment alleviates akynesia. Preliminary data show a possible synergistic effect of the two compounds, suggesting that targeting mGlu4 receptor with a PAM crossing the BBB is an option for treating PD in combination with greatly reduced L-DOPA doses.
This work has been supported by ANR, Lundbeck Research USA, the CNRS and Aix-Marseille Université.
1) Cuomo *et al.*, J Neuroschem 2009
2) Beurrier *et al.*, FASEB J 2009

S06 Barrière Hémato-Encéphalique et pathologies cérébrales. / Blood-Brain Barrier and cerebral pathologies.

S06.1
Des brèches dans le cerveau: trafic des cellules immunitaires au cours de la sclérose en plaques

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Central nervous system (CNS) homeostasis is a prerequisite for the proper communication of neuronal cells. To this end, the endothelial blood-brain barrier (BBB) and the epithelial blood-cerebrospinal fluid barrier (BCSFB) tightly seal off the CNS from the continuously changing milieu within the blood stream. It is now well established that despite the presence of these barriers, the CNS is subject to immune surveillance and immune mediated pathogenic events. Numerous studies in an animal model for multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), have elucidated that memory T cells can cross the non-inflamed BBB or BCSFB using specific molecular keys and gain access to the cerebrospinal fluid (CSF) drained ventricular, subarachnoidal and perivascular spaces. If these pioneer T cells encounter their specific antigen on antigen presenting cells strategically localized immediately behind the brain barriers, reactivation of the T cells will trigger a local inflammatory response, leading to the stimulation of the BBB. The activated BBB will then provide novel traffic signals allowing for the entry of large numbers of circulating inflammatory cells into the perivascular spaces and finally across the glia limitans into the CNS parenchyma, where they progress to initiate tissue injury.

S06.2

Neisseria meningitidis interagit avec l´endothelium vasculaire cérébral et envahit les méninges

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Neisseria meningitidis (Nm or meningococcus) is a bacterial pathogen responsible for meningitis. The ability of *Nm* to colonize the human brain is a characteristic property of this pathogen, however, little is known about the causes for this tropism. Type IV pili are the critical bacterial attribute mediating the adhesion of meningococci to human brain endothelial cells. We have shown that pilus-mediated adhesion of *Nm* triggers complex signalling events resulting in the formation of cellular protrusions that come in close contact with adherent bacteria[1-4]. Bacterial invagination within these protrusions confers to bacteria the ability to resist the high mechanical forces exerted by the blood flow to persist at the endothelial cell surface[5,6]. These events also constitutes the initial step of an invasion process enabling bacteria to translocate through endothelial barriers[2]. Additionally, infection of brain microvessels by *Nm* affects the integrity of the brain endothelial cell junctions by promoting the recruitment of components of the polarity complex and of adherens and tight junctions to sites of bacterial adhesion, thereby enabling the exit of bacteria from the bloodstream by a paracellular route[7, 8].

Until recently, the cellular receptor(s) for meningococcal pili involved in these key initial adhesion events were still largely unknown. Our recent findings indicate that the G-protein-coupled β2-adrenergic receptor is an essential “signalling receptor” for *Nm. A*lthough it cannot mediate initial adhesion, the activation of the β2-adrenergic receptor is required to promote the pilus-mediated signalling events[9]. These data strongly suggest that at least two cellular receptors cooperate to promote firm adhesion of *Nm* and activation of signalling events.

1. Hoffmann et al. **J Cell Biol** (2001).
2. Eugene et al. **J Cell Sci** (2002).
3. Lambotin et al. **J Cell Sci** (2005).
4. Doulet et al. **J Cell Biol** (2006).
5. Mairey et al. **J Exp Med** (2006).
6. Mikaty et al. **PLoS Pathog** (2009).
7. Coureuil et al. **Science** (2009).
8. Lemichez et al. **Nat Rev Microbiol** (2010).
9. Coureuil et al. **Cell** (2010).

S06.3

Cibler le VEGF pour protéger la Barrière Hémato-Encéphalique: une cible thérapeutique pour les épilepsies réfractaires ?

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In human and in rat model of temporal lobe epilepsy, we observed that BBB permeability was associated with an aberrant angiogenesis, assessed by an overexpression of VEGF and its main receptor VEGFR2. Using an integrative in vitro model (organotypic hippocampal cultures: OHCs), we showed that vascular endothelial growth factor (VEGF) was induced by seizures in neurons and/or astrocytes and was responsible for the neo-vascularisation of the epileptic focus. In the present study, we investigated the role of VEGF/VEGFR2 signalling pathways in BBB disruption.
Seizures were induced in OHCs by kainate (25µM). At different time-points, we checked the expression of Zonula Occludens-1 (ZO-1), an essential protein of tight junctions. We evaluated the activation of VEGFR2 and its downstream effectors by measuring the phosphorylation of VEGFR2 and Src. Then, to precise their roles in tight junction degradation after seizures, we tested the effects of a neutralizing monoclonal anti-VEGF antibody (1µM) and of a selective inhibitor of Src: PP2 (10µM).
ZO-1 expression was significantly decreased in OHCs from 4 hours to 24 hours after seizures. At 4 hours after seizures western blot showed an increase of VEGFR2-P in microvessels, concomitant with Src activation. Both anti-VEGF antibody and PP2 inhibited the phosphorylation of VEGFR2 and prevented the degradation of ZO-1. However, VEGF neutralization had deleterious effect (toxicity) but not Src inhibition.
These results demonstrate that VEGF/VEGFR2 system plays a pivotal role in BBB permeability, specifically via Src pathway. Targeting Src to protect the BBB could provide alternative strategies for intractable epilepsies.

S06.4

Protéases et intégrité de la Barrière Hémato-Encéphalique après accident vasculaire cérébral

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Thrombolysis with tissue-type plasminogen activator (tPA) is used for the treatment of patients with acute ischemic stroke. However, a growing body of evidence indicates that besides its the unquestionable benefit from its thrombolytic activity, tPA also has a deleterious effect on the ischemic brain, including cytotoxicity and increased permeability of the neurovascular unit with development of cerebral edema. Because an increasing number of acute stroke patients are treated with tPA, it is important to know the mechanisms of tPA's harmful effects on the ischemic brain. Here, the best studied pathways of tPA's neurotoxicity will be discussed, along with future directions for a safer use of tPA as a thrombolytic agent in the setting of acute ischemic stroke.

S06.5

Rôle des cellules souches cancéreuses dans la perméabilité des cellules endothéliales cérébrales

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Cancer progression is a complex process where cells acquire aberrant proliferative, survival and migratory properties, as well as the ability to trigger the formation of a dedicated blood supply. One striking feature of tumour blood vessels is the loss of barrier function and abnormal increase in vascular permeability. Of note, vascular leak is used as a diagnosis criterion and a prognosis tool in brain tumours. Importantly, we recently found that the cell-cell adhesion molecule, VE-cadherin, is playing a central and dynamic role in the modulation of barrier integrity in both physiological and pathological angiogenesis. Moreover, a recent series of studies from several labs including ours had unveiled the intimate interactions between endothelial cells and glioblastoma stem-like cells in the tumour microenvironment. For instance, cancer stem cells reside within a vascular niche that might help to maintain their identity, while they may also directly contribute to neovessel formation. Our project aims to decipher how endothelial cells convert local cues such as tumour stem cell-derived chemokines and semaphorins to an integrated signal, culminating in gene transcription and tissue plasticity. For this, we have developed an original system to mimic the tumour vascular niche based on

the co-culture of human brain endothelial cells with patient-derived glioblastoma stem-like cells. We are now exploring the signalling mechanisms modulating VE-cadherin adhesion and vascular permeability. Through a unique bench to bedside approach, we offer here the perspective to open new avenues in the treatment of brain tumours, as well as central nervous system pathologies that are frequently characterised by a deviant function of the brain vasculature. In addition, elucidating the mechanisms underlying normal and abnormal vascular formation is an exciting and important area of current investigation as it may provide new targets for the treatment of many disease conditions, including cancer, ocular and inflammatory disorders, asthma, diabetes, and bacterial infections.

S07 Modélisation des mécanismes de la plasticité: du neurone à la dynamique de population. / Modeling of plasticity mechanisms: from single neurons to population dynamics.

S07.1

Plasticité dépendante des interactions temporelles: une règle de plasticité de l´excitabilité intrinsèque des neurones CA1

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Long-lasting plasticity of synaptic transmission is classically thought to be the cellular substrate for information storage in the brain. The spike-timing dependent plasticity (STDP) rule initially defined in hippocampal circuits has been verified in many excitatory synapses of the brain and is now considered as an ubiquitous learning rule for associative plasticity in vivo. Recent data indicate however that synaptic modification is not the unique substrate for brain plasticity and persistent changes in the intrinsic neuronal excitability have been shown to occur in parallel to the induction of long-term synaptic modifications. We will discuss experimental evidence showing that both long-term synaptic potentiation (LTP) and depression (LTD) induced by correlative paradigms in CA1 neurons are associated with modifications in the input-output function at the post-synaptic side (Campanac & Debanne, J Physiol 2008). This plasticity is input specific, requires the activation of NMDA receptors, and depends on the regulation of voltage-gated ion channels located in the dendrites. In particular, we will show the role of the hyperpolarization-activated cationic h-current in the persistent facilitation of dendritic integration occurring in parallel with LTP (Campanac et al., J Neurosci 2008). In conclusion, STDP is a common learning rule for long-term plasticity of both synaptic transmission and dendritic integration, thus contributing a form of functional redundancy that insures significant changes in the neuronal output when synaptic plasticity is induced.

S07.2

Modèles biophysiques de la STDP

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Multiple stimulation protocols have been found to be effective in changing synaptic efficacy by inducing long-term potentiation or depression in the hippocampus
and the cortex. Parts of the biochemical machinery involved in long-term plasticity have been identified. However, the underlying mechanisms linking specific activity patterns to observed synaptic changes remain elusive. Using a synapse model, we show how calcium dynamics evoked by pre- and postsynaptic spikes induces
synaptic changes through activation of potentiating and depressing signaling cascades. Applying the model to a large body of experimental data allows us to relate differences in plasticity outcomes to differences in the underlying synaptic
machinery. We calculate plasticity outcomes analytically and provide insights in how spike-timing and firing rate of pre- and postsynaptic neurons shape plasticity through activation of signaling cascades.

S07.3
STDP et renforcement de l´apprentissage dans une population de neurones

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Learning by reinforcement is important in shaping animal behavior, and in particular in behavioral decision making. Such decision making is likely to involve the integration of many synaptic events in space and time. However, using a single reinforcement signal to modulate synaptic plasticity, as suggested in classical reinforcement learning algorithms, suffers from the spatio-temporal credit assignment: many synapses will have contributed differently to the behavioral decision, and for the same synapse the many releases at different times will have had different effects. We show how we can solve this spatio-temporal credit assignment problem in a population of spiking neurons. The learning rule is spike-time dependent and maximizes the expected reward by following its stochastic gradient. Synaptic plasticity is modulated not only by the reward, but also by a population feedback informing the neurons about the population decision. Hence, we predict that in the context of reinforcement learning, spike-timing dependent plasticity (STDP) depends on 4 factors: the pre- and postsynaptic activities, the reward signal, and the population feedback.

S07.4
From Hebb to STDP to reward modulation: synaptic plasticity models under the influence of neuromodulators

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Recent experiments have shown that spike-timing-dependent plasticity is influenced by neuromodulation. We derive theoretical conditions for successful learning of reward-related behavior for a large class of learning rules where Hebbian synaptic plasticity is conditioned on a global modulatory factor signaling reward. We show that all learning rules in this class can be separated into a term that captures the covariance of neuronal firing and reward and a second term that presents the influence of unsupervised learning. The unsupervised term, which is, in general, detrimental for reward-based learning, can be suppressed if the neuromodulatory signal encodes the difference between the reward and the expected reward— but only if the expected reward is calculated for each task and stimulus separately. If several tasks are to be learned simultaneously, the nervous system needs an internal critic that is able to predict the expected reward for arbitrary stimuli. We show that, with a critic, reward-modulated spike-timing-dependent plasticity is capable of learning motor trajectories with a temporal resolution of tens of milliseconds. The relation to temporal difference learning, the relevance of block-based learning paradigms, and the limitations of learning with a critic are discussed.
[1] *Fremaux et al. Journal of Neuroscience*, Vol. 30, Nr. 40, pp. 13326-13337

S07.5
Plasticité synaptique dans les états stochastiques

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One of the problems identified with spike-timing dependent plasticity (STDP) models is that such models are sensitive to spontaneous activity. For instance, it was shown that networks displaying spontaneous irregular activity cannot show stable learning with STDP, because the spontaneous activity constantly affects synaptic weights, which always return to their steady-state distribution. Thus, STDP cannot be used to learn in realistic network states. To avoid this "catastrophic forgetting" effect, we propose a new class of STDP learning rule with local floating thresholds, which slow dynamics accounts for metaplasticity (mSTDP). This mSTDP model accounts for known properties of STDP such as frequency sensitivity, and in addition accounts for priming experiments on LTP and LTD. The floating threshold also accounts for other well-known plasticity rules such as the BCM rule with sliding threshold, which is an emergent property of the mSTDP model. Finally, because of its floating

threshold, the mSTDP model is robust to spontaneous activity, and can be used for stable learning in realistic network states.
This work was dsupported by CNRS, ANR (HR-Cortex) and European Community grants (FACETS, Brain-i-Nets and BrainScaleS). SEB was supported by a FRM fellowship.

S08 Nouvelles méthodes optiques d'enregistrement et de contrôle de l'activité neuronale. / Advanced optical methods to follow and modify neuronal activity.

S08.1
Contrôle spatio-temporel de l´activité cérébrale par des patrons lumineux en microscopie mono et bi-photonique

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The advent of optogenetics molecules has opened the route for elucidating neural circuit basis of behavior with a previously unheard precision.
However, these tools imply a number of constraints on the opto-stimulation method to be used. A perfect light-delivering method should be: efficient (minimal power loss throughout the system), flexible (capable of targeting a wide range of samples, from a single dendritic spine to a whole 3D population of neurons), allow millisecond temporal resolution and µm spatial resolution, and robust to scattering. Here we present a novel microscopy system for high-resolution patterned photoactivation of optogenetics molecules based on the temporal control of ultrafast pulses for axial localization of the illumination pattern. For lateral light patterning, the system can use either digital holography or the generalized phase contrast method.
We present examples where sculpted two-photon illumination is used to activate Channelrhodopsin-2 (ChR2) in mouse cultured neurons and cortical slices with sufficient efficacy to reliably fire action potentials with millisecond temporal resolution and low excitation power when the light was shaped over the cell body, one or more dendritic subdomains or multiple cells simultaneously.

S08.2
n/a

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We have combined a spatial light modulator (SLM) based microscope, which uses diffraction to pattern an incoming laser source, with two-photon activatable neuromodulators and dyes, to offer precise control and monitoring of cortical tissue with single cell precision. The use of a phase-only SLM provides for efficient multiplexing of the incoming laser beam to allow for simultaneous imaging or photostimulation of different regions of a sample with three-dimensional precision at high frame rates. We demonstrate the utility our system, and of two-photon activation in general, for neuronal circuit studies by mapping the connectivity of somatostatin-positive and parvalbumin-positive interneurons to pyramidal cells in the neocortex, where both classes of interneurons show relatively dense, non-specific connectivity.

S08.3
Imagerie rapide des transitoires calciques subcellulaires par la technique de microscopie multiphotonique RAMP

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Multiphoton laser scanning microscopy has been widely used to probe the intricate and specialized architecture of neurons and networks in the depth of intact brain tissue. However, matching the temporal resolution of optical recordings to the millisecond timescale of electrical neuronal signalling

constitutes an ongoing challenge. The sequential nature of laser scanning techniques imposes a reduction of the dimension of the scanned area as the main strategy to increase frame rate. Using Acousto-Optic Deflectors (AODs) we have developed a Random-Access MultiPhoton (RAMP) microscope, which can address any voxel in the field of view in a few microseconds. AODs are inertia-free diffraction-based pointing devices which induce both spatial and temporal dispersion of femtosecond laser pulses. We will present a simple strategy to mitigate these undesired interactions and describe the performance of the resulting scanning head.
Intracellular calcium concentration transients are the most widely used optical markers of neuronal activity both at the cellular and network levels. We will illustrate with several examples how RAMP microscopy can reveal the spatial and temporal features of neuronal calcium signalling. RAMP microscopy is optimally adapted to map calcium concentration transients in the dendrites of neurons in response to synaptic inputs, revealing the location and nature of calcium influx. Ultrafast RAMP imaging (5 kHz), which yields recordings with unmatched signal to noise ratios, can be used to resolve the time course of both subthreshold and suprathreshold voltage-gated calcium influx. Finally we will present the potential of RAMP microscopy for continuous monitoring of network activity at high frame rate. We show that spikes can be detected optically with millisecond precision, an order of magnitude faster than with previous techniques.

S08.4

Organisation dendritique des afférences visuelles sur les neurones corticaux dans le cortex visuel de souris

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In sensory cortex regions, neurons are tuned to specific stimulus features. For example, in the visual cortex, many neurons fire predominantly in response to moving objects of a preferred orientation. The characteristics of the synaptic input that visual cortical neurons receive to generate their output firing pattern remain unclear. A novel approach was developed for the visualization and functional mapping of visual inputs to the dendrites of cortical neurons *in vivo*. By combining two-photon imaging with electrophysiological recordings, we identify local subthreshold calcium signals that correspond to orientation-specific synaptic inputs. We find that even inputs that share the same orientation preference are widely distributed throughout the dendritic tree. At the same time, inputs of different orientation preference are interspersed, so that adjacent dendritic segments are tuned to distinct orientations. Thus, orientation-tuned neurons can compute their characteristic firing pattern by integrating spatially distributed synaptic inputs coding for multiple stimulus orientations.

S08.5

Imagerie multiphotonique des réseaux neuronaux in vivo

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Optical measurements of neuronal network dynamics in the intact brain have become possible by using two-photon calcium imaging techniques. While two-photon microscopy offers high spatial resolution, sufficient to resolve single neurons, the temporal resolution of standard galvanometric scan mirror systems is limited. To enable in vivo measurements of neuronal population activity on a fast time scale we built a two-photon microscope that employs a pair of acousto-optical deflectors (AODs) for high-speed scanning of the laser beam. With this system we could obtain in vivo images of neuronal populations in mouse neocortex stained with the calcium indicator Oregon Green BAPTA-1 AM down to 300 micrometer depth. Using a novel random access pattern scanning (RAPS) mode we could simultaneously measure calcium signals from neuronal populations of 30-90 cells with a sampling rate of up to 500 Hz. Using combined electrical recordings we demonstrated that single action potential-evoked calcium transients are resolved and that spike times can be inferred with near-millisecond precision. Moreover, a novel spike reconstruction algorithm allowed the extraction of complex spike trains underlying the observed calcium signals. In the future, high-speed AOD-based calcium imaging will facilitate optical studies of neuronal information processing in the intact brain.

S09 Nouvelles avancées dans la connaissance du système olfactif de la souris: des récepteurs aux comportements. / New insights into the mouse olfactory system: from receptors to circuits and behavior.

S09.1
Détection de phéromones d´alarme par le ganglion de Grueneberg chez la souris

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The Grueneberg ganglion (GG) was first described by Hans Grueneberg in 1973, as a ´ganglion´ of unknown function. With the limited histological methods available at the time, Grueneberg concluded that this ganglion-like cell mass might belong to the complex of the Nervus terminalis. These cells were “rediscovered” in 2005-2006 thanks to the inspection of whole-mount specimens from one particular gene-targeted mouse strain called OMP-GFP. These mice express GFP as a histological reporter under the control of the OMP promoter. OMP (olfactory marker protein) is a mature olfactory-sensory neuron-specific marker. In these mice, an uncharacterized OMP-positive structure was observed on both sides of the nasal septum, at the tip of the nasal cavity close to the opening of the naris. Further observation of OMP-GFP adult mice showed that from 300 to 500 cells can be found in each GG. These cells are not innervated by the Nervus terminalis but instead project to the necklace complex in the olfactory bulb. The development of the GG starts around embryonic day 16 and appears to be complete at birth; cell numbers then undergo a minor decrease during postnatal development.
We reported, using immunohistochemistry and electron microscopy, that the mouse GG is composed of different cell populations of neuronal and glial origin. We also observed that GG neurons bear multiple primary cilia. On average, 30 primary cilia are found on a single GG cell. These cilia of 5 µm length and 0.1 µm diameter may be key structural elements of the GG chemosensory nature. We demonstrated that alarm pheromones, the volatile chemicals widely used throughout the plant and animal kingdoms to signal danger to conspecifics, evoked calcium responses in GG neurons *in vitro* and induced freezing behavior *in vivo*. A behavior which completely disappeared when the GG was deleted by axotomy. On the basis of these findings, we also developed a new acute tissue preparation that allowed whole-cell patch-clamp recordings of GG cells to verify their chemosensitivity while preserving their morphology. We found cells with electrophysiological characteristics different from vomeronasal or main olfactory neurons. We conclude that mice detect alarm pheromones through the activation of olfactory GG neurons.

S09.2
Des récepteurs pour survivre: du système immunitaire aux neurones olfactifs

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Mammalian species rely heavily on olfaction to adequately interact between individuals. At the core of this sensory system are large superfamilies of G-coupled receptors that are present on dendrites of main olfactory and vomeronasal sensory neurons. These receptors define the agonist profile of sensory neuron populations, and thus define specific neural circuits, some of which are highly specialized. We recently uncovered a family of formyl peptide receptor-like, whose members are exclusively expressed by vomeronasal sensory neurons. Their corresponding genes are characterized by monogenic transcription and a punctate expression pattern in the sensory neuroepithelium. In vitro expression of these receptors provides sensitivity to disease/inflammation-related ligands. Finally, axons emanating from neurons expressing the same formyl peptide receptor-like converge in the accessory olfactory bulb, where they form a specific topographical projection map. Taken together, these data suggest the existence of a specific olfactory circuit in rodents, potentially involved in the identification of pathogenic states, or in the discrimination of pathogens.

S09.3

La neurogenèse adulte est requise pour l´apprentissage perceptuel olfactif

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Olfactory perceptual learning is a critical component of basic olfactory function. This learning is based on the fact that odor discrimination is enhanced by prior experience. Mechanisms of that implicit and robust learning which is the core of basic olfactory function remain elusive. We first show that the discrimination of odorants is improved in mice by the odor enrichment. More specifically, perception of odorants is only modulated by enrichment with odorants that activate at least partially overlapping regions of the olfactory bulb. Second, we show that this improvement of perception is due to an increase of inhibition due to an increase of newborn granule survival of the olfactory bulb in regions involved in odor processing. Third, we show that bulbar neurogenesis is essential for this learning because its blockade during the enrichment period prevents from the improvement of discrimination. Because the noradrenergic system projects massively onto the bulbar interneurons and modulates their activity, we went further by testing the potential role of noradrenaline in mediating olfactory perceptual learning and changes in neurogenesis. We found that noradrenaline acts upon adult-born cells to support learning. These data indicate that noradrenergic transmission is a key mechanism selecting adult-born neurons during learning and more generally, support the view that top-down neuromodulation acts directly on neurogenesis to modulate learning performances.

S09.4

Premiers pas dans le bulbe olfactif: rôle de l´activité synaptique dans la maturation des interneurones produits chez l´adulte?

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In mammals, olfactory bulb granule cells are continuously renewed throughout life. Granule cells represent the largest neuronal population subjected to continuous replacement, with more than 30,000 newborn granule cells reaching the rodent olfactory bulb every day. This neurogenesis provides a striking form of structural plasticity in the adult olfactory bulb circuit.
Using lentiviral labeling of adult generated cells, electrophysiology, confocal and electronic microscopy, we have shown that immediately after their arrival in the olfactory bulb, the granule cells are receiving functional GABAergic and Glutamatergic synapses. Then, we have described the functional and morphological maturation of these inputs (Nissant et al., 2009; Panzanelli et al., 2009; Katagiri et al., 2011). Our goal is now to understand the role of synaptic activity in the process of cell differentiation and integration in the mature OB network. For example, to challenge the role of GABAergic signaling in the maturation of adult generated granule cells, we are using transgenic mice floxed for the alpha2 subunit of the GABAa receptor (*Jean Marc Fritschy*, Zurich). We are injecting a lentiviral vector expressing the cre-recombinase and the GFP in the rostral migratory stream of these mice. Only the neuroblasts migrating toward the olfactory bulb at the time of the injection are infected and express the cre-recombinase and the GFP. We are then able to follow the maturation of genetically modified adult generated neurons in which the GABAergic transmission has been silenced in a “cell autonomous” manner. We have shown that some aspects of morphological and functional maturation of these cells are impaired.

S09.5

Traduction locale dans l´axone des neurones sensoriels olfactifs: un nouveau mécanisme participant à la mise en place et à l´entretien de la carte sensorielle olfactive chez la souris ?

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Local translation occurs in dendrites or axons of numerous types of neurons and takes part to various processes among which dendritogenesis, synaptogenesis, axon growth and synaptic plasticity[1]. Odorant receptors (ORs) have 3 main functions in olfactory sensory neurons (OSN) in mice: besides their conventional role in the detection and transduction of odorant molecules, they also play a critical role in regulating OR monoallelic expression and in controlling the sorting and coalescence into glomeruli of axons of the same OR identity[2]. This latter function may involve the OR proteins located at the level of OSN axons. We demonstrated that axonal OR mRNAs are translated in this compartment, indicating that axonal OR proteins may have a local origin[3]. Furthermore, we observed that OR mRNA transport and local translation in axons are developmentally regulated. So far, the molecular mechanisms involved in this regulation are unknown, and no RNA-binding protein that may bind OR mRNAs has been identified. Recently, Christie and colleagues demonstrated that the RNA-binding Fragile X Mental Retardation Protein (FMRP), encoded by the Fmr1 gene, is present in so-called Fragile X Granules within the axonal compartment of OSNs[4]. Since FMRP is a key regulator of the transport and local translation of a number of mRNAs in dendrites and axons[5], we hypothesized that it may be involved in the transport and/or translation of OR mRNAs (or other mRNAs) in the OSN axons. To address these issues, we undertook a series of analyses in both Fmr1-KO[6] and wild-type mice, including the assessment of the translation rates for several OR mRNAs in axons, and of their axonal transport index. Furthermore, in view of characterizing further the role of FMRP in this system, we are currently analyzing the glomerular map using bicistronic OR-IRES-reporter mice in either wild-type or Fmr1-KO backgrounds.

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S10 La dimension canalopathie dans l'épilepsie. / The channelopathy side of epilepsy.

S10.1

Canaux sodiques et épilepsie génétique

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Mutations of Nav1.1 (SCN1A) voltage-gated Na^+ channel are the most common known cause of genetically determined epilepsy, causing epileptic syndromes that range in severity from relatively mild disorders such as simple febrile seizures (sFS) and generalized epilepsy with febrile seizures plus (GEFS+) to the epileptic encephalopathy termed severe myoclonic epilepsy of infancy (SMEI) or Dravet syndrome. They can cause also familial hemiplegic migraine (FHM), a severe inherited subtype of migraine with aura. The functional effects of Nav1.1 mutations have not been completely clarified yet, impairing the identification of their pathogenic mechanism and the development of targeted therapies.
We have shown that in an animal model of SMEI, Nav1.1 knock out mice, loss of function of Nav1.1 causes reduced excitability of GABAergic interneurons and reduced network inhibition in hippocampal slices. We have also obtained evidences that Nav1.1 epileptogenic mutations can cause loss of function of Nav1.1 by inducing folding defects that can be rescued by interacting proteins and drugs. Moreover, our results show that FHM mutations cause gain of function both in cell lines and in neurons.
Therefore, our data point to a loss of function as the main effect of epileptogenic $Na_v1.1$ mutations and to a gain of function as the effect of FHM mutations.

S10.2

Un canal potassique au seuil de l´épilepsie

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Erg-like (Elk, Kv12) voltage-gated K^+ channels are expressed throughout the nervous system but their role in neuronal physiology has yet to be described. The characteristic biophysical feature of these channels is a hyperpolarized activation range which suggests a role in determining the sub-threshold excitability of neurons. We produced a mouse knockout of Kv12.2 (Elk2), a channel that is abundantly expressed in forebrain excitatory neurons, in order to determine how Kv12 channels contribute to neuronal signaling. EEG recordings from Kv12.2 -/- mice revealed continuous interictal spike-wave activity accompanied by sporadic spontaneous non-convulsive seizures. Both the knockout and heterozygotes show hypersensitivity to the chemoconvulsant pentylenetetrazole (PTZ). Locomotor activity, coordination and stress responses are not affected in open field and rotarod tests. The mouse phenotype is recapitulated at the cellular level, as cultured hippocampal neurons from KO mice have depolarized resting potentials, increased input resistance and low action potential thresholds. As a result, spontaneous firing is greatly increased relative to WT and maximal firing rates can be elicited with significantly less current injection. We propose that Kv12.2 provides an important and previously unrecognized resting conductance that protects against synchronous discharge in seizure-susceptible circuits.

S10.3

Une question d'âge: dysfonctions des canaux potassiques (type M) et HCN dans l´épilepsie

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The development of the brain and its neuronal networks is an astonishing sequence of events during which neurons are born, migrate, arborize, and establish transient or persistent synaptic connections (1). Changes in any of these complex processes may result in neurodevelopmental disorders that may persistently affect learning ability, memory, and behavior. As dysfunction of Kv7/M or HCN/h channel activities plays an important role in human inherited or acquired epilepsy syndromes (2-5), we generated Kv7/M and HCN/h current-deficient mice to address their physiological roles. To create a “functional ion channel knockout”, we suppressed these ion channel activities through transgenic expression of dominant-negative Kv7 or HCN subunits. In addition, we used the Tet-Off system to limit transgene expression to defined developmental periods (6) by doxycycline (Dox) application. Using a Dox On-Off regime, we found that both mouse lines with brain-specific loss of M or h channel function only showed marked and persistent behavioral changes throughout adolescence and adulthood when the ion channel activity was attenuated during the postnatal preweaning period (until three weeks of age in mice). Our data suggest that Kv7/M and HCN/h channels play a critical role in controlling network activity in the developing mouse brain. Furthermore, our results indicate that treatment of neonatal hyperexcitability in a critical time window of brain development by, for example, chronic application of the NKCC1 antagonist bumetanide, may effectively prevent the development of chronic epilepsy and other long-term sequelae, even in the presence of an inherited or a transgene-induced channelopathy.

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S10.4
n/a

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Brain neurons contain substantial amounts of Zn^{2+}, which plays multiple roles in cellular functions. Whereas the release of Zn^{2+} into the interstitium reportedly modulates various neurotransmitter receptors and ion channels, only little is known about the effects of intracellular Zn^{2+} (Zn^{2+}_i) on transcription of genes critical for neuronal excitability. Here, we address whether Zn^{2+}_i controls the transcription of Ni^{2+}-sensitive Ca^{2+} channels, *i.e.* R/T-type Ca^{2+} currents mediated by the a_1 subunits $Ca_V2.3$ and $Ca_v3.1$-3.3. In NG108-15 neuroblastoma cells, transient exposure to extracellular Zn^{2+} (200 µM) under depolarizing conditions (50 mM KCl), led to Zn^{2+} influx via L-type Ca^{2+} channels and to increased mRNA transcription of $Ca_V3.2$, but not of other R/T-type Ca^{2+} channel subunits. Promoter analysis of $Ca_V3.2$ revealed a 1.251bp fragment within the 5´ UTR-flanking genomic sequence harboring several metal regulatory elements (MRE) for the metal-responsive transcription factor-1 (MTF-1). In a Luciferase assay, exposure to Zn^{2+} strongly induced transcription of this 1426 bp $Ca_V3.2$ promoter fragment. Similar effects were induced by the NO-donor Na^+ nitroprusside, which causes liberation of intracellular Zn^{2+} tightly bound to endogenous chelators. Overexpression of MTF-1 mimicked the exposures to Zn^{2+} or to NO in augmenting $Ca_V3.2$ promoter activation level. Conversely, functional inhibition of MTF-1 by overexpression of a dominant negative MTF-1 construct reversed the effects of Zn^{2+} on $Ca_V3.2$ promoter activation. Our findings implicate $Ca_V3.2$ as a novel target for MTF-1-mediated transcriptional upregulation via transient increases in free Zn^{2+}_i. Given that brain injuries are accompanied by marked elevations in free Zn^{2+}_i, and that $Ca_V3.2$ upregulation profoundly enhances intrinsic neuronal excitability, we propose that the novel upregulation of $Ca_V3.2$ transcription by zinc may be a key process and future therapeutic target in injury-induced epileptogenesis.
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S10.5
Mécanismes épigénétiques des canalopathies dans l´épilepsie

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Both human and experimental temporal lobe epilepsies (TLE) have been associated with enduring, abnormal expression and function of the neuronal ion channel hyperpolarization-activated cyclic-AMP gated channel type 1 (HCN1). Here we examined the nature of the underlying mechanisms, and queried if interfering with these mechanisms could modify disease course. Experimental TLE was provoked by status epilepticus (SE) generated by systemic kainic acid (KA), and HCN1 channel repression was examined at mRNA, protein and functional levels. Chromatin immunoprecipitation was employed to identify the transcriptional mechanism of repressed *hcn1* expression, and the basis for their endurance. In addition, physical interaction of the repressor, NRSF (REST), to target genes was abolished using decoy oligodeoxynucleotides (ODNs). Video-EEG recordings were performed during 2 weeks following SE to assess the onset and initial pattern of spontaneous seizures. Levels of NRSF and its physical binding to the *hcn1* gene were augmented after SE, resulting in repression of *hcn1* expression and HCN1-mediated currents (I_h), and reduced I_h-dependent resonance in hippocampal CA1 pyramidal cell dendrites. Chromatin changes typical of enduring, epigenetic gene repression were within a week after SE. Administration of decoy ODNs comprising the NRSF DNA-binding sequence (NRSE) *in vitro and in vivo,* reduced NRSF binding to *hcn1,* prevented its repression and restored I_h function. *In vivo*, decoy NRSE-ODN treatment restored theta rhythm and altered the initial pattern of spontaneous seizures. Acquired HCN1 channelopathy derives from NRSF-mediated transcriptional repression, that endures via chromatin modification, and may provide insight into the mechanism of a number of channelopathies that co-exist with, and maycontribute to, the conversion of a normal brain into an epileptic one.

S11 Spécification moléculaire lors de la mise en place des connexions neuronales. / Molecular specification of neuronal connectivity.

S11.1
n/a

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Transcription factors of the RFX family are conserved from yeast to mammals and have been shown to control genes involved in ciliogenesis in metazoans. In *Drosophila*, we have previously shown that *Rfx* is expressed in ciliated sensory neurons of the peripheral nervous system. *Rfx* mutants are defective in chemosensory and mechanosensory behaviors due to abnormal function and structure of neuronal sensory cilia.
We have now identified a second *Rfx* isoform that is only expressed, throughout development, in a restricted number of neurons in the *Drosophila* brain. We observed that this population of neurons sends dense projections surrounding the mushroom bodies, a central brain structure involved in memory. In addition we show that the brain *Rfx* isoform is expressed in a small group of peptidergic neurons that innervate the ring gland, a major endocrine organ in flies. More precisely, dRFX is expressed in four neurons innervating the *corpora allata*, which secretes the juvenile hormone and in the two PTTH expressing neurons that control ecdysone secretion by the prothoracic gland.
We created flies inactivated for the brain specific isoform. The larvae show severe developmental delay with marked overgrowth that can be attributed to defective PTTH and ecdysone signaling. In addition, mutant larvae do not show the characteristic food aversion phenotype that is normally induced in mid third instar, hence leading mutant larvae to pupariate in the food. Such a phenotype has been described for flies deficient in neuropeptide F (NPF) production. However, *Rfx* is not expressed in NPF producing neurons suggesting that *Rfx* defines a novel population of neurons involved in larval feeding behavior. In addition, we show that neurites of *Rfx* expressing neurons are stunted in *Rfx* deficient flies. MARCM analysis demonstrates that axonal and dendritic growth relies on a cell autonomous function of *Rfx*.
Altogether, our observations suggest that *Rfx* is required for proper dendritic morphogenesis in a subset of *Drosophila* neurons required for larval growth and feeding behavior.

S11.2
Voies moléculaires de signalisation régulant les projections axonales dans un nouveau model d´asymétrie gauche-droite

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Several cases of anatomical, functional and molecular Left-Right asymmetric features have been described in the vertebrate brain, while in contrast no evidence has yet been provided on the existence of a L-R asymmetric identity of spinal cord neurons and connectivity. The diaphragm is a respiratory muscle comprising a central tendinous region and two lateral muscles innervated by ipsilateral pools of cervical motoneurons forming the left (L) and right (R) phrenic nerves. Although symmetric in appearance at coarse level, both lateral muscles and phrenic nerves exhibit left-right (L-R) asymmetric features. Our quantitative analysis indicates first that L and R muscles differ in size, the R muscle being larger. Second, while the L phrenic nerve divides into two fascicles making a T-shape, the R nerve splits into several fascicles irradiating from the entry point in a fan shape. Overall, the L and R nerves significantly differ in the degree of defasciculation and length of secondary axon fascicles. These differences are present from the onset of target innervation, suggesting possible contribution of the symmetry-breaking Nodal signaling setting L/R asymmetry of the visceral organs in the early embryo. To assess this possibility we studied embryos lacking Pitx2c, a transcription factor

downstream of Nodal and Rfx3, a transcription factor controlling ciliogenesis whose deletion lead to bilateral expression of Nodal. In Pitx2c null embryos, both nerves adopt a R-like pattern. Conversely, in Rfx3 null embryos, both nerves exhibit a L-like pattern. In these embryos, the muscles becomes symmetric, both having a R morphology. Thus, muscle and nerve patterns are uncoupled, strongly suggesting that L/R innervation features are encoded by phrenic motoneurons. In an effort to identify differentially expressed L/R nerve factors, we undertook a proteomic screen of protein contents in neonatal L and R phrenic nerves. In parallel, we investigated the role of candidates and interestingly, we found that metalloproteinase members contribute to the establishment of the asymmetric L/R nerve pattern of the diaphragm.

S11.3

Mécanismes moléculaires mis en oeuvre lors du développement des cartes somatosensorielles

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In the mouse trigeminal pathway, sensory inputs from the face are topographically mapped onto the somatosensory cortex, via relay stations in the thalamus and hindbrain. Somatotopic representations are generated at each level of the neuraxis in which distinct facial structures, such as whiskers or lower jaw and lip, are mapped at different scales. The molecular mechanisms generating such maps are poorly understood. We focus on the wiring of the facial pattern at the level of the brainstem, the first central relay station of the trigeminal pathway. We have previously shown that the gross topographic organization of the face map in the brainstem is related to the positional (rhombomeric) origin along the rostrocaudal axis of the second order neurons of the principal trigeminal sensory (PrV) nucleus and to their graded *Hoxa2* expression (Oury et al., 2006, Science 313(5792):1408-13).
To understand the impact of face-derived signals in determining the positional identity of first order sensory neurons of the trigeminal ganglion (TG) and their peripheral and central connections, we analysed the connectivity and molecular pattern of TG neurons in mice with an altered whisker facial pattern. On the other hand, to characterize the involvement of target-derived signals in establishing a refined central whisker map, we studied the effects on trigeminal afferent connectivity of brainstem-specific *Hox* gene loss- and gain-of- function. The results of these analyses will be presented.

S11.4

Génèse de la diversité cellulaire au sein des neurones de projection moteurs et sensitifs du télencéphale et diencéphale

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Information from our sensory organs converges in the thalamus, where distinct subclasses of thalamocortical neurons relay sensory signals to their proper area- and cell type-specific neocortical targets. Appropriate cortical motor output is in turn generated by distinct subclasses of cortical projection neurons, including corticospinal neurons, which form cell-type specific connections with motor neurons at precise rostro-caudal segments of the spinal cord. Over the past few years, the molecular mechanisms that control specification and early differentiation of several of the distinct broad classes of forebrain projections neurons have become increasingly understood. However, the finer-grained genetic determinants controlling subsequent differentiation events *within a* given class of neurons, such as the selection of a specific synaptic partner, are only beginning to be explored.
Here we present some of our recent findings on the developmental genetic controls over synaptic target specificity within two critical populations of forebrain projection neurons, namely
(1) distinct subtypes of cervical- and lumbar-projecting corticospinal motor neurons, and
(2) distinct subtypes of motor and sensory thalamocortical neurons.
Using comparative microarray gene expression analysis of select subclasses of neurons at critical developmental stages, these studies identify novel developmental gene expression programs central to the generation of forebrain neuronal and functional diversity.

S11.5

Mécanismes cellulaires et moléculaires nécessaires au développement du corps calleux

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Axonal guidance is a key step that allows neurons to specifically integrate in a functional neural network. Intermediate targets or guidepost cells act as critical elements that help to guide axons through long distance in the brain and provide information all along the path. Subpopulations of midline glial cells have been shown to guide corpus callosum (CC) axons to the contralateral cerebral hemisphere.
Our published results unravelled that, during embryonic development, the CC is populated in addition to astroglia by numerous glutamatergic and GABAergic guidepost neurons that are essential for the correct midline crossing of callosal axons (Niquille et al., 2009). Moreover, with the use of in vitro transplantations in slices, co-explant experiments, siRNA manipulations on primary neuronal culture and in vivo analysis of knock-out mice we have been able to demonstrate that CC neurons direct callosal axon outgrowth, in part through the attractive action of Sema3C on its Npn-1 receptor.
Recently, we have studied the origin of CC GABAergic guidepost neurons, the dynamic aspects of these processes, as well as, the molecular mechanisms involved in the establishment of this axonal pathway. We identified two distinct GABAergic neuronal subpopulations, one originating from the MGE and the other from the CGE, which transiently occupy the developing CC. Interestingly, MGE and CGE GABAergic neuronal subpopulations exert both an attractive activity on callosal axons in transplantation experiments. Finally, we have dissected the molecular basis of these guidance mechanisms by using an extensive screen for genes of interest by sensitive RT-PCR technique, as well as, in situ hybridization.
We have also investigated the potential implication of CC guidepost neurons in agenesis of the CC which occurs in numerous human congenital syndromes. We have found that mice deficient for the ciliogenic transcription factor RFX3 suffer from CC agenesis associated with midline patterning defects accompanied by a marked disorganisation of guidepost neurons.
Taken together, our studies reveal novel functions for transient neurons in axonal guidance and bring new perspectives on the respective roles of neuronal and glial cells in these processes.

S12 Mécanismes psychobiologiques des vulnérabilités à l'usage de drogue et à l'addiction. / Psychobiological mechanisms of vulnerabilities to drug use and drug addiction.

S12.1

Le rôle complexe des peptides hypocrétine/orexine dans les comportements induits par la cocaïne

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Compelling evidence indicates that the Hypocretin/Orexin (Hcrt) system regulates arousal, stress and reward seeking behaviors. Those reports used behavioral, pharmacological and electrophysiological approaches in rats mainly. We report here cocaine reward-related behaviors in Hcrt-deficient mice (KO), and their heterozygous (HET) and wild type (WT) littermates. We first observed that WT, HET and KO male and female mice exhibited behavioral sensitization following repeated cocaine administrations (15 mg/kg ip), but KO males displayed a delayed and attenuated response to chronic cocaine administrations. We then assessed the behavioral conditioning for an environment repeatedly paired with cocaine injections. All mice, whatever their gender or genotype, exhibited a robust preference for the environment previously paired with cocaine administrations. Noteworthy, following two weeks of cocaine abstinence, KO males and females no longer exhibited any preference for the compartment previously paired with cocaine rewards whereas both WT and HET mice continued manifesting a robust preference. Meanwhile, using an operant conditioning approach, we did not observe any difference between WT and KO mice trained to self-administer cocaine (0.5-1.5 mg/kg/infusion) either in fixed or a progressive ratio schedule of reinforcement. Using an optgogenetic approach allowing a selective activation of Hcrt neurons in WT mice, we confirmed that the Hcrt

system does not modulate cocaine intake in mice, corroborating our former pharmacological observation in rats. Taken together and compared to the current literature, the present findings suggest that behaviors seen in Hcrt KO mice likely reflects developmental compensations since only a slightly altered cocaine-induced behavioral sensitization was reported in males compared to HET and WT littermates. Overall, the most striking observation is the constant hypoactive phenotype seen in the KO mice that most likely is accountable for their reduced tendency to explore the environment. Whether this hypoactive phenotype is due to a reduced alertness or reduced motivation for reward seeking remains debatable, but our findings suggest that the Hcrt-deficient mice barely display any altered motivation for cocaine seeking behaviors.

S12.2
n/a

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The glucocorticoid receptor (GR) is a transcription factor mediating adaptation to environmental challenges and stress. Stress-induced glucocorticoid secretion by the adrenal gland activates GRs which in turn trigger changes in gene transcription that initially facilitate adaptation but that in chronic stress conditions lead to behavioral pathologies, such as addiction, anxiety and depression. Since GRs are expressed in most structures and cell types of the brain it remains currently unknown whether GRs influence different pathologies by acting on specific cellular targets or whether they non-specifically modify the reactivity of the entire brain by acting concomitantly on several brain structures. In this context, we investigated the potential cellular target of the influence of GR on vulnerability to drugs of abuse, anxiety and despair. We generated animals in which the GR, or associated proteins, were specifically absent in different component of the dopaminergic or the serotoninergic pathways. We found that elimination of GR proteins in the postsynaptic site of the dopaminergic transmission, but not in the pre-synaptic one, largely reduced the impulse activity of mesencephalic dopamine cells and the reinforcing effects of cocaine, but not morphine. In contrast other stress-related phenotypes normally influenced by GR activity, such as anxiety, were not modified in dopamine-selective GR gene mutants, whereas they are when GR gene is inactivated in 5-HT1A expressing neurones.

S12.3
Environnement enrichi et addiction aux drogues

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In the last decades, several studies have demonstrated that environmental conditions can dramatically influence the behavioral and neurochemical effects of drugs of abuse. For example, stress increases the reinforcing effects of drugs and plays an important role in determining the vulnerability to develop drug addiction. Environmental enrichment (EE), on the other hand, has been shown to produce beneficial effects on a variety of physiological and pathological processes. Accumulating evidence indicates that EE can mimic positive life experiences and prevent the development of drug addiction. More recently EE has also been shown to eliminate already developed addiction-like behaviours and to reduce the risks of relapse. These preventive and curative effects of EE are associated with dramatic plastic changes in several brain areas such as the hippocampus, the frontal cortex and the striatum. EE alters all neurotransmitter systems, produces changes in gene expression and transcription factors, induces chromatin rearrangement, and stimulates hippocampal neurogenesis. In this talk, we will present recent results that help understanding how EE-induced neuroadaptations result in decreased vulnerability to addiction and relapse. Based on our results and the existent literature, we propose that EE can be seen as a functional opposite of stress.

S12.4

De l´usage de cocaïne à l´addiction : une vulnérabilité liée à la plasticité synaptique

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Despite years of research, we have limited knowledge of the neurobiological mechanisms underlying transition from controlled drug use to addiction. This failure could be partly due to the lack of pertinent animal models of this pathological transition, until recently. Drugs of abuse induce countless modifications in brain physiology. Therefore, whether or not a drug-induced alteration actually contributes to addiction is difficult to address without preparations specifically modeling compulsive drug use. We developed a model which allows observing transition to cocaine addiction in rats. As in humans, the transition occurs after prolonged access to the drug, in a limited number of users and is associated with a high vulnerability to relapse. Importantly, it is independent of the amount of drug previously self-administered. Therefore, addicted rats only differ from non addicted rats by their addiction-like phenotype. Using this model, we identified a neurobiological alteration associated with transition to cocaine addiction. Exposure to cocaine rapidly suppresses a form of synaptic plasticity in the nucleus accumbens, i.e. the NMDA receptor-dependent long-term depression (NMDAR-LTD). We showed that rats shifting from controlled drug use to addiction maintained a permanent impairment of NMDAR-LTD. On the contrary, rats keeping control on drug use recovered this form of synaptic plasticity. The failure of an individual to counteract the impairment in NMDAR-LTD induced by cocaine intake could contribute to the transition to addiction by making drug seeking progressively more and more inflexible. Causal relationships between this persistent loss in synaptic plasticity and transition to addiction have now to be established. Understanding the behavioral and neurobiological mechanisms that mediate this lack of adaptation in addicted rats could unravel new targets for the development of efficient therapies. These data challenge the common conceptualizations in which transition to addiction is seen as resulting from the progressive development of specific brain adaptations. Instead, the transition to addiction is associated, at least in the nucleus accumbens, with the inability of addicted rats to engage active processes to counteract a common drug-induced effect.

S12.5

Qui est le plus susceptible de faire la transition vers l´addiction? Données récentes d´épidémiologie et de psychologie

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Epidemiologic research is the essential source of information on population-based risk factors for substance use disorders. This discipline has repeatedly shown that substance dependence is associated with male sex, lower education, and numerous other sociodemographic variables. In addition, epidemiology has documented the highly important role played by comorbid psychiatric disorders in the risk of substance dependence. However, very recent trends in epidemiology have focused on explaining transitions from one stage of substance use to another, rather than focusing on the single outcome of dependence. These new analyses demonstrate clearly that most “classic” risk factors are active at very specific stages of the substance use trajectory, and may even have reverse effects at other stages. Such information has been lacking in the epidemiologic literature but it is crucial for defining targets for prevention and early intervention strategies. Behavioral psychology methods such as computerized ambulatory monitoring have also recently emerged as an important complement to epidemiology, and permit highly detailed investigations of the mechanisms involved in these transitions. This presentation addresses the latest epidemiologic research from adult and adolescent populations concerning risk factors for transitions between different substance use stages, and illustrates the power of ambulatory monitoring for identifying underlying mechanisms of transition.

S13 Réparation neuronale et régénération axonale. / Neuronal repair and axonal regeneration.

S13.1

La réorganisation spontanée et neuroréhabilitation induite du système nerveux central après lésion de la moelle épinière

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A severe spinal cord injury (SCI) induces complete and permanent paralysis below the level of the injury. Despite this lack of functional recovery, marked plastic changes take place in the neuronal systems located below the lesion. We found that a substantial anatomical and functional remodeling of spinal circuitries spontaneously occurs after severe spinal cord damage. However, these complex and multifaceted changes in the structure and properties of spinal motor systems lead to a progressive degradation of functional capacities in the chronic stages of the injury. Could this window of opportunity for enhanced plasticity be exploited to improve function? To address this hypothesis, we evaluated the capacity of multi-systems neurorehabilitation to direct this chaos of plastic changes toward useful remodeling of neuronal systems associated with improved functional capacities. Rats with paralyzing SCI followed a comprehensive locomotor training program enabled by a combination of monoamine agonists, electrical spinal cord stimulations, and robotic systems. After two months of neurorehabilitation, rats regained the capacity to initiate locomotion bipedally, walk freely over-ground, cross obstacles, climb stairs, and even swim. This impressive recovery of function relies on the extensive plastic remodeling of lumbosacral circuitries, spared intraspinal systems, and supraspinal motor networks. These results highlight the delicate balance between bad and good plasticity after a severe SCI, and open promising avenues to restore functional capacities in individuals with spinal cord damage.

S13.2

MAP1B, une protéine du cytosquelette clé dans l´intégration des voies de signalisation au cours de la régénération axonale

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Development and maintenance of axons requires the integrity of the cytoskeleton, implicated in processes as diverse as growth cone elongation and guidance, branching, and axonal transport. Inversely, growth cone collapse and axon retraction are features associated with the failure of axons to regenerate when confronted to an inhibitory environment, such as after CNS damage. The constant cross-talk of neurons with their environment implies signaling pathways that ultimately converge onto the cytoskeleton, changing its dynamics and remodeling the network. However, how exactly such neuron-extrinsic signaling is finally translated into regulation of expression, distribution, and/or activity of cytoskeletal proteins, is not yet fully understood.
This question constitutes the basis of our studies, in particular, investigation of the function of the Microtubule-Associated Protein 1B (MAP1B) in regulating microtubule stability and reorganization, in both axon extension and retraction processes. Our group provided evidence that MAP1B, previously considered as “juvenile” MAP, plays crucial roles in adult nervous system by coordinating cytoskeletal dynamics during guidance and collateral branching of regenerating axons, and also during retraction of neurites via microtubule backfolding (as occurring after induction by e.g. lysophosphatidic acid [LPA], or nitric oxide [NO]). MAP1B function is regulated by phosphorylation, with an axon-specific phosphorylation mode depending on proline-directed protein kinases (PDPK). While phosphorylation through PDPK family member CDK5 is not observed in regenerating axons, we could demonstrate a differential involvement of the three c-jun N-terminal kinase (JNK) isoforms in regeneration of adult axons, via a mechanism dependent on MAP1B. Our more recent results clearly show that also GSK-3ß is involved in axon regrowth, again through regulation of MAP1B phosphorylation. Thus, our data demonstrate that MAP1B is one of the key players in the regulation of axon fate, serving as an integrator of signaling pathways that ultimately influence microtubule reorganization.
Financial supports : CNRS, INSERM, UPMC, IRME, AFM, Egide

S13.3

Traumatisme de la moelle épinière: imagerie de la dynamique des interactions cellulaires participant à la régénération axonale

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The concomitant advances in fluorescence imaging technologies and in mouse transgenesis have opened the way to dynamic investigations of single cell behaviors in their natural environment. These technological progresses represent a breakthrough for studying central nervous system trauma, since the functional regeneration of damaged axons critically depends on complex yet unclear cellular interactions between many cell types.
As a first step to explore the cellular basis of healing after spinal cord injury we have developed a dedicated experimental protocol to dynamically and chronically image the same population of dorsal root ganglion axons and their vascular environment over 4 months in the dorsal spinal cord of adult mice. We then established a "pin-prick" lesion model of spinal cord injury and characterized the influence of post-traumatic angiogenesis on the behavior of severed axons as part of a spontaneous recovery process.
Recurrent observations of the same animals showed that injured dorsal root ganglion axons have the intrinsic ability to regenerate in the central nervous system after lesion, at a speed which correlates positively with local vascular density. At the peak of the angiogenic response, sequential or time lapse acquisitions showed an 8-fold enhancement of sprout elongation in axons growing close to blood vessels versus axons growing distal to blood vessels.
The ability of axon sprouts to grow faster while in close proximity to vessels was unrelated to the diameter of the blood vessels, hence the rate of growth was unlikely due to increased oxygen and nutrient supplies. Rather, the perivascular extracellular matrix might have provided axons with growth promoting substrate through perivascular laminin and/or neurotrophic factors through the recruitment of secreting immune cells.
The latter point is currently being investigated using multicolor mouse lines whose axons, macrophages and blood vessels are simultaneously imaged on different color channels. Massive recruitments of lys-6(+) and CD11c(+) circulating macrophages have indeed been observed seven days after injury while the proximity between macrophage processes and axon sprouts suggests a tight regulation of axon regeneration by immune cells.

S13.4

n/a

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The cerebral cortex consists of several hundreds of different types of neurons, organized into specific cortical layers and areas, that display specific profiles of gene expression, morphology, excitability and connectivity.
The identification and characterization of factors capable of (re)specifying the identity of cortical neurons has important implications regarding our understanding of neurodevelopmental diseases and in the context of therapies for neurological disorders.
Embryonic stem (ES) and other pluripotent stem cells constitute a promising tool for the modelling and treatment of human neural diseases.
Here we describe a novel pathway by which pluripotent stem cells, whether of mouse or human origin, recapitulate in vitro the major milestones of cortical development, leading to the sequential generation of a diverse repertoire of neurons that display most salient features of genuine cortical neurons.
Importantly, the moiuse and human pathways of corticogenesis display many similarities but also striking differences that may be related to species-specific developmental programmes.
In addition, when grafted into the cerebral cortex of newborn mice, or lesioned cortex of adult mice, these neurons develop specific patterns of axonal projections corresponding to endogenous cortical projections in vivo.
These data new light on the mechanisms of neuronal specification, and constitutes an innovative tool to model cortical development, evolution, and disease. In the long run, cortical neurons generated in

vitro could be used also in the perspective of brain repair, for several diseases striking cortical neurons.

S13.5
n/a

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A damage or pathological process that destroys axons in the mature central nervous system (CNS) produces lasting functional deficits. One of the major challenges in this field is to stimulate the re-growth of severed axons and reconstruction of pathways.
We have shown that immature neuroblasts taken from the developing CNS can survive in the lesioned brain of adult recipients and have the capacity to reconstruct specific circuitry over long distances in the lesioned mature host brain.
For instance, embryonic motor cortical tissue derived from GFP transgenic mice and transplanted homotopically into the damaged motor cortex of wild-type adult mice, develop efferent projections to appropriate cortical and subcortical host targets, including distant ones, such as the thalamus and spinal cord, with a topographical organization similar to that of intact motor cortex. Furthermore, the host and transplanted neurons have been observed to form reciprocal synaptic contacts, and numerous graft efferents were demonstrated to be myelinated, indicating integration and maturation of the transplanted neurons within the neocortical circuitry.
Interestingly, studies of neural transplants in other parts of the adult CNS have shown that immature neuroblasts have the capacity to reconstruct specific circuitry over long distances in the lesioned mature host brain. For instance, we have shown that ventral mesencephalon tissue obtained from GFP mouse foetuses and grafted into the 6-hydroxydopamine-lesioned substantia nigra of adult mice can survive, differentiate into dopaminergic neurons and, most importantly, develop significant contingents of projections through the medial forebrain bundle to the dopamine-depleted striatum. Most of the grafted cells expressed the dopaminergic markers. In addition to demonstrable circuit reconstruction in the host mice, increases in striatal dopamine levels and restoration of normal behavior were demonstrated as early as 2 months after transplantation.
Taken together, these results show that implanted fetal neuroblasts have the capacity to reconstruct specific circuitry over long distances in the lesioned adult brain. Such findings have raised new hopes and opened new avenues for cell therapies for CNS disorders.

S14 Nouvelles notions sur la synapse glutamatergique. / Novel insights at the glutamatergic synapse.

S14.1
Mécanismes et architecture moléculaires des récepteurs NMDA

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NMDA receptors (NMDARs) form glutamate-gated ion channels widely expressed in the central nervous system (CNS) and highly permeable to calcium ions. NMDARs have always attracted much attention because of their key involvement in numerous physiological and pathological processes including synaptic plasticity and excitotoxicity. Ever since the discovery of NMDARs three decades ago, it has been acknowledged that native NMDARs do not form a homogeneous population of receptors but rather exist as multiple subpopulations that differ in their functional properties, and presumably physiopathological roles. NMDARs are in fact large multi-subunit complexes arranged into heteromeric assemblies composed of four homologous subunits within a repertoire of over 10 different subunits. In the last years, the combination of structural and functional approaches has spurred great progress in our understanding of the molecular basis of NMDARs functional diversity. I will present our recent data revealing a central, and largely unsuspected, role of the extracellular N-terminal region in generating functional diversity of NMDARs. I will show how the molecular identity of this region, which is distal to the pore domain and precedes the agonist-binding domains, determines key biophysical and pharmacological attributes of the various NMDAR subtypes.

S14.2

Remodelage spatio-temporel des protéines d´échafaudage pour contrôler la transmission synaptique

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Scaffolding proteins can interact with receptors to control their localization and signaling. However, the dynamics of these interactions are poorly understood. Here we show in living neurons that the constitutive multimeric (Homer3) and the inducible monomeric (Homer1a) synaptic scaffolding Homer proteins compete to interact with the metabotropic glutamate receptor mGlu5a. Despite a broad co-localization of the proteins in neurons, this competitive interaction was confined to dendritic spines. Disruption of mGlu5a-Homer3 interaction by the cell permeant competitive TAT-Homer1a protein promoted interaction of mGlu5a with NMDA receptors in dendritic spines, and this resulted in inhibition of NMDA currents. Furthermore, we show that this scaffold remodeling-permissive effect on receptor crosstalk in spine occurred physiologically during long-term potentiation. These results enlighten an activity-dependent negative feed-back loop in which sustained activation of synaptic NMDA receptors would induce Homer1a expression, synaptic scaffold remodeling and mGlu5a receptor-mediated inhibition of NMDA currents.

S14.3

Régulation des récepteurs NMDA par la d-sérine d'origine gliale

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NMDA receptors (NMDARs) subserve numerous neurophysiological and neuropathological processes in the cerebral cortex. Their activation requires the binding of glutamate and also of a co-agonist. Whereas glycine and D-serine (d-ser) are candidates for such a role at central synapses, the nature of the co-agonist in the cerebral cortex remains unknown. We first show that the glycine-binding site of NMDARs is not saturated in acute slices preparations of medial prefrontal cortex (mPFC) and it can be modulated by agonists. Using enzymes that selectively degrade either D-ser or glycine, we demonstrate that under the present conditions D-ser is the only endogenous co-agonist of synaptic NMDARs at mature excitatory synapses in layers V/VI of mPFC where it is controlling the excitability of excitatory neurons and is essential for long term potentiation (LTP) induction. Furthermore, blocking the activity of glia with the metabolic inhibitor, fluoroacetate, impairs NMDAR-mediated synaptic transmission and prevents LTP induction. Such deficits can be restored by exogenous D-ser, indicating that the D-amino acid mainly originates from glia in the mPFC, as further confirmed by double-immunostaining studies for serine racemase or D-serine with known markers of astrocytes. Our findings suggest that D-ser modulates neuronal networks in the cerebral cortex by gating the activity of NMDARs, and that altering its levels is relevant to the induction and potentially treatment of psychiatric and neurological disorders.

S14.4

Fonctions synaptiques et mécanismes des récepteurs métabotropiques présynaptiques au glutamate (mGluR4)

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In the rodent cerebellar cortex, excitatory synaptic transmission at the Parallel Fiber - Purkinje Cell (PF-PC) synapse is reversibly depressed by pharmacological activation of mGluR4 receptors - the only member of the group III metabotropic glutamate receptors functional at this synapse (Abitbol et al 2008). This depression involves the inhibition of presynaptic calcium influx that ultimately controls vesicular glutamate release. In order to investigate the molecular basis of this mGluR4-mediated

inhibition, we combined pharmacological approaches, conventional whole-cell patch-clamp recordings and presynaptic calcium influx measurements applied to cerebellar brain slices. We will present evidence that inhibition of glutamate release at the PF-PC synapse by mGluR4 does not require activation of either pertussis toxin-sensitive Gi/o proteins or the adenylase cyclase / protein kinase A signaling pathway. In contrast, pharmacological inactivation of phospholipase C and/or PKC strongly reduce the mGluR4-mediated inhibition of glutamate release at this synapse. These results suggest that the classical group III mGluR signaling pathway described in heterologous expression systems (involving the regulation of adenylate cyclase) is not the transduction pathway by which native mGluR4s exert their effects on synaptic transmission in the cerebellum. Rather, as reported for another group III member, mGluR7 (Perroy et la 2000), mGluR4 - dependent depression of synaptic transmission requires the activation of phopholipase C and ultimately protein kinase C.

Abitbol K, Acher F, Daniel H (2008). Depression of excitatory transmission at PF-PC synapse by group III metabotropic glutamate receptors is provided exclusively by mGluR4 in the rodent cerebellar cortex. *JNC 105:2069-2079*

Perroy J, Prezeau L, De Waard M., Shigemoto R, Bockaert J and Fagni L (2000). Selective blockade of P/Q-type calcium channels by the metabotropic glutamate receptor type 7 involves a phospholipase C pathway in neurons. *J Neuroscience 20:7896-7904*

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S14.5

Rôle obligatoire de la sous-unité NR2A des récepteurs NMDA dans les effets induits par une privation de sommeil sur la plasticité synaptique dans la région CA3-CA1 de l'hippocampe

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Experience-dependent regulation of synaptic NMDA receptor (NMDAR) subunit composition appears more flexible than previously assumed. Modification goes on throughout brain maturation and continues at adult synapses via different types of behavioural experience, such as sensory deprivation, learning and insufficient sleep.
We studied the consequences of a single acute sleep deprivation (SD) on excitatory synaptic communication in mouse hippocampus. Mild, stress-free SD of young adult mice, lasting 4-6 hours starting at light onset, reversibly increased protein levels of the NMDAR subunit NR2A in membrane fractions of hippocampal nerve endings and in immunogold-labeled synapses, while leaving intact NR2B protein levels. The additional NR2A protein integrated into functional NMDARs, as evident by the comparable NR2A/NR2B ratio found electrophysiologically and electron-microscopically. The SD-induced augmentation of NR2A-NMDARs shifted the synaptic modification threshold of bidirectional synaptic plasticity, facilitating the induction of long-term depression in the theta-frequency stimulation range. Plasticity in NR2A-knockout mice was no longer affected by SD, although the behavioral reaction of these mice to SD, including post-SD sleep rebound, was normal.
The role of NR2A-containing NMDARs in plasticity induction was assessed via quantifying the temporal integration of NMDAR-EPSCs in the theta-frequency stimulation range. Using *in vitro* electrophysiology and computational modeling of NMDAR-EPSCs, we found that NMDAR pools, activated on different time scales, contributed to the synaptic response, generating both phasic and tonic current components. Sleep deprivation interfered with the balanced recruitment of these receptor pools, favoring the rapid recruitment of the phasically activated NR2A-NMDARs, while reducing the contribution of the more slowly recruited NR2B receptors.
In conclusion, dominant effects of sleep loss on CA3-CA1 synaptic plasticity were obligatorily conveyed through the upregulation of NR2A synaptic content. Hippocampal deficits resulting from sleep loss could be separated from effects on sleep-wake behavior, suggesting that NR2A is a potentially useful target for preserving hippocampal cognitive function during periods of sleep restriction.

S15 Les rôles délétères et neuroprotecteurs de l'inflammation. / Neurodestructive versus neuroprotective role of inflammation.

S15.1
Conséquences fonctionnelles de la neuroinflammation sur la neurogenèse adulte

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In pathological conditions of the central nervous system, inflammatory responses can affect the capacity of the adult brain to self-repair. Neuroinflammation can be both detrimental and beneficial for neurogenesis. During this symposium, we will present a recent investigation on the effects of neuroinflammation on adult neurogenesis, and more particularly the impact of reactive microglia, the resident immune cells of the brain, on the continuous recruitment of neurons to adult circuits.
As a model, we have chosen to study the subventricular zone (SVZ)-olfactory bulb (OB) system where new neurons are continuously generated throughout life. SVZ-generated neuroblasts migrate via the rostral migration stream towards the bulb and differentiate into mature OB interneurons. Whether brain inflammation alters the functional integration of the new neurons into existing OB circuitry is still unknown. To trigger local OB inflammation, we used deafferentation of the OB by chemical ablation of the olfactory sensory inputs. We found that within two weeks after dichlobenil administration, sensory neurons degenerated while both astroglial and microglial reactions were turned on in the OB. Already 24 h after the dichlobenil treatment, microglial cells swiftly proliferate in the OB. This proliferation is transient, peaking at day-3, and reverses at day-7 following dichlobenil administration. Immune-deficient mice treated with dichlobenil show similar microglial proliferation suggesting that adaptive immune system is not required for deafferentation-induced microglial proliferation. Surprisingly, several microglial cells still remain activated one month after dichlobenil injection, independent of the mouse genotype.
The radial migration of neuroblasts in the OB remains unchanged during this neuroinflammatory lesion but survival of adult-born neurons is dramatically reduced, leading to olfactory impairments lasting several months. We discuss the possible causes underlying reduced neurogenesis and potential anti-inflammatory, pro-neurogenic interventions aimed at improving olfactory deficits in normal and pathological aging and in neurodegenerative diseases.

S15.2
Les récepteurs à ITAM et ITIM exprimés par la microglie et pathologies neurodégénératives

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Elimination of extracellular aggregates and apoptotic neural membranes without inflammation is crucial for brain tissue homeostasis. In the mammalian central nervous system, essential molecules in this process are the Fc-receptors and the DAP12-associated receptors, which trigger the microglial immunoreceptor tyrosine-based activation motif (ITAM)-Syk-signaling cascade. Microglial ITAM-signaling receptors are counter-regulated by immunoreceptor tyrosine-based inhibitory motif (ITIM) signaling molecules.
Recently, we identified triggering receptor expressed on myeloid cells-2 (TREM2) as a DAP12-associated phagocytic receptor of microglia. Stimulation of TREM2 induced phosphorylation of the ITAM-motif of DAP12, cytoskeleton rearrangement and phagocytosis. Transplantation of myeloid precursor cells over-expressing TREM2 ameliorated repair by myelin clearance in the animal model of multiple sclerosis. In contrast, phagocytic activity of microglia was reduced in cultured murine microglia over-expressing human sialic-acid-binding immunoglobulin-like lectin-11 (Siglec-11) signalling via ITIM. Siglec-11 is a recently identified human-specific member of the Siglec family that binds to 2,8-linked polysialic acids. Phagocytosis of apoptotic neuronal material was reduced in Siglec-11 transduced microglia. Furthermore, stimulation of Siglec-11 by cross-linking suppressed the lipopolysaccharides (LPS) induced gene transcription of the pro-inflammatory mediators interleukin-1beta and nitric oxide synthase-2 in microglia. Co-culture of microglia transduced with Siglec-11 and

neurons demonstrated neuroprotective function of Siglec-11 that was dependent on polysialic acid (PSA) residues on neurons.
Thus, ITAM- and ITIM-signaling receptors modulate microglial clearance and repair function during health and disease.

S15.3
No abstract

S15.4
Interactions microglie/neurones: amicales versus mortelles

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In the past decade, a growing number of functions have been assigned to macrophages and microglia under conditions of altered neuronal integrity. Indeed, accumulating evidence indicates that microglia are able to sense subtle alterations of neuronal functions and, in turn, to engage specific activation programs. However, there are still uncertainties as to how microglia may shape the outcome of disorders that are considered as purely neuronal. In this context, we will present results from a recent study analyzing microglia/neuron cellular interactions in a murine model of dopaminergic degeneration. In this model, the use of CX3CR1-gfp mice and Dap12 Knock-In mice allowed a unique neuron/microglia crosstalk to be demonstrated. The nature and role of such particular interactions will be discussed.

S15.5
Rôle de la réponse pro-inflammatoire dans la mort sélective des neurones moteurs dans la SLA

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Chronic neuroinflammation is a pathological hallmark of many neurodegenerative disorders including amyotrophic lateral sclerosis (ALS), Parkinson's or Alzheimer's disease. Neuroinflammation involves a cross-talk between neurons, glial cells (microglia and astrocytes) and immune cells (lymphocytes, monocytes…). There is substantial evidence that neuroinflammation may encompass neuroprotective as well as neurodegenerative functions.
ALS is an adult-onset neurodegenerative disease that primarily affects motoneurons in the brain and spinal cord, resulting in progressive paralysis and death. Approximately 10% of ALS cases have a familial history of the disease and among these, 20% are caused by dominantly inherited mutations in the *Sod1* gene. Mice expressing human SOD1 mutations develop a motor syndrome with features of the human disease. Accumulating evidence suggests that mutant SOD1 damages non-neuronal cells to release factors selectively toxic for motoneurons. Notably, astrocytes mediate selective motoneuron toxicity through secretory and inflammatory components.
We have recently unravelled a novel motoneuron-restricted death pathway triggered by the activation of the lymphotoxin beta receptor (LT-βR) by LIGHT (TNFSF14). We found that the proinflammatory cytokine interferon gamma (IFNγ), derived from SOD1 mutant astrocytes selectively triggers death of motoneurons in a LIGHT-dependent manner. In addition, we found that the genetic ablation of *Light* in *Sod1* mutant mice delayed progression but not onset of the disease Our results suggest that IFNγ contributes to the cross-talk between motoneurons and astrocytes during the progression phase of the disease.
Interestingly, we and others have documented that abnormal levels of IFNγ are also present in the serum of mutant SOD1 mice and ALS patients. An additional source of IFNγ can be the immune system, in particular activated T lymphocytes and natural killer (NK) cells. However, IFNγ and cells producing this cytokine have not been investigated in the context of the neuroinflammation in ALS. An understanding of the communication signals between motoneurons, glial and immune cells is a challenging issue for the development of therapies.

S16 Bases neuronales des représentations sensorielles dans le système olfactif : du codage spatio-temporel au comportement. / Processing of olfactory information: from spatiotemporal representations to behavior.

S16.1
Circuits neuronaux et computation dans le système olfactif du poisson zèbre

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We use a small animal model, the zebrafish, to analyze neuronal computations in the olfactory bulb and its cortical target area by a combination of optical, physiological, molecular and theoretical approaches. I will focus on two or three recent findings. First, computational modelling and mathematical analyses revealed that pattern decorrelation, a basic computation in many neuronal and non-neuronal systems, emerges naturally from generic properties of recurrent neuronal circuits. The underlying mechanisms do not require adaptation to statistical properties of inputs and are enhanced by olfactory bulb-like network architecture. Second, we found that odor representations across olfactory bulb output neurons are largely invariant to changes in odor concentration but switch abruptly when one odor is morphed into another. The olfactory bulb therefore classifies sensory inputs into a large number of discrete outputs. This computation creates defined, noise-limited stimulus representations and acts as a sensory filter. Third, we found that the zebrafish homolog of olfactory cortex uses multiple synaptic pathways to integrate sensory information across processing channels in the olfactory bulb and create synthetic representations of olfactory objects. These results provide insights into olfactory computations that may be of general relevance for neuronal circuit function.

S16.2
Circuits glomérulaires responsables de la transmission des entrées sensorielles sur les cellules mitrales dans le bulbe olfactif

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Olfactory sensory neurons (OSNs) expressing the same odorant receptor converge in specific glomeruli where they transmit olfactory information to mitral cells the principal output neurons of the olfactory bulb. In bulb slices, mitral cells respond to a single stimulation of OSNs with unusually long EPSPs lasting several seconds and producing persistent firing. The synaptic mechanisms underlying these long-lasting responses have long remained poorly understood and controversial. Recent studies including ours indicate that they are much more complex than previously thought. Thus, the mitral cell response is initiated by a fast monosynaptic input from OSNs which is followed by a prominent and robust feed-forward component mediated by AMPA, NMDA and mGlu1 receptors. External tufted cells, a population of hyper-excitable juxtaglomerular neurons, drive the feed-forward excitation pathway which involves intra-glomerular dendro-dendritic excitatory interactions between external tufted, tufted and other mitral cells. Highly reliable release of glutamate at these synapses cause spillover-mediated recurrent activation of NMDA and mGlu1 receptors. Thus, a complex sequence of axo-dendritic and dendro-dendritic synaptic events mediates the mitral cell excitation.These intra-glomerular synaptic circuits potentially provide a critical amplification step of the incoming sensory information.

S16.3
Contrôle des cartes et oscillations olfactives par les réseaux neuro-astrocytaires

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Astrocytes are key cellular elements at the interface between neurons and blood vessels. They can detect neuronal activity via glutamate transporters (GLAST and GLT1), and regulate neuronal energetic needs as well as the level of glutamate in the synaptic cleft. In addition, they are organized in cellular networks bound together via gap junction channels composed of specific connexins (Cx43, 30). By consequence, these two families of molecules are likely to play a central role in the regulation

of both neuroenergetics and neuronal activity. However, their functional implication in a physiologically activated network is still unclear.
Using the attractive model of the olfactory bulb in adult animals, we asked whether GLAST and Cx30 could influence sensory-evoked activities in vivo. We answered this question studying mice lacking either GLAST or Cx30and analyzing both metabolic (glucose use and vascular signals) and neuronal (oscillatory synchronies) activities by means of complementary approaches:
1) [14C]-2-Deoxy-D-Glucose (2DG) uptake
2) local field potential (LFP) recording
3) Intrinsic Optical Signal (IOS) imaging
4) behavioral testing.
Results show a marked decrease of radiolabeled glucose uptake in activated glomeruli -the OB functional units- in GLAST-KO mice compared to control animals, revealing that this transporter is involved in the signaling pathway linking synaptic transmission and energy metabolism. Interestingly, the integrity of astrocytic network ensured by gap junctions is also required for metabolic regulations. Indeed, in Cx30-KO mice, glucose uptake in odor-evoked glomeruli is strongly enhanced, and IOS -due to local blood-related changes- reveal an increase in the number of activated areas. In addition to this metabolic role, we find that in the absence of GLAST transporter, oscillatory activities generated by neuronal populations are profoundly changed, leading to the hypothesis that astrocytic glutamate uptake is also implicated in the function of excitatory tripartite synapses very likely by the regulation of glutamate spillover. We also assessed the ability of these animals for odor detection.
Taken all together these results suggest a crucial role of astrocytes for network processing within a sensory structure in vivo.

S16.4

Corrélats neuronaux des représentations olfactives: études en IRM fonctionnelle chez l´Homme

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Mental imagery consists of the reactivation of percept-like memory representations. Its study allows the investigation of the neural correlates of an item representation without being biased by the perception of the item itself. However, this approach is unusual in human olfaction since the ability to create olfactory mental images is rare. Studying olfactory experts is the best way to accurately identify the mental processes underlying the creation of these images. Perfumers are a small population who claim to have a unique ability to generate olfactory mental images in the total absence of odorants. They have learned to form olfactory sensory representations through daily practice and extensive training. Forming mental images of odors is thus a crucial component of the perfumers´ expertise.
To identify the neural correlates of odor representations and to evaluate the impact of the perfumers´ expertise on the brain regions involved in odor processing, we measured brain activity in novice and experienced (student and professional) perfumers while they smelled or imagined odors, using functional magnetic resonance imaging. First, our results show the robust activation of a large neural network, including the olfactory primary (piriform) cortex, when perfumers mentally imagine odors, confirming the role of these structures in the recall of odor representations, and that similar neural substrates were activated in odor perception and imagination. Second, in professional perfumers, extensive olfactory practice influences the posterior piriform cortex, the orbitofrontal cortex and the hippocampus; during the creation of mental images of odors, the activity in these areas was negatively correlated with experience. Thus, the perfumers´ expertise is associated with a functional reorganization of key olfactory and memory brain regions, explaining their extraordinary ability to imagine odors and create fragrances.

S16.5

Circuits neuronaux impliqués dans la prise de décisions pendant le comportement olfactif chez le rat

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Decision-making becomes difficult when information is limited, contradictory or ambiguous. In order to understand how the brain responds to different kinds of uncertainty, we have been studying the performance of rats in odor-guided decisions tasks in which the value of a left/right spatial choice depends on the identity of the odor presented. We create uncertainty by lowering the concentrations of odors (detection task) or by using highly overlapping mixture stimuli (categorization task). By obtaining many thousands of trials under highly controlled conditions, we are able to quantify in detail how the performance of the subjects, measured primarily in terms of accuracy and reaction time, depends on the task parameters. We find that rats adopt different strategies depending on the nature of the problem. In the detection task, response times increase with difficulty, whereas in the discrimination task they do not. We show that simple mathematical models of neural integration can account precisely for many features of the data. These analyses suggest that the ability to solve the task by integration over depends strongly on the source of uncertainty. In the detection task, uncertainty appears to arise from rapid fluctuations that are subject to integration while in the categorization task, uncertainty arises from slow, trial-to-trial fluctuations that are not. Therefore the strategy of the rat is optimized to the problem at hand, with rapid responses to hard category decisions and slower responses for hard detection problems.

S17 Les fonctions intégratives du cortex préfrontal chez le rongeur. / Integrative functions of the rodent prefrontal cortex.

S17.1

Corrélats neurophysiologiques du cortex préfrontal et de l´hippocampe dans des tâches de navigation vers un but

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The key role of the hippocampus (Hpc) in spatial information processing is supported by the existence of place cells. Such cells are active when the animal occupies particular locations in particular behavioural contexts. However, little evidence has been found in support of the hypothesis that the Hpc could be involved in the generation of navigation paths and coding of spatial goals. The medial prefrontal cortex (mPFC), in agreement with its role in planning, could be a key structure in the mechanisms involved in goal-directed behaviour. The objective of the research presented here is thus to understand how these two structures (Hpc and mPFC) take part in the emergence of goal-directed behaviour. We previously showed that, when the animal performs a goal-oriented navigation task, mPFC neurons display a spatial-selective activity, especially at locations with a high motivational value. We also reported that hippocampal place cells recorded in animals trained in the same conditions do have a goal firing pattern which is time-locked to particular phases of the task. This signal could subserve path planning in combination with prefrontal neurons activity. Additional evidence showed that even though ventral hippocampal-lesioned animals still perform the task, they tended to leave the goal-zone prematurely. We also found that anticipatory activity in the prefrontal cortex is altered, suggesting a dependency on similar activity in the hippocampus. Overall, these unit-recording data suggest joint coding of goal location by the dorsal Hpc and mPFC. In another set of experiments, we investigated how the prefrontal-hippocampal system is involved when the animal has to update the status of a goal-zone (from attractive to aversive) during spatial navigation. Inactivation of either the mPFC or Hpc alone does not impede the system to update the valence of the goal-zone. When tested 24 hours after inactivation in the appetitive version of the task, Hpc-inactivated and sham animals showed a late-onset of goal-zone crossing compared to mPFC-inactivated rats. These last results suggest that the mPFC and the Hpc are not required to update on-line the valence of a goal-zone, but that the medial prefrontal cortex is necessary for the long-term retention of this update.

S17.2

Implication de la dopamine dans les oscillations et la réorganisation des décharges neuronales liées à l´apprentissage

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En 1989, Buzsaki a proposé un modèle de consolidation mnésique en deux étapes. Pendant l´apprentissage, le rat encode les informations, période durant laquelle des oscillations à 5-10Hz (rythme thêta) sont observées dans l´hippocampe. Ces informations seront rejouées pendant le sommeil durant des oscillations à haute fréquence (200Hz) observées dans l´hippocampe et appelées « ripples », aboutissant à leur consolidation puis leur transfert vers des structures corticales. Cependant, aucune étude n´a jusqu´à présent de relation de cause à effet entre ripples et apprentissage. De plus, il reste à détailler la façon dont les informations importantes sont sélectionnées pendant l´acquisition pour être consolidées dans la mémoire à long terme.
Nous avons tout d´abord montré que la suppression des ripples dans le sommeil suivant l´apprentissage d´une tache spatiale entraine une diminution de la performance des rats, démontrant ainsi le rôle causal des ripples dans la mémorisation.
Nous avons ensuite enregistré simultanément dans l´hippocampe et dans le cortex préfrontal de rats apprenant une tache comportementale sur un Ymaze, Nous avons mis en évidence une forte cohérence entre l´hippocampe et le cortex préfrontal au point de décision lorsque le rat a compris la règle. Pendant ces périodes, certains neurones du cortex préfrontal se synchronisent et s´organisent en assemblées cellulaires grâce à une augmentation de l´inhibition d´interneurones fortement modulés par le thêta hippocampique. Ces assemblées sont ensuite réactivées pendant les ripples hippocampiques, dans le sommeil qui suit la tache comportementale. De façon intéressante, nous avons également montré que l´application de dopamine dans le cortex préfrontal de rat anesthésiés provoquait exactement les mêmes effets que pendant le comportement naturel et l´apprentissage : les deux structures se synchronisaient à nouveau.
Ainsi, la dopamine, un neuromodulateur libéré lors de le prise ou la prédiction de récompense, permettrait de marquer l´activité cérébrale dans le cortex préfrontal pour que celle-ci soit rejouée et consolidée pendant les sommeils suivants. Ces différents processus permettent d´expliquer comment sont sélectionnées les informations qui doivent être consolidées dans la mémoire à long terme.

S17.3
Rôle du cortex préfrontal dans les comportements flexibles chez la souris

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Flexible behaviors, the ability to switch appropriately from one task to another or one motivation/reinforcer to another, are known to be compromised in several psychiatric conditions in humans. Here, we describe a serie of behavioral paradigms of increasing difficulty up to the ability to show flexible oriented behaviors, a highly adaptative function exhibited by mammals when confronted to changing environments. Using these paradigms, we investigated the contribution of the neuronal nicotinic receptors containing the beta2 subunit -beta2*nAChRs- using knockout - beta2KO- mice. We showed that beta2KO mice exhibit striking behavioral similarity with mice with prefrontal lesion, despite the fact that beta2*nAChRs are not located specifically into the PFC but are present virtually in all brain areas, and in all cell types. Using c-Fos expression quantification and lentiviral re-expression approaches combined with behavioral tasks that emphasize different aspects of conflict management and flexible decision making, we show that prefrontal beta2*nAChRs are needed to show flexible and adapted behaviors, particularly when conflicting motivations have to be dealt with.

S17.4
Cortex préfrontal et représentation du but

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Identifying relationships between actions and events is a critical aspect of decision making, leading to the selection of actions according to current needs. Many of the basic cognitive mechanisms of selection processes can be identified during instrumental conditioning in both rodents and primates, including humans. In rats pressing a lever to gain access to a food reward, action is thought to be

mediated by goal-directed action-outcome (A-O) associations, requiring both the encoding of the contingency between the action and its specific outcome and the representation of the outcome as the goal. These two aspects can be specifically assessed using contingency degradation and outcome devaluation procedures.
The present talk aims at providing the community with recent advances demonstrating a specific role of the rat medial prefrontal cortex (mPFC) in goal representation. More precisely, three lines of evidence will be presented. The first one concerns the role of the mPFC in goal encoding during training. The second one deals with a specific role of the brain area in adapting to contingency changes. Finally, the third one concerns the role of prefrontal dopamine in goal representation.

S17.5
Contribution de la plasticité inadaptée du cortex préfrontal aux maladies psychiatriques

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The pathophysiology of stress-related disorders, such as depression, involves reductions in neuronal connectivity in specific limbic circuits. Neuronal plasticity is likely to be an important mechanistic component of those malfunctioning cortical networks. In rodents, the so called prelimbic/infralimbic cortex represents the apparent homolog of the medial and subgenual prefrontal cortex in humans that have extensive connections with subcortical regions like the hippocampus and the amygdala.
In recent work, we demonstrated that exposure to stress and even brief periods of stress in animals is sufficient to cause impairment in synaptic plasticity in prefrontal networks by reducing long-term potentiation (LTP) in the hippocampal outflow to the prefrontal cortex. Antidepressants reverse the stress-induced changes in prefrontal plasticity, but with marked differences in efficacy depending on their mode of action. We examined the effects of pharmacologically distinct, antidepressants, on stress-induced synaptic alterations in frontal cortex. Altered synaptic functioning is linked to dysfunctions in signalling cascades, receptor regulation and transcription factors that are key regulators of synaptic plasticity and these changes are dependent on glucocorticosteroids. The data indicate a potential effect on AMPA receptor (AMPAR) phosphorylation as a possible mechanism of the reversal of LTP by specific antidepressants. We further investigated the effects of stress on the different AMPAR subunits in different limbic regions (prefrontal cortex, hippocampus, amygdala) and found changes in AMPAR functioning that are subunit and brain region specific. Thus, from a therapeutic point of view, these results put forward a region-oriented approach.
A balanced interplay between the three core limbic regions may predict the stress symptoms in human. Understanding these adaptations, particularly those changes that are sensitive to psychotropic drugs, is important for the development of more potent and specific treatments of depression. Efforts are under way to combine research in both human and animals and this interchange between basic animal models and human pathophysiology should help to refine understanding of these complex psychiatric disorders.

S18 La pertinence clinique des méthodes de neuroimagerie modernes. / The clinical relevance of modern neuroimaging methods.

S18.1
L´utilisation de neuroimagerie dans l´étude de la maladie d´Alzheimer - nouveaux concepts

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The application of modern computerized automated techniques for analyzing structural and functional brain images have led to real advances in the application of advanced neuroimaging to clinical practice in ways undreamed of only a short time ago. One major advance is the development of image classification techniques that puts diagnosis of the individual at the centre of the enterprise. This approach is currently based on machine learning techniques, some of the best results being obtained with support vector machines (SVM). There is a lot of activity in this area at present and new methods of analysis and results are constantly being reported. MR scanner manufacturers are becoming interested in translating these encouraging results into potential products.

Thus, neuroimaging techniques, in addition to their traditional diagnostic role are currently expanding understanding of the structural and functional changes that occur in dementia. Further research may allow identification of early pathological signs of AD, before clinical symptoms are evident, providing the opportunity to test preventative therapies.
The lecture will review imaging in Alzheimer's disease and other neurodegenerative diseases and attempt to project into the future how the field will develop. Additionally obstacles to such developments will be highlighted and approaches to validating image classification as a diagnostic tool and a means of monitoring treatment discussed.

S18.2
L´utilisation de neuroimagerie pour étudier des déficits cognitives

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How does brain damage translate into a clinical deficit? This is a longstanding question of neurology that has inspired the study of lesion-deficit relations. The tacitly assumed dominant view on brain function in this endeavour has been that of functional segregation. In other words, the functional consequences of lesions were equated with the loss of specialized neurons. Along these lines, generations of researchers have accumulated a large fundus of evidence for functional specialization in the brain. Yet, segregation is only one principle of brain organization, the other being integration. Recently, functional brain imaging studies have proven a powerful way to establish brain-behaviour correlations and to demonstrate the interplay between segregation and integration from which functional specialization emerges. From this perspective, other mechanisms of how brain damage translates into cognitive deficits must be interrogated than just death of neural populations, namely disconnection and diaschisis. The talk will cover recent brain imaging results from healthy participants and patients that speak to these issues. Specifically, we will illustrate how selective agnosias can be tied to functional specialization in the ventral visual stream, and how an enigmatic syndrome as that described by Gerstmann (acalculia, finger agnosia, agraphia and left-right confusion) can be tied to a disconnecting lesion in parietal white matter. The latter result leads to a proposal for expanding the classical disconnection concept to also embrace specific syndromes arising from lesions to crossing (or kissing) fibre populations. Finally, we will show diaschisis effects in intrinsic functional connectivity of stroke patients and discuss how they relate to clinical deficit and recovery.

S18.3
L´utilisation de neuroimagerie pour étudier des troubles affectifs et neuropsychiatriques

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While traditional approaches to relate particular human cognitive or affective functions to their underlying neural substrates have often focused on the implication of particular brain areas, as demonstrated for example by lesion studies or early neuroimaging studies, more recent work has begun instead to emphasize the critical role of distributed brain networks and dynamic connectivity in various mental processes and disorders. On the one hand, using neuroimaging techniques such as functional MRI in patients with brain lesions has allowed us to identify the impact of focal damage on distant structurally intact areas, and thus to better understand the mechanisms underlying some behavioral disturbances as well as the effect of rehabilitation strategies. On the other hand, methodological advances in network analysis and multivariate statistics have given us new tools to assess functional interactions between distant areas within large-scale brain networks, in both health and disease conditions. The talk will illustrate these applications in different clinical conditions ranging from neurological disorders, such as neglect syndrome after stroke, and neuropsychiatry disorders, such as depression and conversion.

S18.4
L´utilisation de neuroimagerie pour étudier les alterations de la conscience

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Probing consciousness in non-communicating patients is a major medical and neuroscientific challenge. While standardized and expert behavioral assessment of patients constitutes a mandatory step, this clinical evaluation stage is often difficult and doubtful, and calls for complementary measures which may overcome its inherent limitations. Several functional brain imaging methods are currently developed within this perspective, including functional magnetic resonance imaging (MRI) and cognitive event related potentials (ERPs). I will briefly review some of these works, and present a new ERP test capitalizing on the “global workspace” theory of consciousness. When subjects were exposed to both local and global regularities with the instruction to detect and count occurrences of global regularity violations, we could observe an ERP response the presence of which seemed to be a specific neural signature of consciousness. I will discuss the power and limits of this approach.

S18.5
L´utilisation de neuroimagerie pour étudier les réseaux épileptiques

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In this overview, the use of modern non-invasive functional neuroimaging techniques for the characterization of epileptic networks in the human brain will be discussed. The fast propagation of epileptic activity within large-scale neuronal networks that implicate cortical and sub-cortical structures requires imaging techniques that have high temporal and high spatial resolution. Recent advances in electric source imaging (ESI) using high-density EEG and the direct combination of ESI and fMRI give the possibility to localize the regions implicated in seizure initiation and propagation with high spatial precision, and to follow the temporal dynamics of this propagation in real time. Several studies combining ESI and fMRI have demonstrated the feasibility and clinical yield of this combined imaging approach. These studies will be summarized in this overview and illustrated by several concrete examples.

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

SP02.1
Des Sushis synaptiques: de la jonction neuromusculaire de C. elegans au cerveau humain

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Sushi domains (also referred to as ´complement control protein´ CCP or ´short concensus repeat´ SCR domains) are structural modules of approximately 60 amino-acids that are found in the extracellular regions of various transmembrane and secreted proteins, where they provide binding sites for protein or glycan interactors. They are frequently found in proteins of the immune complement system in mammals, but they are also abundant in proteins expressed in the nervous system, with poor or absent functional characterization.
In the nematode *C. elegans*, a screen for mutants with declustered acetylcholine receptors (AChRs) at the neuromuscular junction identified LEV-9, a protein containing 8 CCP domains. LEV-9 is secreted by the muscle cells and is exclusively detected at neuromuscular junctions. It is engaged in a multimeric complex involving AChRs, the small secreted protein OIG-4, which only contains a single immunoglobulin domain, and LEV-10. LEV-10 is a transmembrane protein also expressed by the muscle cells, but its ability to cluster AChRs is solely contained in its ectodomain. Hence, synaptic

clustering of AChRs at the *C. elegans* neuromuscular junction is achieved by a novel mechanism that strictly relies on extracellular interactions.
The involvement of Sushi-containing proteins in extracellular scaffolds might have been conserved during evolution to build and regulate neuronal networks. We are currently investigating the role of a protein distantly related to LEV-9 in vertebrates, which has been implicated in the etiology of rare autistic syndromes.

SP02.2

Développement morphofonctionnel de synapses hippocampiques dans des modèles murins de retard mental

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Le retard mental et l'autisme sont des pathologies neurodéveloppementales qui affectent potentiellement le développement structural et fonctionnel des contacts synaptiques. Il est dont important de comprendre en quoi les mutations génétiques chez l´homme qui sont responsables de ces pathologies affectent la maturation des contacts synaptiques dans des régions du cerveau impliqués dans l´apprentissage. Le gène *grik2*, code pour la sous-unité GluK2 des récepteurs du glutamate de type kaïnate, est associé à ce type de pathologies. Nous avons analysé la maturation fonctionnelle d´une synapse glutamatergique fortement impliquée dans l´encodage d´informations nouvelles: la synapse entre fibres mousses et cellules pyramidales de CA3 dans l´hippocampe. Nous avons comparé, chez des souris contrôles déficientes pour la sous-unité GluK2 ($GluK2^{-/-}$), les principales étapes de maturation électrophysiologique et morphologique de la fibre moussue hippocampique. Nos données montrent un délai dans la maturation fonctionnelle des contacts synaptiques chez les souris $GluK2^{-/-}$, aussi bien de la composante AMPA que NMDA postsynaptique. Sur le plan morphologique, nous avons mis en évidence une augmentation de la complexité des éléments pré- et postsynaptiques au cours du développement postnatal chez la souris contrôle qui est retardée chez les souris GluK2-/-. Nous avons complété cette approche globale par l'étude de la mise en place des protéines pré (Munc13.1) et post (SAP102/PSD95) synaptiques à la synapse fibre moussue/CA3. Nous avons observé une augmentation du nombre de protéines pré-synaptiques apposées aux protéines post-synaptiques au cours du développement postnatal chez la souris contrôle ainsi qu'une désorganisation de leur pattern d'expression à la synapse chez les souris GluK2-/-. L'ensemble de ces résultats soulignent l'importance d'étudier le rôle d'une protéine impliquée dans des pathologies neurodéveloppementales au cours de la maturation synaptique.

SP02.3

n/a

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Huntington´s disease (HD) is a neurodegenerative disorder due to an abnormal polyglutamine extension in the N-terminal region of huntingtin protein (Exp-Htt). This mutation causes protein aggregation, neuronal dysfunctions and death. One particular cerebral region affected in HD is the striatum. Alteration in chromatin remodeling and transcriptional regulation is thought to be a prime event in striatal dysfunctions in HD. We have shown that Mitogen- and stress-activated kinase (MSK-1), a nuclear protein kinase involved in chromatin remodeling through histone H3 phosphorylation, is deficient in the striatum of HD patients and model mice. We restored MSK-1 expression in cultured striatal cells, and prevented neuronal dysfunction and death induced by Exp-Htt. We further extended these observations in a rat model of HD based on striatal lentiviral expression of Exp-Htt (LV-Exp-Htt). MSK-1 overexpression attenuated Exp-Htt-induced down-regulation of DARPP-32 expression 4 and 10 weeks after infection. It also enhanced NeuN staining after 10 weeks. LV-MSK-1 induced constitutive hyperphosphorylation of H3 and CREB, indicating that MSK-1 has spontaneous catalytic activity. MSK-1 overexpression also upregulated PGC1-a, a transcriptional co-activator involved in mitochondrial biogenesis. Chromatin immunoprecipitation indicated that transcriptional regulation of PGC-1a is directly linked to increased binding of MSK-1, along with H3 and CREB phosphorylation of the PGC-1a promoter. MSK-1 knock-out mice showed spontaneous striatal atrophy as they aged, as well as higher susceptibility to systemic administration of the mitochondrial neurotoxin 3-NP. These results indicate that MSK-1 activation is an important and key event in the signaling cascade that

regulates PGC-1a expression. Strategies aimed at restoring MSK-1 expression in the striatum might offer a new therapeutic approach to HD.

SP02.4
De nouveaux neurones pour le cerveau âgé

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The mammalian brain continues to produce neurons throughout adult life, both in rodents and humans. This capacity for continued neurogenesis originates from neural progenitor cells located in discrete brain regions including the subgranular zone of the hippocampal dentate gyrus. Lifelong, newborn neurons become structurally and functionally integrated into the hippocampal circuitry where they are believed to contribute to learning and memory processes. With aging, the rate of hippocampal neurogenesis decreases dramatically, suggesting that it might contribute to the cognitive decline that accompanies senescence. Thus, the development of effective methods for the enhancement of adult neurogenesis represents one of the most promising directions in the treatment of neurodegenerative and neuropsychiatric disorders. The proliferation of new born cells seen in the aging brain and in disease like AD may represent an endogenous brain-repair mechanism, the further stimulation of which could have a therapeutic potential. As a first step towards the development of such strategies, we will show that endogenous hippocampal progenitors can be genetically manipulated and instructed to differentiate into neurons in their *in vivo* niche.
Work sponsored by Fondation pour la Recherche sur le Cerveau (FRC), France Alzheimer, CNRS, Université Toulouse III.

SP02.5
Régulation spatio-temporelle de la machinerie de sumoylation dans le Système Nerveux Central de rat

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Small Ubiquitin-like MOdifier protein (SUMO) is a key regulator of the nuclear function. However the role of this post-translational modification outside of the nucleus is still largely unknown, particularly in the Central Nervous System. Here, we report that the levels of SUMO-modified proteins as well as the components of the sumoylation machinery are temporally and spatially regulated in the developing rat brain.
Using brain fractionation experiments at various developmental stages, we find that the nuclear and cytosolic expression levels of both SUMO1 and SUMO2/3 substrates are developmentally regulated. Interestingly, the expression levels of sumoylation and desumoylation enzymes follow the same pattern in the developing rat brain. Furthermore, while the overall level of SUMO substrates and enzymes is decreasing overtime, there is a progressive accumulation of sumoylation enzymes in the synaptic compartment. These data indicate that sumoylation is probably involved in the regulation of synaptic functions and are in agreement with our previous work on the role of the sumoylation process in kainate receptor-mediated synaptic transmission (*Martin et al., Nature, 2007*).
Furthermore, using immunocytochemistry on primary cultures of rat hippocampal neurones, we show that there is a redistribution of SUMO enzymes during neuronal maturation with a targeting of these enzymes towards the synaptic compartment further suggesting that sumoylation participates to synaptic formation and/or stabilization during the early steps of brain development and then at a later stage to the regulation of synaptic communication and/or plasticity.
Overall, our data indicate that the SUMO system might be linked to synaptogenesis during the rat brain development. Therefore, we hypothesize that default within the sumoylation pathway during brain development may participate in developmentally associated mental retardation illnesses.

GDRI and NEUROMED: Building Capacities for Mediterranean Neuroscience

RT02.1
GDRI & N€UROMED: construire les neurosciences en Méditerranée

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GDRI and N€UROMED: Building Capacities for Mediterranean Neuroscience

Neuroscience is one of the world's largest and most important scientific endeavors. Yet, the know-how and the resources are concentrated in relatively few countries, while laboratories in the EU's Mediterranean Partner Countries (MPC) struggle to build research facilities and to keep up. Brain dysfunction is a critical problem not only for developed but also for developing countries such the MPC, which face a heavy economic and social burden due to the impact of child malnutrition on cognitive development, the increasing incidence of neurodegenerative diseases (Alzheimer's and Parkinson's), as well as mental and addictive disorders (schizophrenia, depression). In short basic and translational research on brain function and dysfunction is becoming a Mediterranean priority for many decades to come, which requires close regional cooperation. This social gathering will present some of the tools that have been initiated in recent years in order to develop research centers, training networks and exchange programs that allow sharing the know-how and resources. First, a French-Moroccan *Groupement de Recherche International* (GDRI) of Neurosciences, which is supported by the CNRS and INSERM (France) and the CNRST (Morocco), has started to structure a bi-lateral network 27 teams from the two countries. This has led the way for N€UROMED, a FP7 Cooperation program, funded by the EU for 3 years. This dynamic network gathers 7 countries, including Algeria, Egypt, France, Italy, Morocco, Spain and Turkey. Finally, a *Mediterranean Neuroscience Society* (MNS) has been created to sustain a regular conference of neuroscience. These and other training (ISIS, a Tempus International Master of Neuroscience, Bordeaux) and research programs aim to build a neuroscience network, with sustained cooperation activities within the Mediterranean region.