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FROM THE MOLECULE TO PATHOLOGY

P1- **Toward translational exploration of alpha-synuclein**

Team BioRaN (Radiopharmaceutical & Neurochemical Biomarkers)

Alpha-synuclein (α-syn) aggregation is a neuropathological hallmark of many neurodegenerative diseases including Parkinson's disease and other neurodegenerative diseases with dementia, collectively named as synucleinopathies.

If substantial advances in clinical criteria have allowed to improve the detection and the differential diagnosis of these brain disorders, there is no clear imaging or biochemical biomarkers that afford a reliable differential diagnosis between the different forms of dementias (to distinguish to Alzheimer dementia) or that could facilitate tracking of disease progression and future evaluation of therapeutics.

Our approach is translational, from the α-syn protein modeling to its biochemical analysis in patient's blood and tissues, from the chemistry of PET candidate-molecules to their radiopharmacological evaluation in animal models of synucleinopathies and in patient's brain tissues. The main objective of our project is to reach the proof-of-concept of α-syn biomarkers before their translation to studies in patients.

P2- **Complexity and developmental changes in the expression pattern of claudins at the blood-CSF barrier**

Kratzer I, Vasiljevic A, Rey C, Fevre-Montange M, Strazielle N, Ghersi-Egea JF

The choroid plexus (CP) epithelium is a barrier that controls the movement of solutes between the blood and the cerebrospinal fluid. It has been considered as a functionally more immature interface during brain development than in adult. The tightness of the interepithelial choroidal junction has been attributed to the presence of claudins. We used quantitative real-time PCR, Western blot and immunohistochemistry to identify different claudins in the CP of developing and adult rats. Claudin-1, -2, and -3 were highly enriched in the CP as compared to brain or parenchyma microvessels and were localized at epithelial junctions. Besides, four additional claudins displayed a choroidal specificity, while claudin-5 was enriched in the cerebral microvessels. The choroidal pattern of tight junction protein expression in prenatal brains was already complex and differed from the adult pattern in that the pore-forming claudin-2 increased during development, while claudin-3 decreased. Imunohistochemical analysis of human fetal and postnatal brains demonstrated early presence and localization of tight junction (TJ) proteins at the apico-lateral border of the CP epithelial cells. Overall, choroidal epithelial TJs are already complex in the developing brain. The observed differences in claudin expression between developing and adult choroid plexuses may indicate developmental differences in selective blood-cerebrospinal fluid transport functions.

P3- **Macrophages/microglia as sensors of CNS disorders**

Lhuillier A, Akram N, Ulrich J, Touret M, Chanal M, Boussaid A, Watrin C, Champier J, Pays L, Nataf S

Macrophages encompass a family of tissue-resident immune cells that are considered to pay a crucial role in a large array of developmental, homeostatic and immune processes. Among this family, microglia represent the CNS-resident macrophages and have been assigned an increasing number of functions in the past decade. These include, in particular, the elimination of specific neuronal populations during development, the synthesis of so-called gliotransmitters and the support to non-cell autonomous mechanisms in neurodegenerative disorders. Macrophages as well as microglia express a number of receptors that allow danger signals to be sensed and to induce, in turn, specific activation programs. Finally, we and others previously reported that under CNS pathological conditions, profound alterations of the whole macrophage/microglia lineage may be demonstrated in bone marrow myeloid progenitors and in blood-circulating monocytes. In this context our group aims to characterize the impact of specific neuronal of glial alterations on the behavior of macrophages/microglia in order to eventually unravel new pathophysiological mechanisms and therapeutic targets. To achieve this goal different strategies have been or are currently developed that are listed below: i) mapping physical interactions between microglia and their neural environment in murine or human CNS pathological tissues, ii) performing a transcriptomic analysis of human CNS tissues using actual or virtual microdissection approaches, iii) performing a transcriptomic analysis of blood-derived macrophages in human patients suffering from CNS disorders, iv) modeling in vitro microglia/neuron interactions using stem-cell based technologies. Methods, results and perspectives are summarized here.

P4- **Autoimmune channelopathies: autoantibodies and glutamate homeostasis alteration in the central nervous system**

Cavagna S, Cavillon G, Confavreux C, Giraudon G, Honnorat J, Marignier R, Meissirel C, Nicolle A, Rogemond V, de Rossi P, Touret M, Watrin C

Antibody-mediated central nervous system disorders are an emerging field in Neurology. Autoimmune channelopathies are associated with a broad spectrum of clinical presentation including autoimmune synaptic encephalitides associated with N-methyl-d-aspartate receptor (NMDAR)-antibodies (Ab) and Neuromyelitis Optica (NMO), a demyelinating disorder of the spinal cord and the optic nerve associated with Ab to water channel aquaporin 4 (AQP4). These exciting developments raise interesting questions regarding the etiological and pathogenic mechanisms mediating these diseases.

To study the effect of Ab to NMDAR, we used a unique combination of high-resolution nanoparticle and bulk live imaging approaches. We demonstrate that anti-N-methyl-d-aspartate receptor autoantibodies from patients with encephalitis strongly alter, in a time-dependent manner, the surface content and trafficking of GluN2-NMDA receptor subtypes. Autoantibodies laterally displaced surface GluN2A-NMDA receptors out of synapses and completely blocked synaptic plasticity. This loss of extrasynaptic and synaptic NMDAR is prevented both in vitro and in vivo, by the activation of EPHB2 receptors. We demonstrate that the anti-NMDAR Ab from patients with encephalitis alter the dynamic retention of synaptic NMDAR through extracellular domain-dependent mechanisms.

To study the effect of Ab to aquaporin 4 we used in vitro and ex vivo models based on antibody-treated primary glial cultures (astrocytes and oligodendrocytes) and rat optic nerve. We confirm the pathogenic role of AQP4antibody purified from the serum of NMO patients. Flow cytometry analysis showed a reduction of membrane aquaporin 4 and glutamate transporter type 1 on astrocytes following Ab exposure. The activity of glutamine synthetase decreased in parallel, while extracellular glutamate progressively accumulated, indicating astrocyte dysfunction. Co-treatment of glial cultures with AQP4 Ab and competitive antagonist of NMDAR partially protected oligodendrocytes. This supports the hypothesis of Ab-mediated disruption of glutamate homeostasis in neuromyelitis optica.

These data shed new light on the pathology of demyelinating diseases and neurological and psychiatric disorders mediated by autoantibodies, opening possible new therapeutic strategies.

P5- **CRMP5 in Glioblastomas and its relation to Notch signaling pathway**

Moutal A, Bertrand C, Malleval C, Watrin C, Chounlamountri N, Benetollo C, Honnorat J, Meyronet D, Thomasset N

Glioblastomas (GBM) are very aggressive brain tumors with a poor clinical outcome. Stem cells are identified in these tumors and contribute to the resistance from conventional therapy. Among the markers used to characterize the stem cells, Notch receptors i) participate to one of the most conserved mechanism controlling cell proliferation, tumor growth and stem-cell maintenance in GBMs, ii) and are commonly over-expressed in GBMs tissue and cell lines. Interestingly, Notch also regulates transcription of EGFR and Nestin. Furthermore, Notch, Nestin, and EGFR gene amplifications are related to classical subtype in the Verhaak's classification characterised by a profile of highly proliferative cells.

CRMP5 belongs to the Collapsin Response Mediator Protein (CRMP) family, which is strongly expressed in adult brain neurogenesis zone (Veyrac et al, 2005). In the human lung tumors, we identified CRMP5 as a marker of aggressivity in neuroendocrine lung tumors (Meyronet et al, 2008). Genomic analysis of 20 GBM published by Liang et al (2005) has revealed that CRMP5 emerges from a cluster of genes related to proliferation whose expression correlates with a poor overall survival. We confirmed these results at the protein level by immunohistochemistry in a preliminary study of a continuous series of 55 GBMs: patients with higher CRMP5 expression had a significantly lower median survival (5,9 months) than those with low or negative expression (15,5 months) (log rank, p=0,0026). The objective of our research is to uncover the influence of CRMP5 on GBM stem cells biology in relation with Notch signaling pathway.

Our results showed in GBM-derived cells a positive correlation between CRMP5 protein expression and stem cell markers using Western blot and Flow Cytometry analysis. The blockade of CRMP5 decreases GBM cell proliferation by 86%, concomitantly with a G1/S cell cycle phase transition blockade and extinction of Notch expression. To investigate the mechanism of CRMP5 effect on the Notch signaling dependent-proliferation, we generated stable transfected GL15 cell line using plasmids containing specific shRNA to knockdown CRMP5 expression or control scrambled shRNA. BrdU incorporation analysis showed a decrease by about 80% of the proliferation in the CRMP5 knockdown cell lines compare to control scrambled. Western blot analysis of those cell lines showed a decrease in Notch2 receptor expression with a decrease of cyclinD1, marker of the G1/S cell cycle phase transition. These results suggest that CRMP5 may modulate, in a positive manner, the Notch signaling dependent proliferation through cyclin D1 in glioblastoma.
The characterization of the mechanism by which CRMP5 positively modulates the Notch signaling pathway in glioblastoma may have tremendous implications for patient prognosis and elaboration of new antitumor therapies.

SLEEP AND ALTERED STATES OF CONSCIOUSNESS

P6- **Filtering the reality: Functional dissociation of lateral and medial pain systems during sleep in humans**
Bastuji H, Mazza S, Perchet C, Frot M, Mauguière F, Magnin M, Garcia-Larrea L
Behavioural réactions to sensory stimuli during sleep are scarce despite préservation of sizeable cortical responses. To further understand such dissociation, we recorded intracortical field potentials to painful laser pulses in humans during waking and all-night sleep. Recordings were obtained from the three cortical structures of the spinothalamic cortical input 95% receiving in primates namely the parietal operculum, posterior insula and mid-anterior cingulate cortex. The dynamics of responses during sleep differed among cortical sites. In sleep stage 2, evoked potential amplitudes were similarly attenuated relative to waking in all three cortical régions. During paradoxical, or REM, sleep, opercular and insular potentials remained stable in comparison with stage 2, whereas the responses from mid-anterior cingulate abated drastically, and decreasing below background noise in half of the subjects. Thus, while the latéral operculo-insular system subserving sensory analysis of somatic stimuli remained active during paradoxical-REM sleep, mid-anterior cingulate processes related to orienting and avoidance behaviour were suppressed. Dissociation between sensory and orienting-motor networks might explain why nociceptive stimuli can be either neglected or incorporated into dreams without awakening the subject.

P7- **Influence of familiar music on cognitive processes in comatose patients**
Castro M, Tillmann B, Cadart C, Corneyllie A, André-Obadia N, Perrin F
Music can be a highly familiar and emotional stimulus that conveys beneficial effects on cognitive processes both in normal and brain-damaged participants.
The aim of our study was to evaluate the effect of music exposure on cognitive processes and perceptual awareness. We recorded electroencephalogram (EEG) in comatose patients and control participants while presenting several sequences of different first names, one of them being the patient's/participant's own first name. These sequences were preceded by either familiar music chosen by close relatives of the patients or the participants themselves or music noise.
Our results replicated the previously reported P300 component related to one's own first name in both control participants and some patients in altered states of consciousness. More importantly, in patients with a P300 evoked by the first name, the presentation of familiar music before the sequence of names increased the similarity of the evoked P300 component to that observed in the control participants. Indeed, the P300 had a greater amplitude and shorter latency after the music than after the noise.
Our results will be discussed in link with the previously proposed hypothesis suggesting that music induces positive emotional states, which are correlated with increased arousal. The observed heterogeneity of results among patients can be, at least partially, explained by the patients' varying etiologies. Finally, we discuss the potential interest of developing such a protocol to estimate the perceptual awareness of patients.

P8- **Which cerebral activity differentiates high and low dream recallers ? ERPs and PET studies**
Eichenlaub JB, Morlet D, Daltrozzo J, Bertrand O, Redoute J,Costes N, Nicolas A, Ruby P
Dreaming is still a mystery of human cognition. In the fifties, dreaming was associated with rapid eye movement (REM) sleep (Dement & Kleitman 1957; Sastre & Jouvet 1979) but this hypothesis, which cannot explain all the characteristics of dream reports has been challenged (Solms 1997; Nir & Tononi 2010). We used event-related potentials (ERPs) and positron emission tomography (PET) during wakefulness and sleep, to measure brain activity in subjects who report dreams frequently (High recallers, H-R) *versus* rarely (Low recallers, L-R). During EPRs data acquisition, participants (18 H-R and 18 L-R) passively listened to sounds while they were either watching a silent movie or sleeping at night. PET data were acquired in the afternoon while participants (21 H-R and 20 L-R) were resting (wakefulness) or sleeping (N2, N3 and REM sleep). ERPs results revealed that the primary steps of auditory processing (N1 and MMN) match in High recallers and Low recallers. However, latter responses, reflecting higher cognitive processing, dramatically differ in the two groups during pre-sleep wakefulness and during sleep. In the PET study, H-R vs L-R contrast showed rCBF increases in TPJ during REM sleep, N3, and wakefulness, and in MPFC during REM sleep and wakefulness. This study reveals for the first time functional neuroanatomical correlates of the ability to recall dreams in healthy subjects and argue in favor of the forebrain "dream-on" hypothesis (Solms 2000). Results of the two studies support the hypothesis that high/low dream recall frequency is associated with particular cerebral functional organisation independent of the state of vigilance.

P9- **Selective paradoxical (REM) sleep deprivation in mice using a new unsupervised automatic method**
Arthaud S, Libourel PA, Gervasoni D, Fort P, Luppi PH
An increase in PS quantities always follow paradoxical sleep (PS) selective deprivation (PSD), a process named PS homeostasis. PS deprivation has long been used in rats to study the neuronal networks and mechanisms responsible for PS genesis and homeostatic regulation. However, in the recent years, mice are increasingly used to take advantage of optogenetic method or transgenic models. It is therefore of particular interest to develop sleep deprivation and hypersomnia methods in this species. Here, we describe the adaptation to mice of two deprivation methods: the flowerpot and a new automatic method.
Mice were implanted with 2 muscle (EMG) and 3 cortical (EEG) electrodes for polygraphic recordings. After habituation and baseline recordings, platform PSD mice (n=12) were put in a barrel with 2 platforms (2.6 cm diameter) surrounded by water. After 48h, they were put back in their home cage for 3h of PS recovery. For automatic PSD, mice remained in their home barrel. A real-time detection and quantification of wake, SWS and PS *via* an adaptive algorithm analyzing EEG/EMG signals was performed. As soon as PS was detected, a TTL pulse was applied to a mechanical device that moved the barrel floor. The stimulation was applied during 24h (n=6) or 48h (n=3) and followed by 3h of PS recovery.
During PSD, quantities of residual PS were identical for platform and automatic PSD (1,6% *vs* 6.7% in baseline). The latency to the first PS episode was of 241 min for platform PSD and 20 min for automatic PSD. SWS quantities during PSD were of 31% for platform and 44% for automatic PSD (*vs* 40% in baseline). At the onset of PSR, the latency to PS was of 105 min for platform and 6 min for automatic PSD. Over the 3h of PSR, PS amount was of 16% after 48h of platform PSD, 19% after 24h of automatic PSD and 16% after 48h of automatic PSD (*vs* 8% in baseline).
In summary, platform and automatic deprivation methods both induced during PSD and PSR similar decrease and increase in PS quantities. However, PS latency was much longer and SWS quantities were more decreased with the platform than with the automatic method clearly indicating that automatic PSD is less

stressful (no handling, less hostile environment, absence of water) than platform method. In summary, our results indicate that automatic PSD is a suitable, easy to use and more ethical method for performing PSD in mice than the platform method.

P10- **Short modulation of REM sleep quantity bidirectionally modulates hippocampal synaptic plasticity and memory.**
Hamieh M, Ravassard P, Fraize N, Le Barilier L, Luppi PH, Touret M, Malleret G, Salin PA
Growing evidence supports that rapid eye movement sleep (REMS) plays a crucial role in memory. Previous studies have shown that long-term REM sleep deprivation (RSD) impairs synaptic plasticity, encoding and memory consolidation in rats. However, long-term RSD induces stress, which is known to alter memory. Thus, we performed a mild-non stressful- RSD in order to assess a potential role of REM sleep in synaptic plasticity and memory. Then, we examined whether this RSD or REMS rebound (RSR) obtained 4 hours after RSD affects CA1 hippocampal synaptic plasticity, encoding and memory consolidation of contextual fear conditioning (CFC).
RSD was induced using a dedicated protocol to induce short (4h) and selective deprivation in order to avoid any stress. RSD was carried out before and after CFC encoding. Animals were examined 1 hour later to test the effect on encoding or 24 hours later to test the effect on consolidation.
The results demonstrated that RSD decreases synaptic LTP selectively in dorsal CA1 and RSR rescues these deficits. RSD performed immediately following encoding impaired consolidation of CFC at test. In contrast, animals subjected to RSR before encoding showed an increase in the amount of freezing response during training. Moreover, increase in REMS quantity (RSR) after encoding facilitated consolidation of CFC at test. Our results suggest that an increase in the amount of REMS facilitates LTP, memory consolidation and encoding, while a decrease in REMS impairs LTP and memory consolidation.
Conclusion: These results suggest that REMS quantity may regulate synaptic plasticity, encoding and consolidation of memory in a bidirectional way.

P11- **Sleep restriction in middle-aged obese subjects: impact on leptin levels, hunger and food intake.**
Guyon A, Morselli LL, Balbo M, Van Cauter E, Spiegel K
Epidemiological studies have provided evidence for an independent link between short sleep and obesity risk. We evaluated the effect of sleep restriction, as compared to sleep extension, on appetite regulation in middle-aged, obese adults.
Eleven subjects (7 men, 38±6yo, BMI 34±3kg/m^2) underwent, in a randomized cross-over design, 4 nights of restriction or extension of their habitual bedtime schedule by 2-3 hours/night. An *ad libitum* buffet was served at the end of each sleep condition. Blood was sampled at 10-30 min intervals during the daytime on the previous day for the measurement of leptin while caloric intake was controlled. Hunger and appetite were assessed on these 2 days.
Hunger, appetite and leptin levels were not affected by bedtime duration. In contrast, energy intake at the *ad libitum* buffet was increased by 323±138 kcal after sleep restriction (+15±6%; p<0.05), mainly due to an increase in protein consumption (17±6%, p=0.04) and to a trend for increased carbohydrate intake (11±6%, p=0.10). The difference in caloric intake between bedtime conditions tended to be correlated to the difference in daytime leptin levels (r=0.54, p<0.11); paradoxically, the stronger the increase in leptin, the stronger the increase in food intake.
Conclusion: These results demonstrate that sleep restriction in middle-aged, obese subjects promotes food intake, despite unchanged hunger. However, the present findings differ from our previous report of consistently decreased leptin levels in healthy sleep-restricted lean subjects. The role of leptin-resistance known to be associated with excess weight needs to be evaluated to elucidate these findings.

P12- **Notch dependent neuroglia signaling and sleep regulation**
Aguirre A, Seugnet L
Maintenance of neurotransmission, regulation of energy metabolism, and learning and memory processing have been identified as potential sleep functions. Importantly, all these processes are modulated by glial cells in response to neuronal signals. Neuron-glia interactions may thus play a key role in sleep function. We have previously identified a neuroglial signaling pathway dependent on the Notch receptor (in glia) and its ligand Delta (in neurons). Notch and Delta modulate sleep homeostasis and performance following sleep deprivation in Drosophila. Here we dissected the function of this signaling pathway using Drosophila molecular genetic tools to understand its role in sleep regulation.
Using the Gal4-UAS system to target gene expression in astrocyte-like glia, we evaluated the role of Notch signaling in the regulation of the expression of the glutamate transporter dEaat1, and its potential interactions with the epidermal growth factor receptor (EGFR) signaling pathway, another sleep regulator in Drosophila. dEaat1 expression was assessed using a dEaat1-Gal4 construct coupled to GFP expression. Our results indicate that dEaat1 is independently regulated by Notch and EGFR at the transcriptional level. The influence of Notch signaling on brain dopamine and octopamine levels will also be presented.

PERCEPTION, MEMORY, ATTENTION, COGNITION

P13- **Altered alpha-activity related to impaired short-term memory of tone sequences in congenital amusia**
Albouy P, Caclin A, Tillmann B
Congenital amusia refers to a lifelong disorder of music perception and production. The deficit seems to be related to pitch perception and memory, and to functional and anatomical abnormalities in a fronto-temporal pathway. We investigated the cerebral correlates of the short-term memory (STM) deficit in amusia using behavioral measures and MEG. Amusics and matched controls performed two STM tasks with melodies (a Contour Task (CT); and an easier Transposition Task (TT)). Participants had to indicate whether sequences of six tones presented in pairs were the same or different. In comparison to controls, amusics' STM was impaired for the CT, but not for the TT. By studying oscillatory brain responses during the delay period using beamforming, we investigated the mechanisms underlying the maintenance of pitch information in STM. Given that alpha-activity (8-12 Hz) has been shown to reflect the disengagement of task-irrelevant regions in working memory tasks, we investigated whether alpha-modulation could be a marker related to the STM deficits of amusics. For control participants, alpha-power was enhanced in left auditory, frontal and in bilateral temporo-occipital regions during the CT in comparison to the TT, suggesting a reduced excitability of these areas. This difference was not observed in right primary auditory regions and less extended in the right frontal regions, which are well known to be involved in music perception and memory. However, these task-related modulations were not observed in amusic participants – thus suggesting abnormal neurophysiological mechanisms of memory processing of musical material in amusia, notably in this distributed fronto-temporal network.

P14- **Competition between top-down and bottom-up mechanisms of auditory attention in Human**
Bidet-Caulet A, Bottemanne L, Bertrand O
Attention is the brain function by which we, voluntarily or not, improve the processing of specific information in our environment. The entry of information to the limited-capacity system is controlled by top-down (TD) and bottom-up (BU) processes. On one hand, TD attention enables the good performance of an on-going task by selecting relevant information. On the other hand, one's attention can be involuntarily captured by an unexpected salient stimulus and thus diverted from the previously on-going task. This BU form of attention is necessary to be aware of important events that are nonetheless irrelevant to the on-going task (e.g. fire alarm). A good balance between BU and TD mechanisms is thus crucial to be task-efficient while being aware of our surrounding environment. BU and TD mechanisms of attention have been mostly explored in separated trials or experiments; really few studies have explored how these mechanisms dynamically interact.
We set up a new paradigm to assess both BU (attentional capture) and TD (anticipation) attention mechanisms, at the same time, and scalp EEG was recorded from 18 young adults. The TD controlled attention state of subjects was found to modulate the processing of distracting sounds and BU attentional capture mechanisms. Moreover, the impact of BU attentional capture by distracting

sounds on target processing was revealed as a delayed latency of the N100 sensory response to target sounds.
These results provide crucial information on how BU and TD mechanisms interact and compete in the human brain.

P15- **Brain development in children with idiopathic and cryptogenic localization related epilepsy**
Ciumas C, Saignavongs M, Ilski F, Heckemann RA, Herbillon V, de Bellescize J, Panagiotakaki E, Ostrowsky-Coste K, Ryvlin P
Epilepsy is a common neurological condition, frequently diagnosed in children and adolescents. Among the various existing forms, localization related epilepsies of unknown or genetic cause (cryptogenic and idiopathic epilepsies) are the most prevalent. No lesions are usually detected on conventional magnetic resonance imaging (MRI) examination. However, abnormalities at the cellular level affecting the neuronal microstructure may be associated with these syndromes. In this study, we explored the gray and white matter in children suffering from idiopathic (benign epilepsy with centro-temporal spikes; BECTS) or cryptogenic (partial cryptogenic epilepsy; PCE) epilepsy and in age- and sex matched controls. We used a region of interest approach to assess whether there where structural differences between groups. We conclude that alterations in the microstructure of the white matter are present in BECTS and PCE. We also observed syndrome-specific alterations in the frontal lobes in individuals with PCE. Ongoing longitudinal follow-up with emphasis on structural and functional development in these patients will enable further analyses of white matter alterations present in PCE and BECTS.

P16- **Emotions Alter Pain Perception without Changing the "Pain Matrix"**
Godinho F, Magnin M, Frot M, Perchet C, Garcia-Larrea L
Background. Seeing human pain scenes modulates a concomitant painful perception, but little is known about the cortical areas subserving such phenomenon.
Methodology/Principal findings. In this fMRI study, subjects observed images illustrating pleasant and unpleasant somatic sensations while receiving painful or innocuous shocks. Pain reports increased significantly when concomitant to images showing human pain. This modulation was associated with higher activity in polymodal cortical areas including the pregenual anterior cingulate, the anterior and dorsolateral prefrontal, the temporo-parieto-occipital junction and the posterior parietal cortex. In contrast, the central core of the "Pain Matrix" (the brain areas commonly activated in response to painful stimuli) remained stable.
Conclusion/Significance. These data suggest that the emotional context imposed activity in a specific high-order network, resulting in a different encoding of painful perception, without changing the sensory processing characterizing the Pain Matrix. Consideration of such supramodal activity is a fundamental step in the search of any "objective correlate" of the pain experience.

P17- **A good sniff for a good smell**
Amat C, Buonviso N, Courtiol E, Fourcaud-Trocmé N, Litaudon P
Sensory function depends on a combination of feedforward flow of information from sensory organs to the brain and the ensuing readjustment of sense organs by feedback from the brain. An example of this process is eye movements to gather information about the relevant parts of visual environment, an active process that is integral to vision. In olfaction, the active sampling process is sniffing. Very little is known about how sampling activity contributes to odor discrimination while it strongly impacts neural activity and perception. In our group, we work at understanding the role and impact of the sensorimotor activity, namely the olfactomotor control, on odor coding.
To achieve this goal we use several methodological approaches in rats from intracellular recording to brain imaging to behavior. These complementary approaches allow us to study how sampling parameters (frequency, flow rate) can act either independently or synergistically to shape the neuronal message. The olfactory system likely takes advantage of this flexibility to adapt sniffing strategies according to the odor, task and/or context as demonstrated by behavioral experiments. Overall, our study provides additional support for the idea that sniffing and olfaction function in an integrated manner.

P18- **A physiological increase of insulin in the olfactory bulb decreases olfactory detection in response to food-related odors by modifying the coding properties of mitral cells (MC).**
Palouzier-Paulignan B, Kuczewski N, Aimé P, Savigner A, Fourcaud-Trocme N, Hegoburu C, Garcia S, Messaoudi B, Thevenet M, Mouly AM, Julliard AK
Insulin is involved in multiple regulatory mechanisms, including body weight and food intake, and plays a critical role in metabolic disorders such as obesity and diabetes. An increasing body of evidence indicates that insulin is also involved in the modulation of olfactory function. However, a role for insulin in odor detection and sniffing behavior remains to be elucidated. Using a behavioral paradigm based on conditioned olfactory aversion (COA), we demonstrated that an intracerebroventricular (ICV) injection of 14 mU insulin acutely decreased olfactory detection of fasted rats to the level observed in satiated animals. In parallel, we showed that the OB and plasma insulin levels were increased in satiated rats compared to fasted rats, and that 14 mU insulin ICV injection elevated the OB insulin level of fasted rats to that of satiated rats. To determine the mechanism of action of insulin we recorded mitral cell (MC) activity from OB slices in vitro. We showed that physiological concentrations of insulin affect MC response to olfactory nerve stimulation acting at two different levels: 1-by modifying spontaneous MC firing activity, 2-by reducing the evoked synaptic transmission between olfactory nerve and MC ; the combination of these two effects resulting in a modification of the distance between evoked (signal) and spontaneous (noise) MC firing. A computational model shows that insulin effects on the OB neuronal network can account for the reduction of odor detection observed in vivo. Together, these data suggest that insulin acts on the OB network to modulate olfactory processing and demonstrate that olfactory function is under the control of signals involved in energy homeostasis regulation and feeding behaviors.

P19- **Neural basis of olfacto-tactile memory in rats**
Ferry B, Boisselier L, Sauvagon M, Humblot P, Gervais R
Most rodent models devoted to the study of neural basis of learning and memory are based on tasks in which the conditioned stimulus is processes by one sensory modality (a tone, an odor…). Here we developed a new behavioral paradigm allowing investigating on neural basis supporting cross-modal olfacto-tactile associations. In rat this two modalities are of prime behavioral importance for object exploration. The task consists in finding among 3 cups which one is baited (+) according to a specific odor texture combination. Neural substrate for acquisition, recall and flexibility was revealed using transient ilidocaïne nactivation of either the lateral entorhinal cortex (LEC) or the dorsal hippocampus (DH) . We found that inactivation of either structure did not impair recall of the previously learned task 1. Interestingly, LEC inactivation severely impaired acquisition of a new set of combinations. In contrast, DH inactivation produced no affect on acquisition but selectively impaired performance during the flexibility test. As a whole the experiment suggests a role of LEC for the formation of new olfacto-tactile associations, while DH is important for flexibility of this cross-modal associations.

P20- **Left, right, but not both: a monkey fMRI study of the neuronal bases of visual competition**
Hadj-Bouziane F, Monfardini E, Gaveau V, Salemme R, Hynaux C, Comte JC, Ibarrola D, Sappey-Marinier D, Jacobs S, Procyk E, Ungerleider LG, Farnè A, Meunier M
Sensory stimuli compete for conscious awareness. A paradigmatic example is extinction, a pathological condition following brain damage, whereby patients lose awareness of contralesional stimuli when ipsilesional stimuli are presented concurrently. However, extinction can also occur in the intact brain, leading healthy subjects to extinguish one of two simultaneously presented stimuli. The objective of this study was to identify the neural bases of the competitive processing underlying this physiologic form of extinction by using fMRI in awake behaving monkeys.
We scanned 4 macaque monkeys, using contrast-enhanced (MION) fMRI in a 1.5T or 4.7T scanner. The block-design experiment included 3 conditions where a white dot (diameter: 2°; eccentricity: 7°) was presented unilaterally (right or left) or bilaterally to the monkeys while they maintained fixation on a central red cross. Each condition was presented for 30 seconds, interleaved with 20 seconds blanks. Within each condition, the visual stimuli were flashed at 1Hz (30 ms ON and 970 ms OFF).
Compared with unilateral stimulations, bilateral stimulations yielded stronger activations in parietal regions, including areas LIP and 7, as well as in frontal regions, including FEF. In addition, these regions exhibited an enhanced functional coupling during bilateral compared to unilateral stimulations. This network plays a fundamental role in attentional mechanisms, which may be disrupted in pathologic extinction and neglect. Comparison of these preliminary data in monkeys with those previously reported in

humans by Çiçek et al. (2007) suggests that robust similarities exist between the two species in the processing of visual competition, thereby confirming the validity of the monkey model for studying sensory competition.

P21- **A simple test battery reveals the slow maturation of visuo-spatial perception**
Pisella L, André V, Gavault E, Le Flem A, Luc-Pupat E, Glissoux C, Barrière A, Vindras P, Rossetti Y, Gonzalez-Monge S
We propose a battery of simple clinical tests inspired by adult neuropsychology to assess the development of perceptual functions of the visual dorsal stream. We selected elementary visuo-spatial tasks likely to involve the occipito-parietal cortex (comparison of lengths and sizes, midline localization, angle processing, and relative dot/square localizations). We tested 96 children aged 4 to 12 years old, 14 adults, and two adult patients with acquired bilateral occipito-parietal damage. Unexpectedly, none of the elementary visuo-spatial abilities tested was acquired at 4 years old.The significant increase of performance observed in all subtests between 4 and 6 years old allowed children to reach the adult performance only for length and size comparisons. Capacity for dot localisation further increased between 6 and 10 years old to reach adult performance. Ability to judge angles and midlines did not reach the adult performance even in the oldest group of children, suggesting further maturation through adolescence. Adding a multi-choice selection to the dot localisation increased performance in healthy children as soon as 6 years old but decreased the performance of children of the youngest group and of the patients with attentional deficits. The performance of patients with specific lesions of the occipito-parietal cortex allows us to propose neuroanatomical bases for slow vs fast maturing visual functions. The data collected in healthy children will serve as control for age-specific comparisons with children suffering from developmental disorders potentially linked to visuo-spatial perceptual and/or attentional selection defects.

P22- **Molecular complexity determines the number of olfactory notes and the pleasantness of smells**
Kermen F, Chakirian A, Sezille C, Joussain P, Le Goff G, Ziessel A, Chastrette M, Mandairon N, Didier A, Rouby C, Bensafi M
One major unresolved problem in olfaction research is to relate the percept to the molecular structure of stimuli. The present study examined this issue and showed for the first time a quantitative structure-odor relationship in which the more structurally complex a monomolecular odorant, the more numerous the olfactory notes it evokes. Low-complexity odorants were also rated as more aversive, reflecting the fact that low molecular complexity may serve as a warning cue for the olfactory system. Taken together, these findings suggest that molecular complexity provides a framework to explain the subjective experience of smells

P23- **Role of the noradrenergic system in olfactory learning and adult neurogenesis**
Richard M, Vinera J, Moreno M, Sacquet J, Didier A, Mandairon N
The main olfactory bulb is the first cortical relay involved in the transmission, processing and integration of olfactory information. It is also one of the brain regions receiving strong noradrenergic innervation from the *locus coeruleus*. Noradrenergic inputs play a critical role in several olfactory functions, such as odor discrimination, and various forms of olfactory memory. In addition, the olfactory bulb is one of the rare brain regions where neurogenesis persists during adulthood. Adult neurogenesis is differently required for specific forms of olfactory learning. Indeed, neurogenesis is necessary for the acquisition of perceptual learning (a form of learning where two undiscriminated odors become discriminated after a 10-day exposure to these two odors), but only for the long term retention of associative olfactory memory (the animal learns to associate a reward to the presence of a specific odor).
In this study, we aimed at identifying the cellular and molecular basis of the different requirement of neurogenesis in perceptual and associative olfactory learning. We first investigated the role of noradrenaline in these two forms of learning. We performed *in vivo* intrabulbar infusion of noradrenergic receptor antagonist to locally block the noradrenergic signaling pathway during perceptual and associative learning. We showed that bulbar noradrenaline is necessary for perceptual learning but not for associative olfactory memory.
We then investigated the mechanisms linking adult neurogenesis, olfactory learning and noradrenaline. We showed that newborn neurons receive noradrenergic synaptic contacts at crucial time points during their maturation and integration in the bulbar neuronal network.
Altogether our results support the hypothesis of noradrenaline being a key regulator of adult neurogenesis during olfactory learning.

NEURAL PLASTICITY AND NEW THERAPEUTIC APPROACHES

P24- **Non-Invasive Brain-Computer Interfaces for communication: The P300 Speller.**
Maby E, Perrin M, Sanchez G, Bertrand O, Mattout J
A Brain Computer Interface (BCI) can be used as a communication system to help patients suffering from severe motor impairments controlling a computing device by means of brain activity alone. Imagined by Farwell and Donchin (1988), the so-called P300-speller uses EEG to select items displayed on a computer screen. This system operates by detecting the P300 electrophysiological response evoked by attention to rare stimuli presented among numerous standard events (oddball paradigm).
We describe recent efforts to implement, improve and evaluate this BCI communication tool, through several experiments conducted in healthy volunteers and one patient suffering from the locked-in syndrome (LIS).

P25- **Saccadic plasticity and posterior parietal cortex**
Pélisson D, Gérardin P, Miquée A, Panouillères M, Habchi O, Urquizar C, Salemme R
Exploring our visual environment requires saccadic eye movements. Saccade accuracy is maintained over the long-term despite changing conditions (e.g., growth, aging, lesions) by saccadic adaptation processes. Here, we present direct evidence for a role of the oculomotor area of the intra-parietal sulcus (IPS) in saccadic adaptation. First, a fMRI study delineated the brain network specifically related to saccadic adaptation induced in a target double-step paradigm. The timing of the backstep target was manipulated to yield a systematic visual error either 50 ms (adaptation paradigm) or 500 ms (reference paradigm) after saccade termination. Subjects were tested for reactive and voluntary saccades in separate sessions. Multi-voxel pattern analyses of fMRI data (discrimination between adaptation and reference paradigms) disclosed a network of cerebellar and parieto-frontal areas involved in saccadic adaptation, with marked differences between reactive and voluntary saccades. Notably, the oculomotor IPS was responsive only in the case of voluntary saccades adaptation. Second, the preliminary results of a fMRI-guided TMS study confirm the contribution of the oculomotor IPS in adaptation of voluntary saccades. Taken together, these studies suggest that, besides the well-documented contribution of the cerebellum, saccadic plasticity involves several areas of the cerebral cortex, including the oculomotor area of the intra-parietal sulcus.
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P26- **Breaking the boundaries of somatosensory plasticity: improved touch at the fingers transfers to the lips**
Muret D, Dinse H, Urquizar C, Reilly K, Farnè A
Understanding how cortical plasticity takes place and its functional consequences are major issues in Cognitive Neuroscience. We looked at the somatosensory consequences of passive tactile co-activation, a technique known to induce transient cortical plasticity. Applied during three hours on the distal phalanx of the right index finger (RD2), this protocol resulted in an enhanced spatial discrimination at this fingertip, but also at both sides (left and right) of the upper lip area. No effects were found at either the left index fingertip or at any body-part region of the control group. These results demonstrate that experimentally induced plasticity following RD2 coactivation improves participants' tactile discrimination performance not only at the coactivated body site, but also at cortically adjacent body sites. Thus, coactivation-induced somatosensory plasticity appears to cross somatotopically defined boundaries between cortical body-parts representations, spreading its functional

consequences to cortically adjacent, but peripherally unstimulated body parts.

P27- **rTMS-induced changes in the cortical representation of the human hand**

Houzé B, Bradley C, Magnin M, Garcia-Larrea L

Shrinking of deafferented somatosensory regions after neural damage is thought to participate to the emergence of neuropathic pain, and pain-relieving procedures other than rTMS have been reported to induce normalization of altered cortical maps. While repetitive magnetic stimulation (rTMS) of the motor cortex can lessen neuropathic pain, no evidence has been so far provided that this is concomitant to changes in sensory maps. Here we first assessed the effect of different sites of hand stimulation and of the density of spatial sampling (64- vs 128-EEG electrodes) to optimize the modelling of the somatotopic representation of the hand in area S1 in healthy volunteers. Then, we used this methodology to evaluate possible changes in hand cortical representation induced by high frequency rTMS. The most robust separation of somatosensory sources was achieved by comparing the cortical representations of the first digit and the distal ulnar nerve territories using the 128-electrode montage. Twenty minutes of high-frequency (20 Hz) rTMS significantly increased the cortical representation of the hand on high-density EEG source analysis.

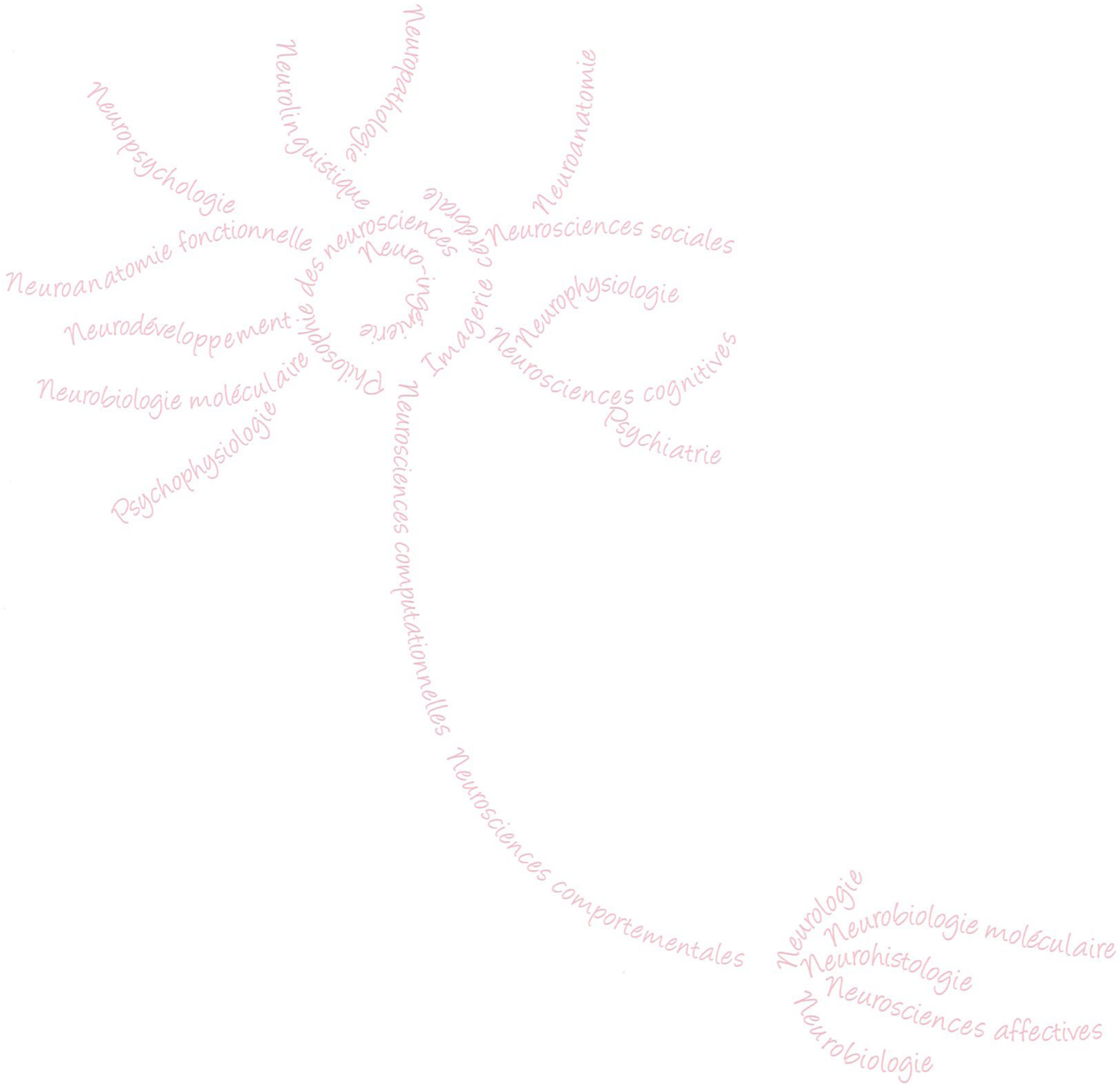
Conclusion: Assessment of tangential SEP components to stimulation of first digit versus ulnar nerve appears the best option to assess plastic somatosensory changes, especially when using relatively low-EEG electrode sampling. rTMS-induced changes might partly counterbalance the plasticity induced by a nerve lesion, and thus substantiate the use of rTMS to treat human pain. However a mechanistic relation between S1 plasticity and pain relieving effects is far from being established.

(see also: Houzé et al., Changes in sensory hand representation and pain thresholds induced by motor cortex stimulation in humans, Cerebral Cortex 2012 in press).

P28- ***Cortical plasticity and perceptual changes during attention to and distraction from pain***

Balança B, Delpuech C, Perchet C, Frot M, Garcia-Larrea L

Focal lesions of the somatosensory system can entail profound long-lasting anatomo-functional changes in mammals, including primates, one of these being a modification of cortical somatotopic maps. In humans, a reorganization of SI cortex has been evidenced after severe deafferentation (limb amputation) but also in the absence of deafferentation, following extensive use of body parts (eg during learning a musical instrument). No study has assessed the possible modulation of SI-3b cortical representations, and the corresponding perceptual changes, during attention to, or distraction from, painful stimuli, which we explored in this study using cortical MEG source reconstruction. Since pain is by itself a powerful attentional attractor, we compared 'soft' intra-modal distracters (attention to opposite hand) with stronger cross-modal distraction procedures (attention to an auditory task). Dynamic changes in the cortical representation of digits were paralleled by simultaneous changes in the subjective reports of stimulus intensity during attention / distraction procedures. The present results add new data to the accumulated evidence that somatosensory plastic phenomena are behaviourally relevant, can operate within minutes and respond to relatively subtle manipulations. To our knowledge, the present study is the first to suggest that attention-driven plasticity *does* affect the very earliest cortical fields in SI sub-area 3b. The net effect in them is not a magnitude enhancement of responses, but rather a modification in the cortical representation of the stimulated territory. Cross-modal distraction (directing attention to auditory input) was more powerful than intra-modal distraction (toward the contralateral hand) to decrease the cortical representations and the perception ratings. This may have practical implications for the management of pain with cognitive procedures, as the magnitude of pain-relief by such procedures should be enhanced if attention is diverted towards a non-somatosensory modality (ie visual and/or auditory), rather than simply oriented toward a different part of the body.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