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Abstract book

INSTITUTE OF NEUROSCIENCE

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Maisin Auditorium

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Program

8h45 – 9h15	Registration - Coffee
9h15 – 9h30	Introduction by Prof. JN OCTAVE IoNS President
09h30 – 11h00	**First session of oral presentations:** - 9h30: **Sylvie Nozaradan,** *Music entrains humans to move, but entrains also their neurons: tagging the neuronal entrainment to the beat with electroencephalography* - 9h50: **Elodie Lerens**, *Early visual deprivation changes the spatial distribution of auditory attention* - 10h10: **Karolina Kabayiza**, *Expression and roles of the Onecut transcription factors in spinal dorsal interneurons* - 10h30: **Nathalie Pierrot** , *Amyloid Precursor Protein Regulates Neuronal Cholesterol Turnover Needed For Synaptic Activity*
11h00 – 11h30	*Coffee break*
11h30 – 12h30	**Second session of oral presentations :** - 11h30: **Nathalie Muls**, *Upregulation of IL-17, but not of IL-9, in circulating cells of CIS and relapsing MS patients. Impact of corticosteroid therapy on the cytokine network* - 11h50: **Amélie Dumont**, *Influence of inflammation on the regulation of glutamate transporters in primary cultured astrocytes and microglia during amyotrophic lateral sclerosis* - 12h10: **Morgane Van de Stadt**, *Homologous and heterologous regulation of dopaminergic transmission*
12h30 – 13h30	*Lunch*
13h30 – 14h30	**Third session of oral presentations:** - 13h30: **Maxime Gilliaux**, *A robotic device as a sensitive quantitative tool to assess upper limb impairments in stroke patients* - 13h50: **Stéphanie Lefèbvre**, *Impact of non invasive brain stimulation on motor performance in chronic stroke patients* - 14h10: **Sophie Leclercq,** *Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects*
14h30 – 15h30	**Posters session**
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Oral Presentations
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Music entrains humans to move, but entrains also their neurons: tagging the neuronal entrainment to the beat with electroencephalography

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Feeling the beat and meter is fundamental to the experience of music. However, how these periodicities are represented in the brain remains largely unknown. Here, we test whether this function emerges from the entrainment of neurons resonating to the beat and meter. In a first experiment, we recorded the electroencephalogram while participants listened to a musical beat and imagined a binary or a ternary meter on this beat (i.e., a march or a waltz). We found that the beat elicits a sustained periodic EEG response tuned to the beat frequency, or *steady-state evoked potential* (SS-EP). Most importantly, we found that meter imagery elicits an additional frequency tuned to the corresponding metric interpretation of this beat. These results provide compelling evidence that neural entrainment to beat and meter can be captured directly in the electroencephalogram in the form of SS-EPs. In a second experiment, we tested whether this technique could reveal a dynamic coupling of cortical activities related to the binding of auditory and visual inputs conveying congruent vs. incongruent temporal periodicities, or *beats*. We evidenced the binding by synchrony of distant cortical areas involved in the multisensory integration of dynamic, temporally-coherent, multimodal stimuli. In a third experiment, we explored the sensorimotor synchronization to the beat, that is, the ability to be entrained to move on periodic sensory inputs and to synchronize movements to the beat. We showed that the frequency-tagging approach with SS-EPs constitutes an effective tool to explore the neural dynamics of sensorimotor coupling in the human brain, by tagging beat-related and motor-related cortical activities separately. More generally, our results suggest that music constitutes a unique context to explore entrainment phenomena in dynamic cognitive processing at the level of neural networks

Early visual deprivation changes the spatial distribution of auditory attention

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Early blind people compensate for their lack of vision by developing superior abilities in the remaining senses such as audition (Collignon et al., 2006; Gougoux et al., 2004; Wan et al., 2010). Previous studies reported supra-normal abilities in auditory spatial attention (Chen et al., 2006 ; Collignon et al., 2006 ; Kujala et al., 1997) and particularly for the localization of peripheral stimuli in comparison with frontal stimuli (Lessard et al., 1998; Roder et al., 1999). However, it is unknown whether this specific supra-normal ability extends to non-spatial attention. Here we compared the performance of early blind and sighted control participants who were blindfolded during an auditory non-spatial selective attention task (target detection based on the sound frequency). In particular, we measured the potential effect of the sound source location (peripheral vs. frontal) on the accuracy and on the speed of the target detection. Blind subjects displayed shorter reaction times and made fewer errors than sighted subjects for both peripheral and frontal stimuli. Moreover, an interaction effect between the group and the sound source location was observed: blind subjects were better to detect peripheral stimuli than frontal stimuli whereas sighted subjects were better to detect frontal stimuli than peripheral stimuli. We conclude that early blind people compensate for the lack of vision by enhancing their ability to process auditory information but also by changing the spatial distribution of their auditory attentional resources.

Expression and roles of the Onecut transcription factors in spinal dorsal interneurons

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The dorsal spinal cord contains functionally distinct classes of interneurons that process, integrate and relay somatosensory information from peripheral sensory neurons to higher brain centres. The correct establishment of regional neuronal identities during embryogenesis is necessary for proper formation of these somatosensory circuitries. In the mouse spinal cord, dorsal horn interneurons (dI) arise in two neurogenic waves that generate six subpopulations of early-born neurons (dI1-6) and two late-born neuronal populations (dIL^A and dIL^B). Onecut (OC) proteins, namely HNF-6, OC-2 and OC-3, are transcription factors expressed in the developing CNS of several species. Previous studies showed that OC factors control neuronal differentiation and migration in murine encephalon and ventral spinal cord.

Here, we report that OC factors are also expressed in dorsal spinal interneurons. Between embryonic days (e)10.0 and e12.5, OC proteins are detected in subsets of early-born dorsal populations dI3 to dI6 as soon as these cells cease to proliferate and initiate differentiation. While most of the postmitotic dorsal interneurons show expression of OC proteins at early stages, OC expression is restricted to a few cells of each subpopulation at e12.5. This suggests that expression of OC factors in early-born spinal interneurons is very transient and that these transcriptional regulators may play an early role in differentiation and/or migration of dorsal interneurons. Ongoing gain-of function or loss-of-function experiments will enable to address this hypothesis.

Amyloid Precursor Protein Regulates Neuronal Cholesterol Turnover Needed For Synaptic Activity

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Neuronal function of Amyloid Precursor Protein (APP) that generates β-amyloid peptide remains largely unknown. Expression of human APP (hAPP) in primary cultures of rat neurons decreased HMG-CoA reductase mRNA levels and therefore cholesterol biosynthesis. However, in cultured astrocytes, expression of hAPP did not affect cholesterol biosynthesis.

In the nervous system, synaptic transmission and plasticity are supported by synchronous calcium oscillations. These synchronous calcium oscillations are known to be generated by glutamatergic synapses, and are mainly mediated by L-type voltage-dependent calcium channels. Recently, we have reported that expression of human APP in primary culture of rat cortical neurons leads to inhibition of calcium oscillations in all the cells of the network. Since spontaneous neuronal activity is known to be tightly control by cholesterol level in membranes, we wonder whether APP could regulate spontaneous calcium oscillation through a cholesterol dependant mechanism. Indeed, we showed in neurons, expression of hAPP decreased both HMG-CoA reductase and 24-S-cholesterol hydroxylase mRNA levels, leading to inhibition of both cholesterol synthesis and hydroxylation. Reinitiating cholesterol turnover in hAPP expressing neurons rescued synaptic activity reflected by calcium oscillations.

Altogether, these results suggest that APP regulates neuronal cholesterol turnover needed for synaptic activity both *in vitro* and *in vivo*.

Upregulation of IL-17, but not of IL-9, in circulating cells of CIS and relapsing MS patients. Impact of corticosteroid therapy on the cytokine network

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Symptoms of MS usually appear in episodic acute periods, called relapses, and are treated by methylprednisolon (MP). There is growing evidences that interleukin (Il-)17 producing lymphocytes, the Th17, are involved in the disease. The TGF-β, in association with IL-6 or IL-21, is required to differentiate naïve Tcells into Th17 cells. The participation of TGF-β in the differentiation of Th17 cells places the Th17 lineage in relationship with regulatory Tcells (Tregs), as TGF-β also induces differentiation of naïve Tcells into Tregs. An impaired balance between these cell types could determine the development of MS. It has recently emerged that IL-9 could affects this balance by differentiating naïve Tcells into Th17 and enhancing the suppressive functions Treg.

Using blood samples from MS patients, we analysed the effect of ivMP on the cytokines expression during clinical relapses both *ex vivo*, by flowcytometry, and *in vitro*, by RT-qPCR after stimulation. We have showed that IL-17 but not IL-9 expression by CD3+ cells was increased during MS relapses. Co-expression of IL-17 and IL-9 was marginal. In addition to Th1 and Th2 cytokines, IL-17 and IL-9 were down-regulated by ivMP but TGF-ß and Foxp3 were not. This change in Th17 and Treg balance could be an additional mechanism by which corticosteroids shorten the duration of a MS relapse and promote recovery.

Influence of inflammation on the regulation of glutamate transporters in primary cultured astrocytes and microglia during amyotrophic lateral sclerosis

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Functional alterations associated with glutamate excitotoxicity and inflammation have been documented in several neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). This study aims at investigating the influence of an inflammatory environment on the glutamate transporters expression and activity in newborn derived astrocytes or microglia cultures, particularly in the context of ALS.

In this aim, we have maintained callosal or cortical astrocytes in culture and exposed these cells to tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine. Indeed, it was previously shown that astrocytes from the corpus callosum or the cortical grey matter show distinct glutamate transporters expression. Also, a culture of microglia was activated with the bacterial endotoxin lipopolysaccharide or with TNF-α. The expression of the glutamate transporters GLT-1a, GLT-1b and GLAST was characterised by quantitative RT-PCR and Western-blotting. Similar experiments were conducted using cells derived from a transgenic rats strain developing ALS by expressing a mutated form of human superoxide dismutase 1 ($hSOD1^{G93A}$).

These experiments indicated the expression of the glutamate transporters was modified after an exposition to an inflammatory environment in the culture from the wild-type rats for both the microglia and the astrocytes. These regulations concerned mainly GLT-1a and GLT-1b, but GLAST was also implicated although regulations were opposed. Furthermore, the inflammatory stimuli induced exacerbated responses in the $hSOD1^{G93A}$ cultures, indicating a higher susceptibility to inflammation.

This study reveals differences in the regulation of glutamate transporter subtypes in astrocytes and microglia under inflammatory conditions. A better understanding of the regulation of the glutamatergic transmission and the mechanism implicated could give rise to opportunities for intervention in neurodegenerative disorders.

Homologous and heterologous regulation of dopaminergic transmission

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Modulation of dopaminergic transmission is the main pharmacological approach to treat numerous psychiatric and neurological diseases such as Parkinson and schizophrenia. However, there is growing evidence that systems involving glutamate, serotonin, adenosine or cannabinoid substances could be used as key pharmacological targets to modulate central dopaminergic transmission. With this in mind, we decided to analyse the impact of heterologous subtances on the cellular response to dopaminergic ligands. Interactions between dopaminergic and adenosinergic transmission interested us at first. Increasing evidence suggest that the antagonistic interaction between specific subtypes of adenosine and dopamine receptors plays an important role in striatal function. Furthermore, behavioural studies suggested that response to adenosine receptor ligands is actually dependent of dopaminergic system. In this context, rats were treated with adenosine and with the adenosine receptor antagonist, caffeine. Dose-response curves with dopaminergic ligands were carried out on striatal homogenates. We observed that, in a particular environment, cellular response to dopamine ligands was decreased after administration of high doses of caffeine. In order to approach the physiological mechanism of such interaction, more specific substances and transfected cells will be used. Modulators of adenosinergic transmission could become a useful pharmacological tool in order to target more specifically the dopaminergic system.

Morgane Van de Stadt is research fellow of the F.N.R.S.

A robotic device as a sensitive quantitative tool to assess upper limb impairments in stroke patients

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Recent systematic reviews of literature have recommended the use of kinematic measures to quantitatively and objectively assess stroke patients' upper limb. The goals of our study were to compare kinematic indices in age-matched healthy subjects and stroke patients, by evaluating various tasks performed with a robotic device, and provide an objective and standardised protocol to assess upper limb impairments in stroke patients.

We performed a prospective cohort study comparing age-matched healthy subjects (n=10) and stroke patients (n=10). Various kinematic indices were analysed from three randomly assigned tasks performed by the affected arm in stroke patients and the dominant arm in healthy subjects. These tasks, composed of large amplitude, targeted and geometrical movements, were standardised and performed with the ReaPLAN robotic device. The ReaPLAN corresponds to a distal effector robotic device that allows displacements of the upper limb in the horizontal plane.

For large-amplitude movements, the stroke patients' path lengths were less constant in amplitude, less rectilinear and less smooth than healthy subjects ($p<0.001$). For the targeted movements, the stroke patients' path lengths were less rectilinear than the healthy subjects ($p<0.001$). For the geometrical movements, the stroke patients had greater difficulty drawing the requested shapes compared with the healthy subjects ($p<0.01$).

Our study proposes an objective and standardised protocol to assess stroke patients' upper limb with any robotic device. We suggest that further randomised controlled trials could use this quantitative tool to assess the efficacy of treatments as robot-assisted therapy.

Impact of non invasive brain stimulation on motor performance in chronic stroke patients

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Background: Numerous stroke patients suffer from hand paresis in chronic stage. Several neurorehabilitation methods have been tested to improve patients' performance. Transcranial direct current stimulation (tDCS) is an appealing therapeutic option with regards to its ease of use and lack of adverse effects. Since 10 years, tDCS has demonstrated its potential to improve transiently performances in simple tasks (like pinching).

Our studies explored the capacity of tDCS to improve patients' performance not only (1) in simple (whole hand movement) but also in more complex (digital dexterity) tasks as well as to improve motor learning capacity (2).

Material and methods: tDCS was used at 1mA in a dual montage: anodal stimulation over the ipsilesional primary motor cortex (M1) and cathodal stimulation over the contralateral M1. tDCS sessions were performed in a double blind (sham/real), randomized order.

1: Performances of 19 chronic stroke patients were evaluated in two sessions. During each session, patients performed 10 grip-lift movements with a manipulandum and Purdue Pegboard Test (PPT) before, during, after and after 20 min of 20min tDCS.

2: Motor learning capacity of 8 chronic stroke patients were evaluated in two blocks of 2 sessions : a stimulation session (real/sham) and a recall session. During the stimulation session, a motor learning task was performed during 30 min under tDCS and after 30min and 60min. At the recall session, patients were asked to perform the task they learned previously.

Results: 1: 20min after real tDCS, grip-lift performance improved of 10% and PPT improved of 30%, when compared to sham tDCS.

2: Motor learning improved during real tDCS when compared to sham; at 1 week, the recall was better after real tDCS.

Conclusion

We demonstrated the capacity of tDCS to improve not only transiently motor performances but also long-term motor learning in chronic stroke patients.

Role of intestinal permeability and inflammation in the biological and behavioral control of alcohol-dependent subjects

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Aims: Alcohol-dependence is commonly investigated in relation to modifications of neurotransmitters in brain. Our hypothesis is that the development of alcohol-dependence could also involve peripheral mechanisms and especially gut-brain interactions. Our first goal was to test whether intestinal permeability, lipopolysaccharides (LPS) and inflammatory cytokines are increased in alcohol-dependent subjects and recover after withdrawal. To explore the possible role of gut-brain axis in alcoholism, our second goal was to test correlations between the biological and the behavioral variables that are known to play a central role in alcohol-dependence, such as depression, anxiety, alcohol craving. **Methods**: 40 alcohol-dependent subjects hospitalized for detoxification program were tested both at onset (T1) and end (T2) of withdrawal and compared for biological and behavioral markers with a control group. Participants were evaluated for gut permeability, LPS, systemic inflammation (TNFα, IL-6, IL-10, hsCRP) and for depression, anxiety and alcohol craving. **Results**: Intestinal permeability and LPS that were largely increased in alcohol-dependent subjects at T1 recovered completely at T2. A low-grade inflammation was observed at T1and recovered partially after withdrawal in parallel with the psychological variables. We found that pro-inflammatory markers were positively correlated with depression and craving. The anti-inflammatory cytokine IL-10 was negatively correlated with depression and craving. **Conclusion**: Leaky gut-induced inflammation is correlated to emotions and craving for alcohol. We can therefore consider that gut-brain axis may play a significant role in the development of alcoholism. IL-10 could be a protective factor in relation to emotional disturbances and the probability of relapse. Moreover, recent animal and human studies have shown that chronic alcohol consumption altered gut microbiota. An interesting perspective would be to test pro- or prebiotics that are known to improve the composition of gut microbiota and therefore restore the gut barrier to reduce inflammation, depression and craving to help patients to remain abstinent.

Adaptive control of grip force to compensate for static and dynamic torques during object manipulation

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Manipulating a cup by the handle requires compensating for the torque induced by the moment of the mass of the cup relative to the location of the handle. In the present study, we investigated the control strategy of subjects asked to perform grip-lift movements with an object with center of mass located away from the grip axis. Participants were asked to lift the manipulandum with a two-fingers precision grip and stabilize it in front of a visual target. Subjects showed a gradual and slow adaptation of the grip force scaling across trials: the grip force tended to decrease slowly and the temporal coordination between grip force and load torque rates displayed gradually better-coordinated patterns. Importantly, this adaptation was much slower than the stabilization of the same parameters measured either when no torque came into play or after previous adaptation to the presence of a torque. In contrast, the maximum rotation induced by the torque was efficiently controlled after only few trials, and an unexpected decrease in the tangential torque produced significant overcompensation. An unexpected increase in torque produced a consistent opposite effect. This shows that the compensation for the dynamic torque was based on an anticipatory dynamic counter-torque produced by the arm and wrist motor commands. The comparatively slow stabilization of grip force control suggests a specific adaptation process engaged by the presence of the torque. This paradigm including tangential torques clearly constitutes a powerful tool to extract the adaptive component of grip control during object manipulation.

Velocity visuomotor transformation for manual tracking

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Humans perform hundreds of visually guided arm movements every day, with ease and even without thinking about it. However, the brain faces a challenging problem: transforming the visual information into a set of adequate motor commands for the arm. In our research, we focus on the motor planning stage for manual tracking movements towards moving targets. The visual information is obviously encoded in retinal coordinates, while the motor plan for the arm should be expressed in shoulder coordinates. Most of the time, the retinal and shoulder reference frames are not aligned because their relationship depends on the 3-dimensional (3D) eye-head-shoulder geometry and kinematics. The brain could use the retinal information as a crude motor plan and using delayed sensory feedback to correct the initial error in the motor plan, or the brain could compute a spatially accurate motor plan by also taking extra-retinal signals (3D eye and head positions and velocities) into account. In order to answer this question, we designed two behavioural experiments in which subjects had to manually track a moving target in different eye-head postures in complete darkness: 1) different head roll angles, 2) different oblique gaze positions and 3) different eye velocities (in terms of speed and direction). We computed the initial arm movement direction over the first 100ms of the arm movement (open-loop phase of the arm movement), and compared for each trial this observed direction to the retinal (extra-retinal signals not taken into account) and spatial directions (3D eye-head kinematics taken into account) of the target. We showed that the brain computes a spatially accurate motor plan for the arm, fully taking the head roll into account, and partially taking the ocular counter-roll, eye velocity and oblique gaze angle into account.

Monitoring brain reorganization elicited by learning with transcranial magnetic stimulation

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Motor learning in general, and force-field adaptation in particular, entails changes in the primary motor cortex (M1). In the force-field task, subjects reach to targets displayed on a screen while holding the manipulandum of a robotic arm. The robotic arm can deviate the hand from its trajectory. The large initial deviation observed at the introduction of the perturbation is then reduced over the course of trials.

To explore M1 reorganization, we used a force field paradigm and delivered a single pulse of TMS around 100ms before movement onset in one third of the trials. We compared 3 groups of subjects. In group 1 (ABR, n=20), the force field was introduced at full strength on the first trial for 240 trials. In group 2 (GRA, n=20), the field was introduced gradually over 185 trials and maintained for an additional 55 trials. We measured the MEP size in the biceps, triceps and deltoid muscles throughout the experiment.

By the end of the learning, the ABR and GRA groups exhibited comparable performance. The force-field elicited an increase in muscle activity for the biceps during movements towards SE and for the triceps and deltoid during movement towards the NW. The size of the MEPs also changed during force-field adaptation. An index measuring the imbalance between the sizes of MEPs before movements in either direction demonstrated a significant change in MEP index for the ABR group but not for the GRA group. For the ABR group, the change in MEP index was correlated with the strength of the motor memory.

In conclusion, corticospinal reorganization can be monitored during force-field learning. In addition, we demonstrate that the MEP changes are not a mere reflection of upcoming muscle activity as we did not observe any change in the gradual condition.

Posters Abstracts

Exploration of nociceptive cortical processing with steady-state evoked potentials

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Studies have shown that the periodic repetition of a stimulus induces, at certain stimulation frequencies, a sustained electro-cortical response of corresponding frequency, referred to as steady-state evoked potential (SSEP). Using infrared laser stimulation, we recently showed that SSEPs can be used to explore nociceptive cortical processing. Here, we implemented a novel approach to elicit such responses, using a periodic intra-epidermal electrical stimulation of cutaneous Aδ-nociceptors (Aδ-SSEPs). Using a wide range of frequencies (3-43 Hz), we compared the scalp topographies and temporal dynamics of these Aδ-SSEPs to the Aβ-SSEPs elicited by non-nociceptive transcutaneous electrical stimulation, as well as to the transient ERPs elicited by the onsets of the 10-s stimulation trains, applied to the left and right hand. At 3 Hz, we found that the topographies of Aβ- and Aδ-SSEPs were both maximal at the scalp vertex, and resembled closely that of the late P2 wave of transient ERPs, suggesting activity originating from the same neuronal populations. The responses also showed marked habituation, suggesting that they were mainly related to unspecific, attention-related processes. In contrast, at frequencies >3 Hz, the topographies of Aβ- and Aδ-SSEPs were markedly different. Aβ-SSEPs were maximal over the contralateral parietal region, whereas Aδ-SSEPs were maximal over midline frontal regions, thus indicating an entrainment of distinct neuronal populations. Furthermore, the responses showed no habituation, suggesting more obligatory and specific stages of sensory processing. Taken together, our results indicate that Aβ- and Aδ-SSEPs offer a unique opportunity to study the cortical representation of nociception and touch.

Numerical and temporal magnitude comparisons in neglect patients

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Interactions between numerical, spatial and temporal magnitude processing are commonly reported, suggesting that these magnitudes could all be represented within a common processing system (Walsh, 2003). Numbers might be represented spatially along a mental number line, with small numbers on the left and larger numbers on the right. Whether this spatial organization also applies to nonsymbolic numerosities and durations is still a matter of debate. It has been shown that patients suffering from spatial neglect deviate towards larger numbers in number bisection tasks (e.g., Zorzi, Priftis, & Umiltà, 2002) or present difficulties to process small symbolic numbers (Vuilleumier, Ortigue, & Brugger, 2004). Here we assessed in neglect patients whether this spatial bias observed in symbolic comparison also extends to (1) nonsymbolic numerical judgment (i.e., rapidly flashed dot sequences) and to (2) duration processing (i.e., comparison of the duration of single dot). In each task, neglect patients and healthy age and sex matched controls had to judge whether the stimulus was smaller or larger than a standard value (i.e., either "5" or 500 ms). The results showed that neglect patients have global difficulties to process symbolic and nonsymbolic numerical and temporal information. Accordingly to previous observations, in symbolic numerical comparison, the neglect patients responded to "4" slower than to "6". In nonsymbolic comparison, they were also less accurate to respond to sequences of 4 dots. In the duration task, performance of the neglect patients was globally worse than controls, whatever the size of the relative interval duration.

Shielding cognition from nociceptive distraction with working memory

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The control of pain by attention should be under the supervision of executive functions in order to decrease the ability of a nociceptive stimulus to capture attention. That hypothesis was tested in the present experiment during which participants performed cognitive tasks on visual targets while concomitantly being presented to task-irrelevant tactile stimuli. Occasionally, in order to distract the participants, standard tactile distracters were replaced by novel nociceptive distracters that disrupted task performance, reflected by increased reaction times in trials with novel nociceptive distracters relatively to trials with standard tactile distracters. When the participants were using working memory to perform the tasks, distraction was reduced suggesting an inhibition of the attentional shift to the nociceptive distracters. Two working memory tasks were used, a high demanding task requiring rehearsing the sensory-perceptual features of the targets, a less demanding task requiring rehearsing the response code. Three main results were showed. First, reduction of behavioral distraction was observed independently of task demands suggesting the specific involvement of working memory in the control of nociceptive distraction. Second, the recording of the laser-evoked potentials – reflecting the cortical processing of nociceptive information – has shown a reduction of magnitude of early-latency potentials (N1/N2) during the two working memory tasks suggesting that the reduction by working memory of attention toward the nociceptive stimuli is mediated by a modulation of the first cortical responses to the nociceptive inputs. Third, the reduction of late-latency potentials (P2) was only significant during the "motor" working memory tasks, suggesting that such electrophysiological responses reflect the selection of the appropriate action to the nociceptive stimulus. These data supports the important but complex role of attention and executive functions for the processing of nociceptive stimuli, and, provably other threat-related stimuli.
(http://nocions.webnode.com/).

Vibrations in the forearm during active touch of rough textures

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Roughness is an important attribute of objects we touch. Humans can discriminate fine variations of surface roughness using active touch. We have recently shown that humans after digital ring block anaesthesia remained able to discriminate textures with the fingertip (Libouton et al., SFN2009). Since anaesthesia eliminates skin sensations in the digit, one must conclude that the somatosensory system is able to collect texture information from other sources. One possibility is that the vibrations caused by scanning a rough surface propagate through the finger and the hand and stimulate sensors in regions far away from the contact area.

We asked volunteers to perform lateral scans on different rough surfaces (periodic and non-periodic). They maintained different levels of normal force and speed. The vibrations were recorded by a microphone inserted in the chest-piece of a stethoscope with the bell side fastened to the subjects' wrist. The position of the fingertip and the contact forces were recorded.

The analysis showed that for periodic stimuli, the frequency content of the vibrations was correlated with the ratio of scanning velocity to spatial period, whereas it was not the case for non-periodic stimuli. However, for all kind of stimuli, the intensity of the vibrations allowed us to discriminate the different levels of roughness.

Holistic perception of faces: direct evidence from frequency-tagging stimulation

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We investigated how the human brain integrates object parts into coherent global visual representations by means of frequency-tagging (Regan & Heron, 1969). Participants saw a whole face whose left and right halves flickered at 5.87 and 7.14 Hz (counterbalanced). In a first control condition, half faces were spatially separated by 0.29 visual degrees. In order to control for interpretation of the interaction terms as reflecting a border effect, vertically misaligned half faces sharing the same amount of border as in the normal whole face condition were presented. Inverted faces were also presented in a third control condition. EEG signal showed posterior responses at fundamental frequencies of stimulation (5.87 and 7.14 Hz), and at several interaction terms (e.g., 5.87 + 7.14 = 13.01 Hz) at occipito-parieto-temporal sites, with a right hemisphere advantage. EEG power of the first order interaction term (13.01 Hz) decreased significantly for the three control conditions: spatial separation, misalignment and inversion of half faces. Importantly, this effect could not be accounted for merely by considering the sum of EEG amplitude of the fundamental frequencies. Overall, the presence and behaviour of interaction terms in the frequency-tagging method provides direct evidence for integration of facial parts into a holistic representation.

Phase-locked and non phase-locked EEG responses elicited by intranasal nociceptive chemosensory stimulation to explore trigeminal function in humans

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Background and aims: Brief and selective chemical stimulation of olfactory and trigeminal receptors of the nasal mucosa can be used to elicit chemosensory event-related potentials (ERPs) and, thereby, study chemosensation. In particular, intranasal stimulation with gaseous $C0_2$, which produces an odorless stinging and burning sensation, can be used to selectively activate chemosensitive nociceptors of the second trigeminal branch. The aim of this study was to characterize the phase-locked ERPs, as well as the non phase-locked event-related synchronization and desynchronization (ERS and ERD) triggered by nociceptive trigeminal chemosensory stimulation in healthy subjects, and to compare the obtained responses to those elicited by thermal laser stimulation of heat-sensitive skin nociceptors.

Methods: The EEG was recorded in ten healthy volunteers, using 64 scalp electrodes. A constant airflow olfactometer was used to deliver 60 pulses of CO_2 (concentration: 50%v/v; rise-time: 20 ms; ISI: 30 s). Time-domain averaging was used to characterize ERPs. A time-frequency decomposition based on the Morlet wavelet transform was used to characterize ERS and ERD.

Results: In all participants, nociceptive chemosensory stimulation elicited clear ERPs consisting of a negative wave (391±55 ms) followed by a positive wave (554±57 ms), as well as ERS (490 ±74 ms, 3.48 ±0.94 Hz) and ERD (813 ±140 ms, 8.94 ±1.21 Hz). The obtained responses were very similar to the EEG responses to thermal stimulation of skin nociceptors.

Conclusion: Selective stimulation of chemosensitive nociceptive free nerve endings of the nasal mucosa using gaseous CO_2 can be used to study nociceptive trigeminal function in humans.

Holistic face perception impairment in acquired prosopagnosia as evidenced by eye-gaze-contingency: generalization to several cases

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Gaze-contingency is a method introduced by Rayner (*Cog. Psy.*, 1975) to investigate the perceptual span in reading by selectively revealing/masking a portion of the visual field in real time. Recently, we introduced this approach in the field of face perception, showing that a brain-damaged patient with impairment limited to face recognition (acquired prosopagnosia, patient PS) presents with the reverse pattern as normal observers: almost no further decrease of performance when only one feature at a time is available (foveal window condition), but a very large impairment when the fixated feature is masked (mask condition), forcing holistic perception (Van Belle et al., *JOV* 2009: *http://www.journalofvision.org/content/9/8/541*; *Neuropsychologia*, 2010). Here we extend these latter observations to two cases of acquired prosopagnosia with unilateral right hemisphere damage: GG (Busigny et al., *Neuropsychologia*, 2010: lingual, fusiform and parahippocampal damage; Van Belle et al., *Neuropsychologia*, 2011) and LR (Bukach et al., *J. Cogn. Neurosci.*, 2006; anterior pole damage). Both patients also present with impairment in visual recognition limited to faces. They were tested in a delayed face matching task with a full view, gaze contingent window, and gaze contingent mask condition. Similar to PS and contrary to normal observers, both patients were significantly more impaired with a mask than with a window, demonstrating problems with holistic face perception. These observations support a generalized account of acquired prosopagnosia as a selective impairment of holistic face perception, and imply that holistic perception is a key element of normal human face recognition. Furthermore, the similar behavioral pattern of all three patients despite their very different lesion locations supports a distributed network view of the neural face processing structures, meaning that the key function of face perception requires the activity of several brain areas of the right hemisphere and their mutual connectivity.

The composite face illusion and its disappearance with misaligned faces : an effect of metric distance or part separation?

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Strong evidence that faces are perceived holistically/configurally comes from the composite face effect/illusion: identical top halves of a face are perceived as being slightly different if they are aligned with different bottom halves. The illusion disappears when the bottom half of the face is moved away from the top half, so that the top and bottom halves are spatially misaligned. One unresolved issue is whether the composite illusion disappears in the misaligned condition because the two halves do not form a whole object (i.e., they form two segmented parts), or because the bottom part is located away from the top part. To address this issue, 12 participants had to match two top halves of composite faces presented sequentially. The experiment was characterized by 3 conditions ("same": both halves identical; "different": both halves different; "composite": top half identical, bottom part different) and 7 levels of alignment between the top and bottom halves: from spatially aligned, forming a whole coherent face, to completely misaligned (100% width of the face). Twenty-three base face identities were used. In the composite trials, accuracy rates decreased significantly compared to "same" trials, only in the completely aligned condition. Correct response times were also significantly increased only in that condition. Strikingly, even a small spatial misalignment (16.7% width of the face) between top/bottom parts in the composite face paradigm disrupted completely the influence of the bottom part on the perception of the top part, so there was no difference between all other levels of (mis)alignment. This observation implies, practically, that it is not necessary to use a wide spatial misalignment in such studies. From a theoretical standpoint, these data show that it is the spatial alignment/separation of the facial halves rather than the metric distance between the face parts that explain the presence/absence of the composite face effect.

Lack of TRPC1 channels impairs skeletal muscle regeneration

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We previously showed in vitro that calcium entry through TRPC1 ion channels regulates myoblasts migration and differentiation by activating calpain, a calcium-dependent protease which in its turn is able to cleave MARCKS protein (myristoylated alanine-rich C-kinase substrate), an actin binding protein involved in focal adhesion. To explore, in vivo, whether the absence of TRPC1 channel impairs skeletal muscle regeneration, we used cardiotoxin injections to induce muscle injury in adult $TRPC1^{+/+}$ and $TRPC1^{-/-}$ mice. Interestingly, we observed that $TRPC1^{-/-}$ muscles showed a smaller fibre size and a decreased muscle specific force after 10 days and 14 days of regeneration respectively. Moreover, we observed an increased proportion of centrally nucleated fibres at day 14 of regeneration in $TRPC1^{-/-}$. These observations pointed out a delay of muscle regeneration in $TRPC1^{-/-}$ mice in comparison with their controls. This was corroborated by the fact that, in comparison with their controls, $TRPC1^{-/-}$ muscles showed a decrease in myogenic transcription factors activity and, in particular, a decrease of MyoD , Myf5 and myogenin expression. As expected, the developmental Myosin Heavy Chain (MHCd), a well known downstream target of MyoD during muscle regeneration, was more expressed in $TRPC1^{+/+}$ than in $TRPC1^{-/-}$ muscles at day 3 of regeneration. Moreover, the Akt/mTOR/P70S6k pathway which is involved in regeneration and in regulation of protein synthesis and muscles fibre size, was also down regulated in $TRPC1^{-/-}$ muscles. Indeed, we observed a decrease of phosphorylation of both Akt and P70S6k in $TRPC1^{-/-}$ muscles than in $TRPC1^{+/+}$ muscles. The possible involvement of PI3 Kinase, an upstream regulator of Akt pathway, is under study.

Altogether, our results emphasize the involvement of TRPC1 channels in skeletal muscles development and identify a calcium-dependent activation of the Akt /mTOR/P70S6k pathway during muscles regeneration which is decreased in $TRPC1^{-/-}$ mice.

The transcriptional activator HNF-6 controls the formation of neuromuscular junctions

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The Onecut (OC) family of transcription factors comprises three members in mammals, namely HNF-6 (or OC-1), OC-2 and OC-3. During embryonic development, these transcriptional activators control cell differentiation in pancreas, in liver and in the nervous system. The *Hnf6-/-* newborn mice suffer from paralysis of the hindlimbs. The goal of this project was to identify the causes of paralysis in *Hnf6-/-* mice. Locomotor deficit was quantified by multiple behavioral tests. In mutant animals, we observed an abnormal positioning of the hindlimbs and a reduction of the hindlimb muscle strength. In order to understand the origin of this locomotor deficit, we focused on neuromuscular junctions. These specialized synapses were visualized after alpha-bungarotoxin labeling (motor plate marker) and immunofluorescence for synaptophysin (presynaptic marker) and neurofilaments (axonal marker) on hindlimb muscle sections. In *Hnf6-/-* mice, abnormal organization and morphology of the neuromuscular junctions characterized by defective apposition of the axonal bouton to the motor plate and delayed and incomplete maturation of the junctions were observed from the onset of their development. Hence, HNF-6 is required for proper formation of neuromuscular junctions. Current investigations aim to identify how HNF-6 controls this process. Our preliminary data suggest that the expression of factors involved in the formation of neuromuscular junctions may be reduced in motor neurons of *Hnf6-/-* newborns. We are developing an *in vitro* neuron-myotube coculture system to verify the implication of these factors through rescuing the abnormal neuromuscular junction phenotype observed in the absence of HNF-6.

The Onecut transcription factors participate in the differentiation and migration of distinct subsets of ventral interneurons in the developing spinal cord

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Neuronal networks that control locomotor behaviors are located in the ventral horn of the spinal cord. They are composed of motor neurons and of several types of interneurons that exert various functions. Four cardinal classes of ventral interneurons called V0, V1, V2 or V3 have been identified. During development, these neuronal populations diversify into different subsets which exert distinct functions.

However, genetic programs that control diversity and migration of ventral spinal interneurons are not fully elucidated. In this study, we report that the four ventral classes of interneurons are differentially distributed along the rostro-caudal axis of the spinal cord. Furthermore, each of these classes can be subdivided into several subsets according to combined expression of Onecut transcription factors (a family of transcriptional activators that includes Hnf6/Oc1, Oc2 and Oc3) and of other transcriptional regulators such as Arx, Bhlhb5, mafA, mafB, Nurr1, Olig3, Otp and Prox1. Some of these subsets are differentially distributed at thoracic and at limb levels, respectively. Moreover, analyses of Onecut mutant embryos strongly suggest that Onecut proteins regulate differentiation of distinct subsets of ventral interneurons. Indeed, in the absence of Onecut factors, identity of different subsets of V1, V2a and V2b neurons is strongly affected. In addition, migration flux of V2a and V2b interneurons is altered and subsets of V2a and V2b interneurons migrate dorsally, while subsets of V1 interneurons abnormally migrate ventrally within V2 domain and close to the midline.

Taken together, these results provide evidence that ventral interneurons are differentially distributed according to the rostro-caudal level of the spinal cord, and that cardinal interneuron populations can be subdivided in subsets that may be of functional relevance. Finally, our data suggest that Onecut factors participate in the differentiation program of distinct subsets of ventral interneurons and may control migration of these neuronal populations.

What is the role of motor simulation in action understanding?

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The mere viewing of an agent performing an action causes automatic covert activity in the motor system of the observer as if his own body performed the action (e.g., Aziz-Zadeh et al., 2006). According to the motor simulation theory, this activity reflects the automatic remapping of the observed action onto a motor representation of the same action in the observer's motor system. This process would play a central role in understanding others' actions (e.g., Rizzolatti et al., 2001). However, the functional role of motor simulation in action understanding remains controversial (Mahon & Caramazza, 2008). The simulation theory predicts that an individual incapable of matching an observed action onto his own motor representations should be somewhat impaired in understanding others' actions (e.g., Gallese, 2009). We investigated the functional role of motor simulation in manual action understanding by assessing action understanding in an individual, DC, presenting with a congenital absence of arms and hands (limb aplasia). DC was invited to perform tasks tapping different aspects of action understanding (conceptual categorization of actions vs. kinematic processing of actions) and in conditions varying in the amount of information provided by the visual action stimulus. The results indicated that motor simulation is not necessary for understanding actions when the visual stimulus conveys both form and motion information, even when visual motion is only implied (photographs), target objects are missing (pantomimes), or fine-grained processing of the kinematics of action is required (weight estimation and violation of expectations). They also suggested that motor simulation does contribute to action processing when visual form information is missing (actions as point-light animations). This pattern is consistent with the hypothesis that motor simulation contributes, in a top-down fashion, to the perceptual processing of conspecifics' body motion, especially when visual information is partly missing or ambiguous (e.g., Wilson & Knoblich, 2005).

Influence of action observation on number production

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Recent findings show that the sensory-motor areas underlying finger movement play a critical role in numerical cognition. Moreover, number processing has been shown to be intimately linked to space processing and attention orienting processes. Given these links between embodied action perspectives and numerical concepts, we suggest that observing certain types of actions should have an effect on the selection and the production of numerical responses. Therefore, the present study assessed whether observing finger, hand or eye movements were able to influence a random number generation task, and how the influence effect moderated for the different kinds of movements. The experimental task required that participants randomly produced a number between 1 and 10 after they first perceived an action stimulus of either a closing or an opening finger grip movement, a closing or an opening hand movement, a horizontal or a vertical eye gaze orientation movements, or they perceived stimuli color changes (a control comparison condition). The results revealed that random number production was influenced by the prior presentation of the finger movements, whereby observing a closing finger grip movement led participants to produce more small than large numbers, while observing an opening finger grip movement led participants to produce more large than small numbers. For the hand movement conditions, the number production was not influenced. There was also an effect following observation of the eye movements: observing eye movements oriented leftward or downward led participants to produce more small than large numbers. The final result concerned observation of stimuli color changes, and as predicted, this had no influence on number production. Taken together, these results showed that the characteristics of the observed finger grip and eye movements appeared to automatically prime the number generation task. The findings are discussed in terms of the functional and neural mechanisms that might explain the effect, and support the view that number semantics might be grounded on sensory-motor mechanisms.

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