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FROM THE MOLECULE TO PATHOLOGY

C1- **Amparo ACKER-PALMER**, Institute for Cell Biology and Neuroscience, Goethe Universität, Frankfurt am Main, Germany

Neuronal and vascular guidance in health and disease

The formation of both nervous and vascular systems is regulated by a combination of attractive and repulsive cues. It is now well known that vessels and nerves share molecular mechanisms for both their development and later during plasticity phenomena in the adult organism, including pathological situations. In our lab we study the molecular mechanisms of such guidance cues using a broad array of techniques including in vivo mouse models, tissue explants and cellular and biochemical assays. At the molecular level we have learned that in both systems receptors cluster in close proximity at the membrane and regulate each other functions by controlling for example the rate of their internalization. In the talk I will review different examples of receptor crosstalk important for neuronal migration during development and synaptic plasticity in the adult and how these molecular players are conserved in the development of vascular structures that might serve as scaffolds for the nervous system.

C2- **Michael HENEKA**, Clinical Neuroscience, Dept. of Neurology, University of Bonn, Bonn, Germany

Multiple level interactions between neurodegeneration and neuroinflammation in Alzheimer's disease

Generation of neurotoxic amyloid-ß peptides and their deposition along with neurofibrillary tangle formation represent key pathological hallmarks in Alzheimer's disease (AD). Recent evidence suggests that inflammation may be a third important component which, once initiated in response to neurodegeneration or dysfunction, may actively contribute to disease progression and chronicity. Various neuroinflammatory mediators including complement activators and inhibitors, chemokines, cytokines, radical oxygen species and inflammatory enzyme systems are expressed and released by microglia in the AD brain. Degeneration of aminergic brain stem nuclei including the locus ceruleus and the nucleus basalis of Meynert may facilitate the occurrence of inflammation in their projection areas given the antiinflammatory and neuroprotective action of their key transmitters norepinephrine and acetylcholine. While inflammation has been thought to arise secondary to degeneration, recent experiments demonstrated that inflammatory mediators may stimulate amyloid precursor protein processing and ß-amyloid deposition, thereby establishing a vicious cycle. Despite the fact that some aspects of inflammation may even be protective for bystander neurons, antiinflammatory treatment strategies should therefore be considered. Non-steroidal anti-inflammatory drugs have been shown to reduce the risk and delay the onset to develop AD. While, the precise molecular mechanism underlying this effect is still unknown, a number of possible mechanisms including cyclooxygenase 2 or c-secretase inhibition and activation of the peroxisome proliferator activated receptor-gamma may alone or, more likely, in concert account for the epidemiologically observed protection. Data on microglial activation in AD along with suggestions to modify and alter the pro- into an antiinflammatory phenotype will be reviewed and discussed.

C3- **Luc ZIMMER,** CRNL/Bioran

Serotonin receptors and neurodegenerative processes. A Focus on 5-HT$_{1A}$ receptor PET imaging

Serotonin (5-hydroxytryptamine, 5 HT) and its various receptors are involved in numerous central nervous system functions. Among the currently known 5-HT receptors, the 5-HT$_{1A}$ receptor is the best characterized subtype, tightly implicated in the pathogenesis of mood disorders.

Recent preclinical and clinical studies suggest that 5-HT$_{1A}$ receptors are involved in cognitive impairments during Alzheimer's disease or Parkinson's disease and may constitute a possible therapeutic target. Receptors can be visualized and quantified *postmortem* by autoradiography and *in vivo* by positron emission tomography (PET), facilitating the translation from animal research to man. However, these imaging studies of 5-HT$_{1A}$ receptors have produced conflicting results. One explanation of these discrepant findings could be that all PET studies used radiolabelled antagonists which bind unspecifically to functional 5-HT$_{1A}$ receptors, pharmacologically mobilizable, and to non-functional receptors. The use of PET 5-HT$_{1A}$ agonists could therefore provide a measure of the remaining functional receptors during the neurodegenerative processes.

Although questions are still pending regarding the correlation between 5-HT$_{1A}$ functional state at a pathophysiological process and the following therapeutic efficacy, this approach illustrates the potential value of PET pharmaco-imaging.

C4- **Claire MEISSIREL**, CRNL/Oncoflam

VEGF in neuronal development and synaptic plasticity

VEGF, for vascular endothelial growth factor, is a prototypic angiogenic factor that was originally known for its critical role in blood vessel formation. Emerging evidence however has revealed that VEGF also regulates a wide range of developmental and adult neurobiological processes, including neurogenesis, neuroprotection and axon guidance. This lecture highlights recent advances in understanding how VEGF directly affects neuronal guidance, referring to studies that employed various mouse models to demonstrate the requirement for VEGF / VEGF receptor signaling. Novel findings uncovered the underlying molecular mechanism involving a cross-talk between VEGF, its receptor VEGFR and the glutamate receptor NMDAR, that is able to modulate non-synaptic NMDAR function. The implication of such a cross-talk between an angiogenic factor and a classic receptor of a neurotransmitter will be discussed in the context of the regulation of hippocampal synaptic transmission.

C5- **Patrick EDERY**, CRNL/Tiger

Mutations in U4atac small nuclear RNA: from splicing to brain malformations

The spliceosome is a ribonucleoprotein complex containing small nuclear (sn) RNAs, which catalyzes RNA splicing through intron excision and exon ligation to produce mature mRNAs, templates for protein translation. No mutations in human snRNAs have been described in humans, or linked to diseases. We identified four point mutations in the *U4atac* snRNA component of the minor spliceosome in patients with severe brain malformations and unexplained postnatal death (Taybi-Linder syndrome, TALS or microcephalic osteodysplastic primordial dwarfism type 1, MOPD1, MIM 210710). Minor intron splicing and expression of a subgroup of genes, possibly linked to the disease phenotype, were affected in cell lines derived from TALS patients. Our findings demonstrate the crucial role of minor spliceosome component, *U4atac* snRNA, in human brain development and postnatal survival.

SLEEP AND ALTERED STATES OF CONSCIOUSNESS

C6- **Barbara JONES**, Dpt of Neurology and Neurosurgery, McGill University, Montreal Neurological Institute, Montreal, Quebec, Canada

Homeostatic regulation of neural activity across the sleep-wake cycle

Neural activity in the brain is altered across the sleep-wake cycle, allowing periods of rest alternating with activity. Yet, some neurons decrease their discharge during sleep, whereas others increase their discharge during sleep, relative to waking. Such different cell populations within the brainstem, hypothalamus and basal forebrain generate the different states of wakefulness, slow wave sleep (SWS) and paradoxical sleep (PS, or rapid eye movement sleep, REMS). As revealed by juxtacellular recording and labeling of neurons in the basal forebrain (BF), sets or pairs of excitatory (glutamatergic or cholinergic) and inhibitory (GABAergic) cells function either in parallel, to promote by their discharge cortical activation or behavioral arousal (together with postural muscle tonus), or in opposition, to effect cortical de-activation or behavioral quiescence (together with postural muscle atonia). The activity of each neuron is likely regulated in a homeostatic manner, such that prolonged activity results in changes in its receptors

with mobilization of inhibitory receptors and desensitization of excitatory receptors. The excitability of wake-active neurons would thus be decreased with prolonged wakefulness, while that of sleep-active neurons would be increased, enhancing the probability for sleep. Conversely with sleep recovery, the excitability of wake-active neurons would be restored and that of sleep-active neurons diminished, decreasing the probability or need for sleep. These changes in neuronal excitability of specific cell populations as a function of sleep and waking would in turn underlie the homeostatic changes in sleep, whereby sleep deprivation results in sleep rebound and a decrease in waking.

C7- **Steven LAUREYS**, Coma Science Group, University and University Hospital of Liège, Belgium

The neural correlates of conscious awareness revealed by the study of coma & related states

The past 15years have provided an unprecedented collection of discoveries that bear upon our scientific understanding of recovery of consciousness in the human brain following severe brain damage. Highlighted among these discoveries are unique demonstrations that patients with little or no behavioral evidence of conscious awareness may retain critical cognitive capacities and the first scientific demonstrations that some patients, with severely injured brains and very longstanding conditions of limited behavioral responsiveness, may nonetheless harbor latent capacities for recovery. Included among such capacities are particularly human functions of language and higher-level cognition that either spontaneously or through direct interventions may reemerge even at long time intervals or remain unrecognized.

When patients in “persistent vegetative state” (recently coined unresponsive wakefulness syndrome) show minimal signs of consciousness but are unable to reliably communicate the term minimally responsive or minimally conscious state (MCS) is used. MCS was recently subcategorized based on the complexity of patients' behaviors: MCS+ describes high-level behavioral responses (i.e., command following, intelligible verbalizations or non-functional communication) and MCS- describes low-level behavioral responses (i.e., visual pursuit, localization of noxious stimulation or contingent behavior such as appropriate smiling or crying to emotional stimuli). Patients who show non-behavioral evidence of consciousness or communication only measurable via ancillary testing (i.e., functional MRI, positron emission tomography, EEG or evoked potentials) can be considered to be in a functional locked-in syndrome.

Taken together, recent studies show that awareness is an emergent property of the collective behavior of frontoparietal top-down connectivity. Within this network, external (sensory) awareness depends on lateral prefrontal/parietal cortices while internal (self) awareness correlates with precuneal/mesiofrontal midline activity. Of clinical importance, this knowledge now permits to improve the care of patients with disorders of consciousness.

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C8- **Dominique MORLET**, CRNL/Dycog

Cognition markers in altered states of consciousness

For many years researchers and clinicians in Lyon have been interested in the investigation of altered states of consciousness. Auditory event-related potentials are a powerful bedside tool for the assessment of the functional state of patients, from the outcome prognosis at the acute phase of coma to the search for islands of awareness in behaviorally non-communicant patients. They marked a new step in coma care. The research work carried out in Lyon Neuroscience Research Center in close collaboration with Catherine Fischer at the Neurological Hospital of Lyon and with Steven Laureys in the Liège Coma Center will be presented.

C9- **Jian-Sheng LIN**, CRNL/Waking

The multiple faces of wakefulness, histaminergic and orexinergic control

Despite the presence of various behavioural/cognitive activities during wakefulness (W), this vigilance state has long been regarded as relatively homogeneous and defined on the cortical EEG as a low voltage and fast activity. Recent studies have shown, however, that cortical oscillation and neuronal properties undergo major changes from quiet to active W. We hypothesize that each brain arousal system exerts a distinct control of different behavioural contexts of W and have investigated using knockout (KO) mouse models the role of histamine (HA) and orexins (Ox), two W-promoting systems of the posterior hypothalamus, in controlling W during different behavioural situations such as locomotion, exploration, motivation, anticipation and sexual arousal.

We found that 1) Ox KO but not HA-deficient mice showed impaired W when they were subjected to a voluntary wheel test, indicating that Ox but not HA promotes W by enhancing locomotion. 2) HA-deficient mice were unable to remain awake in a new environment while Ox KO mice preserved their W enhancement. 3) In a test of motivation, wild type (WT) and Ox KO mice were motivated enough to catch difficult-to-reach palatable food and maintained highly awake, while HA deficient mice, though interested by the food, made no effort to catch it and slept as usual. The two last tests show that as compared to Ox, HA is more involved in the cognitive aspects of W. 4) When WT mice were fed with a predictable restricted schedule (11am-17pm) instead of *ad libitum*, they developed an anticipatory W of 70±9 min before the meal time. This anticipatory W was significantly reduced in Ox KO or HA-deficient mice. Moreover, Ox KO, but not HA-deficient mice exhibited W deficit during the feeding period. Finally, anticipatory W disappeared in double KO mice lacking both HA and Ox; 5) In sexual arousal test, defined as an increased W in a male mouse facing a female, acute inhibition of HA synthesis or antagonism of Ox1-receptor abolished sexual arousal while this function was maintained in Ox KO or HA-deficient mice, indicating a compensation under long term loss of HA or Ox. This compensation became ineffective when both HA and Ox were deficient as sexual arousal was absent in KO mice lacking both HA and Ox.

These data indicate that the regulation of W is context-dependent and support our hypothesis according to which, W is a heterogeneous state with multiple faces. Each arousal system contributes complementarily and synergistically to the maintenance of cortical activation during W, while in different behavioural and cognitive contexts, their individual participation and specific functional role are distinct.

C10- **Pierre-Hervé LUPPI**, CRNL/Sleep

Mechanisms responsible for Paradoxical (REM) sleep genesis: where are we 50 years after its discovery by Michel Jouvet?

Paradoxical or REM sleep characterized by cortical activation combined with muscle atonia and rapid eye movements has been discovered at the end of the fifties by Michel Jouvet and William C. Dement. The studies of the next twenty years suggested that the onset and maintenance of paradoxical sleep is due to a reciprocal inhibitory interaction between brainstem monoaminergic neurons inhibiting PS (PS-off neurons) and cholinergic neurons generating PS (PS-on neurons) localized in a small nucleus of the pontine reticular formation named sublaterodorsal tegmental nucleus. In my talk, I will review our most recent studies indicating that the key PS-off and PS-on neurons are in fact GABAergic and glutamatergic. Further, I will show that two populations of brainstem PS-on GABAergic neurons and a population of hypothalamic PS-on neurons co-expressing GABA and a peptide, melanin concentrating hormone play crucial roles in PS control. These new results might open new avenues for treatments of pathologies such as narcolepsy, REM sleep behaviour disorder and sleep apnea.

PERCEPTION, MEMORY, ATTENTION, COGNITION

C11- **Pascal FRIES**, Ernst Strüngmann Institute (ESI) for Neuroscience in Cooperation with Max Planck Society, Frankfurt, Germany

Attention networks revealed through high-resolution electrocorticography

Brain-wide networks operating at a millisecond timescale are thought to underlie our cognitive functions, but have never been observed directly. Neuroimaging studies based on hemodynamic signals visualized the precise topographies of brain-wide functional networks, but at low temporal resolution. Neurons and areas within these networks likely cooperate through rhythmic synchronization in multiple frequency bands. However, limitations of current recording methods have restricted our ability to detect and investigate these putative brain-wide synchronization networks. Only if extended corticocortical synchronization networks are observed directly and in behaving subjects, will we simultaneously reveal their topographies, frequencies, directions of information flow and cognitive functions, and thereby the relations among those properties. I will present data from large-scale, high-density electrocorticography grids, combining millisecond temporal and millimeter spatial resolution with coverage of large parts of one hemisphere. I will show that a given brain area may simultaneously participate in different networks that synchronize in distinct frequencies and mediate influences in counter-streams. A gamma-band (50-90 Hz) network synchronizes visual-occipital areas and parts of parietal cortex, and gamma-mediated inter-areal influences are bottom-up. A beta-band (peaking at 14-18 Hz) network synchronizes parietal and frontal areas and parts of visual cortex, and beta-mediated inter-areal influences are mostly top-down. Both networks subserve the cognitive function of attention: gamma- and beta-mediated inter-areal influences are enhanced when they mediate behaviorally relevant signals. The direct topographical demonstration of rhythmic synchronization-defined networks constitutes a new quality of brain network investigation and opens an important window onto their function.

C12- **Kia NOBRE**, Oxford Centre for Human Brain Activity and Brain & Cognition Laboratory, University of Oxford, United Kingdom

How temporal expectations change perception

It is increasingly recognised that we can orient attention flexibly in the temporal domain to anticipate relevant events occurring at predicted moments. This ability is highly adaptive in our dealings with the environment since temporal regularities are common and relevant events often occur in rhythmic streams. The mechanisms by which temporal expectations can change neural processing, however, remain largely uncharted. There is still considerable debate about whether and how temporal information is explicitly coded in the brain and, consequently, about what network(s) may provide sources of predictive temporal signals to modulate perceptual mechanisms. Equally, or even more, mysterious is how temporal information can come to bias perceptual mechanisms in the apparent absence of any receptive-field properties for coding timing. In order to characterise the psychological and neural mechanisms by which temporal expectations come to optimize behaviour, we have developed a series of novel paradigms that manipulate temporal expectations about visual target items using predictive cues or rhythms. We have shown consistent benefits of temporal expectation to response speed, and have documented enhancement of contrast sensitivity in psychophysically demanding tasks. Studies using hemodynamic and electrophysiological methods to image human brain activity have started to reveal the neural mechanisms involved in biasing information processing by temporal expectations. Our results show strong interactions between predictive signals about the anticipated timing and spatial location of relevant target events, and suggest that modulation of oscillatory activity may play an important role in carrying temporal regularities or associations to organise neural excitability around critical moments.

C13- **Anne DIDIER**, CRNL/Neuropop

Neurogenesis and memory

The olfactory bulb is the first cortical relay for processing and memorization of olfactory information coming from sensory neurons located in the nasal cavity. It harbors a permanent neurogenesis providing newborn neurons all life long to the olfactory bulb neuronal network. We were interested in the role of these adult-born neurons in learning-induced olfactory bulb plasticity. Indeed, olfactory associative learning increases the number of newborn neurons in the olfactory bulb. In a series of recent experiments, using neurogenesis measurements or neurogenesis blockade combined to the behavioral assessment of learning and memory, we showed that adult-born neurons in the olfactory bulb are required for long-term associative olfactory memory.

C14- **Jean-Philippe LACHAUX**, CRNL/Dycog

High-frequency neural activity and human cognition: insights from intracranial EEG research

Human intracranial EEG (iEEG) recordings are primarily performed in epileptic patients for presurgical mapping purpose. When patients perform cognitive tasks, iEEG signals reveal high-frequency neural activities (HFA, between 40 Hz and 150 Hz) with exquisite anatomical, functional and temporal specificity. Such HFA were originally interpreted in the context of perceptual or motor binding, in line with animal studies on gamma-band ('40Hz') neural synchronization. Today, our understanding of HFA has evolved into a more general index of cortical processing: task-induced HFA would reveal, with excellent spatial and time resolution, the participation of local neural ensembles to the task-at-hand and the neural communication mechanisms allowing them to do so. This review promotes the claim that studying HFA with iEEG provides insights into the neural bases of cognition that cannot be derived as easily from other approaches, such as fMRI. We provide a series of examples supporting that claim, drawn from studies on memory, language and default-mode networks, and succesful attempts of real-time functional mapping.

C15- **Jane PLAILLY**, CRNL/Cmo

Neuroimagery of olfactory perception and memory in humans

Modern methods of neuroimaging are opening new windows to brain functions, among which the generation of mental images. Mental imagery consists of the reactivation of percept-like memory representations. This approach is unusual in human olfaction since the ability to create olfactory mental images is rare. Perfumers are a small population who have learned to form olfactory sensory representations through daily practice and extensive training.

To identify the neural correlates of odor representations and to evaluate the impact of long-term odor training on the brain regions involved in odor processing, we measured brain activity in perfumers while they smelled or imagined odors, using functional magnetic resonance imaging. Additionally, we used voxel-based morphometry to compare the gray-matter volume in perfumers as well as in untrained control subjects to investigate expertise-related structural reorganization.

The functional data confirmed that similar neural substrates were activated in odor perception and imagination. More importantly the level of activity of specific olfactory and memory brain regions in perfumers was negatively correlated with experience during the creation of mental images of odors. In addition, the structural data showed that the gray-matter volume in several olfactory brain regions was positively correlated with experience in perfumers.

Thus, extensive olfactory training leads to the acquisition of acute olfactory knowledge, which is paralleled by both a functional and a structural reorganizations of olfactory brain areas.

C16- **Barbara TILLMANN**, CRNL/Cap

Language, music, complex sounds: What to expect? And when?

Perceivers' brains track complex sound structures, keep signals in memory, learn regularities between sounds, build up knowledge and use this information to expect and anticipate future events. These expectations shape the perception of upcoming signals (whether auditory or visual): processing of an expected event is faster and more accurate, less stimulation is necessary and less neural resources are engaged. Listeners'

expectations can be based on perceptual, sensory information only (i.e., previous sounds stored in an auditory memory buffer) and/or on cognitive influences, such as attention or listeners' knowledge about systems underlying the auditory signals (e.g., linguistic and musical systems of one's culture). Our research is investigating these perceptual and cognitive expectations with their behavioral and neural correlates. The used auditory materials cover complex sounds (specially constructed for the experimental purposes) as well as verbal and musical sound structures. The presentation will cover an overview of some of our fundamental research projects, with a particular reference to a theoretical framework of attention, which conceptualizes temporal attention as oscillatory processes in a dynamical system. Originally proposed for music perception, this theory of dynamic attending has now been used for language processing, auditory scene analysis and implicit learning.

NEURAL PLASTICITY AND NEW THERAPEUTIC APPROACHES

C17- **Walter PAULUS**, Göttingen, Germany
How to induce neuroplastic alterations non-invasively?
Transcranial electric stimulation techniques have been developed as cheap and efficient tools for modifying cortical plasticity. Repetitive transcranial magnetic stimulation (rTMS) allows increasing or decreasing the excitability of corticospinal or cortico-cortical pathways depending on the intensity and frequency of ultrashort stimulation pulses. Here magnetic stimulation is the vehicle which allows transferring transcranially short-pulsed electric energy without inducing skin pain. Direct transcranial electric stimulation of the human brain can be used painlessly if less steep voltage gradients are involved. Weak transcranial direct current stimulation (tDCS) with a homogenous DC field fulfills this requirement ideally (Nitsche and Paulus, 2000). TDCS induces plastic aftereffects via membrane polarization: cathodal stimulation hyperpolarizes, while anodal stimulation depolarizes the resting membrane potential, whereby the induced after-effects depend on polarity, duration and intensity of the stimulation. Transcranial alternating current (tACS) (Antal et al, 2008) and random noise stimulation (tRNS) intend to interfere with ongoing cortical oscillations (Terney et al., 2008). Using these techniques, we can induce and modify differently neuroplastic changes with different advantages and disadvantages of tDCS, tACS and tRNS. Plastic aftereffects need a minimal stimulation duration time and may reverse with too long stimulation. Whereas in the normal stimulation duration range of about 10 minutes tDCS allows for excitability increase and decrease, tACS and tRNS induce only excitability increases in particular with higher frequencies between 100 and 600 Hz. The latter induce less skin sensation than tDCS and accordingly can be blinded better. They are also less current direction sensitive. These effects are strongly modified by neuropharmacological co-application: L-DOPA leads to a focusing effect in analogy to its otherwise found U-shaped dose dependency. Dopamine agonists may reverse anodal excitatory tDCS into inhibition, SSRI provide the opposite effect. In conclusion continuous transcranial electrical stimulation techniques allow for targeted modulation of cortical plasticity.

C18- **Niels BIRBAUMER**, Institute of Medical Psychology and Behavioral Neurobiology, University of Tuebingen and Ospedale San Camillo, IRCCS, Istituto di Ricovero e Cura a Carattere Scientifico, Venezia-Lido, Italy
Brain Computer Interfaces (BCI) in paralysis and psychological disorders
We provide an overview of recent advances in clinical applications of the BCI technology and its potential for technological multiplication. BCIs using Electroencephalographic recordings were shown to allow verbal brain communication in amyotrophic lateral sclerosis (ALS), also in the locked-in state. Completely locked-in patients could not communicate even after neurosurgical implantation of electrodes in the brain. Reasons for this situation and solutions are presented. BCI for brain communication is now ready for multiplication. In motor restoration in chronic stroke and spinal cord paralysis only one controlled study of the author's group is available (Buch et al 2008 in Stroke) demonstrating complete control of hand opening and closing in chronic stroke with a magnetoencephalographic BCI but no generalization outside the laboratory. Preliminary results of a new controlled study on chronic stroke using EEG and implanted electrodes will be presented.
Behavioral psychiatric disorders usually are caused by subcortical brain dysfunctions. A new BCI for subcortical brain areas using functional magnetic resonance imaging (fMRI-BCI) and near infrared spectroscopy (NIRS) was developed and tested in attention deficit disorders, criminal psychopaths and schizophrenia, in addition to memory disorders and addiction. Results are highly encouraging and would allow technological application at a large scale using NIRS.

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C19- **Yves ROSSETTI**, CRNL/Impact
From sensori-motor adaptation to brain stimulation induced plasticity for rehabilitation
Our group has been investigating various forms of sensori-motor plasticity for several decades. Sensori-motor adaptation is a simple correlates of human brain plasticity, In addition, altering sensori-motor coordination through eye movement adaptation (e.g. saccadic adaptation) or hand movement adaptation (e.g. prism adaptation) may affect untrained functions. Given the fundamental place of eye and hand movements in the interplay between the body and the environment and their central role in the elaboration of bodily and external space representations, consequences of adaptation may be expected at the cognitive level. We have been exploring for 15 years the effects of prism adaptation on spatial cognition in brain-damaged patients and described numerous aspects of this peculiar expansion of sensori-motor after-effects to cognition. Knowing that adaptation to laterally-shifting wedge prisms produces compensatory after-effects in the direction opposite to the optical shift, we used right-shifting glasses to bias sensori-motor responses to the left. When this protocol is used in patients with left spatial neglect, who tend to ignore left-sided stimuli and fail to produce movement to or mentally represent the left-side, therapeutic effects are obtained. These effects are crucially not restricted to the exposed sensori-motor modalities but expand to audition or mental number representation, and are accompanied with benefits in the patients' daily life. Current investigations attempt to define the ideal regime for patients through clinical trials. In addition, recent results showed effectiveness of this approach on other syndromes (CRPS) and its synergy with brain stimulation.

C20- **Luis GARCIA-LARREA**, CRNL/Neuropain
Pain relief with transcranial magnetic stimulation: what are we doing in the brain?
Brief description: Although the exact mechanisms of pain relief through motor cortex stimulation remain elusive, much has been learned in the last 10 years. In this talk we shall explore what is currently known about the neurophysiological and metabolic actions of this type of cortical stimulation, and will compare the local and distant effects of direct (epidural) versus transcranial (magnetic) modes of application. It will be shown that a number of commonalities exist between both modes, especially in their distant effects, whereas local changes in sensorimotor cortex are most probably dissimilar. An intriguing common aspect of both epidural (and transcranial (rTMS) modes of stimulation is the participation of opioid mechanisms in their long-lasting effects.

C21- **Laurent BEZIN**, CRNL/Tiger
Brain plasticity sustained by environmental enrichment: hopes for patients with epilepsy
Epilepsy is a complex and multifactorial pathology, affecting about 50 million people worldwide, and about half of patients newly diagnosed with epilepsy are children. Epilepsy does not affect only the health but every aspect of daily life, causing

psychological or social distress, for both patients and their children with epilepsy do not dissipate with age and might contribute to the poor vocational and social outcome of these patients, as well as high rate of psychopathology and a poor quality of life at adulthood. Therefore, in addition to the need for an early identification of children at risk for psychiatric diagnoses, treatment of their psychopathology has clinical and humane importance and should be provided shortly after diagnosis is established. Cognitive-behavioral therapy has proven efficacy in reducing anxiety, social and specific phobias in children with epilepsy. Our objective is to test whether a holistic approach, providing to the children a better control over their activity, can by itself improve their quality of life and that of their parents, and their cognitive skills. This has been motivated by data obtained in animals demonstrating that the severe anxiety and cognitive disorders that develop with epilepsy are dramatically reduced when animals are raised in an enriched environment, combining novelty and complex inanimate and social stimulations. In this presentation will be presented the design of the first study aimed at testing the efficacy of an add-on holistic approach in reducing the severity of anxiety, poor self-esteem and cognitive skills in children with epilepsy aged from 8 to 12.