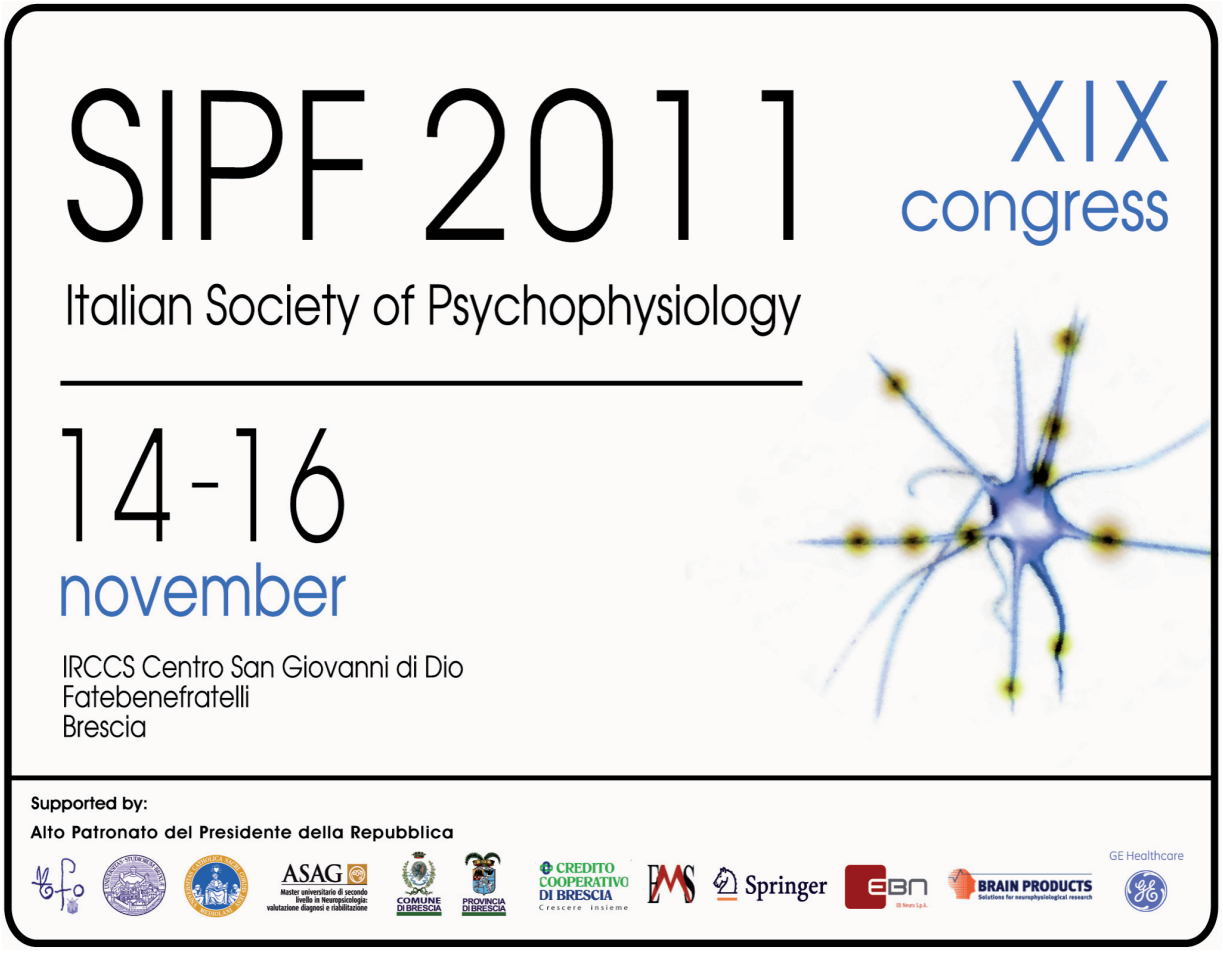
VOLUME 149 • NUMBER 3 (S) • SEPTEMBER 2011

Archives Italiennes de Biologie

A Journal of Neuroscience

Chief editors
P. Pietrini and B. Ghelarducci



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1. Spatial response codes in the representation of time

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One of the most ubiquitous attributes of our external and internal world is the temporal duration of the events that populate it. Yet time is an elusive phenomenon that is difficult to grasp with our senses. There is evidence on how the cognitive system represents such an abstract concept as time. In particular, there is a family of spatio-temporal congruency effects which demonstrate that spatial representations often lie beneath temporal ones, while the converse is not necessarily true. For instance, individuals who have been exposed to left-to-right orthographic systems are better at judging short durations or words referring to the past with their left hand, and long durations or future-related words with their right hand, than vice versa. A first control experiment excludes the possibility that this phenomenon could be due to a bigger temporal preparation effect (shorter FPs for longer durations) for the right hand than for left one. Other alternative interpretations concerning manual or hemispheric asymmetries are excluded on the basis of empirical evidence that shows how this spatial-temporal congruency effect occurs for accuracy when the responding hands are crossed and again for speed when two fingers of the same hand are used for responding. This series of experiments suggests that time, similarly to other ordered sequences, is represented under certain circumstances by means of a spatial reference frame that influences motor performance: a mental line running from left to right. A final study tested, by means of Event-related Potentials (ERPs), how this hypothesized mental time line could dynamically pre-activate a corresponding spatial response code from left to right. In congruent conditions (short-left/long-right), a negative-going ERP component developed over the right motor scalp region around the short duration, suggesting an early pre-activation of left-hand responses. This negativity gradually moved to the left motor region towards the long duration, compatibly with a pre-activation of right hand responses. Pre-activations in the opposite direction, however, were not present for the incongruent conditions. These results confirm that, in such tasks, elapsing time is represented from left to right, and this representation generates corresponding response codes which bias behavior. More generally, the studies reviewed here represent multifaceted contributions to the hot debate on how mental and neural representations of abstract concepts that cannot be directly experienced through our senses may partially rely on our richer perceptual and motor representations.

2. Activity-dependent modification of intrinsic electrical properties in human motoneurones

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There is increasing evidence that neural intrinsic excitability can be modulated by activity. Activity-dependent modification of intrinsic electrical properties are common in the developing brain and during behavioural learning tasks in adult animals. However, this important issue has been never addressed in humans. The changes in excitability of distal motor axons and motoneurones (Mns) produced by natural activity were measured in eleven healthy subjects using maximum voluntary contractions (MCV) of the abductor digiti minimi (ADM) lasting 5, 15, 30 and 60 s. Axonal excitability was studied by recording the changes in the size of a compound muscle action potential (CMAP) that was ~50% of the maximum. On cessation of the contractions, there was a prominent decrease in the size of the test CMAP due to motor axonal hypoexcitability: the same intensity required to produce the test CMAP generated a response ~10-50% lower than the control value, which recovered in ~2-20 min, depending on the contraction's duration. The antidromically evoked recurrent responses (F-waves) of the ADM Mns showed quantitatively similar activity-dependent depression both in terms of magnitude and recovery time, as the CMAP. Motor-evoked potential (MEP) to transcranial magnetic stimulation also showed a clear-cut activity-dependent component, with a peak depression (~10-40%) and a recovery time (~4-20 min), both depending on the contraction's duration. Statistically, there were a significant correlation (Pearson's coefficient) and a structure dependence (coefficient of correntrophy) between the activity-dependent CMAP depression and depression of Mn responses (F-waves and MEP). Our results show that human Mns decrease their intrinsic excitability according to the ongoing level and duration of electrical activity. This activity-dependent Mn hypoexcitability correlated with the decrease in excitability of distal motor axonal membrane. It is, therefore, plausible that similar changes also occurred in axonal initial segment, that is the site of action potential initiation, thus causing alterations in current thresholds for action potential spiking. The activity-dependent reduction of Mn excitability following natural movements could be a negative feed-back mechanism to tune the Mn output firing according to ongoing levels and pattern of electrical activity. For example, it could provide a toolbox that a MN can draw upon to stabilize and reduce its firing during fatiguing contractions. This possibility should be viewed with interest as, although progress has been made in the study of muscle fatigue, we are still unable to specify the mechanism responsible for Mn impairment during fatiguing contractions.

3. Newborns' preference for goal-directed actions

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The central role of sensory-motor representations in cognitive functions is almost universally accepted. However, the process determining the link between motor execution and its sensory counterpart and when, during ontogenesis, this link originates are still under investigation. The aim of the present study was to investigate whether at birth this link is already present and 2-day-old newborns are able to discriminate between visual cues indicating goal-directed or non goal-directed actions. In a preferential looking technique study a hand grasping a ball was the observed movement and the three factors necessary to successfully reach the goal were orthogonally manipulated: a) the presence of the ball (Present vs Absent), b) the direction of the arm movement (Away from the body vs Toward the body), and c) the hand shaping (Grasping vs Reaching).
Results showed first that different hand shapes are discriminated only when the movement was directed away from the body. This is a necessary prerequisite for reaching something in the external world. Second, the away from the body movement was looked longer only when the object was present. That is the direction of the movement assumes a specific meaning only when it may develop into a purposeful movement, the potentiality of which is determined by the presence of the to-be-grasped object. Very interestingly, the presence or absence of the object did not influence the capacity to discriminate between different hand shapes. The preference found for Grasping with respect to Reaching cannot, therefore, be attributed to the movement suitability in grasping the ball: this preference is present independently from the presence of the ball. Numerous are the developmental findings indicating that others' action recognition depends on action experience (Sommerville and Woodward, Cognition, 95, 1-30, 2005) and the lack of significance of the interaction between different hand shapes and presence/absence of the object may be considered as a further result in this direction. No doubt 2-day-old newborns have absolutely no knowledge of the most suitable type of hand shaping for successfully grasping a ball, and, therefore, they are not able to visually recognize it.
Present findings can't be explained simply by perceptual and/or kinematics differences between the two stimuli but they necessarily refer to the presence of goal-directedness in the observed action. Furthermore, among goal-directed actions, newborns seem to prefer those rich in sensory feedback (such as the wrapping up of a ball with the entire hand), reflecting in perception the research of sensory satisfaction driving the initial phases of motor behavior development (von Hofsten, Scand J Psychol, 50, 617-623, 2009). Overall, present results support the existence of a primitive form of sensory-motor associations since the first days of life, and strongly suggest that goal-relatedness has a primary role in the building process of them.

4. Cross-modal recognition of object properties between vision and touch in human newborns

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This research aims to study the ability to coordinate object information between vision and touch in newborn infants. Firstly, we investigate cross-modal recognition of shape. Using intersensory procedure, we show that newborns can visually recognize the shape of an object that they have previously held in their right hand, but they fail when they previously manipulated it with their left hand. Secondly, we compare newborns' cross-modal recognition of shape and texture between the visual and the tactual modalities. Our results reveal that cross-modal transfer of shape is not bi-directional at birth. Newborns visually recognize a shape previously held but they faile to tactually recognize a shape previously seen. In contrast, a bi-directional cross-modal transfer of texture isobserved. Taken together, the results suggest that cross-modal transfer is present from birth but it depends on object property and also on modality specificities.

5. Frequency-dependent tuning of human motor system induced by transcranial oscillatory potentials

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Background. Oscillatory currents delivered through the scalp by Transcranial Alternate Current Stimulation (tACS) at different frequencies seem able to entrain specific electroencephalographic (EEG) brain activities, thereby reinforcing physiological phenomena specifically related to the frequency bands of the stimulated brain region.
In human sensorimotor regions, the main detectable oscillatory activity is an "idling" beta activity peaking at about 20 Hz (beta range), which typically occurs in the absence of processing sensory information or motor output. Solid evidences indicate that beta oscillations of sensorimotor

areas usually undergo to desynchronization during preparation, execution, imagination or observation of movements. However, the causal relationships between the beta idling oscillatory activity of the motor areas and the related human corticospinal output still needs to be elucidated.
Objective. Here we used a novel approach which combines on-line simultaneous single-pulse Transcranial Magnetic Stimulation (TMS) with tACS at different frequencies (5 to 40 Hz), in order to investigate if the corticospinal output measured by Motor Evoked Potentials (MEPs) of the left primary motor cortex (M1) may be modulated by frequency-dependent tACS.
Methods: Twelve right-handed subjects underwent to seven random and counterbalanced conditions: two basal sessions (no-tACS), tACS of the left M1 at 5 Hz (theta), 10 Hz (alpha), 20 Hz (beta), 40 Hz (gamma), as well as 20 Hz of the right parietal cortex (control site). Each session of stimulation lasted 1.5-2 minutes. TMS was applied over the sponge electrode used for tACS overlying the left M1. MEPs were recorded from the right First Dorsal Interosseus, during online neuronavigation. In order to control any effect due to biophysical interactions of the tACS and TMS electric fields, the experiment was then repeated by applying the same protocol (5 and 20 Hz) on the ulnar nerve.
Results. ANOVA showed that the corticospinal output resulted in a better reactivity when tACS was applied on the left M1 at 20 Hz. This was reflected by a significant enhancement of the MEPs size obtained during tACS at 20 Hz with respect to all the other conditions. Peripheral tACS was uneffective.
Results originally provided causal evidence that 20 Hz rhythm of the motor cortex plays a specific role in corticospinal facilitation by showing a robust enhancement of the MEPs size with respect to all the other conditions.
Conclusions. Current findings represent the first attempt to directly quantify the corticospinal output in living humans during tACS applied at a physiological range on the motor system. The strict frequency-dependence and regional specificity of tACS effects make this approach potentially worth to be applied in the investigation of motor output dysfunctions, as Parkinson's disease or other movement disorders.

6. Neurophysiology of auditory-motor synchronization

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Introduction. Synchronization of body movements to an external beat is a universal human ability, which has also been recently documented in non-human species. The neural substrates of this rhythmic motor entrainment are still under investigation. Correlational neuroimaging data suggest an involvement of the dorsal premotor cortex (dPMC) and the supplementary motor area (SMA).
Objectives. To investigate the role of these cortical areas in auditory-motor interaction processes more specifically using a causal approach by repetitive transcranial magnetic stimulation (rTMS).
Methods. In twelve right-handed healthy volunteers, 1 Hz rTMS was delivered to different cortical areas using an established rTMS protocol which produces a focal suppression of cortical excitability outlasting the stimulation period. Subjects were asked to synchronize right index tapping with different rhythmic auditory cues and to continue reproducing the rhythm after cessation of the external cues. All tasks were performed at the baseline and immediately after the 15 min long train of rTMS.
Results. Accuracy of voluntary synchronization between rhythmic cues and right index finger tapping, as measured by the mean time lag (asynchrony) between the onset of motor and auditory events, was significantly affected when the right dPMC was transiently disrupted by 'off-line' focal rTMS. This effect was seen with metrical rhythms of different complexity, but not with non-metrical or isochronous sequences. Conversely, no change in rhythmic motor entrainment was observed with rTMS of the SMA, of the left dPMC or over the midline occipital control site.
Conclusions. The current data strongly support the view that the right dPMC is crucial for rhythmic auditory-motor entrainment in humans. This contributes to clarify the neurophysiological substrate of musical abilities and represents a potential tool to plan rehabilitative strategies based on auditory cues such as those used in Parkinson's disease.

7. Understanding others: evidence from clinical and normal population studies

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Empathy, the ability to understand and share the feelings of another person, a major component of what has been termed "social intelligence," is one of the crucial elements of successful human interactions. According to the recent model proposed by the social neurosciences (de Vignemont and Singer, 2006), different components of empathy can be pointed out, with bottom-up and top-down information processes constantly engaged: 1) the affective component, activated either in a spontaneous or voluntary way by perceptual input, is related to the sharing of the feeling with the other; and 2) the self-other distinction, which is related to the ability to keep track of the source of the affective state and disentangle our own feelings from the feelings of the others, and being distressed and overwhelmed by the emotional state of the other. At the same time, several factors modulate our ability to be empathic with others: i.e. the

ability to take the perspective of the other and understand his internal world and mental states (also referred to as Theory of Mind - ToM) is a cognitive skill that predisposes us to experience empathy. Finally, the ability to empathize with others probably could not take place without the capacity to be aware of our emotions and feelings, strictly related to the ability to read the signals coming from our body and make a correct representation of our internal bodily states (interoceptive awareness). In the past few years, several functional neuroimaging studies have provided initial insight into *how* empathy is implemented in the human brain (for an overview, see Singer and Lamm, 2009). The most consistent finding of these studies is that empathy recruits a core network consisting of anterior insular cortex (AI) and anterior medial cingulate cortex (aMCC; Lamm et al., 2011, for recent meta-analysis). These brain structures jointly seem to be engaged in the representation of emotional states, and in behavioral and autonomic nervous system regulation required by these states. Notably, both AI and aMCC play important roles in coding the affective and motivational components of directly experienced pain. Hence, it has been suggested that some sort of "embodied simulation" lies at the root of empathizing with the affective experiences of others. A lack of such "embodied simulation" could cause a reduction of empathic behavior. In two studies involving subjects with alexithymic traits (alexithymia is a sub-clinical phenomenon marked by difficulties in identifying and describing feelings (Nemiah, Freyberg, and Sifneos, 1976)), we recently tested the mechanisms underlying the ability to understand one's own emotions, and its relationship to the ability to empathize (Silani et al., 2008, Bird et al.. 2010). Notably, we showed that deficits in the understanding of one's own feelings are associated with hypoactivation of AI both when inferring one's own emotional state and when empathizing with another's emotional state.

8. Study of the connectivity of the fronto-parietal circuits in humans by means of TMS/EEG co-registration

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Objectives. Knowledge of connectivity of parietal and frontal regions in humans is fundamental in order to understand networks and possible mutual connections of these structures. Transcranial Magnetic Stimulation (TMS), when used in co-registration with Electroencephalography (EEG), is a promising tool to study cortical connectivity. Here, a TMS/EEG approach will be presented, focused on the connections of the parieto-frontal networks.

Material and Methods. Single-pulse TMS was applied during EEG recording. 10 healthy subjects were stimulated over the left intraparietal sulcus. 13 healthy subjects were stimulated medially over the left parieto-occipital area. 12 healthy subjects were stimulated over the left premotor cortex. Blocks of TMS were intermingled with sham stimulations. Subjects were asked to remain relaxed with closed eyes during stimulation. TMS was delivered at 110% of resting motor threshold (RMT) in the first experiment, at 120% RMT in the second and ranging from 110% to 120% RMT in the third experiment. Different intensities were used to manage problems related to the TMS artifact and presence of motor evoked potentials. TMS evoked potentials were then computed and sLORETA/eLORETA were used for current density analysis by comparing TMS to sham data. Statistical significance was set at $p < 0.05$ (corrected for multiple comparisons).

Results. TMS of intraparietal sulcus resulted mainly in activation of right frontal areas (Brodmann Areas -BA- 9, 46), 102-167 ms after the stimulus. Ventral stream areas (BA 20, 36, 37) resulted activated between 171-177 ms. Stimulation of left parieto-occipital region resulted mainly in the activation of left temporo-parieto-occipital regions (BA 17, 18, 19, 23, 30, 31, 37, 39), 23-33 ms after TMS. Left sensorimotor and frontal regions (BA 1, 4, 6, 9) were activated between 186-191 ms, while a right frontal region (BA 11) was activated around 223 ms. Finally, left premotor stimulation showed activations that ranged mainly from a left frontal region (BA 45) around 57 ms after TMS, to activation of right frontal and sensorimotor regions (BA 2, 3, 4, 6, 8, 9, 10, 45, 46), and an insular region (BA 13), at 132-139 ms after TMS. A right frontal region (BA 11) was activated around 215 ms.

Discussion. Results show distributed connection patterns in the brain, ranging from dorsal-ventral stream connections, to ipsilateral parieto-frontal connections in discrete time ranges. Also contralateral parieto-frontal connections were observed as well as left premotor connections that flowed toward the right hemisphere. This pattern of connectivity could be the result of both direct and/or indirect links among the above indicated areas.

Conclusion. Present data suggest a high complexity in brain connections, which might be both direct or mediated by the same or different regions. The described connectivity could represent the neural substrate for various types of tasks, ranging from visuo-motor to attentional ones.

9. Prognostic value of standard EEG in traumatic and non-traumatic disorders of consciousness

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It is difficult to predict the extent of recovery in patients with acute brain injuries who survive coma and develop

various degrees of disorders of consciousness. While the prognostic role of standard EEG in comatose patients has been evaluated extensively, few studies have investigated its value for predicting the outcome of severe disorders of consciousness. For standard EEG to be a prognostic tool, it must accurately quantify abnormalities. Recently, we recorded standard EEG in patients suffering from disorders of consciousness (vegetative state, minimally conscious state, emergence from minimally conscious state) due to different aetiologies[1,2]. We quantified abnormalities using the 5-grade Synek scale (1988)[3]: 1) dominant reactive alpha activity with some theta activity; 2) dominant theta activity; 3) dominant widespread non-reactive delta activity; 4) various patterns: burst suppression, epileptiform discharges, low-output non-reactive activity or alpha/theta coma patterns; and 5) isoelectric activity. EEG abnormalities were correlated with the level of cognitive functioning (LCF) scale score and with LCF variation after three months. We found a good correlation between EEG abnormalities and the degree of cognitive improvement, expressed as variation of the LCF score, and this correlation was present regardless of aetiology of the disorder of consciousness (traumatic brain injury, cerebrovascular diseases, anoxic injury). Although these results are valid for group analysis, they may also have applications to individual patients. Indeed, three months after brain injury, none of the patients with EEG Synek scores of 1 were still in the vegetative state (good prognosis), while almost all patients with scores of 4 had no significant improvement in their level of consciousness (poor prognosis). Patients with scores of 2 or 3 had greater variability in the cognitive outcome. In conclusion, standard EEG is a simple and readily-available tool with significant prognostic value in patients with disorders of consciousness due to different aetiologies. Its sensitivity in individual patients is not completely satisfactory, but might be improved in the future, for example by developing EEG evaluation scales specifically designed for patients with disorders of consciousness.

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10. Neural Basis of Sport Benefits on Cognitive Functions

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Positive effects of physical activity on health and wellness are well known, less is known about the sport effects on cognitive functions. However, growing evidence suggests that exercise has a positive impact on cognitive processing. Many cognitive functions decline in persons confined to a wheelchair (following spinal cord injury, amputation or neural infections, such as poliomyelitis), and with age. Previous studies on these population showed that the processing speeds of these functions can be particularly affected.

We investigated the effect of sports activity on physically-disabled and middle-age individuals using behavioral and electrophysiological techniques in visual Go/No-go response task.

In one study participants included disabled athletes from open-skill (wheelchair basketball) and from closed-skill (swimming) sports, and age-matched healthy non-athletes. Reaction times of disabled athletes were slower than those of healthy non-athletes. Intra-individual variation of reaction times, switch cost and number of false alarms were higher in the swimmers but comparable to healthy non-athletes in the basketball group. Event-related potentials (ERPs) early components P1, N1 and P2 had longer latencies in the disabled. The late P3 component had longer latency and smaller amplitude in the disabled. Differently, the N2 component, which reflected inhibition/execution processing, was delayed and reduced in the swimmer group but was comparable to healthy subjects in the basketball group. Results show that a) ERPs components related to perceptual processing and late components related to executive processing are impaired in disabled subjects; b) open-skill sports such as basketball may partially compensate for executive control impairment by fostering the stability of motor responses and favoring response flexibility.

In a second study, Young and middle-age fencers and non-athletes were studied. RTs were slower for the older subjects, but other measures were not impaired. In particular, the early ERP component P1 and late cognitive component P3 were delayed in older subjects. Participation in sports prevented this age-related decline in performance. The RTs of middle-aged and young fencers were comparable: the P1 latency of middle-age fencers was similar to the younger subjects; the N1 was enhanced in older, as well as younger, fencers; the N2 component of fencers had shorter latencies and larger amplitudes than non-athletes; and in no-go trials, the P3 component was enhanced in fencers independent of age. In conclusions open-skill sports may counteract the decline in executive function that occurs following physical disabilities during middle age.

11. Music as a model of sensori-motor integration and neural plasticity

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Psychophysiology has often used special populations to study specific brain functions plasticity. In this context, musicians are a particularly interesting population since they train a complex skill for years, several hours a day. In fact, a musician is a sensor-motor expert. For this reason many cornerstone studies have been carried on musicians about auditory field plasticity (Pantev et al., 1998), somatosensory maps use-induced alterations (Elbert et al., 1995), motor cortex plasticity (Pascual-Leone et al., 1995), white matter training-induced changes (Schlaug et al., 1995), pathological plasticity (Candia et al., 2003). Furthermore, more recent trends used musicians as a good model of sensori-motor resonance in a mirror-like fashion. These studies showed that passive listening to trained pieces of music induced motor activities in musicians (D'Ausilio, et al., 2006). At the same time, listening to musical notes in performing musicians altered actual motor execution as if auditory-presented notes could activate competing motor programs (D'Ausilio et al., 2010). Finally, an emerging trend of research is using musician as model of sensor-motor (non verbal) communication. In fact, (orchestra and ensemble) musicians besides training their instrument are expert in coordinating their performance with other musicians. Coordination is actually the main goal shared by all participants in order to produce an esthetically pleasing experience in the listeners. This coordination indeed, requires accurate and fast mechanisms to decode others' motor intentions via auditory and visual information in order to plan the appropriate movement and adapt to unexpected changes in others' performance (D'Ausilio et al., Submitted).

12. Entrainment and cognitive processes

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Neural oscillations of ongoing brain activity are ubiquitous mechanisms associated to cognitive processes. However, the fundamental and so far unresolved problem for neuroscience remains to understand how oscillatory activity in the brain codes information for human cognition. The recently introduced brain stimulation techniques are a promising tool for studying the nature of brain oscillations and understanding whether they are correlative or causally linked to brain functions (Thut and Miniussi, 2009; Thut et al., 2011).

In the current study we used transcranial alternating current stimulation (tACS) to entrain specific frequency oscillations and to verify whether this entrainment produce behavioural modulations. We focused on the posterior alpha rhythm (8-14 Hz), which is the most prominent oscillation in the visual areas. It has been proposed to reflect functional inhibition, is related to the state of excitability of the visual cortex and is modulated by the focus of spatial attention. Usually an increase of alpha power is associated with inhibitory effects and inversely related to perception. We applied tACS over the occipito-parietal areas while subjects were performing a gabor detection and discrimination task under five contrast levels. Whether the tACS was effective in increasing the natural alpha power, an impairment in visual perception was expected.

A group of subjects received alpha stimulation (10 Hz), a group of subjects received sham stimulation and another group received a control frequency stimulation (25 Hz). In each group there were twenty-four subjects. For all subjects we collected data during three baseline blocks of behavioral task only and during three tACS blocks of behavioral task and concurrent tACS application. The analysis of the data revealed that alpha stimulation induces a general decrease of the detection rate in comparison to sham stimulation. Importantly, this worsening was not observed with the control stimulation.

These data confirm that tACS at 10 Hz in occipito-parietal areas is able to interfere with visual perception, according to the inhibitory role of alpha rhythm in brain functioning (Klimesch et al., 2007). Thus, they provide decisive evidence on the causal link between alpha oscillations and perception. In addition, these results show that tACS is a promising tool for investigating the functional role of brain frequencies in cognition. Its ability of inducing an entrainment of neural oscillations could also be exploited for inducing facilitatory effects helpful in neuro-rehabilitative approaches.

13. Molecular and structural imaging in frontotemporal dementia

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The role of structural and molecular imaging in Fronto Temporal Lobar Degeneration (FTLD) has expanded greatly over the last few years. Using Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) techniques, investigators have demonstrated that imaging can detect specific abnormalities in the brains of FTLD patients that help to differentiate FTLD from other diseases such as Alzheimer's disease.

PET molecular imaging has been included in the recent guidelines for dementia diagnosis. Various factors will

improve its applicability at a single subject level, such as the higher accuracy of PET reading through automatic analysis (i.e. SPM) and the availability of large data-bases of normal subjects for analysis and comparisons. Cerebral glucose metabolism is the mostly applied in the support for diagnosis and differential diagnosis of dementia. FTD with its behavioural (bv-) and aphasia variants has to be differentiated from psychiatric disorders and other types of dementia. The frontal metabolic impairment is characteristic of the bv-FTD, whereas distinct brain metabolic patterns characterize the other variants. PET functional imaging has helped to explain the behavioural and language deficits that develop in FTD. In vivo neurotransmission PET studies offer the possibility of a multi-tracer approach in dementia research. Specific targets such as dopaminergic, serotoninergic and cholinergic neurons, and reactive glial cells are evaluated with PET. The main neurochemical alterations in FTD are the serotonine and dopamine depletion. The measurement of dopaminergic system by PET is crucial in the study of FTLD with associated parkinsonism. Few in vivo reports have focused on the serotoninergic system in FTD, showing significant reductions of 5-HT2A receptor densities. Despite the increasing reliance of the biomedical sciences on molecular imaging, the development of new radiotracers with the specificity and kinetic characteristics which are required for the quantitative analysis in vivo remains a slow process. The new challenge for molecular neuroimaging in the study of FTLD will be the development of new tracers and methods allowing the in vivo quantification of specific endogenous neurotransmitters, specific protein changes, and neuroinflammation in disease progression and degenerative cascade events. The expected development of new drugs able to slow the degenerative process would give also relevance to the
(MRI) is also a useful tool in the evaluation of FTLD that leads to loss of gray and white matter brain tissue that is measurable with MRI techniques, such as voxel-based-morphometry (VBM) and Diffusion tensor Imaging (DTI). There is evidence of an early reduction of fibre tracts volume and integrity, as well as of characteristic patterns of focal atrophy that might help in differentiating the underlying FTLD variants.
Researchers have begun to look into the utility of using imaging to study FTD over time.

14. Study of a BCI Multimenu system based on the P300 component to allow an efficient way to communication.

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Objectives. A brain-computer interface (BCI) is a man-to-machine communication channel operating only on brain signatures that are independent from muscular output. We studied a BCI communication system based on the late event related potential (ERP) component P300, which enables the user to sequentially select alphanumeric characters from a keyboard-like matrix on the screen. We aimed at creating an adaptation of this BCI paradigm with the purpose to be faster and more reliable than the classical ones in satisfying the specific needs of each user.
Materials and Methods. A total of 7 healthy subjects took part to the experiments. EEG was recorded from 8 electrodes with a standard 32 channel cap based on the International 10-20 system (Fz, Cz, P3, Pz, P4, O1, Oz, O2; referenced to the AFz electrode and grounded to the POz). A general-purpose BCI software platform (BCI2000, http://www.bci2000.org/) controlled stimulus presentation, data collection, and online processing. A calibration phase was made with the P300 Speller Matrix (6 x 6) and was performed using 20 characters divided into 4 runs. Each row/column of items flashed for 125 ms, followed by a 125 ms inter-stimulus interval. The flashes were organized into sequences (each sequence included the flash of each row/column once = 12 flashes). We made 20 sequences for each selection, giving a total number of 240 flashes per selection. To identify the characteristics of the EEG signal associated with different categories of character (target vs nontarget) the Stepwise Linear Discriminant Analysis (SWLDA) was used. Then, an online phase started where autoinducted (30 items) and ordered selections (30 items) were made. Data were analyzed through a Wilcoxon test for paired data.
Results. Users were able to express at least 15 consecutive wishes over 60 selections, an amount that was considered sufficient to cover person's wishes for several minutes. There were not significant difference ($V = 13.5$, $P = 0.595$) between the accuracy reached with the "order method" and that of the "auto-inducted" one. By the way, users reported to find the "auto-inducted" method funnier, less boring and less tiring. The same experiment was carried out on a locked-in patient. Data obtained in the calibration phase were similar to those obtained in healthy subjects. Till now, the patient underwent the "order method" phase, where he performed quite well, making 3 errors over 17 items.
Discussion. The Multimenu system, based on a semantic scheme instead of a syntactic one, largely decreases the rate of redundancy of communication. In this way, the subject does not make any selection that is not strictly necessary and this reflects on the fact that communication is less tiring and boring, leading to increased accuracy and feedback to the subjects.
Conclusion. The Multimenu system represents an easy way to communicate a person's wishes and needs in a fast and efficient way.

15. Neural bases and cognitive processes of temporal discrimination

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The objective of the present work was to provide evidence that supports the hypothesis of a differential involvement of neural circuits and cognitive processes in discriminating durations in the sub-second and supra-second ranges (Lewis and Miall, 2006). To this end, a group of experiments were performed using behavioural methods, electrophysiological recordings (EEG), or transcranical magnetic stimulation (rTMS). The task required to explicitly discriminate the duration of pairs of visual stimuli, presented in succession. The first (standard) stimulus could have duration of either 500 or 1500 ms, the second (comparison) stimulus could have a duration shorter or longer than the standard one. Participants were asked to judge the duration of the second stimulus relative to the first one. Behavioural results revealed that the discrimination threshold in the 500 ms range was higher than in the 1500 ms range. Furthermore, a consistent response bias was present which showed an opposite trend when perceiving durations above or below 1 second. The analysis of the slope of a slow electrical potential (the contingent negative variation, CNV), which developed during the whole duration of the comparison stimulus, clearly demonstrated that the discrimination process first occurred online, i.e. during the comparison stimulus, and engaged memory processes. The scalp distribution of the CNV was centro-frontal. The analysis of ERPs locked to the offset of the comparison stimulus revealed that the duration modulated the amplitude and the latency of a positive deflection, peaking at about 150 ms. The event-related synchronization and desynchronization analyses (ERD/ERS) in the alpha and theta bands provided further evidence of these modulations in the frequency domain. Interestingly, the bias in responding could be manipulated in an rTMS experiment. Trains of three magnetical pulses were administered to the right or left angular gyrus (AG), either at the onset or at the offset of the comparison stimulus. The results showed that the left AG mostly contributed to the processing of durations below 1 second when delivered at the offset of the stimulus, whereas the right AG intervened at the onset of the stimulus to be discriminated. Taken together, the results seem to be in line with a recent model proposed by Wiener, Mattel and Coslett (2011), which suggests that time processing is mediated by multiple, overlapping neural systems, acting independently and adaptively, depending on the required task and on the involved stimulus duration.

16. Blink-related delta oscillations are located in the precuneus and correlate with levels of consciousness.

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Recently, blink-related oscillations (BROs) in the EEG delta band were observed during spontaneous blinking at rest in healthy subjects. It has been proposed that these oscillations are associated with the continuous gathering of information from the surrounding environment. This function has been classically attributed to the precuneus. Moreover, fMRI studies have shown that precuneus activity is reduced or missing when consciousness is reduced or absent. We therefore hypothesized that the cortical source of delta BROs is located in the precuneus in healthy subjects and that delta BROs are absent or reduced in patients with disorders of consciousness (DOC).

To test this hypothesis, the EEG activity at rest was recorded in 12 healthy controls and 9 patients with DOC (4 vegetative states, VS, and 5 minimal conscious states, MCS). Three seconds-lasting blink-centered EEG epochs were analyzed in both time- (BROs) and frequency-domain (Event-Related Spectral Perturbation, ERSP, and Inter-Trial Coherence, ITC). Cortical sources corresponding to the maximum power of the delta BROs were estimated with sLORETA.

In control subjects, as expected, delta BROs cortical sources were located in the precuneus, while in DOC patients delta BROs were barely recognizable and, hence, they were not localized in the precuneus but in scattered and not homogeneous sites. In addition, both ERSP and ITC was significantly reduced in both VS and MCS groups compared with controls. This reinforces the hypothesis that delta BROs reflect neural processes associated with awareness of the self and environment. In addition, the direct relationship between spectral indexes and LCFS scores suggests that delta BROs might serve as a biological paraclinical indicator of levels of consciousness.

17. Psychophysics of pain perception differences between males and females

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It is obvious that many pain conditions have a higher prevalence in females as compared with males (e.g. fibromyalgia, TMD, migraine, tension type headache, whiplash, IBS). Human experimental pain research involves two

separate topics: Standardised activation of the nociceptive system and measurements of the evoked responses. The ultimate goal of advanced human experimental pain research is to obtain a better understanding of mechanisms involved in pain transduction, transmission and perception under normal and pathophysiological conditions. Human experimental pain research bridges the gab between basic animal studies and clinical applications and provides better characterisation of pain mechanisms in healthy volunteers and characterise sensory dysfunction in patients with chronic pain. One topic to investigate is gender differences in pain mechanisms and perception. Experimental approaches for studying gender differences can be applied in:

1. Laboratory settings for basic mechanistic studies on gender differences (e.g. pain sensitivity, central hyperexcitability).
2. Laboratory settings for studying drug efficacy in males and females.
3. Clinical settings to characterise male and female patients with sensory dysfunctions and/or pain (e.g. neurogenic pain).
4. Clinical setting to monitor male and female patients responses to treatment.

The primary advantages of experimental approaches to assess gender differences in pain mechanisms under normal and pathological conditions are:

1) Stimulus intensity, duration and modality are controlled and not varying over time.
2) Differentiated responses to different stimulus modalities.
3) The physiological and psychophysical responses can be assessed quantitatively and compared over time.
4) Pain sensitivity can be compared quantitatively between various normal/affected regions.
5) Experimental models of pathological conditions (e.g. hyperalgesia) can be studied.

As pain is a multi-dimensional perception it is obvious that the reaction to a single standardised stimulus of a given modality can only represent a very limited fraction of the entire pain experience and hence less likely to show gender differences. Therefore it is necessary to combine different stimulation and assessment approaches to gain advanced differentiated information about the nociceptive system under normal and pathophysiological conditions.

The experimental possibilities available for studying cutaneous, muscle and visceral pain are far from equal. There is a need for more experimental and clinical studies on deep pain to provide new knowledge to this clinically relevant area.

There are at this stage no simple clear cut differences between males and females but different gain in different pain mechanisms (e.g. descending pain modulation, response to intramuscular glutamate, pressure pain thresholds, distension of the esophagus) can be shown.

18. Wired to be social: twin fetuses plan other-directed movements

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Newborns come into the world wired to socially interact. But, is a propensity to interact with others demonstrable before birth? Twin pregnancies provide a unique opportunity to investigate the social pre-wiring hypothesis. Unlike ordinary siblings, twins share a most important environment – the uterus. If a predisposition towards social interaction is present before birth, one may expect twin fetuses to engage in some form of social interaction. Although inter-twin contact has been demonstrated starting from the 11th week of gestation, no previous study investigated the critical question of whether twin fetuses plan and execute movements directed towards each other. Put differently, whether intra-pair contact is the result of motor planning rather than the accidental outcome of spatial proximity. Here we addressed this question by investigating the kinematics of movement in five pairs of twin fetuses. Arm movements were studied using four-dimensional ultrasonography (4D-US) during two separate recording sessions carried out at the 14th and 18th week of gestation. We demonstrated that by the 14th week of gestation twin fetuses do not only display movements directed towards the uterine wall and self-directed movements, but also movements specifically aimed at the co-twin, the proportion of which increases between the 14th and 18th gestational week. Kinematic analysis revealed that movement duration was longer and deceleration time was prolonged for other-directed movements compared to movements directed towards the uterine wall. These differences in kinematic profiles were surprisingly consistent across fetuses and held independently of the gestation period considered, suggesting that already starting from the 14th week of gestation intra-pair contact resulted from the planning and performance of social movements obeying specific kinematic patterns. Interestingly, the kinematic profile of movements directed towards the co-twin displayed an even higher degree of accuracy then self-directed movements: movement du These findings force us to predate the emergence of social behavior: when the context enables it, as in the case of twin fetuses, other-directed actions are not only possible but predominant over self-directed actions.

19. Salience detection system of environmental stimuli: a "bottom-up" component of attention

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Objective. Although behavioral evaluation of awareness in disorders of consciousness (DOC) is difficult it remains the clinical standard. The refinement of Neurophysiological techniques would improve our characterization of those patients. Most of Researchers have used active protocol of stimulation which have the disadvantage of being too demanding for patients with DOC. In patients recovering from DOC preservation of "bottom-up" processing of sensory stimuli is a prerequisite for subsequent "top-down" processing of salient stimuli. "Bottom-up" processing related to short term habituation/dishabituation, can be detected using simple passive paradigm in which after stimuli of identical modality a stimulus of different modality is presented. In order to verify the applicability in a clinical context we studied a group of healthy subjects to obtain normative data.

Methods. In 16 healthy subjects multichannel EEG was recorded while participants received trains of three stimuli (S1-S2-S3) at 1-sec ISI. The time interval between each triplet ranged between 8 and 12 sec. S1 and S2 always belonged to the same sensory modality somatosensory or auditory, whereas S3 belonged either to the same modality as S1 and S2 (triplet same) or to the other modality (triplet different). To test repetibility of cortical responses seven subjects were recorded twice at least a month a part. A one-way repeated measures ANOVA was used to explore the effect of "modality change" (two levels: "same," "different").

Results. Both for auditory and somatosensory stimuli the magnitude of N1 and P2 waves were significantly lower (auditory $F(2,14) = 102.2$, $p < 0.0001$; somatosensory $F(2,14) = 44.5$, $p < 0.0001$) when the S3 stimulus was preceded by S1 and S2 of the same modality (triplet same). The amount of attenuation was 57% (SD 13%) for auditory modality and 39% (SD 14%) for somatosensory modality. When S3 was preceded by S1 and S2 stimuli of different modality (triplet different) the amplitude of N1 and P2 was not significant different from amplitude of S1 of the same modality. The inter trials variability was very low: subjects recorded in a second session showed no significant difference in the amount of S3 changes compared with the former session.

Significance. We provided normative data on short term Habituation and Dis-habituation process in healthy subjects and we showed the consistency of these indexes, a requisite necessary for a potential clinical application based on evaluation of a single patient. Bottom-up process is a fundamental component of attention, the prevoluntary filtering of saliency of environmental stimuli. Remaining processing capacities are reduced for VS and MCS according to underlying entity of structural brain damage. This protocol can be able to pick-up remaining information processing capacities ("bottom up") in patients with DOC.

20. TMS-interference with primacy and recency mechanisms provides evidence of separate encoding mechanisms in the human brain

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Background. During immediate free recall, the probability of a word being recalled correctly is typically highly dependent on its serial position during presentation: the first words (primacy effect) and the final ones (recency effect) showing the best recall, to the detriment of the middle items, showing that the position has an effect on learning The U-shaped serial position curve is one of the most well-established recall memory findings (Murdock, 1962; Robinson and Brown, 1926).

Objective. To verify in causal manner whether primacy and recency mechanisms share or not the same cortical networks.

Method. In 13 healthy subjects, 20 lists of 20 unrelated words (1 word/1 second) were acoustically presented via headphones. Lists and words were randomly divided in 4 conditions: Baseline, during rTMS of the left dorsolateral prefrontal cortex (DLPFC), during rTMS of the left intraparietal lobe (IPL) and during rTMS at the vertex as control. The navigated rTMS train (90% of RMT, 10 Hz, 500 ms) started 100 ms before the end of the listened word, according to a previous study (Rossi et al. 2011). Immediate free recall was subsequently tested without rTMS interference.

Results. A double dissociation occurred: rTMS applied to the left DLPFC significantly worsened the accuracy for the words presented at the beginning of the list (primacy effect) versus all other conditions. rTMS applied of the left IPL significantly worsened the accuracy for the words presented at the end of the list (recency effect) versus all other conditions.

Conclusion. We showed a clear-cut double dissociation between rTMS-induced detrimental effects on memorization abilities following stimulation the left DLPFC, which

selectively impacted on the primacy effect, sparing the encoding of the last presented words, and rTMS applied on the left IPL, which impacted selectively with the recency effect, leaving unaltered the encoding of words presented early in the lists. These effects, which are extremely consistent interindividually, are regionally specific, since rTMS applied on a control brain region (i.e., the vertex) did not impact memorization. Current rTMS results fit nicely with previous neuropsychological studies in brain damaged patients, showing double dissociations between post-lesional memory performance for early and late presented items (Warrington and Shallice 1969; Baddley and Warrington 1970; Vallar and Papagno 1986). Accordingly, it can be hypothesized that a double independent, but functionally linked and possibly inter-changeable systems, are responsible both of the short-term (recency) and the long-term (primacy) encoding. The short-term encoding, which would explain the recency effect, could have a direct access from the IPL region, through an explicit elaboration of the encoded items. The direct demonstration of a "double route" for encoding in healthy humans is entirely original and represents a striking example of the causal utility of rTMS in cognitive neuroscience.

21. Psychophysiological mechanisms underlying spatial attention in children with primary headache

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Objective. Neurophysiological studies to evaluate spatial attention in children with primary headache are lacking. Tactile spatial attention modulates the N140 somatosensory evoked potential (SEP) amplitude. The aims of the study are: 1) to investigate the effect of spatial attention on the N140 amplitude in children with migraine and tension-type headache (TTH) and in healthy children, and 2) to correlate the neurophysiological results with a neuropsychological test for spatial attention.
Methods. We studied 16 patients with migraine without aura (MoA), 12 TTH children and 10 healthy subjects. "Deux Barrage" test for spatial attention was administered. SEPs were recorded in a neutral condition (NC) and in a spatial attention condition (SAC).
Results. No significant differences in neuropsychological measures were found between MoA, TTH and healthy subjects. The N140 amplitude increase during SAC, as compared to NC, was significantly higher in patients than in healthy controls. Migraineurs showed a positive correlation between the N140 amplitude increase during SAC and their neuropsychological performance.
Conclusions. Although spatial attention performances in children with headache are as good as in controls, the N140 amplitude increase during SAC in headache patients suggests that the psychophysiological mechanisms subtending spatial attention are different from those in healthy children.

22. Glutamatergic neurotransmission in migraine motor-cortex: effects of transcranial direct current stimulation (tDCS) preconditioning on high-frequency repetitive transcranial stimulation (rTMS)

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Background. Brief trains of 5-Hz repetitive transcranial magnetic stimulation (rTMS) delivered at stimulation intensity equal or up to 120% of the resting motor threshold (RMT) determine in healthy subjects a progressive facilitation of the motor evoked potentials (MEPs). There is evidence that this facilitation mainly depends on presynaptic mechanims of glutamatergic neurotransmission. In a recent work we showed an opposite response of migraine motor-cortex to the trains of 5-Hz rTMS when delivered at different stimulation intensities: MEP facilitation at 110% and paradoxical MEP inhibition at 130% of the RMT. These results provide evidence of both hyper-responsivity and self-limiting hyperexcitability capacity in migraine, in line with studies supporting the concept that under conditions of cortical hyperexcitability inhibitory mechanisms of homeostatic plasticity could be activated. To support this hypothesis, in the present study we applied in migraine patients cathodal transcranial Direct Current Stimulation (tDCS) to reduce experimentally the level of motor-cortical excitability and subsequently assess the motor-cortical response during the 5-Hz rTMS trains delivered at high stimulation intensity.
Methods. Ten patients affected by migraine with aura received brief trains of 5-Hz rTMS to the motor cortex at an intensity of 130% of the RMT, with recording of the EMG traces evoked by each stimulus of the train from the contralateral abductor pollicis brevis (APB) muscle. This interventional protocol was preconditioned by 10 min of cathodal or anodal tDCS delivered at 1 mA intensity.
Results. As previously observed MEP decreased significantly in size during trains of 5-Hz before tDCS preconditioning. The inhibitory preconditioning with cathodal tDCS was able to restore the normal facilitatory response during the 5-Hz rTMS trains. Instead, after anodal tDCS MEP inhibition during the trains was further increased.

Conclusions. Our findings support the hypothesis that in migraine a condition of basal cortical hyperexcitability could be responsible for the MEP inhibition in response to trains of high-frequency rTMS given at high stimulation intensity. Indeed, we showed that the inhibitory cathodal tDCS can restore the normal facilitatory response to the trains by reducing the level of cortical excitability. Moreover, our results seem to be in line with studies suggesting that an abnormal glutamate neurotransmission could play a major role in migraine physiopathology.

23. The effect of observed biological and non biological movements on action imitation: an fMRI study

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Past research has indicated that when individuals observe biological movements many areas in the observer's motor system become active. Nonetheless, recent behavioral evidence showed that observed movements can interfere with execution of incompatible movements, especially the biological ones. However, the hypothesis that the interference originates within a common neural network, encoding both movement observation and execution, and responding preferentially to biological movements, still awaits confirmation. To test this hypothesis, in the present fMRI study we compared patterns of activation obtained when participants executed finger-movements after having observed either a biological or a non biological model performing compatible (imitative) or incompatible (non imitative) movements. Moreover, we tested the possibility that imitative responses are influenced by the emotional facial expression (sad, neutral, angry) presented before the observed movement. Behaviorally, participants showed a marginally larger compatibility effect (compatible movements faster than incompatible movements) in the biological condition than in the non biological condition. In the imaging data, the interaction testing for areas more active when the observed model was biological (compared with non biological) and performed compatible movements (compared with incompatible movements), activated a network including the motor, premotor and parietal cortices. Notably, the interaction was significant for the neutral and sad facial expressions only. We showed that observing biological movements modulates the activation of motor-related regions, by facilitating the execution of compatible movements and/or interfering with the execution of incompatible movements.

24. A multimodal imaging study for the investigation of the neural mechanisms of the TMS induced analgesia

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Objective. To examine the effect of continuous theta burst stimulation (cTBS) applied over the primary somatosensory cortex (S1) and the primary motor cortex (M1) on the cortical processing of nociceptive and non-nociceptive somatosensory inputs in humans. This allowed us to determine whether or not S1 is involved differently in the cortical processing of nociceptive and non-nociceptive inputs. It also allowed us to characterize better the effect of cTBS applied over M1, a technique used increasingly to reduce pain in patients. We compared the brain responses elicited by stimuli delivered ipsilateral vs. contralateral to the hemisphere onto which cTBS was applied to discriminate between specific and unspecific effects of cTBS.

Methods. Non-nociceptive (transcutaneous median nerve stimulation) and nociceptive (CO_2 laser stimulation) somatosensory evoked potentials (SEPs) were recorded following stimulation of the left and right hand, before and after applying cTBS over the left or right S1 (localized using coregistration of individual MRI data) or M1 (localized based on the motor response elicited by single pulses). For each of the peaks characterizing non-nociceptive and nociceptive SEPs, the finding of an interaction between the 'time' (before vs. after cTBS) and 'stimulation side' (stimuli ipsilateral vs. contralateral to the hemisphere onto which cTBS was applied) was considered as evidence that the cTBS applied to that cortical region exerted a specific effect on the processing of nociceptive or non-nociceptive input.

Results. 11 subjects underwent cTBS over S1, 9 over M1. cTBS did not modulate the amplitude of the N20, P27, N30, P45 and N60 waves of non-nociceptive SEPs, neither when applied onto S1, nor when applied onto M1. The magnitude of the P100 wave elicited by stimuli delivered contralateral to the cTBS site was significantly decreased following cTBS applied over M1, and significantly increased following cTBS applied over S1. The opposite pattern was observed for stimuli delivered ipsilateral the site of cTBS. Late-latency non-nociceptive SEPs (P200 but not N140) and nociceptive SEPs (N160, N250, P360) were reduced after cTBS, both when applied over S1 and over M1, and both for stimuli ipsilateral vs. contralateral to the cTBS site. Finally, cTBS applied over S1 and M1 both produced a significant analgesic effect on the percept elicited by nociceptive stimuli delivered to the contralateral hand, but not the ipsilateral hand (interaction

p = 0.004). In contrast, cTBS did not modulate the perceived intensity of the non-nociceptive stimuli.
Discussion & Conclusion. cTBS applied over S1 an M1 had a significant analgesic effect on the percept elicited by nociceptive stimuli delivered to the hand contralateral to the hemisphere onto which cTBS was applied. This *specific* effect of cTBS was not reflected in the magnitude of the nociceptive ERP components, which were reduced after cTBS regardless of the stimulated side.

25. Task-dependent coupling between eye and hand motor systems: a transcranial magnetic stimulation (TMS) study

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A tight motor coordination of eyes and hand is critical for accurate interactions with objects. Our previous transcranial magnetic stimulation (TMS) studies showed excitability changes in the corticospinal system (CSS) of the relaxed upper-limb when visual stimuli are targeted by eyes alone. Thus, eye and hand motor systems are coupled even when only one effector is engaged. The present study was aimed at investigating the nature of this coupling. By applying TMS to the motor cortex, we tested whether upper-limb CSS excitation changes: 1) are also induced by covert shifts of visuospatial attention, 2) vary with the saccadic task in a context-dependent manner. In Experiment 1 (27 subjects), the colour of a peripheral cue randomly demanded either the execution of a saccade (GO), or the maintenance of a central fixation (NO-GO). In Experiment 2 (29 subjects), the cue colour demanded a prosaccade or an antisaccade. During the task, participants kept their upper-limb muscles fully relaxed. A single-pulse TMS was applied on the left motor cortex and motor evoked potentials were recorded in three muscles of the contralateral arm: first dorsal interosseous (FDI), *abductor digiti minimi* (ADM) and *extensor carpi radialis* (ECR). TMS was randomly delivered before (baseline) or at a variable delay (within 1 s) after the onset of the peripheral cue. In Experiment 1 no change of upper-limb CSS follows covert shifts of visuospatial attention (NO-GO condition). Conversely, in FDI muscle, GO trials show a direction-dependent modulation of CSS excitability, which occurs within a narrow time-window at 120 ms after saccade onset. Experiment 2 unveils that saccades do not always enforce a motor coupling between eye and upper-limb. In fact, no CSS modulations are observed in antisaccade trials. By contrast, a generalized facilitation turns, in all muscles, to a long-lasting inhibition after the occurrence of a prosaccade. On the top of this inhibition, FDI and ECR muscles show direction-specific changes, which are confined around a time delay of 480 ms after saccade onset. Accordingly to our previous studies, visually-guided saccades induce CSS modulations compatible with a sub-threshold motor program of the hand towards the gaze target, which are absent after covert shifts of visuospatial attention. These findings disclose the motor nature of the signal guiding oculo-manual responses, that however does not slavishly yoke the engagement of an effector with that of the other. On the contrary, eye-hand coupling depends on task contest. Indeed gaze movements driven by cognitive factors only (e.g. antisaccades) are not inherently coupled with a motor activation of the relaxed arm. One may surmise that circumstances of stimulus-response compatibility and practice to perform a combined movement of eyes and hand are mandatory for an implicit motor coupling of both effectors.

26. Random noise stimulation improves neuroplasticity in perceptual learning

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Perceptual learning is considered a manifestation of neural plasticity in the human brain. We investigated brain plasticity mechanisms in a learning task using non-invasive transcranial electrical stimulation (tES). We hypothesized that different types of tES would have varying actions on the nervous system, which would result in different efficacies of neural plasticity modulation. Thus, the principal goal of the present study was to verify the possibility of inducing differential plasticity effects using two tES approaches [i.e., direct current stimulation (tDCS) and random noise stimulation (tRNS)] during the execution of a visual perceptual learning task.
107 healthy volunteers participated in the experiment. High-frequency tRNS (hf-tRNS, 100-640 Hz), low-frequency tRNS (lf-tRNS, 0.1-100 Hz), anodal-tDCS (a-tDCS), cathodal-tDCS (c-tDCS) and sham stimulation were applied to the visual areas of the brain in a group of volunteers while they performed an orientation discrimination task. Furthermore, a control group was stimulated on the vertex (Cz). The analysis showed a learning effect during task execution that was differentially modulated according to the stimulation conditions. Post-hoc comparisons revealed that hf-tRNS significantly improved performance accuracy compared with a-tDCS, c-tDCS, sham and Cz stimulations.
Our results confirmed the efficacy of hf-tRNS over the visual cortex in improving behavioral performance and showed its superiority in comparison to others tES. We concluded that the mechanism of action of tRNS was based on repeated subthreshold stimulations, which may

prevent homeostasis of the system and potentiate task-related neural activity. This result highlights the potential of tRNS and advances our knowledge on neuroplasticity induction approaches.

27. Early and late modulations of the motor system by action observation

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Objective. In this experiment we aim to describe the time course of covert motor modulation occurring during the observation of others' actions before and after a behavioral anti-simulative training.
Methods. The experiment was organized in 3 parts: 1) baseline recording; 2) behavioral anti-simulative training and 3) test recording. In the baseline recording we presented participants with movies of right hands turning a round box in a clockwise or in a counter-clockwise direction. We applied single suprathreshold transcranial magnetic stimulation (TMS) pulses over the left motor cortex (M1) at four different inter-stimulus intervals (ISIs) from the onset of observed movements (100 ms, 150 ms, 250 ms, 320 ms). The arm's motor responses to TMS were recorded by means of an accelerometer that was placed on the participants' right wrist. In this way, rather than the electrical activity of TMS-evoked muscular contraction (motor evoked potentials), we recorded the kinematics of the motor response. Then the participants underwent a behavioral training in which they were presented with the same movies and were instructed to turn as fast as possible a round box in the direction opposite to the one in the movie. The test recording was identical to the baseline one.
Results. In baseline recordings a clear simulation effect (i.e. TMS evoked movements congruent to the observed ones) was found at 250 ms and 320 ms. After training the simulation effect was evident at 150 and 250 ms and only at 320 ms did a counter-simulation effect appear.
Discussion. These results show that a short anti-simulative training produces associative visuo-motor responses in the anti-simulative direction that are elicitable only 320 ms after the onset of observed movement. In earlier intervals only simulative responses are elicited. These findings show two temporally separated phenomena occurring in the motor system during action observation: early responses are stable and not susceptible of changes by associative training, while late responses are modulated in the short term by recent visuomotor behavior.
Conclusion. These data are at variance with the hypothesis that a short associative training is sufficient to remap visuo-motor transformations performed by the mirror system (Catmur et al., 2007). We propose an alternative hypothesis in which not one but two distinct pathways are triggered by action observation: a fast, not flexible, automatic pathway matches the observed action with the motor programs allowing to perform the same action (a mirror neuron pathway), while a slower but flexible route computes the visuo-motor association required to perform the counter imitative task.

28. The N400 as electrophysiological marker of semantic incongruity in Mild Cognitive Impairment (MCI)

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Background. A peculiar feature of early cognitive impairment in MCI patients is the loss of semantic memory processing (Petersen et al., 1995, 1999; Ritchie and Touchon, 2000; Joubert et al., 2010; Carter et al., 2011). The N400 is a component of linguistic ERPs elicited by semantic incongruity which generate a larger wave to incongruous words than to congruous words within the semantic context. The N400 is described as the electrophysiological expression of linguistic semantic comprehension (Kutas and Hillyard, 1984; Friederici, 1997, Kutas et al., 2000). Literature data suggest that the N400 amplitude is a sensitive marker of semantic processing demands in MCI and it is supposed to be a reliable tool in early detection of incipient Alzheimer's disease (AD) (Olichney et al., 2002, 2006, 2008).
Objective. Recording of the N400 ERPs to explore the semantic processing in MCI patients.
Patients and methods. A simple word-pair reading paradigm was administered to 15 MCI patients and 15 elderly normal controls during a 30 channel EEG recording in order to elicite and measure linguistic ERPs (N400). Adjective-pairs were selected according to the frequency of word-use, cloze probability and length-word and each stimulation paradigm was set up with semantically congruous (60%) and semantically incongruous (40%) pairs. Auditory and visual P300 ERPs were recorded as well to evaluate cognitive decline. A selective neuropsychological battery was administered to assess general cognitive status, short- and long-term verbal memory, episodic memory, constructional praxia.
Results. Abnormal N400 (decreased amplitude or absent) was found in 12/15 of MCI patients. As a group, no significant differences between the N400 amplitude to incongruous words and congruous words were recorded in MCI patients with respect to the controls. Neither N400 latency to incongruous words and congruous words showed significant differences in patients compared to controls. No significant correlations emerged between N400 amplitude with age and depression.

Conclusions. N400 abnormalities found in this study suggest that it may represent a useful electrophysiological index to evaluate semantic memory deficits in MCI patients. Recording of linguistic ERPs can provide meaningful insights to better understand the neurocognitive basis of language comprehension. Longitudinal studies are needed to assess the predictive value of N400 in detection and staging the progression from MCI to AD.

29. Physical activity and cognitive experiences anticipates synaptogenesis onto adult-generated neurons in hippocampus

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Dentate gyrus (DG) of hippocampus generates new neurons (neurogenesis) throughout adulthood in a wide range of species, including humans. These newly-generated neurons become integrated into functional circuits and seem to play a role in spatial pattern separation, in spatial learning, and in improving memory consolidation; thus, promoting adult neurogenesis could ameliorate mnemonic function. Many factors modulate adult neurogenesis, including experiences involving hippocampal activation; in particular we previously showed that hippocampus-dependent learning in the Morris Water Maze (MWM) enhances new neuron survival, and that it induce the early appearance of GABAergic synapses and voltage-dependent Ca2+ current in very immature neurons. The MWM is a complex experience that involves, besides the cognitive aspect, motor activity and exploration. This work is addressed to discriminate the role of these different components in the modulation of synaptic and Ca2+ current appearance on new neurons in DG. Five-week-old Sprague-Dawley male rats were in situ injected with GFP-expressing retrovirus to in vivo label newly-generated neurons in DG, and, at fourth day from surgery, were divided into the following groups: enriched environment (EE); voluntary running (RUN); forced running in treadmill (TM); control rats. Seven days after infusion, rats were killed to perform patch-clamp recordings on GFP-positive cells. No synaptic activity was recorded in 7 day-old immature neurons of control group. On the contrary, all the groups exposed to behavioral experiences exhibited GABAergic synaptic activity, indicating an anticipation of the appearance of the first synaptic contact; in detail, more than 20% of the recorded cells showed functional GABAergic synapses in EE and RUN groups, while around 15% only in TM rats. Voltage-dependent Ca2+ current was detected in about 17% of recorded immature neurons in controls. A higher percentage of newborn neurons showed voltage-dependent Ca2+ current in EE, RUN, and TM rat groups, but it was significantly different from control in RUN only. The main results of this work are: 1. both physical activity and environment enrichment per se caused an anticipation of GABAergic synapse formation onto very immature neurons, this anticipation is greater following a training into a pool maze; 2. voltage-dependent Ca2+ current was detected in higher number of 7 day-old immature neurons in rats exposed to behavioral experiences. These findings indicate that behavioural experiences involving hippocampus activation are able to change synapse formation and ion-channel expression onto newborn neurons in adult DG, and therefore the hippocampal circuitry; this could affect information processing related to future experiences. The mechanisms underlying synaptogenesis anticipation could involve one or more paracrine factors, among which the likeliest one may be BDNF due to its roles played in neuronal plasticity.

30. The role of the motor system in speech perception: TMS studies

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Classical models of language localization in the brain consider an antero-posterior distinction between perceptive and productive functions. In the last 15 years, this dichotomy has been weakened because of empirical evidence suggesting a more integrated view. A large amount of data is accumulating against the reality of such a strict anatomo-functional segregation in speech and language processing. Passive listening to phonemes and syllables activate motor (Fadiga et al., 2002) and premotor areas (Wilson et al., 2004). Interestingly, these activations were somatotopically organized according to the effector recruited in the production of these phonemes (Fadiga et al., 2002; Pulvermüller et al., 2006), and in accordance with the premotor activities in overt production (Pulvermüller et al., 2006; Wilson et al., 2004). However, a distinctive feature of action-perception-theories in general and in the domain of language specifically, is that motor areas are considered necessary for perception. All the above mentioned studies are inherently correlational, and it has been argued that in absence of a stringent determination of a causal role played by motor areas in speech perception, no final conclusion can be drawn in support of motor theories of speech perception (Toni et al., 2008). In fact, the mere activation of motor areas during listening to speech might be caused by a corollary cortico-cortical connection that has nothing to do with the process of comprehension itself. A possible solution might come

from the selective alteration of neural activity in speech motor centers and the evaluation of effects on perception. Therefore, we designed a series of TMS experiments to tackle the causal contribution of motor areas to speech perception (D'Ausilio et al., 2009). We demonstrated that activity in the motor system is causally related to the discrimination of speech sounds and might be more critical under adverse listening conditions (D'Ausilio et al., 2011a; 2011b) or when coping with inter-speaker variability (in preparation). Interestingly, this functional association is somatotopically organized according to an effector-sound motor map. In fact, listening to reproducible speech sounds might activate the same motor gestures necessary for production and thus help sensory classification and decision.

31. Flexibility of mirror mechanisms: the effect of cognitive context

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The function of the mirror neuron system (MNS) is highly debated and has been linked with several aspects of cognition such as action understanding and imitation. Based on recent suggestions that the MNS may be employed for multiple functions (Rizzolatti and Sinigaglia, 2010), we reasoned that mirror mechanisms may be top-down regulated by higher cognitive processes according to contingent cognitive demands. We examined event-related potentials in a delayed go/no-go task known to induce bi-directional interference between the motor system and the visual system. Images of hand gestures were presented as a go stimulus after participants had planned either a matching (congruent) or non-matching (incongruent) gesture. Participants performed the task in two cognitive contexts. At the end of each trial, participants were asked to select among four hand gesture images either: the action they had seen (image context), thereby attending most to the observed action depicted in the image; or the action they had performed (action context), thereby attending more to their own performed action. We measured the N170 elicited from presentation of the go-stimulus (Bortoletto et al., 2011) in order to study the influence of action plans on action observation (motor-to-visual priming). We also measured movement-related activity lateralized over the left hemisphere, i.e. left-lateralized readiness potentials (L-LRPs) following the go stimulus, in order to study the influence of action observation on action planning (visual-to-motor priming). We found stronger motor-to-visual priming (congruency effects on N170) in the action context compared with the image context, i.e. when participants were required to focus more on their performed actions. Viceversa, we found stronger visual-to-motor priming (congruency effects on L-LRPs) in the image context compared with the action context, i.e. when participants focused more on the observed action. In general, the aspect of the task that was most relevant and specifically attended was not influenced by the congruency between observed and executed actions; it was only the non-relevant aspect of the task that was affected by congruency. Interestingly, both action and image contexts produced similar effects on reaction times to initiate movements. We suggest that top-down regulation of mirror mechanisms can change not only the strength of interaction between visual system and motor system (Chong et al., 2008) but also its direction. This study is consistent with previous findings that network connectivity, in this case the MNS network, depends on the subject's state and cognitive contingencies (Silvanto et al., 2008: Schippers and Keysers, 2011) and supports the multifunctional role of mirror mechanisms in cognition.

32. Effects of transcranial direct current stimulation on esophageal motility and pathological waves in gastroesophageal reflux disease patients

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Aims: to evaluate, through esophageal manometry, the effects of transcranial direct current stimulation (TDCS) on esophageal mean distal waves amplitude, pathological distal waves and lower esophageal sphincter (LES) mean pressure in patients with GERD. Methods: we studied 16 patients with clinical diagnosis of GERD who previously underwent endoscopy to differentiate erosive reflux disease (ERD) from non-erosive reflux disease (NERD). We performed an esophageal manometry before and during cortical stimulation with TDCS (2 mA) on the right esophageal motor area. Randomly 9 patients were assigned to anodal stimulation, 7 patients to sham stimulation. We asked each patient to swallow a 5 ml water bolus for 10 subsequent times, distal waves amplitude (considered as distal amplitude < 30 mmHg or as not propagated distal peristalsis), number of pathological waves (over 10 swallows) were measured 5 and 3 cm over the esophageal sphincter. LES pressure was obtained as well. In order to compare mean distal waves amplitude, number of distal pathological waves and mean basal LES pressure, before and during TDCS in both groups of patients, statistical analysis was performed by repeated

measures ANOVA with Group (two levels: anodal-sham) as between subject factor, Time (two levels: before-during TDCS) and Swallows (ten levels) as within subject factors. Results: mean distal waves amplitude increased significantly ($p = 0.01$) and the number of distal pathological waves decreased significantly ($p = 0.03$) during anodal TDCS, while sham stimulation didn't influence both parameters. LES mean pressure was significantly decreased during anodal ($p = 0.05$) but not during sham stimulation in our patients. Conclusions: although preliminary, our data suggest that TDCS can influence cortical control of esophageal motility and reduce pathological motor pattern in GERD patients.

33. Direct current stimulation of the right inferior frontal cortex modulates control of locational-based information in the Simon task

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Objective. Different regulative mechanisms are supposed to affect behaviour when spatial representations compete for response selection. The term 'response inhibition' refers to the ability to suppress within-trials the activation of an incorrect response; in contrast the term 'sequential adaptation' is used to define between-trials behaviour adjustment. In the Simon task, the correspondence between irrelevant stimulus location and response position (associated with task demand) affects reaction times (RTs) speed: RTs are faster when stimulus and response positions spatially correspond then when they do not correspond. Interestingly, the magnitude of the Simon effect (i.e. the difference between non-corresponding and corresponding conditions) is reduced when RTs are longer and after a preceding (N-1) non-corresponding trial. Aim of the present study was to evaluate the different involvement of the right and left inferior frontal cortex (IFC) in response inhibition and sequential adaptation.
Material. Two experiments are reported in which transcranial direct current stimulation (tDCS) was applied on the right or left IFC while participant were engaged in a Simon task.
Method. Cathodal, Anodal, and Sham tDCS (2 mA for 20 minutes) were delivered to all the participants (Exp.1 N = 11; Exp.1 N = 12) in three different sessions during the execution of a Simon task. In experiment 1 and experiment 2, the active electrode (2.5 cm^2) was placed between F4 and F8 or between F3 and F7 (10-20 sys), respectively. The reference electrode (3.5 cm^2) was positioned over the contralateral supraorbital region.
Results. In experiment 1, a significant reduction of the Simon effect was obtained when cathodal stimulation was applied over the right IFC, and this effect mainly depend to slower RTs. In addition, with this montage, sequential adaptation was eliminated as a reduction of the Simon effect was observed when the trial N-1 was a corresponding trial. In experiment 2, stimulation of the left IFC did not reveals any effect on both within-trials inhibition and between-trials sequential adaptation.
Discussion. The present results show that cathodal stimulation of the right IFC ameliorates the ability to inhibit within-trials the activation of an incorrect response and interferes with between-trials sequential adaptation.
Conclusions. In accordance with dual-route models, the present study demonstrates for the first time a specific involvement of the right IFC in within-trials inhibition of incorrect response activation when relevant and irrelevant spatial information compete for response selection. In addition, in line with a possible role of the right IFC in updating response selection and action planning, our data suggest that sequential adaptation may operates not only by reducing the activation of irrelevant information when previously competing with task demand, but also by enhancing its influence when it was previously adaptive.

34. Stimulus- and response-locked ERPs in patients with liver chirrosis

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Objectives. To evaluate stimulus- and response-locked P300 evoked by a Go-NoGo spatial stimulus-response conflict task in patients with liver cirrhosis.
Methods. 13 patients with liver cirrhosis and 16 age-matched healthy controls were enrolled in the study. A visual Simon task including Corresponding, NonCorresponding and NoGo conditions was performed to obtain behavioural and P300 responses. The electroencephalogram (EEG) was continuously recorded using a 30 electrodes-cap according to the international 10/20 system. The peak of P300 was determined at Fz, Cz, and Pz as the largest positive peak within 250 and 550 ms in stimulus-locked averages and within -100 and 200 ms in response-locked averages. Behavioural and ERPs data were analyzed using Repeated Measures ANOVA and Pearson's Correlation.
Results. *Behavioural performance*: statistical analysis showed a significant main effect of Condition in reaction times (RTs) and accuracy indicating a better performance in Corresponding condition both in patients and controls. *Stimulus-locked P300*: we found a main effect of

Condition and a Condition by Group interaction for P300 latency. Multiple comparisons showed a delayed latency in NoGo condition, mainly in patients. Analysis of amplitude revealed main effects of Electrode and Condition and an interaction between Electrode and Condition. Post Hoc Test showed that amplitude was higher in NoGo condition and followed an anteroposterior gradient. *Response-locked P300*: analysis of P300 latency showed a main effect of Group indicating a higher latency in patients. Concerning amplitude we found a main effect of Electrode and an interaction between Electrode, Condition and Group. Post Hoc Test showed an anteroposterior gradient of amplitude. *Correlation analysis*: in control group, but not in patients with cirrhosis, a significant correlation between RTs and response-locked P300 latency was found at Fz and Pz in Go conditions (Corresponding and NonCorresponding).

Discussion. Behavioural results highlighted slower RTs and lower accuracy in NonCorresponding compared to Corresponding condition. Delayed RTs in NonCorresponding condition, however, was not reflected on latency of stimulus- and response-locked P300. The positive correlation of RTs with P300 response-locked latency in controls could suggest that RTs are correlated to response selection rather than stimulus evaluation process. This correlation was not found in patients with liver cirrhosis probably because of the increased variability of RTs which was frequently observed in these patients. The delayed latency of stimulus-locked P300 in NoGo condition could indicate an impairment of stimulus evaluation process mainly detectable when higher attentional resources are required.

35. Alterations of effective connectivity in vegetative state patients: an EEG study

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Objective. Alteration of the cortical connectivity pattern has been suggested to be an important key to understand disorders of consciousness (DOC). This study was aimed at evaluating the pathological alterations of the effective connectivity from EEG signals, in a cohort of post-anoxic patients (ABI) in vegetative state (VS).

Materials and methods. Standard EEG recorded in resting condition was analyzed by means of a frequency domain linear index of connectivity, the Partial Directed Coherence (PDC), estimated from a multivariate autoregressive model (MVAR). Ten patients in VS following anoxic damage were selected for the study and compared with 10 healthy controls. Resting EEG activity was analyzed by dividing one minute of EEG into 30 non-overlapping epochs of 2 s, each of which underwent MVAR analysis. The in- and out-density, two basic indexes deriving from graph theory, were used to characterize changes of the network connectivity. EEG electrodes were grouped into five regions (frontal, central, posterior, left and right temporal), and connections within each region (short-range connectivity) and between pairs of regions (long-range connectivity) were identified.

Results. Our findings indicated that significant connectivity changes involved the EEG activities in delta and alpha bands. A widespread significant decrease of connections occurred in delta band in patients compared with controls. By contrast, the alpha activity resulted hyper-connected in the patients, namely in central and posterior regions.

Discussion. The decrease of connectivity in delta band occurring in our patients in VS could be interpreted as a consequence of a subcortical differentiation. Conversely, alpha hypersynchronization might result from a pathological network, taking place in highly damaged brains due to an anoxic injury, leading excessive synchronization among residual or aberrant EEG-alpha sources.

Conclusion. Our study indicates that connectivity patterns associated to delta and alpha EEG activities are affected in VS patients. The results show that PDC and simple indexes derived from graph theory are tools capable to detect abnormal connectivity changes of cortical networks in patients affected by severe DOC and to identify opposite mechanism of network alteration depending on the different frequency bands.

36. Photosensitive epilepsy and corpus callosum: an unexpected link

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Introduction. Photosensitive Epilepsy (PE) is a form of epileptic seizure induced by powerful triggers. The exact kind of stimuli that trigger epileptic seizure differs about subjects, and severity of resulting symptomatic cases. Here, off-line low-frequency rTMS of one occipital lobe was employed to disclose the contribution of callosal input to visual responses in both healthy subjects and PE patients.

Materials and Methods. We enrolled 10 healthy subjects (5 males and 5 females; mean age 16.8 ± 3.4 yrs) and 5 patients (15.9 ± 4.2 yrs) Visual evoked potentials (VEPs) triggered by grating stimuli of different contrasts were recorded before and after functional inactivation of the occipital cortex of one hemisphere via off-line low-frequency repetitive transcranial magnetic stimulation (rTMS; 0.5 Hz stimulation for 20 min). VEPs were recorded in V1 before (T0), immediately after (T1) and 45' following the completion of rTMS (T2).
Results. We found that low-frequency rTMS had an inhibitory effect on VEPs amplitudes at all contrasts in the treated side in controls and patients. Reduction of VEP amplitudes in the inhibited hemisphere at T1 was accompanied by an increase in VEP amplitudes in the contralateral side at mid-high contrasts (50-90%) in healthy subjects ($p < 0.05$). This disinhibitory effect was observed with both central and hemifield stimulation; in PE patients, we showed both a larger potentiating of VEPs amplitudes at T1 ($p < 0.01$) and a persistence of the disinhibitory effect at T2 ($p < 0.01$). No changes in VEP amplitudes were observed when rTMS was applied to a cortical site more anterior than V1.
Discussion and Conclusion. In patients with photosensitive epilepsy VEPs amplitude increases considerably when contrast rises, and so there is no saturation of evoked responses. That could suggest an impairment of transcallosal inhibitory loops, underlying the phenomenon of contrast gain control. In fact, some forms of photosensitivity tend to improve spontaneously around 18 years old, there is the time in which is completed the maturation of trancallosal projections.

37. Recovery of aphasia: a case study with "dual" tDCS

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Objectives. In the present study we used a "dual" tDCS (Vines et al., 2008; Giglia et al., 2011) training on inferior frontal gyrus's (IFG) areas in order to improve the linguistic performance of EBE, an Italian female, left-handed, presenting a global aphasia following a stroke of right middle cerebral artery.
Materials. For the picture naming task, 20 object and 20 action images, selected from a set of picture standardized for frequency, were presented on a paper sheet one at time.
Method. Stimulation was used at 1 mA for 15 minutes. Dual tDCS was given over both IFGs, anode in the right (damaged areas) and cathode in the left (preserved areas) daily for two weeks (weekend-free). The position of the electrodes was based on a previous pilot study on EBE, in which tDCS efficacy was greater when the cathode was positioned over the right Broca's area and the anode over the left Broca's area, compared to the opposite placement. One week after the end of the treatment, sham tDCS was delivered for another week. EBE performed the naming of the complete set of 40 pictures at the following times: before real tDCS (T0), immediately after the end of real tDCS (T1), before sham tDCS (T2) and after sham tDCS (T3). Since EBE was able to name no picture without a phonological cue (the first or the two first letters of the stimulus), the images in the picture naming task was first presented without cue, then with a first letter and, if no response was obtained, with the two first letters. The following scores were used: 0 = incorrect response; 0.5 = correct response with two letters of phonological cue; 1 = correct response with one letter; 2 = correct response without cue. Thus, a higher score means a better performance. These scores obtained at the four different times (conditions) of examination were compared by means of repeated measures one-way ANOVA.
Results. ANOVA showed a statistically significant main effect of conditions. As showed by Duncan's post hoc analysis EBE made significantly less errors after real tDCS (T1) with respect to baseline (T0) ($p < 0.05$), while no significant changes in performance were observed after sham tDCS (T3 vs T0).
Discussion. Our study is the first in which dual stimulation is used in order to improve the linguistic performance of an aphasic patient. In our patient, considering left-handedness and aphasia following a right lesion, a right hemisphere dominance for language can be presumed. So, anodic stimulation of the left frontal areas could favor the recruitment of this area to compensate the function of the damaged language area; while cathodic stimulation of the right damaged area could have played its effect reducing transcallosal inhibitory drive to the homologue area.
Conclusion. Dual tDCS could be a promising tool for aphasic recovery. This study shows that an intense training (at least ten days) improves linguistic performance also for severe nonfluent chronic aphasia.

38. Can Wii modulate visuospatial attention lateralization?

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Objectives. In a previous study we found that "open-skill" high level athletes (volleyball players) performing a line-length judgment task responded significantly faster and

were also more accurate, as compared with closed skill athletes (rowers) and controls. As the design of the study did not allow to know if such results were due to training rather than self-selection of ability, in the present study, differences in visuospatial attention lateralization were investigated in healthy volunteers before and after a short period of virtual "open skill" sport playing.
Materials. Subjects: 18 sedentary participants.
Experimental procedure. Computerized line length-judgement task using Psyscope X software on a portable apple computer 13". Virtual open skill sport (tennis) on an active system game consolle, the "Nintendo Wii", and the "Wii Sports games" software "tennis". The controller used was a "Wii remote", a wireless 3-axis accelerometer that works with gesture recognition.
Method. Subjects responded to a computerized line-length judgment task, before and after a short period (7 days, 1 hour/day) of virtual "open skill" sport playing (tennis). Five lines, differing in the length of their right and left segments, were randomly presented; the respondent made a forced-choice decision about the respective length of the two segments. Reaction times (RTs) and percentage of errors towards left and right were recorded and analized by means of ANOVA.
Results. In baseline condition subjects showed a tendency to bisect lines slightly to the left, a phenomenon known as pseudonenglect. The one-way ANOVA for the percentage of errors Pre vs Post- Wii showed a significant main effect, with a significant reduction in the post-wii condition ($p < 0.05$). The two-way ANOVA comparing leftward versus rightward errors between conditions: pre- vs Post-wii, with Errors (leftward and rightward) and Condition (pre- vs Post-wii) as within subjects factors showed a statistically significant main effect ($p < 0.05$). Duncan's post hoc analysis showed that in the Post-wii condition, subjects made statistically significantly fewer errors to the left compared to the pre-wii condition. The one way ANOVA for RTs showed no significant differences between conditions.
Discussion. Visuospatial attention is a cognitive function considered to represent an important determinant of success in open skill sports. In such sports, the environment is constantly changing and movements have to be continually adapted. The ability to process spatial information and perceive differences or asymmetries correctly in both hemi-visual fields allows athletes to perform successfully. The main result of the study was that a short period of virtual open skill sport playing was able to counteract the physiological hemispheric imbalance, improving visuospatial attention isotropy.
Conclusions. The results may suggest the possibility of changing the distribution of visuospatial attention by virtual training.

39. Spatio-temporal pattern of brain activity to Stroop Task in early multiple sclerosis revealed by estimation of EEG cortical sources

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Objectives. Multiple sclerosis (MS) patients, compared with controls, have shown abnormal activity in several brain networks during different cognitive tasks. The present study was aimed to examine whether brain activation abnormalities in MS patients are developed across specific stages of information processing during performance of the Stroop test. To address this issue, we used event-related potentials (ERPs) combined with individual magnetic resonance imaging (MRI) anatomy increase the spatial-temporal resolution which could be used to identify brain regions involved in information processing.
Methods. Thirty-three subjects (15 relapsing remitting patients with low EDSS disability and 18 healthy controls) completed a visual Stroop task during 64-channel EEG recording. ERPs were computed separately for congruent, incongruent and neutral condition. The cortical sources of these activities were estimated using two modeling: weighted minimum norm estimate (wMNE), and standardized low resolution brain electromagnetic tomography (sLORETA) techniques. Second, the spatio-temporal reconstructions of ERP sources were estimated using the individual anatomy (MRI) of each participant.
Results. Results in the control group showed activation of large distributed networks with a well defined temporal course which was similar for different conditions of the Stroop test. For the condition with higher cognitive conflict, the dorsolateral prefrontal cortex showed a significant increase of activity during early (120-250 ms) and late (400-450 ms) periods. In comparison with the controls, MS patients showed an increased activity in different brain networks mainly involving the associative visual cortex as well as parietal regions. However, MS patients showed also a decreased activity in fronto-temporal regions during early stages (150-250 ms). In addition, the time course of activity in some of these brain regions was delayed in MS patients compared to the control group.
Discussion. Cortical reorganization in different stages of MS appears to limit the impact of lesions through compensatory mechanisms by calling on cognitive resources from brain areas adjacent to those essential to perform the Stroop test. Multimodal integration of ERPs and MRI information can be a useful tool for the study of the time course of activity in brain networks involved in a cognitive test.
Conclusions. The finding, in early MS patients, of cortical overactivation during specific stages of information pro-

cessing may account for similar performance compared with controls. On the other hand, abnormal activation patterns in fronto-temporal regions may explain some early cognitive deficits found in these patients.

40. Idiopathic environmental intolerance attributed to electromagnetic fields: neuropsychophysiological approach to decode a new self-reported condition

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Introduction. A growing number of people are concerned about potential health risk from environmental exposure. Idiopathic Environmental Intolerance attributed to electromagnetic fields (IEI-EMF) formerly "electromagnetic hypersensitivity", is a self-reported condition in which subjects attribute a range of non-specific symptoms (dermatological, neurasthenic, vegetative disturbances) to exposure to man-made EMF. The collection of these disturbances is not part of any medically explained syndrome. The relationship between experienced symptoms and exposure is yet to be demonstrated; any reliable tool is currently available to identify these individuals. A causal relation between EMF and symptoms has never been demonstrated in provocation studies. Approximately 10% of reported cases of IEI-EMF were considered severe.
Objective. Aim of the study was to characterize a neuropsychophysiological endophenotype of IEI-EMF subjects.
Methods. Eight subjects with IEI (7 F, 1 M) (29-69 yrs, mean 48,50 ± 14,37) and 8 control subjects, matched for age and sex, participated in this study. Chronic diseases, history of neurological and psychiatric illness, medication use or drug abuse were excluded. A semi-structured interview defined life habits and exposure. Neurobehavioral aspects, personality traits and quality of life were assessed (BDI, GHQ, MMPI, PSQI, STAY Y1-2, Electromagnetic Hypersensitivity Questionnaire). Neurophysiological investigations included determination of electric perception thresholds and Intensity Dependence of Auditory-evoked Potentials (IDAP). P3 component (Oddball, Novelty, Reaction-Time paradigms) of Event-related potentials (ERPs), and Contingent Negative Variation (CNV) were recorded.
Results. IEI-EMF subjects exhibited different scores in BDI ($p < 0.05$), GHQ ($p < 0.01$), STAY Y1 ($p < 0.01$). MMPI scores showed differences in some neurotic profiles. Intergroup differences neither in perception thresholds nor intensity dependence of N1/P2 amplitudes were evident. Reliable ERPs components were obtained in all subjects. Intergroup differences in P2 ($p = 0.06$) and N2 latencies, a decrease in P3 latency during novelty and RT paradigms were evident in IEI-EMF subjects. P3b latency was similar in two groups. A decreased amplitude of W3 (200 ms pre-S2) was observed at grand average CNV in these subjects.
Discussion. An internal consistency regarding neurobehavioral and neurophysiological investigations was evident in IEI-EMF group. The perception threshold and intensity dependence of the N1 and P2 component of AEPs showed similar patterns in two groups. Conversely to what observed in diseases reflecting low serotonergic activity and deficient inhibition to noxious stimuli (migraine, depression, fibromyalgia), our findings seem to exclude generalized hypervigilance of sensory stimulation, suggesting a preserved inhibitory system against overstimulation. P2/N2/P3 activity reflects information processing with attention; reduction in P2- N2 latency could reflect a faster transmission of the relevant stimuli, filtered at the preattentive stage, to the attentive processing stage. However, decreased amplitude of terminal CNV is suggestive of impairment in sustaining attention.

41. Orienting response in essential tremor: role of involuntary and voluntary attention

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Background. Essential Tremor (ET) is one of the most common neurological disorders and is the most common pathologic tremor in humans. Since that many studies have now documented mild deficits in ET patients in cognitive tests measuring verbal fluency, word recall, and selective aspects of attention, working memory and executive functions, the traditional view that defined ET as a monosymptomatic and benign disorder has been reconsidered. As in several other progressive movement disorders in facts, cognitive deficits appear to be a part of the disease in addition to motor disturbances.
Objectives. The aim of this study was to investigate the attention, either in its involuntary and voluntary component, in ET patients, using Mismatch negativity (MMN) and novelty P3, for they are evoked independently from motor ability of the subject.
Methods. 15 non demented patients with ET and 15 age and sex-matched healthy controls underwent an EEG recording. MMN (with 2 deviant tones) and P3a in a three stimulus paradigm were evoked. Their latencies and amplitude were evaluated. $\chi 2$ and unpaired t-tests were used for statistical analysis.
Results. Reliable ERPs components were obtained in all patients. Grand averaged potentials showed a significant

difference in MMN latencies for both the two deviants (DEV1 $p < 0.05$; DEV2 $p < 0.01$) between ET and control groups, and a significant prolonged latency of novelty P3 ($p < 0.05$) in the ET patients.

Discussion. Our data demonstrated that ET patients present deficits in orienting response which is a rapid response to new, unexpected or unpredictable stimuli, that essentially functions as a "what-is-it" detector. In particular the prolonged latencies of MMN with respect of both deviant stimuli (the more similar to the standard and the easier one to detect) could indicate that the automated processing of the stimuli is compromised. The prolonged P3a latency could indicate that the redirection of attention monitoring, when a perceptually novel "distracter" stimulus commands frontal lobe attention, may also be impaired. Cerebellum, which is thought to play a major role in the pathophysiology of ET, may interfere with cognitive functioning, due to the strong bidirectional fronto-cerebellar connectivity, in particular to the dorsolateral prefrontal cortex. It is reasonable to suppose that ET patients showed a difficulty in tasks strongly related to frontal attentive circuits, because of their cerebellar pathological involvement.

Conclusions. Our data indicate that patients with ET present selective cognitive dysfunction in attentional networks regarding both voluntary and involuntary attentional orienting.

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42. ERPs in sporadic amyotrophic lateral sclerosis: utility of a multitasking approach in cognitive assessment of clinical subtypes

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Purpose. Amyotrophic Lateral Sclerosis (ALS) was traditionally believed to spare cognitive functions, but subtle executive deficits have been recently reported in most patients with sporadic ALS. The aim of this study was to investigate the presence of cognitive dysfunction in non-demented ALS patients using Event-related Potentials (ERPs), a measure of cortical activity that can be recorded non-invasively from humans during cognitive tasks, without interference by motor action.

Methods. 33 non-demented patients with sporadic ALS (22 with spinal-onset, 11 with bulbar-onset) and 32 age and sex-matched controls underwent an EEG recording. Mismatch negativity (MMN), P3a, P3b and Contingent Negative Variation (CNV) were recorded. MMN, P3a, P3b latencies and CNV amplitude (total and in three different temporal windows - W1, W2, W3) with CNV onset were evaluated. The results of ERPs were correlated with respiratory function and clinical scales.

Results. No differences were found between ALS patients and controls with respect of MMN, P3a, P3b latencies and total CNV area, while CNV onset showed a significant delay in ALS patients ($Fz\ p < 0.03$ - $Cz\ p < 0.02$ - $Pz\ p < 0.02$). A subgroup analysis revealed that total CNV amplitude ($Cz\ p < 0.01$) and W1-CNV area were significantly reduced ($Fz\ p < 0.07$ - $Cz\ p < 0.05$ - $Pz\ p < 0.03$) and the onset of the CNV was significantly delayed ($Fz\ p < 0.001$ - $Cz\ p < 0.002$ - $Pz\ p < 0.005$) in bALS vs controls, while no differences were found between sALS and controls.

Discussion. Our data indicate that a subtle cognitive impairment involving selective cognitive functions is present in non-demented patients with sporadic ALS; in particular the prolonged onset of CNV probably reflects a difficulty in attentional shift when a demanding stimulus arrives. In addition, the decreased amplitude of CNV in bALS patients, which is thought to vary as a function of the amount of attentional resources allocated to time-information processing, supports the finding of a predominantly executive frontal lobe dysfunction in a clinical sub-type of patients. The normal MMN latency in the same group of patients presumably indicates that the attentional delay is not due to a primary arousal problem and automated types of stimulus processing are not prolonged by the disease process.

Conclusion. A multitask psychophysiological approach seems to be an useful tool in order to detect selective and subtle cognitive dysfunction in non-demented ALS patients.

43. The gating role of the thalamus to protect sleep: an F-MRI report

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Objective. Neuroimaging is an innovative technique to study brain functiong during sleep. Most data regard nuclear neuroimaging, and only recently the potentials of functional Magnetic Resonance (fMRI) have been applied.

Materials and methods. During an fMRI recording acquired on a 3 T scanner (MAGNETOM Allegra, Siemens, Erlangen, Germany) with contemporary electrical stimulation at the right median nerve at different frequencies (3 and 10 Hz), two subjects fell asleep during the 3 Hz session, and woke up when the frequency was shifted to 10 Hz. Functional data were analyzed using BrainVoyager and activated voxels identified with a GLM approach.
Results. During electrical stimulation, subjects reported falling asleep, and were not responsive to commands. While asleep, BOLD signal increase was evident in thalamus, ascending-reticular-system and cerebellum, while BOLD signal decrease was observed over the bilateral occipital (Brodman areas 18 and 19), temporal (41) and posterior parietal cortex (7), with a minor area in the supplementary motor (6) and motor cortex (4). During wake, BOLD signal increase was recognized in the controlateral supplementary motor area (6), contralateral primary somatosensory cortex (7), bilateral secondary somatosensory cortex (5), bilateral insula and cerebellum.
Discussion and conclusion. We report the first cases of fMRI of spontaneously sleeping healthy subjects during somato-sensory stimulation. A dissociation of BOLD signal activation/deactivation emerges: increased metabolism in thalamus and ascending-reticular-activating-system versus a BOLD decrease in heteromodal associative cortex (visual, auditory, parietal, prefrontal). This may be a visual rendering of the "thalamic gating hypothesis" of the sleeping brain. Reduced brain responsiveness during sleep depends on the disruption of signal transmission from the periphery to the cortex. As an integrating station of the sensitive pathways, the thalamus selects information to be projected or not to the pertinent cortices: in short, it protects the sleeping cortex. A limit of our data is the lack of EEG-coregistration. Sleep was recognized by the examiner and referred by subjects. Nonetheless, we can reliably belive the subjects fell asleep due to the activation-deactivation pattern congruent with previous data and the BOLD pattern mismatch between the wake/asleep scans.

44. The effect of music on corticospinal excitability is related to the valence of the perceived emotion: a TMS study

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Objective. TMS and neuroimaging studies suggest a functional link between the emotion-related brain areas and the motor system. Music is a powerful universal medium to express and evoke strong emotions with both a positive and negative valence, and its neural substrate is under investigation. It is not well understood whether the primary motor cortex (M1) activity is modulated by specific emotions experienced during music listening. In the current study, we used TMS to evaluate whether listening to musical pieces affects the corticospinal excitability and to assess whether this modulation is related to the emotional valence of the stimuli.
Methods. In 23 right-handed healthy volunteers, non-musicians, we recorded the motor evoked potentials (MEP) following TMS from the first dorsal interosseous (FDI) muscle of the left hand while subjects listened to music pieces evoking different emotions (happiness, sadness, fear, and displeasure), an emotionally neutral piece, and a control stimulus (musical scale). Musical pieces were selected in a preliminary phase in which other subjects were requested to judge the emotional valence and to rate the intensity of the emotion expressed by each piece. The intensity of the magnetic pulse was adjusted to elicit MEP of about 0.5-1 mV in peak-to-peak amplitude in the relaxed left FDI when the subject performed no task. In a subgroup of 12 subjects the following psychophysiological measures were also recorded: skin conductance level, heart rate, respiratory rate, and skin temperature.
Results. Fear-related music significantly increased the MEP size compared to the neutral piece and the control stimulus. This effect was not seen with music inducing other emotional experiences and was not related to the intensity of the perceived emotion. In addition, no significant correlation was seen between MEP amplitude modulation and psychophysiological measures.
Conclusion. Current data indicate that also in a musical context, the excitability of the corticomotoneuronal system is related to the emotional valence of the listened piece.

45. Cortical areas involved in facial physical features and face identity processing: preliminary data by rTMS

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Objective. Face recognition is enabled through a distributed neural network but the relative contribution of the single components of this network has not been clarified. Functional neuroimaging data suggest a role of face-selective occipito-temporal region in the perception of facial physical features (occipital face area, OFA) and invariant aspects of faces such as face identity (posterior superior temporal sulcus, pSTS). We used an on-line interference appoach by focal rTMS to invesigate the role of the OFA and pSTS in face processing.

Methods. Fifteen healthy volunteers participated in a match-to-sample discrimination task. Stimuli were manipulated by morphing technique that changes (morphs) one image into another at different levels. Two faces were successively presented for 250 ms: a match-face and a target face. The target face could be the same (no morphing), different in terms of physical features (low morphing), or different both for physical features and identity (high morphing) compared to the match face. Focal 20-Hz rTMS at an intensity of 90% resting motor threshold was delivered simultaneously to the target face presentation (250 ms). Four blocks of 45 pairs of stimuli (15 for each level of morphing) were randomly presented in four different experimental conditions: 1) baseline (without rTMS); 2) rTMS of the right OFA; 3) rTMS of the right pSTS; and 4) rTMS over Cz (cortical control area). Dependent variables were accuracy (percentage of correct response), reaction times (RT) and the response confidence on a scale from 1 to 3.
Results. rTMS of the right OFA did not produce significant effect on accuracy ad RT. The interference with the right pSTS function produced a slight worsening of the accuracy in the 'high morphing' condition (75 ± 12%) compared to baseline (82 ± 16%), rTMS of the right OFA (85 ± 15%) and rTMS over Cz (83 ± 12%) conditions. However, this effect did not reach statistical significance.
Conclusion. These preliminary data suggest that OFA could not play a crucial role in the holistic face processing. The present task implied a global stimulus analysis that likely involves neural regions at higher level of the face processing stream. In contrast, OFA is considered to be involved in the early processing of face parts. The evaluation of a larger number of subjects is necessary to clarify the role of the pSTS in this task.

46. Learning, autonomic memory and "Mild Emotive Impairment" in subjects with aMCI

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Introduction. Patients with Alzheimer disease consistently demonstrate impaired performance on tests of facial emotion recognition. Recognition of emotion on faces in AD decreases with the progression of dementia and could be related to the progression of the degeneration of the structures implicated in emotional processing systems. However, it remains unclear how early in the neurodegenerative process these deficits emerge. The aim of the present study was to compare the brain activation patterns during the perception of subliminal emotions vs. supraliminal low frequency filtered emotions on faces in both healthy and a-MCI subjects through psychophysiological indexes. The secondary aim was to assess whether deficits in autonomic memory anticipate and influence cognitive impairment.
Methods. Subjects included 20 patients with aMCI and 20 healthy individuals. The two groups were matched for age, educational level, and gender. *In Experiment 1*: 10 subjects of aMCI group and 10 subjects of COM group were presented with emotional faces in subliminal presentation (six basic emotions: anger, disgust, happiness, fear, sadness and neutral face). Their skin conductance response was recorded through digital electrodes. *In Experiment 2*: all subjects were presented with the same facial emotion expressions in supraliminal condition. *In Experiment 3*: participants were asked to select the correct emotional target that differs in each block of trials (6*6*6). We investigated a possible autonomic memory effect on overt presentation 48 hours after they had been subliminally primed. Accuracy and RTs were measured.
Results. In contrast with COM group, aMCI group failed to show skin conductance response to the face stimuli in the subliminal condition especially as regards negative emotions such as fear. The COM group was significantly more accurate and had better RTs at recognizing target emotions that had earlier been subliminally primed. In this emotional recognition task, aMCI subjects performed worse in negative emotion recognition in particularly of fearful facial expression. These findings corroborated our hypothesis that Mild Emotive Impairment depends on the deterioration of areas of brain activation involved in processing emotional facial expression and takes part in delaying underlying mental processes. Many studies have shown the role of the amygdala in automatic, involuntary appraisal processes. It seems to play a critical role in perceiving fear so we could presume a specific amigdalic deficit in aMCI subjects.

47. rTMS on left DLPFC affects emotional memory retrieval. The contribution of the stimulus valence

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A reduced number of research has examined whether and where emotion and memory could be represented in the brain. A suggestive hypothesis proposed that the Later Prefrontal Cortex (LPFC) may be identified as the site of emotion-memory integration, since it was shown to be particularly sensitive to the activation of the emotional memories. Firstly, prefrontal cortex seems to be involved in memory mechanisms and, secondly, it is implicated in emotional regulation by managing the cognitive control over emotional behaviour. Nevertheless, there is little understanding around how prefrontal areas accomplish both emotional and memory functions.

In the present research we explored the role of the dorsolateral prefrontal cortex (DLPFC) in memory retrieval process of positive vs. negative emotional stimuli. Secondly, the lateralization effect (left hemisphere) was explored in response to positive emotional material. These aspects were analyzed by using a repetitive transcranial magnetic stimulation (rTMS) paradigm that induced a cortical activation of the left DLPFC. Subjects were required to perform a task consisting in two experimental phases: an encoding-phase, where some lists composed by positive and negative emotional words were presented to the subjects (9 lists, each composed of 20 words, 10 with a positive and 10 with a negative emotional content); a retrieval-phase, where the old and new emotional stimuli were presented for a recognition performance. For the retrieval-phase, stimulus material was composed by a total of 270 stimuli (9 lists, each composed by 30 words grouped in the old and new categories). An rTMS stimulation (5 Hz) was provided over the left DLPFC during the retrieval-phase.

We found that the rTMS stimulation over this brain area affects the memory retrieval of emotional material, with higher memory efficiency (reduced RTs) for positive stimuli, whereas memory effectiveness (accuracy index) was not influenced by the stimulation. This result suggests that left DLPFC activation favours the memory retrieval of positive emotional information in comparison with negative information. The valence model of emotional cue processing may explain the decreasing of RT measure, by pointing out the distinct role the left (and right) hemisphere has in emotional cue processing.

The model allowed to elucidate the relationship between emotional information retrieval and hemispheric lateralization effect, supposing withdrawal-related emotions are located to the right hemisphere, whereas approach-related emotions are biased to the left hemisphere. When one of the two cortical systems is hyper-activated, subjects had an unbalanced response in favour to one of the two emotional categories, respectively the positive or the negative one.

48. Cortical response when a semantic anomaly is detected in action representation. A LORETA source analysis

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The strength relationship between action and language was largely discussed. When perception of plausible or implausible actions within a context is performed a specific semantic process is activated, which was shown to be similar in nature to the processing of anomalous linguistic information.

In the present research it was considered the cortical response to the semantic incongruence induced by an anomalous object-related action, within an actions' sequence. We examined the action representation and semantic processes indexed by event-related potentials ERPs (N400 effect) when plausible (congruous) or implausible (incongruous) actions were performed within a dynamic context (video tapes showing a sequence of four action frames). The N400 effect was explored using a paradigm from neurolinguistic studies, which showed the amplitude of N400 was larger for critical words that were semantically incongruous or unrelated to preceding words. However, the cortical regions involved in the semantic anomaly processing need to be examined as a function of the stimulus category (linguistic vs. action). Indeed, the N400 effect was shown to have a more anterior distribution for action than for linguistic contexts.

Seventeen participants performed an explicit task to distinguish congruous from incongruous final target action. We provided specific contextual constraints where the final frame of a sequence of actions (three preceding actions) represented the congruous/incongruous ending. The semantic anomaly consisted of a gesture that did not have the semantic properties required to perform for the action-goal (functionally unusual). That is, the action was in opposition with the goal-related and intention-related requirements to perform that gesture. ERP analysis and cortical source analysis (LORETA) showed a significant N400-like effect more frontally (DLPFC) and tempo-ro-parietally (left supramarginal gyrus) distributed in response to incongruous condition.

Two possible explanations were proposed. The N400-like would be correlated with an increased difficulty to access the semantic memory networks in comprehension or it would be related to the integrative processing capacity necessary to configure new semantic representations. Moreover it can be argued that the N400-like effect is similar in nature to the N400, which is generally evoked by linguistic stimuli. Nevertheless, the present research showed also significant differences between the cortical generators of action processing and linguistic processing. This fact may be explained by assuming that object-related action representations activate a specific cortical network, more frontally distributed, directly related to congruous/incongruous object use comprehension.

49. Near versus far neglect: a TMS study in normal subjects

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Objectives. Spatial neglect (SN) is a general term referred to a variety of acquired neuropsychological disorders, affecting explicit processing of contralesional

spatial information (or of the contralesional sector of a single object) following unilateral brain damage. SN patients following right hemisphere damage fail to respond, report, or orient to stimuli in the left hemispace (Heilman, Watson, and Valenstein, 1979). Hemineglect can affect peripersonal or near space (operatively defined as the space that can be reached by the hand) or extrapersonal (far space) that remains beyond hand reaching. Far and near space could be remodulated through the use of tools. So patients with far space neglect could normalize their performance in line bisection task using a stick that in some way expands hand reaching remodulating far into near space. Advance in understanding of neglect mechanism underlying neglect has been obtained through models in normal subjects with techniques able to induce virtual transitory cortical dysfunction like transcranial magnetic stimulation (TMS). Through this technique far and near space mechanisms have been studied, showing that neglect like phenomena in near space can be induced by virtual lesioning of posterior parietal cortex, while far space neglect can follow to rTMS disruption of right temporo-parietal areas, in agreement with anatomical observation in brain damaged patients. However, the ability of rTMS models to explore reciprocal remodulation of near and far space according to the use of tools has not been yet investigated. This was indeed the aim of our study.

Materials. 15 subjects (seven men, eight women) aged 28.2 ± 6.3 underwent a land-mark visuospatial task (in which they had judge about symmetry of prebisected lines).

Methods. Lines were presented in a computer monitor in near- (at 60 cm distance) and far-space (120 cm distance) from the eyes, in baseline and during an interfering rTMS train on right PPC (10 stimuli a 20 Hz frequency). In far space condition visuospatial performance both in baseline and during rTMS was explored also with a tool (a 70 cm long stick that the subject used to reach the screen), to evaluate the effects of space remapping. Results confirmed the slight bias toward left in baseline (pseudo neglect) and the ability of disrputing right parietal rTMS to induce virtual neglect (rightward bias) in near space as previously reported; moreover, the tool was able to determine an effective remapping of far vs near space both in baseline (revealed through the abolishing of pseudoneglect) and with rTMS where a virtual neglect was observed even in far space when using tool.

Conclusion. Effective remapping of far into near space can be induced through the use of tools. rTMS virtual lesioning can give relevant contribution to the understanding of mechanisms underlying visuospatial attention and near-face space perception and remodulation.

50. Physiological and anatomical investigations on cortico-cortical connections between the parietal operculum and the motor cortex in humans

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Objectives. The parietal operculum is a complex multimodal cortical region that processes somatosensory nonnoxious and noxious stimuli, visual stimuli and also codes motor behaviour. It contains a complete sensory representation of the human body. Its functional role in behaviour is yet to be fully understood. The objective of the present work is to investigate functional connections between the parietal operculum and the primary motor cortex by assessing short-latency interactions in a dual-coil transcranial magnetic stimulation (TMS) paradigm. In a second step we aim to correlate the TMS data with white matter connectivity measures obtained with diffusion tensor imaging (DTI). Methods -TMS STIMULATION: Five healthy participants were tested. Subjects received two stimuli, (conditioning stimuli - cTMS and test stimuli - tTMS) provided by two different coils. The test coil is permanently placed on the left-hemisphere hand motor cortex while the conditioning coil moves repeatedly in sequence on a grid of 12 different points on the ipsilateral parietal opercular region. Three different intervals between cTMS and tTMS (5,7,9 ms). We recorded the motor evoked potential (MEP) of the right first dorsal interosseus (FDI) muscle during rest, from tTMS alone and from cTMS + tTMS. The data were analyzed by computing the ratio between conditioned MEPs divided by test MEPs. Twelve cTMS pulses were applied for each grid point and each time interval. DTI TRACTOGRAPHY: DTI data were acquired with a Siemens 4 T [30 + 5 independent diffusion directions, b = 1000 mm/s^2, 2 x 2 x 2 mm] and probabilistic tractography were performed on data using FSL software.

Results. Significant short latency inhibitory effects of cTMS on tTMS were observed in all subjects for cTMS applied to 1-2 grid points at inter-stimulus intervals of 5 and 7 ms. Probabilistic tractography provided direct connection distributions between the active opercular region and the hand motor cortex.

Discussion. The inhibitory effects of opercular TMS on MEP amplitude at 5 ms intervals represents indirect evidence of cortico-cortical pathways between the parietal operculum and the primary motor cortex. Probabilistic tractography support electrophysiological results providing a slight but coherent distribution of possible pathways connecting a small region of the anterior bank of the central sulcus with the parietal operculum.

Conclusion. The parietal operculum is functionally and anatomically linked to the primary motor cortex in humans.

51. The involvement of fronto-polar cortex in visual-spatial prospective memory: a cTBS study

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Previous behavioural and neuroimaging investigations document the involvement of Broadmann area (BA) 10 in the neural control of prospective memory, i.e. the ability to remember to execute intended delayed intentions in the future. In a recent TMS study we found a specific involvement of the left BA in the modulation of PM processes during the execution of a verbal event-based PM task. Whether left hemispheric lateralization is related to the use of verbal material or it is rather reflecting a dominant role of this hemisphere in PM remains an unresolved issue. Recent findings reported an asymmetrical pattern of neural activity related to the performance of a PM task characterized by a stronger activation of the left than the right frontal pole suggesting a basic dominance of the left hemisphere in PM operation regardless of the kind of material used. To further address this issue, in the present work we used a transcranial magnetic stimulation (TMS) paradigm to investigate the role of right BA10 in prospective memory (PM) during a visual-spatial event-based task.

Twelve right-handed subjects took part to the experiment. They were evaluated after inhibitory theta burst stimulation (cTBS) over the right BA10, left BA10 and Cz. In the PM procedure, sequences of 4 squares each were presented. During the intersequence delay subjects had to repeat the squares sequence forward or backward (ongoing task). Moreover, at the occurrence of a target square subjects had to press a button on the keyboard (PM score). Recall and recognition of the target squares were also tested.

PM accuracy was comparable between cTBS over the left BA10 and Cz ($p > 0.50$). However, PM performance was poorer after cTBS over the right BA10 compared both to cTBS over Cz ($p < 0.01$) and left BA10 ($p < 0.05$). No significant difference between the three conditions emerged on false alarms and scores obtained on the ongoing, recall and recognition tasks.

In conclusion, our results confirm the functional link between BA10 and PM functioning. Differential cTBS effects of left and right BA10 respectively on verbal and spatial material could suggest that the hemispheric lateralization encountered in different studies is material-specific rather than process-specific.

52. Effects of cTBS of lateral cerebellum on mental rotation task during music listening

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Behavioural experiments showed that listening to a Mozart Sonata (K.488) enhances performance in spatial-temporal reasoning tasks. fMRI studies documented that the cerebellar hemispheres are activated during listening of music as well as in spatial-temporal tasks. The aim of this study was to investigate the role of the cerebellum in the association between spatial and musical domain. We used continuous Theta Burst Stimulation (cTBS) as a tool to down-regulate excitability of cerebellar hemispheres in subjects executing mental rotation tasks either during music listening or in baseline conditions.

Fifty six right-handed healthy subjects participated in experiment 1 and fifty-six healthy subjects participated in experiment 2.

In experiment 1, subjects performed an egocentric mental rotation task, while in experiment 2 subjects performed an abstract mental rotation task.

The first task is a modified version of the Ratcliff's mental rotation task, that involves the representation of body image in space. Subjects were requested to mentally rotate the dummy and to give "left/right" responses according to the position of a visual landmark positioned on the dummy's hands.

The abstract mental rotation task is a modified version of Thurstone's primary mental ability test cards. Subjects were presented with pairs of similar two-dimensional abstract figures positioned differently from each other. They were requested to mentally rotate the images on a plan and to give a "same/different" response, according to whether the resulting images were overlapping or "different" (for example mirrored).

Subjects were randomly assigned to 4 different groups: TBS Music (TM); TBS Silence (TS); Sham Music (SM); Sham Silence (SS). TM and TS subjects performed the mental rotation task following inhibitory cTBS stimulation over the left cerebellum; SM and SS subjects performed the mental rotation task following sham stimulation. The mental rotation task was executed either during Mozart Sonata listening (TM and SM) or in silence (TS and SM). Response times and accuracies were recorded for each subject.

Experiment 1: when using the egocentric mental rotation task, there was not any significant difference between SM and SS groups. On the other hand, subjects of the TM group were faster ($p = .052$) and less accurate ($p = .018$) than subjects of the TS group.

Experiment 2: when using the abstract mental rotation task there was not any significant difference between any of the groups.
These results show that left cerebellum is selectively involved in mental rotation tasks requiring to map the space in egocentric coordinates.
Furthermore, the main findings suggest that music listening does not counteract the effects of cerebellar inhibition, and it is rather deteriorating performance leading to a speed-accuracy trade-off. These findings constrain the hypothesis on the neural correlates of the so called "Mozart's effect" and on its putative role in neurological rehabilitation.

53. Network complexity analysis approach could uncovers an intelligence fingerprint in resting state fMRI data

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Objective. Intelligence literature suggests a role for both local and distributed network of a wide range of brain areas in determining individual Intelligence Quotient (IQ), including nodes in the frontal and posterior lobes as suggested by the Parieto-Frontal integration Theory (P-Fit). At the same time "Resting-state fMRI" (RS-fMRI) approaches uncovered an association between performance in single cognitive tasks and the interplay of several steady state Networks, such as the Default Mode Network (DMN) and the Attention Network (Task-Positive Network; TP). The capability of the RS-fMRI to capture network properties of the brain is starting to be exploited in Intelligence research, however an emphasis on global measures of network organization and Total IQ scores makes it difficult to deeply understand neurobiological Intelligence arrangement and didn't help in addressing subtest scores differences that have been shown to be important in the clinical assessment. Here we explore the link between functional connectivity metrics, including Graph Theory topological parameters and Pairwise Timeseries dependency approach, with both Total and subtest IQ scores. We aim to: (1) test P-Fit in the perspective of RS-fMRI; (2) assess the role of DMN and its interplay with TP nodes in the definition of individual intelligence profile; (3) extend observations to subtest scores.
Materials and Methods. 60 subjects (31 female; age 35 ± 11, IQ 100.1 ± 13) underwent IQ assessment through Wechsler Adult Intelligence Scale (WAIS-R) and RS-fMRI (TR 2.5, 178 scans, 1.5 T). Pairwise connectivities (correlation and mutual information, < 0.1 Hz) individual matrices of 100 anatomically defined cortical and subcortical regions entered graph theory and model based analysis. The model based approach pulled and contrasted intrinsic and extrinsic connectivities of networks of the P-Fit, TP and DMN.
Results. IQ levels seemed to be related to: (1) the strength of the connectivities between P-Fit nodes and the rest of the brain; (2) TP-DMN connectivities separation; (3) DMN intrinsic connectivities. Moreover (4) subtest scores showed both overlapping and specific functional connectivity patterns.
Discussion. These results suggest the importance of the functional independence of P-Fit nodes from the rest of the brain. Moreover, looking at the heterogeneity of the connectivities inside the P-Fit, RS-fMRI analysis seems to be able to unveil segregate modules that show different relations with specific IQ subtest. Finally a more general role of DMN and TP-DMN connectivities is suggested.
Conclusion. We provide evidence to reconcile network data-driven approaches with anatomically based model of intelligence. By moving to region specific connectivities we were able to show how heterogeneities in the distribution might help in separating IQ into modules that could suggest new insight in the neuropsychological testing and localization of cognitive deficits.

54. Neuroplasticity induction in a perceptual learning task. Which is the best timing to apply tES?

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In recent years, we have seen the emergence of transcranial electrical stimulation (tES) for the study of the 'plastic mechanisms' that underlie visual and motor functions in the human brain. tES approaches aim to induce changes in the activity of the brain, leading to alterations in the performance of a wide range of behavioural tasks (Nitsche et al., 2008).
Previous studies suggest that timing is important in determining the behavioural effects of brain stimulation (Nitsche et al., 2003; Kuo et al., 2008; Stagg et al., 2011). However this question has been investigated only in the motor system and only with the application of transcranial direct current stimulation (tDCS). We hypothesize that also in the visual system the effects of tES (i.e., tDCS and transcranial random noise stimulation - tRNS) are highly dependent on the state of cerebral activation during stimulation. Therefore the same type of stimulation, applied in different moments, may have different effects.
In a previous work we have shown that high frequency tRNS (hf-tRNS) is more efficacious than anodal tDCS

(a-tDCS) when the stimulations are applied during the execution of an orientation discrimination task (ODT) (Fertonani et al., in press). But what happen when the same stimulations are applied before task execution?
The aim of this study is to understand if there is a critical timing for the application of tES to obtain the induction of neuroplasticity in the primary visual cortex. Therefore we applied hf-tRNS and a-tDCS before (offline) or during (online) a visual perceptual learning task.
70 healthy subjects participated in the experiment, divided in five groups: a-tDCS offline, a-tDCS online, hf-tRNS offline, hf-tRNS online and sham stimulation. Our results confirm that exists an ideal timing of application, depending on the type of stimulation. High frequency tRNS is efficacious only if applied during the task execution, whereas it's better to apply anodal tDCS before the task.
These results provides important indications for the designing of rehabilitation protocols, highlighting which among the two excitatory techniques is better to choose in relation to its timing of application.

55. The effects of transcranial direct current stimulation on oscillatory brain activity in vegetative state: a preliminary study

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Objectives. We based our study on 2 aspects: (i) the interest in the functional role of oscillatory brain activity in specific frequency bands and the coherence analysis between EEG traces; (ii) the increasing use of non-invasive stimulation of the human brain via transcranial direct current stimulation (tDCS). The aim of the study was to assess the potential effects of the combination of these two lines of research on a group of patients in vegetative state (VS).
Materials. Five patients in VS and 5 age-matched healthy controls received anodal tDCS over the central (C3), parietal (P3), dorso-lateral prefrontal areas (DLPF), and a sham stimulation. tDCS was applied for 20 min at 200 microA. 19 channels-EEG was recorded before and after each stimulation session.
Method. EEG was filtered between 0.5 and 30 Hz by elliptic filters. Fast Fourier Transformation was performed on 2 sec-epochs. For each stimulation site, coherence values were estimated within four frequency bands: Delta (0.5-3.5 Hz), Theta (4-7.5 Hz), Alpha (8-12.5 Hz), and Beta (13-30 Hz). Each coherence map was proportionally thresholded, preserving 50% of the strongest coherence values, to produce a weighted adjacency matrix. The estimated functional connectivity patterns were characterized by means of two global network metrics derived from graph theory: modularity and global efficiency. Modularity measures how the network is organized into modules with high level clustering. Global efficiency measures how efficient the network is in exchanging information at the global level. For each frequency band and site of effective stimulation, we performed a repeated measure analysis of variance (RMANOVA) on each graph measure, using Stimulation (Effective vs. Sham) and tDCS (Pre vs. Post) as factors.
Results. RM-ANOVA computed on modularity in the alpha frequency band revealed a significant interaction between the factors Stimulation and tDCS ($p = .035$) when applying tDCS on DLPF of healthy participants. Two paired t-tests revealed a significant increase of the network modularity (pre tDCS: $.16 \pm .007$; post tDCS: $.21 \pm .014$) when stimulating in DLPF ($p = .009$) compared to SHAM ($p = .76$). No significant effect was revealed on other frequency bands and stimulation site on both healthy participants and VS patients.
Discussion. The tDCS-related modifications of the coherence in the alpha frequencies after DLPF stimulation could indicate that the alpha range is important to transmit information between cortical areas in healthy controls. The increased modularity suggests that the coherently synchronous alpha activities can occur within different modular brain areas and appear substantially independent of one another. This mechanism seems to be lack in VS patients.
Conclusion. Our preliminary study revealed that tDCS but not sham stimulation elevates EEG alpha power and thus demonstrates the feasibility of tDCS to modulate specific oscillatory brain activity. tDCS could be considered a powerful tool for diagnosis/prognosis in altered state of consciousness.

56. A case of isolated and prolonged global aphasia: the role of EEG and FDG-PET in differential diagnosis

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The most common cause of sudden isolated and prolonged global aphasia is stroke, affecting the cortical or subcortical language network. However, an aphasic status epilepticus (ASE) has to be considered as a possible differential diagnosis in awake patients presenting with acute and prolonged language impairment. ASE is suggestive of a localized dysfunction of language processing in the domi-

nant hemisphere. ASE is a rare phenomenon and to our knowledge a few cases are described in the literature. In the differential diagnosis between ASE and stroke with aphasia, FDG-PET imaging should be used when EEG shows no clear evidence of ictal activity. We described a case of a 74 year-old woman who presented sudden onset of both isolated and prolonged global aphasia 5 months after a left temporo-occipital haemorrhage and 20 days after a left hemispheric ischemic stroke. A new ischemic and haemorrhagic event was excluded by neuroimaging (CT and MRI, including DWI). Since several EEGs showed atypical patterns in the left temporal region, an FDG-PET was performed, resulting in two hypermetabolic areas in the left temporal and occipital lobes. The aphasia improved after anti-epileptic therapy. In conclusion, this is a case of post-stroke ASE, in which the evidence of hypermetabolism on FDG-PET allowed a definite diagnosis of epilepsy.

57. A comparative study of central and peripheral responses evoked by concentric and standard surface electrical stimulation

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Introduction. A concentric surface electrode (CE) was recently proposed for noninvasive selective stimulation of small nociceptive fibers. According to recent studies, its concentric geometry and small anode-cathode distance can provide relatively low current intensities which limits depolarization to nociceptive fibers in the superficial layer of the dermis without recruitment of deeper lying non-nociceptive fibers. In this study we aimed to evaluate whether this technique could be considered really selective both in the peripheral and in the central nervous system.
Objectives. To verify if it's possible to record a peripheral sensory nerve action potential (SNAP) using the CE in the territory of a common standard nerve; to compare cortical evoked potentials (EPs) obtained using the CE and a pair of standard surface electrodes (SE) in the same experimental conditions (stimulus intensity, stimulation and recording sites).
Methods. First we performed an orthodromic study using the CE as a stimulator in the territory of the Median nerve (proximal phalanx of digit III) in 10 healthy subjects. Recording electrodes were placed along the course of the Median nerve at the wrist. In each subject we built a recruitment curve in order to achieve the minimum intensity able to evoke a reproducible SAP. Then we compared the CE- and the standard SE-thresholds. In the second part of our study, we recorded CE-EPs and subsequently SE-EPs stimulating the same hand area.
Results. we were able to obtain reproducible CE-SNAPs at low current intensities (mean 2.5 mA, range 2.1-5.0 mA), with the CE- thresholds lower than SE-thresholds. Latency and amplitude of the cortical vertex CE-EPs and SE-EPs were not significantly different.
Conclusions. The recording of a reproducible SAP using the CE strongly suggests an A-beta fibers coactivation at range intensities commonly used in previous studies to evoke the so called "pain-related EPs". In addition, the similarity of the EPs obtained using both types of electrodes strongly disagrees with the supposed CE-selective stimulation of small nociceptive fibers. CE-EPs are probably entirely subtended by the few fast fibers co-activated in the peripheral nervous system according to the "first come, first served" theory. In this sense the CE-EPs are likely an example of a multimodal neural response of the salience detection system.

58. Effect of repetitive transcranial magnetic stimulation on the perception of dyspnea induced by inspiratory resistive loads

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Introduction. Neuroimaging and neurophysiological studies have shown that nociceptive stimuli elicit responses in an extensive cortical network including somatosensory, insular and cingulate areas, as well as frontal and parietal areas. This network, often referred to as the ''pain matrix'', is viewed as representing the activity by which the intensity and unpleasantness of the percept elicited by a nociceptive stimulus are represented. Non-nociceptive stimuli, including Dyspnea, can elicit cortical responses with a spatial configuration similar to that of the ''pain matrix'. According to this theory we can expect that repetitive Transcranial Magnetic Stimulation (rTMS) able to modulate pain perception could affect also Dyspnea Perception.
Methods. We studied 12 healthy subjects breathing against progressive inspiratory resistive loads before and after effective and sham rTMS (1 Hz) applied using a standard, figure-of-eight-coil and MagPro X100 stimulator over the right motor cortex. During the loaded breathing ventilation, tidal volume, respiratory frequency, pleural pressure swings, arterial oxygen saturation, end-tidal partial pressure of CO2, were recorded A stimulus train of five impulses of 1 ms duration at a frequency of 250 Hz was used to induce Pain. Dyspnea and pain were rated by a Visual Analog Scale (VAS). The individually averaged VAS values were entered into a repeated-measures two way ANOVA.
Results. Compared with prestimulation, ventilation, tidal volume, respiratory frequency, pleural pressure swings, end-tidal partial pressure of CO2, and arterial oxygen satu-

ration were unchanged. Compared to the control test, the perception of dyspnea intensity was significantly lower during the tests performed after the rTMS; the ratio between the degree of intensity of breathlessness (VAS) and all respiratory variables measured was significantly lower ($F = 26.4$, $p < 0.0001$) during the test run after rTMS. The intensity of pain decreased significantly after magnetic stimulation. The changes in the perception of the intensity of dyspnea induced by rTMS correlated significantly with changes in pain intensity (Wald^2 test: 5.62, $p < 0.018$). There was no difference in the intensity of dyspnea and pain between the first and the second test of the sham protocol.

Significance. rTMS of M1 induces reduction of Dyspnea intensity for each inspiratory resistive load. The significant correlation observed between changes in dyspnea and changes in pain induced by rTMS further supports the hypothesis that the mechanism underlying these phenomena is common to the two sensations. These data suggest that Dyspnea and Pain are processed in common cortical-subcortical structures. This cortical network might represent a basic mechanism through which significant events for the body's integrity are detected, regardless of the sensory channel through which these events are conveyed.

59. Luminant and chromatic VEPs in dyslexic children: magnocellular or parvocellular dysfunction?

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Developmental dyslexia is a specific learning disorder, characterized by reading difficulties affecting accuracy and/or speed, word recognition, and spelling and decoding abilities. These difficulties are realized in the absence of neurological, cognitive, sensory and relational deficits, and with normal school and educational opportunities.

The etiology of dyslexia has not yet been clarified, but the hypothesis of a deficit in the visual system was the first to be made and is still one of the most reliable. In particular, it was hypothesized that in dyslexic subjects the magnocellular system is alterated. This system is responsible for the spatial representation of visual events when reading and detects image movements out of the fovea in order to restore gaze on the target. Its involvement would be reflected in some difficulties presented by dyslexic subjects: frequent replacement and/or reversal of similar graphemes and the inability to maintain binocular fixation. However, this assumption has recently been questioned: in some works based on the registration of Visual Evoked Potentials (VEPs) to luminant stimuli magnocellular system dysfunctions were not shown, but, on the basis of the results obtained, it was rather hypothesized a deficit of the parvocellular system, which is involved in the discrimination of fine details, colours and shapes. Possible malfunctions of the parvocellular system would better explain deficits of letters recognition in these patients and may have important repercussions on the choice of more effective rehabilitative interventions in facilitating reading.

As chromatic stimuli are considered specific for the parvocellular system, the purpose of this pilot study was to investigate its possible involvement by recording chromatic VEPs in 6 dyslexic children and 6 age- and sex-matched healthy controls. The results obtained could be used in the rehabilitation of dyslexia.

60. Detection of human agents in interaction: early ERPs evidences

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In order to interact effectively, we need to swiftly detect other human beings and recognize them as potential interagents. According to direct access theories, the first steps of visual information processing offer us an informed direct grasp of the situation. Biological system detection may be the gateway of such smart processes and then may influence initial stages of perception fostering adaptive social behaviour. Neural markers of human features have been found but classic paradigms used a contextual individual stimuli. To overcome that limitation and investigate early neural correlates of human agents detection in ecological situations, we compared scenes showing a human vs. artificial agent interacting with a human interagent.

20 volunteers participated to the study. Participants were asked to observe dynamic visual stimuli showing realistic interactions. EEG was recorded and then ERP for selected ROI were computed. Each stimulus depicts an arm executing a gesture addressed to a human interagent. Visual features of the arm were manipulated: in half of trials it was real; in other trials it was deprived of some details and transformed in a statue-like arm. The dynamic stimuli was composed by two frames presented in close succession (SOA = 200 ms) and ERP has been time locked to the second frame in order to explore the specific processing phase of intention attribution.

Morphological analysis revealed an early negative deflection peaking at about 155 ms and two positive deflections peaking respectively at 250 and 350 ms. Peak amplitude data have been statistically analysed by repeated measures ANOVA. No statistically significant differences due to Agent (human vs. artificial) have been revealed by the analyses applied to the positive peaks. The analysis of

the N150 peak amplitude, instead, showed a significant simple effect for Agent and significant interaction effects (Agent x Side and Agent x Region x Side). The peak was ampler in the left anterior fronto-temporal region, in particular when the gesturing arm was human.
Two negative deflections have been associated to perception of human features: N170 and N190. They are respectively sensitive to faces and body parts and are ampler in parieto-occipital regions. The different scalp localization and the earlier time frame of the negative component we found suggest that it may be a different potential and may have a different source. The early negative deflection, N150, that we found to be different between the human and artificial conditions, may not depend on luminance or contrast values, it being presumably associated to human agency detection. In fact, the cortical localization of this peak, that is more left fronto-temporally distributed, suggests the hypothesis of an early agent-related category-effect mediated by cortical anterior structures.

61. Serotonin activity in tinnitus: an Intensity Dependence of Auditory Evoked Potentials (IDAP) study

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Introduction. Tinnitus is the most common auditory disorder, affecting million people in the world. It is defined as tone or noise sensation, in the absence of a physical sound source, that patients can refer in one or both the ears or into the head. It has been theorized that the cause of the disorder could be a sensorineural hearing loss (SNHL) leading to a plastic reorganization of auditory cortex and characterized by an altered frequency representation. Furthermore, it has been suggested a central role for limbic and paralimbic structures in a gating process, involved in switching on or off the tinnitus sensation. One of the most limbic-relevant neurotransmitter is serotonin (5-HT) and its depletion has been correlated with symptoms, such as hypersensitivity to noise, reduced REM sleep and depression/anhedonia, co-occurring with tinnitus to varying degrees. The intensity dependence of auditory evoked potentials (IDAP) is a non-invasive electrophysiological technique suggested to be a specific biological marker of central serotonergic activity.
Objective. The aim of the study was to investigate the cerebral serotonin activity in patients with tinnitus as indexed by IDAP.
Methods. Two groups of patients with tinnitus (mean age 43,86 ± 10,99), monolateral (n = 7) and bilateral respectively (n = 8), referring the onset of symptom from no longer than two years, and a control group (n = 9), matched for age and sex, were recruited for the study. All the subjects had a normal hearing or at most a mild hearing loss (≤ 40 dB). All subjects underwent IDAP recording and brainstem auditory evoked potentials (BAEPs) to investigate the functionality of the auditory system; audiometric test and stapedius reflex test with the measure of the dynamic range for the diagnosis of hyperacusis were also performed. STAI, BDI and PSQI tests were administered. Newmann THI test was administered to assess the impact of the tinnitus on life. We had to exclude from the analysis 14 subjects also recruited: 4 subjects presented an altered BAEP pattern, 4 subjects were suffering from migraine and 6 subjects presented technical problems during IDAP recording.
Results. No significant differences were displayed by the groups, concerning STAI, BDI, PSQI scores. A steeper ASF slope and a higher intensity response at each intensity stimulation were evident in patients. A correlation between IDAP and both BDI and Newmann scores was observed. BAEPs showed a normal pattern in all subjects. However a longer interpeak latency III-V resulted in patients for both stimulation intensities.
Discussion. The greater intensity dependence in tinnitus sufferers could be related to the preactivation level theory involving the serotonergic system; low preactivation levels lead to stronger intensity dependence of the evoked response. The correlation between BDI scores and ASF slope could reflect the influence of depression traits on IDAP. The correlation between Newmann scores and ASF slope could provide the physiological basis of the empirical observation of a general worse toleration of monolateral tinnitus relative to the bilateral one.

62. Rhythmic transcranial magnetic stimulation locally entrains natural brain oscillations

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Introduction. The generation of brain rhythms by transcranial brain stimulation and exploring the behavioural consequences thereof ("entrain and measure approach") would allow to test for a causal role of oscillations in shaping behaviour.

Objectives. To test whether brain oscillations can be entrained by Transcranial Magnetic Stimulation (TMS) when delivered at the natural frequency of a brain area. Specifically, we examined the possibility of entraining a right parietal α-generator by TMS at individual α-frequency.
Methods. TMS-site was first individually identified using a parietal α-localizer task (attention orienting), MEG and source localization in MRI. Ten subjects then underwent 62-channel EEG under neuro-navigated TMS in 4 conditions: 5-pulse TMS trains delivered (1) at individual α-frequency (α-TMS) and three control conditions, consisting of (2) arrhythmic 5-pulse TMS, (3) α-TMS at an active but suboptimal coil orientation, and (4) α-TMS at an inactive (sham) orientation. Evoked oscillations were examined using wavelet analysis over the train, detailed waveform analysis per each of the five pulses, and computation of phase locking values (PLV) across trials.
Results. Parietal α-TMS triggered a parietal α-power increase. The α-response at the target site showed a progressive enhancement with a maximum towards the end of the train. This was due to significant phase locking of α-activity to the TMS pulses (PLV), which depended on pre-TMS α-phase, i.e., the on-going α-oscillation. None of these effects were observed in the control conditions.
Discussion. Our results demonstrate that frequency-tuned TMS can drive brain oscillations through a progressive synchronization of the underlying generator. The dependence on pre-TMS phase suggests the entrainment of natural oscillations instead of the imposition of an artificial rhythm. This shows that TMS can generate functionally relevant brain oscillations, and by extension that entrainment is one mechanism of TMS-action.

63. The contribute of FMRI in exploring brain and cognitive function in consciousness disorders: a follow-up case report

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The diagnosis of vegetative state (VS) relates to patients who do not show awareness of self or of the environment, that is, who do not manifest any reproducible, purposeful or voluntary behavioral responses to sensory stimuli, including language comprehension. When these patients become able to respond to commands, the diagnosis shifts to Minimally Conscious State (MCS), and then, if they become able to functionally use an object, they enter the status of Severe Disability (SD).
Clinical assessment of residual cognitive functions in these patients, however, may be particularly difficult due to the extremely reduced or undetectable behavioral output. Over the last decades, functional imaging and electrophysiological techniques have been used to investigate brain activity in relation to residual cognitive abilities in patients suffering from disorders of consciousness, independently from their ability to produce any behavioral or motor output.
Interestingly, functional magnetic resonance imaging (fMRI) recently contributed to demonstrate that patterns of brain activity in subgroups of patients with disorders of consciousness patients may be comparable to those of healthy control subjects and able to predict their clinical recovery (Coleman et al., 2007, Boly, 2011).
Here we report the results of an auditory language listening fMRI study in patient O.A., who clinically transitioned from VS to MCS, and one year later from MCS to SD. His brain activity was evaluated longitudinally at different time-points of his clinical history: here we present the results from the two sessions acquired just prior to the two clinical transitions.
During the VS prior to transition to MCS, the patient showed task-related significant activations bilaterally in the superior temporal gyrus, including auditory cortex, and in the left inferior frontal cortex, similar to the pattern of brain response found in a group of control healthy subjects (N=4). As compared to the first evaluation, a significant increase in both extension and magnitude of brain activity in the left inferior frontal and bilateral temporal cortex, and an additional recruitment of middle frontal and posterior parietal areas, were found in the MCS state a few weeks before the transition to SD.
These results provide further encouraging evidence in support of fMRI for the identification of residual brain and cognitive functions in patients with severely impaired consciousness and for the detection of neural activity predictive of clinical recovery.

64. How sleep and sleep deprivation modulate juvenile myoclonic epilepsy: a combined EEG-TMS study

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Objective. Simultaneous EEG-TMS permits to investigate cortical reactivity to external perturbations. TMS evoked potentials (TEPs) are described in normals during sleep (S) and wake (W) but neither after sleep deprivation (SD) nor in the frame of pathologically enhanced excitability – i.e. epilepsy. The aim of our study is to identify

TEPs and their modifications during W, SD and S in normals and in juvenile myoclonic epileptics using EEG-TMS coregistration.
Materials and methods. Focal TMS was delivered to the left primary motor cortex at 110% of motor threshold in 12 controls and 10 epileptics. Patients maintained therapeutic regimen throughout the study. TMS was delivered randomly 8-15 sec during W, SD and S. At least 150 stimuli were recorded for each condition. EEG was simultaneously acquired from 32 scalp electrodes with the Brain Vision Recorder system.
Results. TMS induced a reproducible sequence of deflections on EEG. An amplitude's statistically significant difference between states was observed for the late peaks (P100 and N190). In normals, after SD P100 amplitude showed a globally distributed increase, while N190 slightly augmented over the posterior areas. In patients, both after SD and during S, amplitude enhancement was evident for the P100 and N190 peak over the antero-central derivations. Comparing the two groups, epileptics showed overall higher amplitude potentials, with P100 more evident over the posterior areas in S2, and N190 more represented anteriorly in S2 and centrally during SD.
Discussion. We demonstrate an overall higher cortical excitability in epileptics. Moreover, the same group showed an amplitude increase of TEPs over the anterior areas after sleep deprivation and during rebound sleep. This phenomenon could relate to the dysfunction of the corticothalamic circuit supposed to cause myoclonic epilepsy and the higher susceptibility to the effects of sleep deprivation of frontal and prefrontal areas.
Conclusion. sleep deprivation is an effective enhancer of cortical excitability, specially in the epileptic, pathologically hyperexcitable, brain.

65. Event Related Potentials Evoked by Incongruous Words with High and Low Frequency of Use in Spoken Language and progression toward Alzheimer's disease in patient with Mild Cognitive Impairment (MCI): a five years longitudinal study

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Aims of the study was to assess if baseline N400 in response to verbal stimuli of different frequency of use in Italian language can predict clinical and neuropsychological progression towards Alzheimer's disease in subjects with MCI.
Subjects: Fourteen subjects, diagnosed as MCI according to the accepted international criteria (1) were enrolled.
Methods: At the baseline N400 was recorded in all subjects. In this study N400 was evoked by a written verbal paradigm, the evoking stimulus was a semantic incongruity in a short phrase. Target stimuli has been selected among words in the Italian language with high (Frequent words) and low (Rare words) frequency of use.
Patients then underwent a five years clinical and neuropsychological follow-up in order to detect conversion to dementia. The difference of baseline N400 latencies obtained from Rare and Frequent (R-FN400) words were compared in converted and non-converted groups of patients. Positive values were obtained if Rare words evoked N400 with longer latencies with respect Frequent words. negative values were obtained when Rare words showed N400 latency values shorter than Frequent words.
Results: five of the fourteen patients converted to dementia while in nine patients cognitive impairment was unchanged or slowly progressing. The group of non converted patients showed a baseline positive R-FN400 mean latency (33 ± 54 msec) while the group of converted patients showed a negative R-FN400 difference (-14 ± 18 msec). Difference was significant between groups.
Discussion and conclusion: A baseline assessment comparing N400 latency differences evoked by Frequent or Rare words detect progression toward dementia in a group of subjects with MCI. Group of MCI subjects not progressing to dementia showed positive R-FN400 latency values as found in normal subjects (2), while MCI subjects converted to dementia had R-FN400 negative latency values. The modification of N400 latency in MCI patients is possibly caused by impairment in semantic memory access, that could cause the loss of the frequent stimulus-induced facilitation, seen in healthy controls.

66. Magnetic stimulation of the left posterior superior temporal sulcus produces remote effects on the posterior parietal cortex during observation of grasping

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Objective. The posterior superior temporal sulcus (P-STS) and the posterior parietal cortex (PPC) are active during observation of others' goal-directed actions. We investigated functional links between the P-STS and PPC using a paradigm that combines offline repetitive transcranial magnetic stimulation (rTMS) and functional magnetic resonance imaging (fMRI) according to a 'perturb and measure' approach.
Methods. Participants were stimulated with 1 Hz (inhibitory) rTMS over the P-STS region for 10 minutes and underwent MRI immediately after. While scanned, participants were shown short video clips of either a hand grasping an object (grasp clips) or a hand moving next to the object (control clips). RTMS-fMRI was applied

in four different blocks. In two blocks the left P-STS region was stimulated and in the other two the right P-STS region was stimulated. For each stimulated side, TMS intensity was set to 95% of resting motor threshold (effective TMS) in one block and to 50% of resting motor threshold (sham TMS) in the other block. The analysis was made on regions of interest defined by contrasting the grasp versus the control clips.

Results. Only rTMS over the left P-STS, but not over the right P-STS regions produced remote effects on the cortical areas of interest compared to sham TMS. The effects consisted in an increased activation in the PPC bilaterally to grasp stimuli compared to control clips.

Conclusions. The present data demonstrate a direct functional connection between the left P-STS and the left and right PPC. This cortico-cortical link is effective during observation of others' praxic hand actions rather than during simple vision of objects and unrelated hand movements.

67. Neurophysiological correlates of motor anticipation in open skill sports

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The ability to anticipate the action of the adversary offers an advantage in open skill sports where attacks and counterattacks depend on the prediction of the opponent's actions. Karate athletes (KA) learn to predict the opponent's next move by interpreting cues from his body kinematics which could precede a move by several tens of ms. Trained KA detect and elaborate these cues to select the best response possibly by optimizing a series of covert brain process linking sensation to action. To study the neuronal substrate of these processes we correlated the predictive and reaction capacity with the movement-related cortical potentials (MRCPs) in a group of 10 KA who were asked to press a computer key as soon as they foresee, on the basis of cues, the next move of an expert karateka (actor) in a video. Since sensorimotor transformation may depend on the internal state of the network at the time of the cue/stimulus processing, we computed a time-frequency analysis of the EEG signals in the pre-cue period. In detail, KA were submitted to two different videos in which the actor performed either a single move (test 1: left leg kick) or one of three different moves in a pseudo-random order (test 2: right or left strike or a kick). During test 1 participants performed a simple reaction time task by pressing with their right index a computer key as soon as they foresee the actor's move, while during test 2 they performed a complex reaction time task, by pressing one of three keys to choose among 3 possible responses. Each move was preceded by 400 ms by a postural setting of the actor (cue) providing information on the type of the following move. MRCPs were obtained from epochs of EEG activity recorded at Cz and Fz sites lasting from -5 to +3 s with respect to the start of the actor's move. The onset of EMG activity of the right extensor digitorum muscle was used to calculate the response time and to sort KA into two groups, fast (F) and slow responders (S). In both tests the time to peak of the premotor positivity (PMP), which precedes the motor cortex potential (MCP) i.e. the outflow from the motor cortex, was simultaneous or even precede the occurrence of the cue, leading the onset of EMG activity to be almost simultaneous with the beginning of the actor's move, although anticipated in F with respect to S. Analysis of MRCPs of S and F athletes revealed a significant difference in the latency of N1, the first component of MCP, but not in the latency of PMP peak, indicating a more prolonged cue processing in S with respect to F. In addition, in the 2 s period preceding the cue, F showed, in test 2, a lower EEG spectral power in the α_1 band and a higher power in β_2 and γ bands as compared to S. In conclusion, we may assume that cue information is used by KA to anticipate the opponent's moves and that a better performance depends on the ability to reduce the time of cue elaboration which is influenced by the attentional state in the pre-cue period.

68. Frontal midline theta is related to error during reaching movements

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We have previously shown that during the execution of a visuomotor tracking task frontal midline theta (fmθ) putatively generated in the anterior cingulate cortex (ACC) increased in an inverse relationship with tracking accuracy. We speculated that fmθ represents the EEG correlate of motor error processing within the ACC in line with the activation of this area in case of conflict or error detection/correction in cognitive tasks. Since tracking is a continuous task, it was not possible to lock θ power changes to any anchor time points, such as the appearance of visual feedback or the beginning of corrective movements. To further study the association of fmθ with error detection and/or correction, continuous tracking was replaced by individual reaching movements performed under visual occlusion of the arm in the first half of the trajectory and in the presence or absence of a variable degree of visual shift (5°, 10° or 15° rightward) induced by prismatic lenses. Wearing the prisms led movement direction to shift to the right of the target until adaptation occurred, while wearing sham lenses, once prism adaptation was achieved, led movement direction to shift leftward. We

expected that when visual feedback of the hand became available, the spatial discrepancy between the predicted and the actual direction of movement generated an error signal able to trigger movement correction. In 12 normal subjects 32-channel EEG activity was recorded simultaneously with acquisition of hand kinematics by an infrared optoelectronic system. The times at which visual feedback of the hand became available and movement correction started were used as anchor points to measure event-locked spectral perturbation (ERSP) in the θ frequency range for a series of EEG sources (ICs) that were extracted from EEG signals by independent component analysis (FastICA algorithm) and exhibited scalp maps and dipole coordinates consistent with a frontal location. For each subject two ERSPs were obtained corresponding to the conditions of low and high motor error calculated as the angular difference between the direction that the movement should ideally have to hit the target and the direction that it actually had at the time of appearance of the feedback. With respect to the ERSPs computed for the low error condition, those obtained for the high error condition showed a significantly higher increase in θ activity starting approximately 200 msec after the appearance of visual feedback. More precisely, such transient increase was centred around the beginning of the corrective movement and was more prominent in an IC provided with a midfrontal topography and with an equivalent dipole location near the ACC. The present results confirm and extend our previous data showing that 1) fmθ increases during the execution of a visuomotor task in close association with the occurrence of motor error, 2) such increase follows the appearance of visual feedback in coincidence with error correction.

69. Clinicoanatomical evidence that white matter injury may lead to signs of neglect: a case report

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Visual neglect has been associated with focal damage of parietal, frontal or temporal lobe, as well as basal nuclei and thalamus. Latest investigations suggest that visual neglect could be also related to damage of the white matter (WM) tracts connecting the frontal and the parietal/temporal lobes in the right hemisphere or damage of the visual pathways up to the calcarine cortex added to the posterior part of the corpus callosum. However, these investigations have evaluated mostly patients suffering from WM injury associated with grey matter damages. Here, we discuss the case of a patient affected by a specific WM damage (i.e. a monophasic, inflammatory demyelinating disease as acute disseminated encephalomyelitis - ADEM). His brain MRI showed multiple areas of altered signal of WM in the right temporal and parietal lobes, in the left corona radiata, in the WM around the calcarine sulcus and in the callosal splenium. Four weeks after injury he recovered from coma and showed extrapersonal neglect and dressing apraxia of the left part of the body. Such a condition lasted about three further weeks. Indeed, a contemporary MRI showed an almost complete remission of the WM damage. On this base, we assume that WM damage per se may cause visual neglect, disrupting the integrated functioning of fronto-parietal or temporo-parietal networks and/or WM visual pathway added to the posterior part of the corpus callosum.

70. Does sleep deprivation modulate cortical reactivity? A combined EEG-TMS study

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Objective. Electroencephalography-transcranial magnetic stimulation (EEG-TMS) co-registration is an innovative tecnique to study cortical reactions to external perturbations and their modulation. TMS evoked potentials (TEPs) have been described during both wake and sleep, but the effect of sleep deprivation on TEPs is unknown.
To study vigilance-related modifications of cortical reactivity by measuring variability in TEP.
Materials and methods. In twelve healthy subjects, EEG-TMS co-registration was performed with compatible equipment (BrainVision Recording System, 32 electrodes) and the dominant motor area was stimulated in a standard wake condition, after partial sleep deprivation, and during sleep. Of the initial twelve subjects, nine fell asleep during the experiment and qualified for analysis. EEG traces were scored off-line according to Rechschaffen-Kales sleep stages; segments were analysed from 100 msec before to 500 msec after the TMS artifact.
Results. TMS induced clear-cut EEG activity lasting up to 300 msec after the TMS artefact and consisting of alternating positive and negative polarity deflections. Sleep deprivation caused an important, statistically significant, amplitude increase of the whole EEG response to TMS, with a prominent anterior distribution.
Discussion. Our results evince increased cortical reactivity after sleep deprivation, with a tendecy for a more anterior topographical distribution of this effect. Neurophysiologically, this finding underpins the notion that the frontal-prefrontal areas are more susceptible to the effects of sleep deprivation. Moreover, while no effect of sleep deprivation in healthy subjects has been detected with

TMS alone, TMS-EEG co-registration seems to be a more sensitive tool for studying vigilance-induced modulations.
Conclusion. Sleep deprivation is a powerful enhancer of cortical excitability, as measured by TEPs. A topographical distribution of this effect can be observed, with consequent neurophysiological implications.

71. Inferior precentral and postcentral gyrus, brain areas for speech articulation: a case of pure anarthria

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Pure anarthria, (or apraxia of speech), concerns a motor speech disorder characterized by an impaired ability to coordinate the sequential articulatory movements necessary to produce speech sounds. Affected patients although aware of what they want to say and how this sound, are not able to perform those articulatory movements. No other oro-facial disorders are present. Focal brain damage, such as stroke, may cause this disorder, however, information on the brain regions entailed in the disorder is controversial. Extant evidence would suggest the involvement of Broca's area, left frontal and temporo-parietal cortex, left superior anterior region of the insula and left sub-cortical structures, as the basal ganglia. Activation in the frontal operculum as well as in the premotor and primary motor cortices was also noted in speech articulation. All these neuroanatomical investigations, however have estimated patients who suffered from both aphasia and apraxia of speech. We report a single case of a pure anarthria/apraxia of speech of a patient affected from focal brain damage of the precentral and postcentral gyrus and the underneath white matter. No evidences for damage of the inferior frontal gyrus including Broca's area, subcortical structures of the brain or anterior insula were observed.

72. Effects of the transcranial direct current stimulation treatment on spontaneous and evoked cortical activity in Alzheimer's disease

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Background. Transcranial direct current stimulation (tDCS) has been shown to be able to induce specific effects on cortical excitability and behavior in a polarity-dependent way. Currently, there is a growing interest in applying this methodology therapeutically, to reduce cognitive deficits in patients with chronic neurodegenerative diseases, as Alzheimer's disease, but the direct impact of tDCS-induced modulation on cortical excitability still remains to be investigated.
Objective. The aim of our study was to investigate the tDCS-induced effects on spontaneous and evoked cortical activity, combining transcranial magnetic stimulation (TMS) and electroencephalography (EEG).
Methods. Fourteen AD patients participated in this study. The patients were randomly assigned to one of two study groups. The first group underwent a 2-week of real tDCS treatment, while the second one underwent a 2-week placebo treatment. Anodal tDCS (2 mA) was delivered for 25 minutes above the left dorsolateral prefrontal cortex (DLFPC). The EEG activity and TMS-evoked cortical potentials (TEPs) were recorded from 19 scalp electrodes. The spectral power of all the EEG frequencies (range: 2-45 Hz) and the spectral coherence were calculated. The tDCS-induced changes on TMS-cortical responses were evaluated analyzing the cortical local field power. The statistical analyses were performed to reveal changes in cortical activity and reactivity after tDCS treatment, in comparison with baseline measure.
Results. We found a significant decrease on cortical reactivity after placebo treatment to the left DLPFC, and no cortical excitability change after real tDCS treatment. The reduction after the placebo treatment was observable both on the stimulated side as well as in the contralateral prefrontal cortex. Moreover after real tDCS treatment, we observed a significant power decrease in the low frequency bands, and in cortical connectivity.
Conclusions. This study shows the cortical reactivity effects of a tDCS neurorehabilitation protocol. The anodal tDCS treatment on DLPFC doesn't induce a specific modulation of the cortical excitability as well as the cognitive performance, in patients with Alzheimer disease. Probably, the stimulation during the execution of a task could potentiate the stimulated area and the engaged network, more significantly than a tDCS treatment during the resting state. However, this study supports the combination of TMS-EEG as a tool for examining the non invasive brain stimulation induced effects in the clinical protocols.

73. EEG connectivity correlates of fatigue in Multiple Sclerosis

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Background. Fatigue in one of the most disabling symptoms in multiple sclerosis (MS). Neuroimaging studies reported a relationship between morphological/functional brain chang-

es and fatigue severity. Electroencephalographic (EEG)-based studies searching for correlation between neurophysiological parameters and fatigue severity are limited.
Objective. To investigate the relationship between fatigue severity and EEG connectivity.
Method. Twenty patients with relapsing remitting form of MS underwent resting EEG analysis and subjective fatigue assessment using a standardized self-administered questionnaire (fatigue severity scale - FSS). Patients had no other neurological and/or psychiatric disturbances and were not disabled. The measure of EEG connectivity was obtained using eConnectome (MatLab-based software). Connectivity analysis was applied for delta (1-3 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta1 (13-18 Hz), beta2 (19-21 Hz) and beta3 (22-30 Hz). QEEG data obtained were used for correlation analysis with fatigue severity values.
Results. Several negative correlations were found between anterior-posterior/posterior-anterior connectivity in the left hemisphere (delta, theta, beta bands) and FSS. Stepwise regression analysis reveled O1-Fp1 connectivity measured for beta2 band as predictor of FSS.
Conclusions. Correlation between long distance connectivity and FSS might reflect the modulation of fatigue on structural changes in the left fronto-occipital fasciculus. The study showed the possibility to objectivate fatigue severity, which is typically a subjective symptom, using QEEG approach. If confirmed and validated, the method could be useful as a paraclinical endpoint for the assessment of fatigue in MS.

Indice degli autori

Archives Italiennes de Biologie

VOLUME 149 • NUMBER 3 (S) • SEPTEMBER 2011