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SECTION I

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Abstracts

The role of neuroimaging in language rehabilitation

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Functional magnetic resonance is the imaging technique that has been most extensively used to investigate the neural mechanisms of recovery of aphasia due to cerebrovascular lesions. The crucial need for longitudinal investigations of recovering patients adds a further layer of complexity to the difficult task of analyzing brain activation in cross-sectional studies of brain-damaged individuals. A dedicated workshop held at Northwestern University (Evanston, Illinois, USA) has adressed, by means of intensive discussion sessions among international experts in this research area, the main problems related to data analysis techniques. In particular, the discussion was focused on pre-processing, statistical analysis and interpretation of the results. While it was generally acknowledged that general procedures are difficult to apply to a wide array of diverse experimental paradigms, the workshop has generated a number of guidelines, which can be useful for investigators willing to enter this complex research field.

Cognitive deterioration, language and non-invasive brain stimulation

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Recent studies have reported enhanced performance on specific cognitive tasks in patients with several types of neurological diseases (Alzheimer – AD, stroke) after receiving non-invasive brain stimulation (NIBS), i.e., repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS). Converging evidence has indicated that intermittent rTMS above 5 Hz (high frequency), which leads to increased neuronal firing, appears to have positive effects on behavior. Moreover it has also been shown that anodal tDCS can induce similar effects, increasing neuronal firing rates. Specifically, it has been showed by several experiments that rTMS reduces vocal reaction times for picture naming in normal young and old subjects and improves the number of correct responses in AD patients. Using tDCS, it has also been shown that anodal tDCS can ameliorate language performance in normal young and old subjects and deficits in AD e stroke patients. Studies have shown evidence of plastic changes in surviving neurons, even in severely affected areas. In AD patients, the NIBS-induced partial recovery of language abilities, may be due to a strengthening of the synaptic activity of the surviving neurons in the stimulated network. The same phenomenon can be observed in stroke patients after a lesion to an adjacent area or when connected areas become "silent" due to diaschisis and lesion-induced effects that result in silent synapses. NIBS might induce a gradual readjustment of an area that remains intact but "functionally" suppressed due to a steady reduction in synaptic strength. Therefore, these data support the idea that brain stimulation-induced changes in synaptic strength are an essential step toward the recovery of function. Indeed, improving the performance of a specific system within the functional network leads to more effective processing. Compensatory networks may be recruited or rebalanced to accomplish the impaired function. TMS or tDCS might induce a gradual readjustment of an intact but "functionally" suppressed area due to a steady reduction in synaptic strength. Therefore, these data supported the idea that brain stimulation-induced changes in synaptic strength are an essential step toward recovery of function. Therefore, NIBS could be used to strengthen or modify a network that is specific to a diminished cognitive function. Studies have suggested that the best way to perpetrate this strengthening is to stimulate the area and activate the network supporting the specific function. This approach can be achieved by combining exogenously induced plasticity (i.e., NIBS) with a specific training-induced plasticity (i.e., cognitive training). In part, this approach resembles the one used to improve motor performance in patients with hemiplegia.

If NIBS is applied when the system is in a given functional state, it will enhance and strengthen the specific distributed functional cortico-cortical (or subcortical) network that is active rather than inducing a non-specific arousal or activation of the system. The potential for inducing a slowing down of the cognitive decline or even a behavioural improvement in AD or Stroke patients, and the further possibility that these effects become long-lasting, are intriguing; and NIBS study's results could lead to the development of a new therapeutic approach.

Relationship between language and gestures in neuropsychology

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In cognitive neuropsychology, recent models of praxis processing have been mapped onto cognitive models of language processing, suggesting that gesture and language make use of parallel cognitive mechanisms. To better understand the relationship between gesture and language, two individuals with dyslexia, two with constructional dyspraxia and one child with both constructional dyspraxia and dyslexia were tested on a series of tasks assessing each mechanism of the cognitive models of language and gesture processing. The integrity of the lexical route for gesture and language processing was assessed using tasks measuring recognition (input lexicons) and identification (semantic systems) of gestures and words, gesture production and reading abilities (output lexicons). The sub-lexical route was tested using tasks assessing the imitation of meaningless gestures and the reading of pseudo-words. Furthermore, the unique dyspraxic pattern of an individual with Asperger syndrome will be discussed. Results showed that the two dyslexic children did not show any sign of limb dyspraxia. On the contrary, the two children with constructional dyspraxia demonstrated difficulties in language and gesture processing, both at the level of the lexical and sub-lexical routes. The child with dyslexia and constructional dyspraxia had difficulty in executing both meaningful and meaningless gestures as well as in reading words and pseudo-words. Since all the children showing limb dyspraxia had difficulties in reading abilities, it follows that some forms of dyslexia might derive from praxis deficits. This is in line with Corballis' evolutionary theory (2012), according to which language originated from manual gestures rather than animal vocal call. The relationship between gesture and language can be also elucidated in the praxic behaviour of JK, a child with Asperger syndrome who did not show difficulties in using objects or executing pantomimes. However, when asked to produce communicative gestures in response to social simulations presented in verbal or visual modalities, he provided an appropriate "verbal response only" without executing the corresponding gesture. Bernardis and Gentilucci (2006) reported that once individuals produce a gesture while simultaneously pronouncing the gesture name, there is interference at the expense of gesture, suggesting that words and gestures are coded as single signal by a unique communication system. JK's performance can be explained by assuming a deficit in this system and his results further confirm the relationship between language and gesture.

tDCS effect on N400 ERP in case of action or sentence representation

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In the present study, we explored the representation of an incongruent action (instrumentally incorrect use of an object) in comparison with sentences ending with an incongruent action word, taking into account the role of left dorsolateral prefrontal cortex (DLPFC) activation. This activity was appositely modulated by tDCS. The effect of tDCS when subjects processed congruent/incongruent object-related actions (Experiment 1) or sentences (Experiment 2) was verified by measuring changes in the ERP (event-related potential) N400, ERs (Error Rates) and RTs (Response Times). In Experiment 1, thirty subjects performed the detection task within a dynamic context (video tapes representing a sequence of four action frames). In Experiment 2, twenty-eight subjects read sentences that represented object-related actions. The stimulation effect (a cathode applied to the DLPFC and an anode to the right supraorbital region) was analysed by comparing the ER, RT and ERP profiles before and after stimulation (or sham treatment). As shown by ERP analysis and LORETA a significant reduction of the N400 was observed for incongruent stimuli in the case of cathodal stimulation of the DLPFC compared with pre-stimulation conditions for Experiment 1, but not Experiment 2. Moreover, ERs were increased, and RTs were reduced in response to incongruent conditions after tDCS, but not after sham stimulation in Experiment 1. It was suggested that perturbation of the DLPFC may limit the ability to analyse a semantically anomalous action sequence, with a reduced N400 ERP effect and increased random responses being observed. Finally, the contribution of the frontal area to the semantic processing of action was discussed, comparing action with sentence representation.

Homeostatic modulation of tDCS-dependent plasticity

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Non invasive brain stimulation techniques have been shown to be able to induce synaptic plasticity. Two important mechanisms are involved in plasticity: gating mechanism, able to trigger the plasticity induction and homeostatic processes, able to guarantee stable level of synaptic activity over time. Recent studies have highlighted that applying transcranial direct current stimulation (tDCS) over primary motor cortex (M1) it is possible improve motor performance in healthy subjects and stroke patients. Aim of the study was to determine if combining tDCS with motor practice (MP) a task that enhances motor skills inducing cortical plasticity, affects motor cortical plasticity and learning in a polarity-dependent manner. To this purpose, we modulated M1 excitability by anodal, cathodal and sham tDCS in healthy subjects during a motor learning task. Thirty-six right-handed subjects took part in the experiment. The motor learning task consisted of a baseline block and six experimental blocks. Each block involved 40 fastest thumb abduction movements of the left hand, at a rate of 0.25 Hz. Visual feedback was provided during each trial, and subjects were asked to maximize the initial peak acceleration of the thumb, as measured by an accelerometer fixed to the distal phalanx of the thumb. tDCS was delivered at 1.5 mA current intensity (electrode surface 25 cm^2; current density 0.06 mA/cm^2) for 20 minutes on the right M1 during the execution of the six experimental blocks. The changes in motor performance, in terms of peak acceleration were evaluated. All data were normalized to the baseline block and analyzed with a 3 (stimulation) by 7 (block) ANOVA. The results show a general learning effect, as reported by a statistically significant increase in peak acceleration across time. Moreover, the data reveal that the learning rates varied between stimulation conditions. Post hoc analysis indicate a tDCS-dependent impairment in early phase of motor learning task in the anodal stimulation compared to sham, and an increase of the peak acceleration in the last two blocks of MP during cathodal compared to anodal stimulation. Planned ANOVA performed to separately contrast anodal condition to cathodal reported a general decrease of peak acceleration during anodal stimulation. In conclusion, the results highlight that neuronal plasticity induced in the motor cortex by tDCS is modified by concurrent motor learning task. Application of tDCS during an implicit motor learning task led to modulation of behaviour in a polarity specific manner. Anodal tDCS impairs performance during motor learning, highlighting that this current polarity combined with a motor task interferes with the gating effect.

Prefrontal mechanisms during unconscious information processing

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The aim of this talk is to review the topic of unconscious processing in executive control. Executive control refers to the ability of the human brain – mostly associated with prefrontal cortex activity – to regulate the processing involved in the execution of novel or complex goal-directed tasks. Previous studies or models of human cognition have assumed that executive control necessarily requires conscious processing of information. This perspective is in line with common sense and personal introspection, which suggest that our choices are intentional and based on conscious stimuli. Nevertheless, in the last few years several behavioral and cognitive neuroscience studies have put under scrutiny this assumption. Cumulating evidence is now showing that prefrontal executive control can involve or be triggered by unconscious processing of information, with consequent effects on observed behaviors.

Motor mirroring meets motor performance

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Motor mirroring consists in the activation of one's motor system in response to, and congruent with, sensory inputs produced by another person's actions. In most social contexts of daily life however, the motor responses to others' acts are not imitative, but rather follow arbitrary rules. How is automatic mirroring and executive control of actions integrated? We investigated with transcranial magnetic stimulation (TMS) the timecourse of covert motor modulations in response to biological acts in different social tasks. We documented that in an early time window (varying between 150 and 250 ms according to the task) from stimulus presentation the observer's motor system resonates with the observed movements irrespective of the motor task to be accomplished. In a later time window (300 ms) the observer's motor system is modulated according to arbitrary responses. We speculate that the biphasic time-course of motor modulation reflects two distinct neural processes: an early automatic "mirror" activation and a later, arbitrary "executive" activation. In a second experiment we showed that the late modulation is not influenced by the duration of an associative visuo-motor training and is likely to be an all-or-none phenomenon linked to the arbitrary instruction rather than a product of neural plasticity. In a further experiment we targeted the dorsolateral prefrontal cortex with repetitive TMS experiment and showed an effect on the late component of the biphasic motor modulation. Finally in a last experiment we showed that early imitative automatic responses are necessarily present only if the observed actions and the arbitrary responses are the same, even though with an inverted response coding. However early responses disappear if the cue actions are not part of the response repertoire, thus showing that executive control can be variably efficient in controlling them.

Instruction-dependent effects on automatic responses to action observation

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The relationship between perception and action is a key factor in unravelling the current debate over how we understand others' intentions, how we are able to imitate and how we select our actions in social contexts. Whereas traditional views considered perception and action as two independent systems working serially, recent neurophysiological and behavioral data have shown that the visual and motor systems are directly linked and inter-dependent. A crucial question is whether the link between perception and action can be regulated by higher cognitive processes to meet contingent demands. In this talk, three studies will be presented as evidence that the cognitive context in which actions are performed might influence visuomotor interactions. The first study supports that the visuomotor interaction is bidirectional so that action planning can influence action observation (motor-to-visual priming) and viceversa action observation can influence action planning (visual-tomotor priming). The second study supports that visuomotor interaction can be modulated top-down by higher cognitive functions, depending on whether own performed actions or observed actions are selectively attended. The third study shows that the effects of cognitive context on visuomotor interference are also dependent on the point-of-view of the observed action. Overall these data suggest that the interaction between the visual system and the motor system may be modulated by higher cognitive processes, so that when our own actions are more relevant to contingent demands, others' actions have much less interference on our behaviour.

Visceral pain and brain response

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Mechanisms underlying visceral pain are far less known than those of somatic pain. Uncertainty concerns the anatomic pathways conveying the nociceptive inputs coming from internal organs to the brain and the cerebral areas constituting the "visceral pain matrix". The functional assessment of the visceral nociceptive system is mostly hampered by the difficulties in obtaining a sufficiently synchronized and reproducible input afferent to the brain. In the last ten years, the stimulation technique improvement has allowed researchers to record more and more reliable brain responses to gut stimulation. Balloon distension has been initially used to evoke pain to stimulation of different gastrointestinal tracts. Although this technique has the advantage to mimic the physiological stimulation, activation of the nociceptive endings may be asynchronous and irregular, so that the responses recorded from the brain have a poor signal/noise ratio. On the contrary, electrical stimulation of the gastrointestinal wall represents an un-ecological method which, however, allows us to obtain brain responses of reliable amplitude and morphology. By using this stimulation technique, it has been possible to record evoked potentials to stimulation of all tract of the gastrointestinal tube. The responses have been analyzed by dipolar modeling technique in order to disclose the cerebral areas involved in gut pain processing. Although the brain responses to heart stimulation cannot be recorded thus far, neurophysiological techniques of somatic pain assessment, such as the laser evoked potential recording, have been used to shed light on the physiopathology of cardiac pain. These studies showed that the central nervous system is involved in cardiac pain, mostly in cardiac syndrome X, characterized by normally patent coronary arteries.

Early neurophysiological assessment of the patients with disorder of consciousness

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While expert neurobehavioral observation remains the "gold standard" for the diagnostic assessment of patients with disorders of consciousness (DOC), neurophysiological investigations (electroencephalography, short latency evoked potentials and event-related potentials-ERPs) help to further understanding of the pathophysiology underlying the state of unresponsiveness, differentiate coma from other apparently similar conditions (i.e., locked-in and locked-in-like syndromes) and potentially integrate prognostic evaluation. Moreover, these techniques have the considerable advantage of being available at the bedside. Short latency EPs are indicators mainly of poor prognosis if absent, while ERPs are indicators of good outcome if present. However the sensitivity of the latter is low because they are identifiable in a minority of DOC patients, so their absence has not prognostic value. In order to add a new test between short latency and EPs and ERPs we studied the modulation of acoustic and somatosensory N100 during repetitive stimuli in patients with DOC. Using a simple passive paradigm with trains of stimuli short-term habituation (STH) can be detected; it is known as a fundamental component of attention as it represents a "bottom-up" filtering for salient stimuli and, at the same time, a prerequisite for subsequent "top-down" processing. We applied STH protocol in 30 DOC patients of different etiologies hospitalized in sub-intensive care units (emerging/high grade MCS/low grade MCS/VS, assessed with standardized neurobehavioral examination [Coma Recovery Scale - Revised, CRS-R]). STH were found in all emerging and high-grade MCS patients. An acoustic STH although sometimes atypical was also detected in every low-grade MCS. STH was absent in 50% VS (6/12) patients while it was someway preserved in the remaining 50% VS patients. Two among of the VS patients showing STH, subsequently became minimally conscious. Our protocol could be able to pick-up preserved elementary information processing in DOC patients since the early stages. Further outcome correlations are however needed in the VS group to assess a possible prognostic significance of STH detection. We all share the need to optimize the evaluation of patients with DOC and discontinuity between the hospital and rehabilitation phases is rightly considered to be one of the critical points. We think that an early neurophysiological characterization will enable to identify which paraclinical diagnostic or prognostic test is necessary, at any given time, for our routine assessment of individuals with DOC.

Separating transcranial direct current stimulation (tDCS) of Broca's area and speech therapy in chronic aphasia: a controlled outcome study

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Objective of this study is to assess the effect of transcranial direct current stimulation (tDCS) and speech therapy separated in time on language recovery in a sample of post-stroke chronic aphasic patients. Eight post-stroke patients with chronic aphasia were submitted to an *off-line* approach of treatment with tDCS on Broca's area and speech therapy. The patients were stimulated daily for two weeks with anodal tDCS (20-minutes, 2 mA) on Broca's area and two weeks with *sham* stimulation as control condition. The patients received also daily one-hour of individual speech therapy. The order of the two conditions and the treatment modalities (tDCS/*sham* and speech therapy) were counterbalanced. The effect of treatments on language recovery was measured assessing object and action naming abilities with a computerized picture naming task. Statistical analysis showed no difference between anodal tDCS or *sham* stimulation, both for objects and actions naming tasks. *Off-line* tDCS had no differential effect on nouns and verbs naming. The results of this study underline the role of simultaneity in time between tDCS and a particular task or positive treatment effect and may discourage clinicians to separate the two treatment modalities in time.

Brain stimulation over frontal area improves everyday life conversation in aphasic patients

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Recent studies have emphasized transcranial direct current stimulation (tDCS) efficacy coupled with language training to enhance lexical retrieval deficit in aphasic patients. However, improvements found in nouns or verbs naming does not always reflect significant changes in the participants' real-life, day to-day communication. In this study, we investigated tDCS efficacy in a more complex context of everyday life scenes to figure out whether spontaneous speech of eight cronic aphasics would improve after an intensive treatment based on "Conversational therapy". Nine short videoclips of everyday life contexts were prepared. Six videoclips were used to elicit spontaneous conversation in the patients during the treatment, while the remaining three were presented to the patients only before and after the therapy. Patients were required to describe each videoclip, with the help of a therapist, while they were treated with tDCS (20 min., 1mA) over the left hemisphere in three different conditions: anodic tDCS over the frontal areas, anodic tDCS over the temporal areas and sham stimulation. Each experimental condition was performed for ten consecutive daily sessions with 14 days of intersession interval. The linguistic analysis was carried out using a multi-level approach focusing on different aspects of the language process which were measured on the spontaneous conversation produced by each patient before and after each experimental condition. First, we run a "microanalysis" on the number of correct lexical elements (e.g. "thematic words" like nouns, verbs, adverbs, adjectives). Secondly, the number of grammatically correctly constructed phrases were considered. Finally, the number of semantically correct "Idea Units", which represent a chunk of information that have a communicative value, were analyzed. After frontal stimulation, patients showed a greater improvement in spontaneous speech in terms of verbs, "Idea Units" and correctly constructed grammatical phrases with respect to the other two conditions not only on the videoclips used during the treatment but also in the three contexts presented to the patients only at the beginning and at the end of the therapy sessions. These last results indicated a generalization of the recovery. Moreover, the follow-up testing revealed retention of the achieved improvement. Our data suggest that anodic tDCS applied over the left frontal area together with a intensive "Conversational Therapy" treatment might improve everyday life conversation in aphasic patients. We believe that positive treatment effect may be further enhanced and maintained by coupling language stimulation with anodic tDCS applied to the left language areas.

Mirror motor mapping of unseen actions: masked presentations of body actions affects cortico-spinal excitability

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Several studies have shown that observation of actions performed by others induces a mirror-like activation in the observer's brain. Mirror motor activation seems to be triggered automatically independently of the explicit requirement of imitation and has also been found during observation of static postures implying actions. Whether mirror motor mapping of observed non emotional actions requires the perceptual awareness of the observer or is also present for subliminally presented actions, however, is unknown. Here we studied motor response to supraliminally and subliminally presented implied actions using a masked priming paradigm, with a sequential presentation of 3 pictures of different right hands: sample, masked prime and target stimuli. The sample stimuli was always static, while the prime and target stimuli could display a static hand, an index finger or a little finger abduction. The prime was presented for 53 ms and was forward and backward masked by a rotating masking stimulus. This masking procedure allowed us to present the prime for a relatively long time and, at the same time, to disrupt its explicit perception. Indeed, sixteen out of 20 subjects weren't able to correctly detect the prime hand in a follow up task. During the experimental task, a transcranial magnetic stimulation (TMS) pulse was delivered over the motor cortex 307 ms after the onset of the prime ("early") or 307 ms after the onset of the probe ("late"). Electromyography was used to record motor evoked potentials (MEPs) from the first digital interosseus (FDI) and abductor digiti minimi (ADM) muscles, which correspond to the driving muscle of the seen implied action. Results showed a mirror-like increase in corticospinal excitability following observation of supraliminally presented target hands (i.e., greater MEP amplitude during observation of the movement involving the recorded muscle as compared to observation of the static hand or of the other movement type). Crucially, a somatotopic response was also obtained after observation of an implied action prime, independently of the target hand implied action. In particular, the amplitude of FDI MEPs was lower during observation of little finger movements when compared to observation of index finger movements and of a static hands. This suggests a somatotopic inhibition of the cortico-spinal representation of a muscle in response to the subliminal presentation of an incongruent action. Thus, subliminal and conscious observation of implied actions yield opposite effects on cortico-spinal excitability, with inhibition for incongruent actions induced at a subliminal level and facilitation for congruent actions induced at a supraliminal level. Our results provide first time evidence that conscious perception of actions is not required for the mirror-like modulation of the activity within the observer's motor system.

Modulation of motor excitability induced by action observation in stroke patients

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A substantial body of evidence indicates that primary motor cortex (M1) is part of a distributed cortical network that go well beyond simple motor production. One of the remarkable properties of M1 is its ability to respond to passive observation of motor acts as though the observer was actually performing the action. At motor cortex level, viewing another person's hand actions facilitates corticalspinal (CS) excitability in an onlooker's motor circuits. TMS-induced motor evoked potentials (MEPs) is a suitable technique used to assess corticalspinal (CS) excitability during action observation. TMS explorations in healthy participants have indicated that changes of corticospinal excitability during action observation are strictly time-locked and largely specific to the muscles involved in the observed action. Within this context, observation of healthy unimpaired motor performance may assist the recovery of hampered hand movements following stroke, simply by activating the affected cortical motor network in a similar way to that during movement execution and thereby enhancing plastic changes within this network. The present study point to better delineate the changes in corticospinal excitability that accompany perceptual to motor transformations when stroke patients are asked to observe an object-related action. We aimed at verifying if the observation of everyday movements made by the upper-limb produces muscle-specific and time-locked motor facilitation in hand muscles of stroke patients. Single pulse TMS was applied to ten right-handed stroke patients while they were watching video sequences containing right or left hand interactions with different size objects. We examined the MEPs modulation of the muscle involved in the observed actions (first dorsal interosseous (FDI)) and (abductor digiti minimi – ADM). MEPs were also recorded at rest at the beginning and at the end of the video sequences to establish baseline values. We found that motor cortex excitability, in patients with right hemisphere damage (RHD), appears to be modulated by the hand movements observed and that object-size MEPs were muscle specifics to the kinematics characterizing observed actions. Conversely, in patients with left hemisphere damage (LHD), we didn't detect any time-locked or muscle specific modulation in CS excitability. Our findings suggest that the specificity of the motor program activated via action observation depends on the phase of the observed movement and it is reflected in CS excitability. This study attempted to identify crucial factors that could increase motor function by helping to regain or maintain a normal cortical representation of the body in order to improve motor rehabilitation outcomes.

McGurk effects require a motor coding

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In speech perception auditory and visual information related to lips movements are coupled to probably improve speech recognition in noisy environments. Mismatching auditory and visual information lead to the McGurk illusion. However, in natural conditions, only a relatively small part of the speech-related visual signal is available because most articulators, such as the tongue, are not visible. Thus, visually showing articulators for which we have no visual experience should not induce perceptual auditory-visual integration, unless more complex mechanisms involving observer's/listener's sensorimotor representations are at the basis of the McGurk effect. Starting from these considerations, we investigated whether visually presented tongue movements, not normally visible in a speaker, elicit a McGurk-like effect. Short video clips showing the sagittal profile of a tongue (ultrasound images) articulating different syllables (ba/ga/pa/ka) were aligned to the sound (ba/pa). The three conditions we investigated were: Matching audio-video stimuli, Mismatching stimuli, and Control condition (visual stimuli formed by scrambled videos). 15 right-handed subjects participated in the study. Subjects had to attend the stimuli and were asked to perform a 2 alternative forced-choice task (two buttons associated to the auditory "ba" or "pa" syllables). Reaction times (RTs) of the three conditions significantly differ from each other. In particular, RTs in the Mismatching condition are slower than the Matching one and faster than Control. The shorter RTs for the identification of the syllable during the Match and Mismatch conditions with respect to the Control demonstrate that tongue-related information have been processed offering a general speeding advantage. This may be interpreted as a larger implicit salience of biologically moving stimuli. However, the difference between Match and Mismatch supports the idea that specific, visually presented, tongue movements are implicitly recognized by the subject, since their congruence with auditory information leads to a further speed advantage. This result offers important implications for the interpretation of the classical McGurk effect as well as of the role of prior motor knowledge for the classification of perceived speech. In fact, the classical interpretation of the McGurk illusion is based on the functional disagreement between two sensory modalities and is considered to take place in multisensory integration areas such as the superior temporal sulcus. However, other lines of research have proposed that both auditory and visual information are first translated into motor codes, suggesting that McGurk-like effects are originated by mismatch in sensorimotor coordinates. Our results support this second view by demonstrating that the audio-visual speech classification may also be mediated by the somatomotor system.

The role of the primary motor cortex on action-verbs comprehension: a rTMS study

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According to Embodied Cognition theory, neural systems deputed to perception and action are also involved in language comprehension, to the extent that conceptual knowledge is mapped within the sensory-motor system. Several researches demonstrated that verbs referring to actions performed with different body parts trigger the same cortical regions activated during the real action. The aim of the present study is to investigate the role of the primary motor cortex (M1) during action-verbs processing. The main hypothesis is that if M1 is necessary for semantic processing of action verbs, than applying rTMS over the portion of M1 that controls hand movements, should allow to detect a modulation of reaction times for verbs describing an action performed with the hand; on the other hand, this changes are not exptected working with abstract verbs. Twenty-four hand-action verbs (e.g to sign) and twenty-four abstract verbs (e.g. to imagine) have been selected and matched for number of letters, numbers of syllables and frequency. We recruited twenty university students who volunteered to join the study; they were all native italian speakers and strongly right-handed. The participants completed a semantic judjment task, in which they had to press one of the 2 allowed keys to indicate wheter the verb was concrete or abstract. Reaction times were recorded. The task was performed before and after an offline session of low frequency (1 Hz) rTMS delivered over the hand portion of the right and left M1. The results indicate that, as a general trend, participants are faster when answering after the right stimulation compared to the left stimulation, and (not surprisingly) when answering to concrete verbs, if compared to abstract verbs. The most interesting finding is the significant interaction between the side of stimulation and the type of verb: data suggeste that RTs for concrete verbs after left stimulation are significantly slower than for concrete verbs after right stimulation, as well than for abstract verb after left stimulation; these results seem to underline a specific effect of left stimulation towards concrete verbs. The goal of the experiment was to address the "necessity question" about the involvement of M1 during language processes. The main result of the research is that the stimulation affected selectively the processing of action verbs and not of abstract verbs, and that this effect is specific for the left primary motor cortex. This laterality effect seems to confirm that the understanding of action-verbs entails motor programs: actually the controlateral motor area is involved only in right-handers, in both action execution and comprehension. In conclusion, the present findings support the hypothesis that the primary motor cortex is functionally involved in semantic action-verb comprehension, and coherently with handedness.

TDCS-induced naming facilitation in healthy-aging subjects: the importance of timing

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Actions or objects naming is a complex ability, that requires the involvement of a wide cerebral network that comprise, among other areas, the left prefrontal and temporal areas. In particular the crucial role of the left dorsolateral prefrontal cortex (DLPFC) in action naming has been previously confirmed by repetitive transcranial magnetic stimulation (rTMS) studies. Transcranial direct current stimulation (tDCS) is a technique, able to generate a long-term increase or decrease in the neuronal excitability that can modulate the performance in cognitive tasks, similar to rTMS. The aim of this study was to explore the effects of anodal tDCS on a picture naming task in healthy-aging subjects. In particular we were interested to understand which was the best timing to apply stimulation (during vs. before the task execution) to obtain the greatest facilitation effect. The stimulation was delivered by a battery-driven, constant current stimulator through a pair of saline-soaked sponge electrodes (7 × 5 cm). The picture naming task was made up of three experimental blocks and a practice block. Each block included 14 object and 14 action images. The subjects were required to accurately name, as fast as possible, the stimuli appearing on the computer screen. Anodal tDCS was applied to the left DLPFC before or during the execution of a picture naming task in 20 healthy-aging subjects (10 males, mean age 66.5 years).The results were compared to that obtained in a placebo condition. We measured the percentage of accuracy and the latency of the verbal reaction time (vRT) of each subject in each condition. Anodal tDCS applied during the task on the left DLPFC improves naming performance, faster vRT ($p < 0.05$), whereas anodal stimulation applied before the task has not statistically significant effects. Recent papers suggests that timing could be a key variable in influencing the effects of tDCS. This study confirm that the state of cerebral activation during the stimulation influences significantly the obtained behavioral results. Based on the Hebbian theoretical hypothesis, from previous and present observations in the neurostimulation fields, we assume that the capacity of the cerebral network, dedicated to lexical retrieval processing, to increase its efficiency is maximized only if anodal left DLPFC tDCS is applied on an "active" neural network. This datum seems in contrast with our previous study on young subjects, in which we observed a facilitation in an offline condition (i.e., stimulation before the task). The absence of offline facilitation could probably be due to the different responsiveness to tDCS of healthy-aging neural networks. Based on our results, in older adults the cerebral network dedicated to lexical retrieval processing may be facilitated only if tDCS is applied on an "active" neural network.

Can Managers compete to increase their vagal tone?

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Many studies showed how competition contributes positively to achievement by enhancing intrinsic motivation and fostering the mastery of a skill. However, competition also represents a considerable source of social pressure, that can elicit heightened sympathetic or decreased parasympathetic cardiac modulation, thus impairing autonomic balance and flexibility and potentially enhancing the risk of cardiovascular diseases. Given the impact of competition on physiological arousal, it is not surprising that many studies have reported using bio-behavioral techniques, such as biofeedback, to reduce sympathetic activation produced by competition. However, only few studies have tried to exploit competition itself as motivation factor for challenging individuals to reduce their physiological arousal. The present study investigated whether a competitive biofeedback (BF) training can be used with high competitive Managers in order to increase their respiratory sinus arrhythmia (RSA), an index of cardiac vagal control. Thirty-one Managers, leading outstanding private or public Companies, were randomly assigned to either a Non-competitive (n = 17) or Competitive RSA-BF group (n = 14). Participants in the latter group had to compete with paired competitors on their ability to increase RSA. All participants underwent five 40 min RSA-BF sessions. The outcome was assessed as changes in RSA, heart rate (HR), blood pressure (BP) and skin conductance level (SCL) from pre- to post-training. After BF-training, an increase in resting RSA was observed in the Competitive group only. A significant decrease in resting HR, SCL and systolic blood pressure (SBP) was observed after the training in both groups. Results showed that competition can be used with Managers involved in high-level work responsibilities, in order to enhance their cardiac vagal control. Moreover, competitive BF, while enhancing Managers' RSA, did not prevent BF-assisted acquisition of reduced general arousal.

Association between depressive symptoms and reduced cardiac vagal modulation in patients after cardiac surgery

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Several lines of evidence indicate that depression is a relevant and independent risk factor for cardiovascular diseases. Reduced heart rate variability (HRV), which reflects altered autonomic nervous system activity, has been suggested as a potential factor linking depression to cardiovascular diseases. While several studies have investigated the association between depression and reduced HRV in patients with cardiovascular diseases, to our knowledge, this relationship has not yet been studied in patients after cardiac surgery. Therefore, the main aim of this study was to examine whether postoperative depressive symptoms could be related to reduced HRV. Patients with depression and without depression, who had undergone cardiac surgery, were enrolled postoperatively. In all patients, HRV was derived from a four-minute blood volume pulse recording at rest. Analyses of covariance and partial correlations, while controlling for anxiety, were used to examine the association between postoperative depression and HRV parameters. The two groups of patients (i.e., with depression and without depression) were comparable in terms of demographic, biomedical and surgical characteristics. Compared to non-depressed patients, patients with depression showed significantly lower standard deviation of N-to-N intervals (SDNN), root mean square successive difference of N-to-N intervals (rMSSD), and high frequency power. Partial correlation analyses showed that depression was inversely related to SDNN, rMSSD, and high-frequency power, whereas it was unrelated to other HRV parameters. Discussion: These novel findings add to the literature on physiological mechanisms underlying the association between depression and cardiovascular disease by showing that a depression-reduced HRV relationship extends to patients after cardiac surgery. Also, our study suggests that postoperative depression is more likely to be associated with reduced cardiac vagal modulation rather than excessive sympathetic influence. Conclusion: Reduced HRV, especially an altered vagal tone, may be considered as a potential mechanism underlying the link between postoperative depression and subsequent risk for cardiac events or mortality after surgery. In particular, the present study suggests that, in addition to cardiac surgery itself, depressive symptoms may further affect HRV in the early postoperative period, potentially contributing to adverse outcome in patients after surgery.

Cerebral vasomotor reactivity modulate by tDCS: could be a fast-track for stroke patients?

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Cerebral vasomotor reactivity (VMR) is the capability of cerebral vessels to change their diameter in response to hypercapnia. One of the techniques to evaluate VMR is the "breath-holding" test. It can be quantified as the percentage increase in flow velocity (PIV) weighted by the time the breath is held (Breath-Holding Index or BHI: PIV / period of breath holding in seconds). In order to minimise haemodynamic changes following deep inspiration the patients should hold their breath at the end of a normal inspiration. Transcranial direct current stimulation (tDCS) can modulate brain function through a focal and prolonged cortical polarization shift. Anodal tDCS (A-tDCS) on primary motor cortex (M1) increases its excitability, whereas cathodal (C-tDCS) produces opposite effects. tDCS effects on cerebral haemodynamic have been poorly studied. In our study we evaluate the change of VMR on 11 healty subjects before and after tDCS stimulation. Eleven healthy subjects underwent anodal/cathodal tDCS (8 female and 3 male, 21-50 years; 5 A-tDCS vs. 6 C-tDCS) on right M1. Before and after tDCS, VMR assessment by transcranial ecocolordoppler (evaluating right middle cerebral artery (MCA) by transtemporal approach) and heart rate variability (HRV) were measured. Normalized low-frequency (LFN) band power of heart rate variability and its reactivity from basal to VMR condition (LFNreact) were estimated as markers of sympathetic activation. We found that tDCS exerted a specific effect on both VMR and HRV. In fact, A-tDCS decreased VMR (Mean BHI 1.12 before tDCS and 0.72 after A-tDCS) increased LFN react, whereas C-tDCS increased VMR (Mean BHI 0.721 before tDCS and 1.32 after C-tDCS) and reduced LFNreact. VMR and HRV are modified by tDCS. The changes of HRV can suggest the modulation of VMR by the sympathetic nervous system. Further studies are needed to confirm this hypothesis, that can support the clinical use of tDCS in order to modulate VMR in stroke patients.

"The more I wait the more I process": a high-density event-related study on the automatic expectancy-related brain activity

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Neuroimaging studies have shown that implicit temporal expectation is represented within cortical areas traditionally associated with action programming and motor preparation, such as pre-motor areas or inferior parietal cortices. However, recent data showed other cortical regions not strictly associated to motor processing, such as the right dorsolateral prefrontal cortex (r-DLPFC), to be also selectively engaged in temporally predicable tasks requiring speeded motor responses, like for example, the variable foreperiod paradigm. Thus, it still remains unclear whether motor preparation/execution and response selection are necessarily implicated in implicit temporal expectation. The aim of the present study was to unravel the contribution of task-related processing (response selection and execution) on the stimulus expectancy-related brain activity. High-density EEG (128 sensors) was recorded in eighteen young adults during a passive interval timing task consisting in the passive viewing of pairs of visual stimuli (S1 and S2) interspersed with empty intervals (ISI). In the standard condition (70% of trials), the ISI lasted 1.500 ms, while in the two alternative, deviant conditions (15% each), it lasted 2.500 and 3.000 ms. The main purpose was to create an implicit temporal rule based on the maximum expectation of a determinate event (S2 onset) in a precise time-point, that is 1500 ms after S1 offset.We expected that when this rule was violated (i.e., in the two low-probability deviant conditions), an up-dating of the conditional probability of S2 occurrence would be automatically engaged in order to allow attentional resources to be re-oriented over time, this mechanism being reflected in a modulation of the S2-locked ERP activity. We found a significant amplitude modulation of the P2 response over the fronto-central right scalp area that was directly proportional to the ISI. In particular, the more subjects passively expected S2, the larger was the P2. Brain source analysis performed with the Brainstorm toolbox localized this effect in the right dorsolateral prefrontal cortex (rDLPFC; Broadmann Area 9/46). The ISI-related proportional modulation of the P2 response elicited by S2 onset accounts for the existence of an automatic temporal monitoring mechanism sensitive to the conditional probability of event occurrence. This mechanism seems to be automatically prompted by statistically constrained temporal structures and consists in the progressively shifting of attentional resources over time in order to unconsciously prepare and anticipate events. When events cannot be predicted according to fixed or informative pre-orienting cues, temporal expectation is automatically updated as a function of the change of signal occurrence conditional probabilities over time. The rDLPFC plays a key role in this process.

ERPs and cerebral perfusion correlates in Mild Cognitive Impairment (MCI)

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Objective of this study was to find ERP and cerebral perfusion correlates of cognitive impairment in MCI patients. Ten patients (age 66.5 ± 5.1; 6 women) underwent ERP recordings (N400 and P300) by means of 30 electrodes and 99 mTc HMPAO SPECT. A selective neuropsychological battery was administered to assess general cognitive status, short- and long-term verbal memory, episodic memory, constructional praxia. Abnormal N400 (decreased amplitude or absent) was found in 8/10 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. No significant correlations were observed between N400 amplitude with age and depression. P300 was normal in 8/10 of patients. In comparison with controls, 9 out 1 patients showed significant hypoperfusion in the frontal, limbic and temporal lobes mainly on the left side. Neuropsychological assessment disclosed a slight involvement on tests exploring verbal and episodic memory in 8/10 of patients. Statistical analyses revealed significant correlations between N400 abnormalities and left frontal lobe SPECT hypoperfusion ($p = 0.04$ $r = 0.7$), verbal memory score ($p = 0.02$ $r = 0.75$) and verbal learning test ($p = 0.03$ $r = 0.6$). Also, left temporal lobe deficit perfusion correlated significantly with verbal memory test patients' performance (($p = 0.04$ $r = 0.6$). N400 abnormalities and cerebral perfusion findings described in this study enable the detection of neuropathological dysfunctions in MCI providing functional informations. Both electrophysiological recordings and SPECT neuroimaging may support neuropsychological evaluation in identify earlier functional biomarkers of cognitive deficits in MCI and even in subjective cognitive impairment (SCI). Such functional correlates could provide useful tools in predicting conversion to dementia.

Covert visuospatial attention-based BCI for ALS patients

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By translating brain signals into commands, brain-computer interfaces (BCIs) allow people to control devices. BCIs represent a concrete solution for the communication problems of patients with amyotrophic lateral sclerosis (ALS). Most of the BCIs rely on visual interfaces, in which patients must move their eyes in order to reach efficient BCI control. This fact represents a limit of BCI use with ALS patients who are in the latest stages of the disease (i.e., locked in state [LIS]) and have impaired eyes muscles control. We aimed to improve visual interfaces for ALS-LIS patients in order for them to control the movement of a cursor on a monitor. To this aim, we designed two new interfaces that required the users to orient their covert visuospatial attention. One interface exploited the principle of Exogenous visuospatial attention orienting, whereas the other exploited Endogenous visuospatial attention orienting. Ten ALS patients with different levels of impairment used the two new interfaces in an event-related potentials (ERPs)-based BCI, developed for controlling the movement of a cursor on a monitor. Their task was to reach with the cursor one out of four icons, which was indicated by the experimenter at the beginning of each session. ALS patients performed 16 sessions with each interface during eight consecutive days. During each session, the ERPs, elicited on each trial, were recorded. By using an ad-hoc classification algorithm, the ERPs were processed on-line and translated into discrete cursor movements. ALS patients reached good performance (i.e., classification accuracy of targets and non-targets in percentage) of about 70% with both the interfaces, but the accuracy in target classification was higher with the Endogenous Interface than with the Exogenous, $t(9) = 1.96$, one tailed $p < .05$. Furthermore, the Endogenous interface was associated both with faster communication speed ($t(9) = 2.31$, one tailed $p < .05$) and with higher rate of target icons reached by the cursor ($t(9) = 3.32$, one tailed $p < .01$), with respect to the Exogenous interface. ALS patients were able to use their covert visuospatial attention in order to control an ERP-based BCI system in real time. Nevertheless, better results were associated with the Endogenous interface than with the Exogenous interface. The results support the idea that ALS patients can use the covert visuospatial attention orienting in order to control an ERP-based BCI, without the need of moving their eyes. Interfaces based on covert visuospatial attention offer a new solution for the communication problems in ALS patients with impaired eyes muscles control. Moreover, the use of the Endogenous visuospatial attention orienting leaded to better performance. This represents a costless improvement in ERP-based BCI interface design. We suggest that more attention be paid to the neuropsychological aspects involved in interfaces design, for researchers to develop more efficient BCIs for ALS patients.

How does buzz the surgeons brain? An EEG coherence study while they work in conventional laparoscopic or robotic modality

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In human, both primary and non-primary motor areas are involved in the control of voluntary movements. However, the dynamics of functional coupling among different motor areas has not been fully clarified yet. There is to date no research looking to the functional changes in the brain of surgeons working in laparoscopy compared with those trained and working in robotic surgery. We enrolled 16 right-handed trained surgeons and assessed changes in intra- and inter-hemispheric EEG coherence with a 32-channels device during the same, simplified motor task with either a robotic or a laparoscopic approach. Estimates of auto and coherence spectra were calculated by a fast Fourier transform algorithm implemented on Matlab 5.3. Because coherence data depend on the recording type and, in particular, are highly sensitive to signal variations at the common reference, we further checked the intra-individual reproducibility of our results under different montage schemes. We off-line converted our initial Cz reference into common average, bipolar, and ipsilateral earlobe reference montages, which all emphasize different properties of the EEG signals. The analysis of coherence revealed a significant increase in intra-hemispheric coherence in the range of theta activity in surgeons using a conventional laparoscopic approach, compared both with resting condition (SMA vs. M1: $F = 7.9$, $p = 0.012$; SMA vs. S1: $F = 7.7$, $p = 0.014$; M1 vs. S1: $F = 14.2$, $p = 0.0019$) and robotic surgery (SMA vs. M1: $p < 0.001$; SMA vs. S1: $p < 0.001$; M1 vs. S1: $p < 0.0001$). Similar results were found by comparing S1 with pre-SMA (laparoscopy vs. resting condition: $p = 0.0025$; laparoscopy vs. robotic surgery: $p = 0.0006$). Concurrently, we revealed a significant increase in inter-hemispheric coherence in the range of beta activity in surgeons using the robotic device compared both with resting condition

(right vs. left M1: $F = 13.7$, $p < 0.001$; right vs. left S1: $F = 12.7$, $p < 0.005$) and laparoscopy (right vs. left M1: $p < 0.0001$; right vs. left S1: $p < 0.0001$). Similar results were found by comparing right M1 with left pre-SMA (laparoscopy vs. resting condition: $t = 6.68$, $p < 0.001$; laparoscopy vs. robotic surgery: $t = 7.57$, $p < 0.001$) and left M1 with right pre-SMA (laparoscopy vs. resting condition: $t = 5.32$, $p < 0.001$; laparoscopy vs. robotic surgery: $t = 5.85$, $p < 0.001$). Our data provide a semi-quantitative evaluation of dynamics in functional coupling among different cortical areas in skilled surgeons performing laparoscopy or robotic surgery. These results suggest that motor and non-motor areas are differently activated and coordinated in surgeons performing the same task with different approaches. To the best of our knowledge, this is the first study that tried to assess semi-quantitative differences between robotic and laparoscopic procedures.

Electrocortical markers of lying

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Lying, as a deplorable behavior, induces changes in the vegetative system because of the sense of guilt and the anxiety of being uncovered, and the current lie-detectors, as the polygraph, register these changes as cues of a deceptive behavior. Such modulations, however, aren't direct measures of deception per se, but products of emotions in general that could also affect an innocent suspect, wrongly accused. But what happens in the brain? Is it possible to define the relationship between lies and emotions? The purpose of this study was thus to investigate the neural correlates of deceptive behavior in response to neutral and affective questions, created ad-hoc, through the analysis of the electrocortical indexes registered in healthy volunteers. ERPs were recorded from 128 sites. From ERP responses it was possible to notice, at anterior brain areas, a late modulation of the electrocortical activity during the lying versus the telling the truth condition, according to the affective valence of the stimuli. This finding is particularly relevant in that it confirms the ambiguity of data coming from studies related to peripheral indexes measures. An earlier peak was found over the prefrontal regions that distinguished between truthful and mendacious responses, irrespective of the affective context. This component would thus represent the neural marker of deception. A swLORETA linear inverse solution was computed on its amplitude. The results showed that a deceptive behavior is related to the activation of anterior brain areas reflecting an increasing need in higher-level cognitive functions, namely working memory, conflict monitoring, controlled- and task switching-processes, also suggested by behavioral responses.

Transcranial electrical stimulation (TES) modulate plasticity in a perceptual learning task

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Transcranial electric stimulation (tES) protocols are able to modulate neural plasticity, offering important insights to focus and constrain theories of the relationship between the brain and behaviour. Previous studies have shown that different types of tES (i.e., transcranial direct current stimulation – tDCS and transcranial random noise stimulation – tRNS) induce different behavioural effects. However to date is not clear which are the best parameters (i.e., timing and presence of pauses) to apply tES to obtain reliable effects. In this work we performed two experiments. In Experiment 1 the goal was to investigate how tDCS and tRNS can modulate plasticity in the healthy adult brain in relation to their timing of application. In Experiment 2 the aim was to understand if the presence of pauses during the stimulation may induce different behavioural effects during a perceptual learning task. The stimulations were delivered by a battery-driven stimulator through a pair of saline-soaked sponge electrodes, one applied on V1 and the other on the right arm. We used an orientation discrimination task (ODT). Participants had to decide whether the presented stimulus was tilted clockwise or counterclockwise relative to the previously presented stimulus.In both experiments the stimulations were applied during (online condition) or before (offline condition) the ODT execution in a between subjects experimental design. In Exp. 1 we had seven stimulation groups: anodal tDCS (a-tDCS online and offline), cathodal tDCS (c-tDCS online and offline), high frequency tRNS (online and offline) and sham. In Exp. 2 we had five stimulation groups of: continuous-c-tDCS (online and offline), intermittent-c-tDCS (online and offline) and sham. In Exp. 1 we observed an improvement of the performance when a-tDCS was applied before the task (offline), whereas with tRNS we had a great improvement in the performance only during the task execution (online). Surprisingly an analogous improvement was present with offline c-tDCS whereas online c-tDCS was similar to sham. In Exp. 2 we observed a difference between continuous-c-tDCS and intermittent-c-tDCS. The main result of this study is the finding that the timing of identical tES protocols yields opposite effects on synaptic plasticity. Indeed, the effects of tES are highly dependent on the timing of the stimulation and on the presence of pauses during stimulation. These results confirm our hypothesis that the state of cerebral activation, when the non-invasive brain stimulation is applied, is important for inducing neural plasticity. Our results confirm that exists an ideal timing of application, depending on the type of stimulation. In addition, it is important to consider that the effects of tES depend on several parameters (i.e, timing and pauses) related to the technique. These results are important for the designing of rehabilitation protocols, highlighting the importance of a careful choice of stimulation parameters.

The effects of musical expertise on reading skills: an ERP study

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Several studies showed that an early music training modifies functional brain structure and enhances connectivity, but little is known about the effects of training in notation reading on brain plasticity. The aim of this study was to compare visual processing of notes and words in 15 professional musicians and 15 controls while EEGs recorded their visual processing. Stimuli comprised 300 words and 300 short (1 measure) music scores that were randomly presented at the center of a PC screen located approximately 114 cm from the viewer's eyes. Thirty healthy right-handed participants (18 males and 12 females) were recruited for this experiment. They were matched for cultural status and education level (except for musical expertise) across groups. All had normal or corrected-to-normal vision and reported no history of neurological illness or drug abuse. Half of them were professional musicians with a Conservatory degree in violin, trumpet, clarinet, piano, composition, orchestra conduction. Musicians usually read their music scores in Violin and/or Bass clefs. The mean age of acquisition (AoA) of musical abilities (playing an instrument) for musicians was 8.57 years. The mean age of musicians was 31.7 years (SD = 12), while of control was 26 ys. (SD = 69). Non musicians (control group) were totally unable to read musical notation as determined by a note reading test (solfeggio) administered prior to recruitment. People who recognized a single note were not enrolled in the study. Handedness was assessed with the Italian version of the Edinburgh Handedness Inventory, a laterality preference questionnaire. All participants reported strong right-handedness and right ocular dominance. In this study 300 Italian words and 300 musical beats were presented for 1600 ms in the central visual field. ERPs were recorded from 128 scalp sites in a group of Italian University students and in a group of professional musicians. The task consisted in paying selective attention to a given note or letter included (or not) in the musical measures or words presented, and in responding to targets by pressing a button as accurately and quickly as possible. Letter processing was strongly left lateralized in controls, while the fusiform (BA37) and inferior occipital gyri (BA18) were activated in both hemispheres in musicians during both word and music reading. The hypothesis is advanced that the recruitment of right occipital/temporal areas during orthographic reading, in musicians, might depend on their early acquisition of music reading ability. Our study provides evidence, for the first time, that the early learning of the musical notation system may affect the neuroanatomical and functional mechanism of visual word recognition.

Reinforcement learning is mediated by medial orbitofrontal cortex: evidences from transcranial direct current stimulation (tDCS)

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Reinforcement learning refers to the ability to use action outcomes to shape knowledge and to make predictions on the consequence of future choices. In a natural environment the outcomes of our choices are frequently characterized by some degree of uncertainty, in other words most of our choices are based on non-deterministic predictions of environmental outcomes. The medial orbitofrontal cortex (mOFC) is considered a key area of the brain that represents events value and that is involved in reinforcement learning, however the causal relation of this area in reinforcement learning was never investigated in healthy individuals. The objective of the present study is to test the role of the mOFC in reinforcement learning. Thirteen healthy individuals participated to the study and undergo to three experimental sessions. In each session, participants perform a probabilistic learning (PL) task while anodal, cathodal or sham transcranial direct current stimulation (tDCS) was applied over the mOFC. In each trial two Japanese ideograms were displayed on the left and on the right of the fixation point and participants were instructed to make choices between the two alternatives. Three fixed pairs of ideograms (AB, CD, EF) were randomly and equally presented during the task and each ideogram was associated to a different probability of receiving positive/negative feedbacks: A = 0.8/0.2, B = 0.2/0.8, C = 0.7/0.3, D = 0.3/0.7, E = 0.60/0.4 and F = 0.4/0.6, respectively. After each choice probabilistic feedback was provided depending on the selected ideogram. Participants were instructed to identify the best alternative in each pairs of ideograms and to use positive/negative feedbacks as reinforce for the future choices. In each session tDCS was delivered at 2 mA for 25 minutes with the active electrode (25cm^2) placed over Fpz (EEG sys) and the reference electrode (64cm^2) placed over Oz. After the PL task (learning phase) a test phase was delivered to evaluate the implicit probabilistic associations derived from the positive/negative feedbacks received during the learning phase. In the test phase, the new pairs AC, AD, AF, AE and BC, BD, BE, BF were presented without feedbacks and participants were invited to make their choices using the knowledge acquired during the PL task. During cathodal stimulation of the mOFC participants were significantly less accurate in performing the PL task, both compared to sham and anodal stimulation. In addition, in the test phase, after anodal tDCS, participants were less confident in their choices when they had to select the alternative that was associated more frequently with positive feedbacks in the preceding learning phase. The present results demonstrate the causal relationship between mOFC and reinforcement learning. Our data support the idea that the mOFC is involved in the representation of the positive value associated to a particular event.

rTMS on the left dorsolateral prefrontal cortex during an emotional memory task improves the performance of the retrieval process as function of level of anxiety and stimulus valence

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Anxiety behaviour showed a consistent attentional bias toward negative and aversive memories, induced by a right prefrontal cortical superiority, based on an "unbalance effect" between the two hemispheres. In the present research we explored the contribution of the left dorsolateral prefrontal cortex (DLPFC) in memory retrieval process of positive vs. negative emotional stimulus, as a function of the anxiety level. The left DLPFC stimulation is supposed to modulate the "right superiority" in high level anxiety profile, by a decreasing of the attentional bias for negative cues. Material: Subjects, who were divided in two different groups depending on their anxiety level (high/low-anxiety, STAI), were required to perform a task consisting in two experimental phases: an encoding-phase (lists composed by positive and negative emotional words); and a retrieval-phase (old stimuli and new stimuli to be recognized). Moreover, new stimuli (distractors) were semantically related or unrelated to the old stimuli to test a possible interference effect induced by the semantic association. The left DLPFC effect was analyzed by using a high frequency rTMS (repeated transcranial magnetic stimulation) sham-controlled paradigm that induced a cortical activation of the left DLPFC. The rTMS stimulation over left DLPFC affected the memory retrieval, as a function of anxiety level and stimulus valence. High-anxiety subjects showed a typical attentional bias for aversive cues in comparison with low-anxiety subjects. However, they benefitted in greater measure to the prefrontal left stimulation with a reduced negative bias (increased accuracy and reduced RT for the positive stimuli) and a significant increased performance for the semantically related distractors (reduced interference effect). These results suggested that left DLPFC activation increases the memory retrieval of positive emotional information and might limit the "unbalance effect" induced by a right hemispheric superiority in high level of anxiety. Moreover, this effect was related to both retrieval of positive old memories and detection of semantically related distractors.

Laser evoked potentials in vegetative and minimally conscious states: case reports

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Pain perception is currently an open question in patients suffering from prolonged disorders of consciousness. In this study we aimed to examine laser evoked potentials (LEPs) in patients with vegetative (VS) and minimal conscious state (MCS), in light of main clinical features, Nociception Coma Scale (NCS), mismatch negativity (MMN) and late cortical responses evoked by innocuous not noxious electric somatosensory stimuli (lSEPs). Three VS, 4 MCS patients and 11 age and sex matched controls were examined. Evoked responses were obtained by 64 scalp electrodes, stimulating the dorsum of the right hand by noxious laser and innocuous electrical stimulus, according to normal controls subjective rating. For MM, the presented stimuli were 1500 pure tones of 1000 Hz (85%, standard) and 1500 Hz (15%, deviant). Topographic analysis was performed for each patient, modeling cortical responses over individual MRI. The MM was present in all patients, though 2 patients with MCS displayed a significant amplitude reduction on frontal derivations. LEP vertex complex was recognizable in all cases, with a significant latency increase of both N2 and P2 and a topographic scalp rearrangement. Late SEPs were absent in all patients except in one MCS case, who showed a significant N2 and P2 latency increase. Our results may suggest that high relevant stimuli may be processed even in patients with severe brain damage. Larger series and multimodal approaches may contribute to confirm that cortical arousal toward pain salience may be a primary function for life persistence.

Detection of short-term habituation (STH) in patients with disorder of consciousness (DOC): preliminary results

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Short-term habituation (STH) is known as a fundamental component of attention as it represents a "bottom-up" filtering for salient stimuli and, at the same time, a prerequisite for subsequent "top-down" processing. STH can be detected using a simple passive paradigm in which trains of stimuli belonging to identical or different modality were presented. Our aim was to ascertain if STH is preserved in patients with different levels of disorder of consciousness (DOC).We selected 30 DOC patients (emerging/high grade MCS / low grade MCS/VS, assessed with standardized neurobehavioral examination [Coma Recovery Scale - Revised, CRS-R]) of different aetiologies (haemorrhagic, traumatic and post-anoxic) Every patient underwent a complete neurophysiological study that included EEG with reactivity evaluation, somatosensory evoked potentials, ERPs with passive oddball protocol and finally STH protocol. STH protocol provides for the delivery of trains of three stimuli (triplets S1-S2-S3): S1 and S2 always belongs to the same sensory modality (auditory or somatosensory) whereas S3 can belong either to the same modality (as S1 and S2),triplet "same" or to the other modality, triplet "different". Amplitude of long latency evoked potentials (N1-P2) in response to different stimuli was then compared in order to detect any STH. In order to verify the reproducibility, seven patients were also retested. Acoustic and/or electric STH was found in all emerging and high-grade MCS patients. STH was qualitatively and quantitatively comparable to that obtained in healthy subjects. An acoustic STH sometimes atypical (N1 modulation), was also detected in every low-grade MCS. STH was absent in 50% VS (6/12) patients while it was someway preserved in the remaining 50% VS patients. Two among of the VS patients showing STH, subsequently became minimally conscious. One VS patient, who did not present any STH phenomenon did not change his clinical status 3-months later. In addition, 1/3 of our patients (everyone with a clear acoustic or electric STH) presented also a P3-a response. STH process is a preserved phenomenon in emerging and MCS patients showing features similar to healthy subjects. An acoustic STH was also found in every low-grade MCS and in some VS patients. Two of these VS patients later regained some grade of consciousness. None of the emerging/high grade MCS and low grade MCS did not show a significative acoustic or electric STH phenomenon. In this view, our "triplet" protocol could be able to pick-up preserved elementary information processing in DOC patients. Further outcome correlations are however needed in the VS group to assess a possible prognostic significance according to triplet responses.

Blink-related alpha and beta oscillations differentiate between minimally conscious state and unresponsive wakefulness syndrome/vegetative state

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Recently, we have shown the existence of EEG delta blink-related oscillations (delta BROs), which are peculiar to the resting state of the healthy subject. The hypothesis is that they can represent the activation of updating and short-term memorization of the context, which are at the basis of the global (gestaltic) awareness of the visuo-spatial environment. As expected, the source of these oscillations was located in the precuneus, whose function is believed to be the surveillance of the internal and external environments and some assessment of salience of stimuli for the individual. In patients with disorders of consciousness (DOC), delta BROs were poorly represented, so that it was not possible to identify unambiguous and homogeneous sources. However, parameters such as power and phase synchronization of delta BROs was directly proportional to the levels of consciousness expressed by the Levels of Cognitive Functioning Scale (LCFS) scores. Nevertheless, at the group level, it was not possible to statistically distinguish minimally conscious state (MCS) from unresponsive wakefulness syndrome/vegetative state (UWS/VS). In an effort to increase our capabilities of differential diagnosis, and taking into account that brain responses are to be considered as the superposition of multiple oscillations, we have extended our analysis to other frequency ranges than delta. EEG activity at rest was recorded in 12 healthy subjects and 9 patients with DOC (5 MCS, and 4 UWS/VS). Three-second-lasting EEG epochs centred on each blink instance were analysed in both time- (BROs) and frequency-domains (event-related spectral perturbation or ERSP). Cortical sources of blink-related band power maxima were estimated by Sloreta. It was thus possible to obtain a statistically significant differentiation between MCS and UWS/VS on the basis of both alpha and beta oscillations within a time window of about 1000ms after the blink. The brain region that turned out to be more active in MCS with respect to UWS/VS was the precuneus (which was however still deficient compared to healthy subjects). The brain regions that turned out to be more active in MCS with respect to both healthy and UWS/VS subjects were the left temporo-parietal junction and, to some extent, the left pre-frontal cortex.The activation of such a fronto-parieto-temporal network in MCS subjects could be interpreted as a compensatory mechanism to the current condition of functional insufficiency of the precuneus.

The tDCS effect on ERP profile for the semantic representation of action. The role of DLPFC

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Representation of action within an object-related dynamic context was considered as a semantic task similar to word comprehension within a linguistic context. Indeed it has been hypothesized that the mechanisms involved in the perception of action sequences may be similar to those associated with the processing of language. That is, action comprehension was seen as a specific semantic processing where context-action representation resulted integrated as in the word-sentence representation. The aim of the present research was firstly to investigate the effect of tDCS on a specific ERP deflection (N400 effect) when subjects processed a congruous/incongruous object-related action. Secondly, the contribution of tDCS to modulate the cortical response of the dorsolateral prefrontal cortex (DLPFC) was explored. We supposed that the inhibition of anterior DLPFC area may induce a decreased ability to produce a concomitant N400 effect. Thirty subjects performed a detection task when congruous or incongruous sequences of action (video tapes). The procedure was subdivided into three phases. Prior to tDCS stimulation, a baseline task was conducted on a separate day, and EEG was registered (phase 1). The participants were required to press a left or right pulse of the mouse depending on whether the final action target frame represented a congruous or an incongruous ending scene. Successively tDCS/sham stimulation was induced (phase 2) on the subjects. Finally, immediately after tDCS/sham stimulation (phase 3) subjects were submitted to the same experimental task of phase 1. The EEG was registered during the task execution using the same procedure of EEG acquisition adopted in phase 1. The stimulation effect (cathode applied on the DLPFC and anode on the control site) was tested comparing the behavioural (RTs) and ERP profile before and after the stimulation (or sham effect) applied on the frontal areas. A significant N400 reduction was observed for incongruous stimuli in case of cathodic stimulation of DLPFC compared with the pre-stimulation condition. Also RTs were modified in case of tDCS application when subjects processed incongruous actions. It was suggested that the inhibition of DLPFC may limit the ability to analyze the semantic anomaly induced by action representation. Secondly, the contribution of the frontal areas for the semantic processing of action was supported. Finally, the N400-like effect was largely modulated by tDCS, as shown by comparing pre- and post-stimulation ERP profiles. The effect of tDCS applied over prefrontal cortex to explore action semantic processing was demonstrated and currently we tested for changes in the RT and ERP cortical responses induced by direct current stimulation.

Affordance encoding in the motor cortex: a TMS state-dependent study

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The term affordance defines an attribute arising from visual properties of objects and motor information, which derives from the possible interaction that an agent can carry out with that object. The motor program that an object evokes in an agent can be represented as a pattern of muscle contractions and joint positions. This pattern of activity (or motor synergy) should therefore be primed by the visual presentation of an object. Although monkey neurophysiological studies show a parieto-frontal network extracting affordance-related features of objects, this system (canonical neurons) remains elusive in humans. Here we tested whether it is possible to selectively pre-activate some pattern of finger-movements when observing objects. Moreover, we are interested in studying the interaction between the mirror and canonical neuron networks by using an adaptation paradigm. In this study we applied the paradigm of visual adaptation in order to segregate neural populations responding to two different intransitive grasp actions: precision and power grasp. In each trial, after visual presentation of one of the two adapting movements, an object offering clear affordance (for precision or power grasp) was presented. A single TMS pulse was delivered over M1 hand representation during the presentation of the object, in order to test the hypothesis of specific motor priming given by the object's features. In addition, a mismatch between visual adaptation and object affordance was introduced so as to test the effect of perturbing the system's stability online and therefore the state-dependency of such effects. Motor evoked potentials were recorded from *Abductor Pollicis Brevis* (APB) and *Abductor Digiti Minimi* (ADM). Reaction times increased when a mismatch was present between the adaptation movement and the object affordance, suggesting a cross-modal adaptation between the observation of an action and of the object presented. MEPs showed an increase in size for the action-affordance matching condition involving precision grasp in APB muscle, whereas a modulation for the action-affordance matching condition involving power grasp was found in ADM. Altogether, the results support the possibility of priming a specific and congruent motor pattern by the visual presentation of an object offering an affordance. The action-affordance mismatching conditions showed an intermediate pattern of motor evoked responses, thus supporting the hypothesis that the state of the system plays a fundamental role in the physiological object-related responses. Therefore, cortico-spinal excitability maps the specifics of the affordance offered by a visually presented object. Nevertheless, these measures can be biased in a state-dependent manner. Here, with an adaptation protocol, we show a cross-system functional link between mirror and canonical neuron neural circuits.

Modulating the effect of learning on spatial conflict: a tDCS study

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Upon encountering stimuli that present action affordances, visual irrelevant information may activate incorrect motor responses with respect to our current goals. When this happens, a conflict arises at the response selection stage. In the Simon task, participants are instructed to respond to a non-spatial attribute of a stimulus (e.g., the color) and to ignore its position. Despite the fact that spatial information is irrelevant to the task, responses are faster when stimulus and response position correspond than when they do not correspond. The Simon effect is defined as the difference in reaction times between non-corresponding and corresponding trials. Although the effect of spatial correspondence is very robust, it has been shown that it can be modulated by prior practice on a spatial compatibility task with incompatible mapping. In particular, the Simon effect disappears if, before performing the Simon task, participants practice with an incompatible mapping. This effect of practice reveals a transfer of learning of new stimulus-response associations from one task to the other. In the present study we investigated whether transcranial direct current stimulation (tDCS) of the premotor cortex can modulate the effect of practice. Three groups of participants performed the Simon task in two sessions (baseline and transfer sessions) interleaved by a spatial compatibility task (practice session). In the spatial compatibility task, participants were required to respond to the location of the target (left response to right stimuli, right responses to left stimuli). The group 1 underwent the experimental procedure without stimulation. In the group 2 and 3, anodal tDCS and cathodal tDCS, respectively, were applied to the premotor cortex of the left hemisphere during the practice session. The analysis of reaction times showed that the SImon effect was reduced from the baseline to the transfer session in all the groups, revealing a clear effect of practice. However, the analysis of responses performed with the right hand showed that tDCS was able to modulate the effect of practice on the execution of the subsequent Simon task. In particular, the effect of practice was increased after cathodal tDCS (group 2) while a tendency to the opposite direction was observed after anodal tDCS (group 3). These outcomes revealed that brain stimulation is able to modulate the effect of learning induced by behavioural practice. These results might contribute to prove the relevance of the development of applied techniques combining cognitive training and tDCS in order to improve mechanisms of cognitive control.

The organization of the neural networks involved in preparing reaching movements in humans investigated by the application of TMS0 and TMS/EEG

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Our previous behavior/TMS findings showed a discrete stream of regions, from the parietal to the frontal cortex, which is involved in the preparation of reaching movements. Focusing the attention on the parietal cortex, we also individuated, by TMS/EEG co-registration, further cortical areas of the temporo-occipital region that could also be involved in movement preparation and execution. Here, additional experiments are presented, in order to extend those results and better define the functionality and dynamics of this network. In the behavior/TMS experiments, 58 healthy subjects underwent single pulse TMS over different cortical regions of the left hemisphere while preparing a reaching movement. A series of points on the skull, located on the lateral parieto-occipital, parietal and premotor areas, were stimulated during the preparation of reaching movements. Subjects performed 42 randomized trials for each stimulated point on the skull: 21 trials with and 21 without TMS. In the TMS/EEG experiment, single TMS pulses were delivered over the left parietal cortex on nine healthy right handed subjects during continuous registration of EEG activity. The real TMS distribution of neuronal activity was computed and compared with respect to sham TMS. A voxel-by-voxel within-subjects comparison of current density distribution of real vs. sham TMS induced activity was performed. No specific effects were found on reaction times as a consequence of TMS delivery in the behavior/TMS experiments. In the TMS/EEG experiment, ERPs showed both positive and negative deflections, the amplitude of which was lower in the case of sham TMS. When considering current density distribution, significant differences were found between real and sham TMS in the time ranges between 116-126 msec, 134-146 msec, and at about 190 msec after the delivery of the stimulus, as well as in the mean neural activity of specific time windows of interest (60-130 msec, 130-245 msec and 245-300 msec, respectively). The propagation of activity, probably related to the preparation of reaching movements, seems to involve wide regions of the brain, distributed in the frontal, temporal, parietal and more posterior cortex. Besides the known serial flow of activation from posterior to anterior direction, a parallel elaboration of information among parietal and premotor areas seems also to exist. Moreover, segregation among these neural systems seems not to be highly restrictive, since present data point in favor of the existence of an overlap between different neural structures that are needed for the implementation of different

movements. The description of the many cortical regions which are involved in the preparation of movement, their organization and dynamics is a fundamental prerequisite for the development of brain-computer interfaces to be used in brain injured patients for rehabilitation and support to physical therapy.

Brain areas involved in temporal discrimination task: a study with ERPs and TMS

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Time processing in the millisecond-to-minute range is reflected by event-related potentials (ERPs), but the neural circuits of timing remains controversial. In the present study we investigated the role of different cortical areas in the processing of basic temporal information using an interference approach with repetitive transcranial magnetic stimulation (rTMS) and ERPs as indices of timing mechanisms. Nine healthy volunteers performed a temporal discrimination task in which they had to decide whether the time interval between two tones was shorter (800 ms), equal to, or longer (1200 ms) than a previously listened standard interval (1000 ms) and press different buttons accordingly. The task was performed at the baseline and immediately after a 15-min-long train of focal 1-Hz rTMS delivered to supplementary motor area, right posterior parietal cortex, right superior temporal gyrus, or Oz (control area). Accuracy and reaction times and ERPs during (contingent negative variation, CNV) and after the end of the comparison interval were analyzed. At the baseline, CNV was modulated by the interval duration and the analysis of the ERP evoked after the end of the comparison interval showed that the amplitude of the positive peak emerging approximately after 200 ms was higher for "Long" compared to "Short" intervals, whereas amplitude for "Equal" was intermediate. RTMS interference had no significant effect on behavioural performance or ERP components. These data may suggest that these cortical areas are less crucially involved than other brain regions (e.g. sub-cortical or cerebellar areas) in the neural mechanisms processing basic temporal information like interval duration.

Can mirror-like properties generalize across effectors? A TMS study

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Observation of others' actions modulates the excitability of the observers' corticospinal pathway involved in the execution of the same movement, revealing the existence of a mirror neuron system also in humans. In the past 20 years a lot of studies explored which features of the observed action are reflected in the observers' motor system. Previous evidences suggested that motor activity mirrors the observed action for muscles specificity, time-course and exerted forces. In contrast with these "low level" sensorimotor features, other studies highlighted the importance of the goal of the observed action regardless of the muscles involved to attain it. Although the facilitation of the motor system during action observation is widely accepted, the issue of granularity and generalization power of this system in humans remains still partly unexplored. Here we explore if the cortical facilitation induced by action observation could be generalized to an abstract representation of the observed action. In fact, the motor system might code fine details of others' action without losing the ability to generalize motor invariants to a more abstract level. Specifically, here we test whether the same pattern of muscle facilitation evoked by the observation of a given action may extend to conceptually similar movements even if performed by different effectors. To address this question we presented videos showing the hand or the mouth executing two different movements (opening/closing) in a lateral view. In 14 subjects we measured the activity of the flexor digitorum superficialis (FDS), a muscle usually involved in the closure movement by using single-pulse TMS. We found that motor evoked potentials (MEPS) were significantly larger during the observation of closing movement than during the observation of the opposite one for the hand as well for the mouth. For the presentation of hand actions we found the classic mirror resonance following the expected pattern of muscle specificity. However, the fact that an analogous pattern was shown also with mouth actions let us speculate that such low-level mirroring can indeed generalize between effectors. In fact, this modulation loses strict muscle specificity (for the mouth) but retains the critical invariances, such as the hierarchically more abstract concept of opening and closing. This result goes into the stream of studies demonstrating the centrality of goal rather than muscle-level resonance and provides evidence that the motor system possess the capability to generalize a given action. This generalization could be at the basis of a conceptual representation of the observed action. It is worth noting, that the two effectors used as stimuli have a strong connection due to their synergic proprieties.

State dependent effects of transcranial alternating current stimulation of the motor system: what you think matters

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Recent evidences suggested that imperceptible transcranial alternating current stimulation (tACS) resonates in a frequency-specific manner with the endogenous cortical oscillatory activity. Such a phenomenon causes behavioral consequences on perceptual, motor and cognitive tasks. In the motor system, 20 Hz tACS in beta range, coincident with the idling rhythm of the motor cortex at rest, increased corticospinal output. To assess how tACS modulates corticospinal excitability in a differential frequency dependent fashion during motor imagery and rest, we delivered transcranial oscillatory frequencies on the primary motor cortex ranging from theta to gamma band. Thus, we aimed to verify whether facilitatory tACS effects persisted during motor imagery, a cognitive task which desynchronizes the rolandic 20 Hz rhythm of quiescent motor areas, thereby becoming theoretically less susceptible to resonance effects of beta stimulation. Eighteen fully healthy right-handed volunteers (8 females, 10 males; mean age 32.2 ± 7.05 years)underwent fourteen different randomized conditions. Both for motor imagery and for resting condition, a "basal 1" session (without tACS), tACS on the left motor cortex at 5 Hz (θ band), 10 Hz (α band), 20 Hz (β band), 40 Hz (γ band), as well as 20 Hz on the right parietal cortex (as a control for unspecific effects on cortical excitability) and a "basal 2" session (again without tACS), were run. Each session of stimulation lasted 1.5-2 minutes. TMS was applied over the sponge electrode used for tACS overlying the left M1. Corticospinal excitability changes during stimulation at different frequencies were indexed by motor evoked potentials (MEPs) through navigated transcranial magnetic stimulation (TMS) of the primary motor cortex. MEPs were recorded from the right First Dorsal Interosseus. For motor imagery tasks, subjects were requested to visually imagine a thumb-index finger pinch grip with their right hand. Each TMS pulse was delivered 1-2 seconds after the initiation of the motor imagery task as well as for rest condition. bA repeated measures ANOVA (factors motor imagery and rest x frequency conditions) showed that the maximal increase of corticospinal excitability took place when tACS was applied at 5 Hz with subjects engaged in a motor imagery task, whereas tACS at 20 Hz confirmed the maximal increase of corticospinal excitability with subjects at rest. On one hand results confirmed the frequency-dependence effects of tACS. On the other hand a state-dependent effect of tACS emerged for the first time. The entrainment in the theta range during

motor imagery might reflect reinforcement of working memory processes required to mentally elaborate and "execute" the task. We infer that tACS induces an entrainment effect by dragging the endogenous oscillatory activity to the one induced by stimulation. This indicates that human brain motor processes might be driven and promoted by application of external sinusoidal electrical forces.

TMS-evoked potentials after low-frequency rTMS: a premilinary study

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Many studies have supported the idea that low-frequency repetitive transcranial magnetic stimulation (i.e. rTMS < 1-Hz) produces a decrement in motor cortex excitability, as revealed by motor-evoked potentials (MEPs). Nevertheless, findings often show contrasting outcomes. Currently, the development of TMS-compatible EEG systems offers an valuable tool for directly investigating the effects of TMS on cerebral cortex by analyzing TMS-evoked potentials (TEPs). The objective of our study was to directly evaluate the effect of a 1-Hz rTMS protocol on cortical excitability by analyzing the modulation of TEPs at rest. Repetitive TMS was carried out using a biphasic magnetic stimulator with a figure-of-eight coil. The EEG signal was acquired by a TMS-compatible amplifier from an array of 30 Ag pellet electrodes mounted in an elastic cap. Eight healthy volunteers underwent an rTMS protocol of 20 min consisting of a train of pulses at 1 Hz, delivered over left primary motor cortex (M1). The protocol intensity was set at 90% of participant's motor threshold (MT). To assess the protocol effects on TEPs, 50 TMS single-pulses at 100% of MT were delivered over M1, before (pre-rTMS session) and immediately after (post-rTMS session) the 1-Hz protocol. During the entire rTMS protocol participants were seated in a comfortable armchair in front of a computer monitor at 80 cm of distance. During the pre- and post-rTMS sessions, they were asked to fix a white cross in the middle of a black screen and to wear ear plugs playing white noise, in order to mask the coil click and avoid possible auditory ERP responses. The analysis of TEPs revealed differences in morphology and amplitude between the pre- and post-rTMS sessions. Early TEP components (such as P13, N18, P30, N45, and P60) were higher in amplitude in the post- compared to the pre-rTMS session. Furthermore, N100 was larger at central site Cz in the post- compared to the pre-rTMS session. Interestingly, such modulations were maximum at electrodes close to the stimulation site. The results confirm the inhibitory nature of N100 as shown by its increment in amplitude after the low-frequency rTMS protocol. Although preliminary, this study provides important insights into the effect of the TMS frequency on cortical excitability.

Neurological and neuropsychological changes induced in 8 right lesion motor stroke by controlesional motor cortex inhibitory rTMS

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Some studies are reported in the literature assessing the neurological and clinical amelioration after a rehabilitation treatment with repetitive transcranial magnetic stimulation (rTMS) in stroke patients. The most treated deficit are motor impairment, aphasia and neglect. The two most used protocols consist in the high frequency excitatory stimulation of the lesioned hemisphere and in the low frequency inhibitory stimulation of the unharmed hemisphere. The rational of the procedure is rebalancing the interhemisphere equilibrium altered by the stroke. The beneficial effects, from a clinical and neurological point of view, could be mild to medium, especially in a portion of patients. We hypothesized that the treatment could also affect neuropsychological scores of cognitive functions more lateralized in one hemisphere. Eight patients (2/6 males/females, age 51 ± 10 y, education 11 ± 6 y) with chronic right motor lesions (> 6 months poststroke) were enrolled for this study. Patients received 10 daily sessions of low frequency 1 Hz rTMS, 80% rest motor threshold, over the intact motor cortex with a focal 8 shaped coil (MAG&more, München). Outcome measures included dexterity, force, spasticity, objective neurological examination and a large battery of neuropsychological and psyschological test including: MMSE, Forward and Backward Digit Span, Corsi Span, Attentional Matrices, Short Story, Phonemic Fluency, Rey-Osterrieth Complex Figure Copy and Delayed Recall, Figures Copy, Bisection Lines Test, Landmark Task, Nelson Modified Card Sorting Test, Diller Letter Cancellation Test, SF36 Quality of Life, Hamilton Depression Inventory. The complete assessment was performed two weeks before rTMS and again two weeks after the end of treatment. We compared the scores with a two sample paired t-test ($p < 005$). Small to mild improvements were detected in some clinical outcome measures (spasticity, strength), three patients showed a greater improvement. Only Phonemic Fluency, Landmark Task and Line Bisection Test showed a significant improvement in the post treatment assessment. Depression and quality of like did not change except for Physical Role Subscale of the SF36. Our findings indicate that inhibitory rTMS effected the interhemispheric balance influencing and improving the neuropsychological scores of the more lateralized functions (language and space perception). This effect was particularly intriguing as we stimulated only the unharmed motor cortex with a focal coil and we did not treat directly areas specialized in the functions as in tradition rehabilitation protocols for aphasia or neglect.

Low frequency rTMS effect over the right dorsolateral prefrontal cortex in Depression resistant patients: effects on affective symptoms, cognitive function and P300 components

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Treatment-resistant depression (TRD) is a major health problem, affecting up to 15-20% of people with Major Depression. Between new therapeutical tools for these patients TMS is an emergent neurostimulation technique. While antidepressant efficacy of rTMS over DLPFC has been assessed in different clinical studies, less data are available on the effects on cognitive functions. The aims of the present study are to confirm the precedent findings about the antidepressant effects, to study the neurocognitive modification after 15 rTMS sessions after the right DLPFC, and to evaluate the possible role of the Event-Related Potential P300 as an indicator of the therapeutical response. Nine patients (age 41-76) diagnosed with Unipolar or Bipolar Depression resistant to at least two antidepressant trials, received low-frequency rTMS (1 Hz) over the right dorsolateral prefrontal cortex (DLPFC) in a 3-week trial (fifteen daily session, 1800 stimuli every session). Hamilton Depression, Hamilton Anxiety, Montgomery-Asberg Depression Scale, were evaluated the day before the treatment and every 5 session of rTMS. Trial Making Test, Stroop Test, Rey Auditory Verbal Learning Test, Rey Complex Figure Test, Verbal Fluency Test were evaluated in each subject at the beginning and at the end of the treatment. ERP were elicide by an acustic oddball paradigm with 20% target stimulus (red ash of light) and 80% non-target stimulus At the beginning and the end of the rTMS treatment auditory ERP was recorded before and immediately after the daily session of rTMS. After 15 rTMS sessions there was a significative reduction of HAM-D (76.46%), MADRS (80.33%), HAM-A (74.80%) scores. Looking at these results six patients were considered as remitters (HAM < 9). The neurocognitive test showed a significative improvement only in the Rey Auditory Verbal Learning Test (RAVLT), after the treatment there was a mean improvement of 10.16 points (immediate recall). This was seen not to be significantly linked to the antidepressant effect of rTMS. The latency of P300 was significantly increased at the beginning of the treatment (60% of patients had a P300 latency longer than the attended value for age) and remained increased at the end of the rTMS treatment. Considering the acute effect of rTMS, whereas at the day 1 no change of latency have been induced by 30 minutes of 1 Hz rTMS, at the day 15 rTMS determined a significant increase of P300 latency. The main finding of our study was: a dissociated effect of rTMS on affective symptoms

compared to cognitive symptoms. Central dopaminergic system play an important role in the generation of the P300 and that central dopaminergic activity could be involved in the modulation of P300 parameters. Our finding in depressed patients responders to rTMS treatment (increase in latency induced by rTMS effect on ERP responses at the end of treatment) can be explained as an indicators of functional restoring of the central dopaminergic system in the in the modulation of P300 parameters.

Time-course of transcranial direct current stimulation and multiparametric evaluation: a safety online TMS/tDCS combined study

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Most of neurophysiological studies demonstrated the effectiveness of tDCS stimulation in modifying cortical excitability,as an off-line protocol. Just a handful of studies documented online effects. Moreover, relationships between cortical excitability changes and vital parameters are still underinvestigated. We monitored tDCS online and after-effects by adopting a novel online transcranial magnetic stimulation (TMS)/tDCS combined protocol, by recording motor evoked potentials (MEPs) prior, during and after tDCS. Simultaneously, vital parameters such as continuous heart rate (HR) monitored in beat per minute (bpm), systolic (sBP) and diastolic (dBP) blood pressures, sympathetic andparasympathetic tones (power spectra analysis of the R-R interval [RRI]) and the heart rate variability (HRV) were measured by using the "Task Force Monitor" device, in order to check whether monopolartDCS may cause potentially dangerous side effects induced by currents spreading through the brainstem. Neurophysiological and vital parameters were recorded in ten healthy subjects. A monopolart DCS montage was adopted by placing the target electrode over the dominant primary motor cortex (M1) and the reference over the ipsilateral shoulder. TMS was applied over the sponge electrode overlying the left M1 and MEPs were recorded from the right first dorsal interosseus (FDI). Ten MEPs were collected every 2.5 minutes time windows. The experimental design was set up by running a no-tDCS condition for 15 minutes and subsequently online tDCS (anodal, cathodal or sham) for additional 15 minutes. tDCS after effects were recorded for 30 minutes post-stimulation. Vital parameters were measured in 5 minutes time windows during the entire experiment, which lasted 60 minutes. Results showed a robust inhibition of cortical excitability induced by cathodal tDCS,occurring starting after 15 minutes online stimulation and persisting during the whole post-stimulation time-windows. Anodal tDCS induced just a slight effect between no-tDCS and post stimulation time windows.. Sham stimulation was uneffective. Analysis of vital parameters did not show significant differences across tDCS conditions. These findings provide new insights on the time course of tDCS effects, both on cortical excitability and safety parameters.

Effects of the low frequency rTMS over the right dorso-lateral prefrontal cortex on contingent negative variation

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The contingent negative variation (CNV) is a slow negative cortical potential related to the attentional effort that occurs between two contingent stimuli, a warning stimulus followed by an imperative stimulus and reflects operant conditioning processes. To test the effects of the modulation induced by low frequency repetitive transcranial magnetic stimulation (rTMS) of dorso-lateral-prefrontal cortex (DLPFC) on the CNV with a motor response. 9 right handed healthy subjects (mean age 23.67 ± 3.31 years), that were naive to the rTMS, underwent, in the same day, three consecutive EEG recordings during which CNV with motor response was evocated in basal condition and after 30 minutes of real or sham 1 Hz rTMS stimulation of the right DLPFC. For the sham stimulation we positioned the coil at 90º over the scalp, in the same place where we put the coil for the real stimulation. The order of real and sham stimulation was randomized using http/random.org. Total CNV amplitude and the areas in three different temporal windows (W1, W2, W3) were evaluated. Reaction times (RTs) were also measured for all CNV recordings. Results showed that 30 min of 1 Hz rTMS induced a significant decrease of total CNV amplitude ($Fz\ p < 0.03$ – $Cz\ p < 0.08$ – $Pz\ p < 0.03$), W1-CNV ($Fz\ p < 0.009$) and W2-CNV areas ($Fz\ p < 0.02$ – $Cz\ p < 0.02$ – $Pz\ p < 0.01$) respect to CNV in basal and sham conditions. No differences were found between basal and sham condition for all CNV characteristics. No difference was found in RTs for all recordings. This study confirms and extends that 1 Hz rTMS produces a real inhibitory effect on neurophysiological parameters as CNV. Transient inhibition of DLPFC could cause a difficulty in sustaining attention during a task of operative conditioning with a critical involvement of orienting and operative choice phases.

Is transcranial alternating current stimulation effective in modulating brain oscillations?

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Transcranial alternating current stimulation (tACS) is a promising tool to modulate brain oscillations, especially regarding possible therapeutic interventions. However, the lack of conclusive evidence for tACS to be able to effectively affect cortical activity still limits its application. The present study aimed at addressing this issue, exploiting on the well-known inhibitory alpha rhythm at posterior parietal cortex in visual perception and attention orientation. Ninety-six healthy volunteers (48 female, mean age 21.7) participated in the study and were randomly assigned to one of four groups of stimulation, each one composed by 24 participants. Each group was tested during a visual stimulus detection (yes/no) and orientation discrimination (leftward/rightward) task. Target stimuli were low-contrast gabor patches at five different contrast levels ranging from 0.034 to 0.052 (Michelson Contrast Index) presented in a random order in the left or right visual hemifield. The central contrast was adjusted at the threshold level estimated in a pilot experiment. All the participants were tested at the baseline and at a selective frequency of tACS, including Sham, 6, 10, and 25 Hz. A small target electrode (16 cm^2) was placed, according to the participant group, over the left or right occipito-parietal areas (PO7 or PO8) as determined by the International 10-20 EEG system. The reference electrode was positioned over the vertex CZ. The results, in terms of arcsine-transformed accuracy (% of correct responses), showed a general decrease of visual perception, over both the visual fields, independently by the site of stimulation (ipsilateral vs. contralateral), and this was found in the groups stimulated both at 10 Hz and at 6 Hz. The lack of retinotopically organized effects and the only marginal frequency-specificity force us to be cautious about the effectiveness of tACS to modulate brain oscillations. In conclusion, the present study does not provide strong evidence that tACS induces modulation of occipital brain oscillations during a visual task.

Impact of low frequency repetitive transcranial magnetic stimulation over right DLPFC on event-related brain potential

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The utility of rTMS technology in the treatment of depression is fully recognized from a lot of studies, but only in the 30% of patients the therapy is effective. Many studies have already demonstrated the connection between effectiveness of rTMS and elder age, drug resistance or presence of comorbidities, but they didn't found a useful link with a neurophysiological marker. Some studies controlled the influence of rTMS over DLPFC on P300 wave in depressed patients, but not in healthy subjects. So our objective is to better understand this last relationship to predict how much useful will be the rTMS for every patient before starting the therapy, so it will be easier to identify who receives more benefits from the treatment. Up to now in the studies was generally stimulated the left DLPFC. Pallanti et al showed similar effect of 1 Hz rTMS on right DLPFC. We studied a population of 9 healthy young volunteers, right-handed with no history of neurological or psychiatric diseases. In particular, all subjects with a history of affective, psychotic, or cognitive disorders were excluded. ERP were elicited by an acoustic oddball paradigm with 20% target stimulus and 80% non-target stimulus All subject were naive to the rTMS. Every subject was recorded twice in one week, once using real rTMS (1 Hz) over the right DLPFC and another time using sham stimuli. For the sham we positioned the coil at 90º over the scalp, in the same place where we put the coil for the real stimulus. The order of real and sham stimuli was randomized using http/random.org. We compared the P300 wave latency and amplitudes before and after the real and sham stimulation. Results showed that 30 min of 1 Hz rTMS OVER RIGHT DLPFC induced a significant increase of P300 latency. There was no effect for early ERP components (N100, P200 and N200). We show effect on P300 amplitude only at Pz electrode. Reaction time showed no significant main effect of rTMS. It is generally admitted that cortical excitation is induced by high frequency rTMS (i.e. 20 Hz), whereas cortical inhibition is provoked by low frequency (i.e. 1 Hz). However, several studies did not report any modification after 1 Hz rTMS on cognitive functions. This study confirms and extends that 1 Hz rTMS produces a real inhibitory effect on Neurophysiological parameters – i.e. P300 latency and amplitude. The data suggest that unilateral rTMS modifies the speed of cognitive processing and in only in part the energetical aspect of information processing, and that cortical inhibition induced by the magnetic stimulation affects principally the controlled cognitive processes and not the automatic ones.

Independent component analysis of the neural correlates of action awareness

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It is assumed that while performing a goal-oriented movement a matching process occurs between its predicted and actual sensory consequences that may contribute to the feeling of ourself as the agent of our's own actions, that is the "sense of agency". If the matching process detects a discrepancy which exceeds a certain threshold then awareness of action discrepancy or a perturbed sense of agency appears. In a previous study we demonstrated that both these perceptions are associated with changes in movement-related high α/low β desynchronization in the parietal cortex. To localize the source/s of such desynchronization we used independent component analysis (ICA) computed on 64 channel EEG recordings of normal subjects performing center-out cued reaching movements under a variable degree of perturbation of the visual feedback. Briefly, the output of an electromagnetic motion-tracking system, whose sensor was located on the subject right finger, was processed by a computer and projected on a mirror where the subjects saw their virtual finger as a cursor, having their hand hidden by the mirror. Computer processing used an algorithm for adding a linear directional bias in clockwise/counterclockwise direction of varying amplitude or for producing a randomly-generated distortion (d). Thus, four experimental conditions were presented pseudorandomly: 0°d, visual displacement of 7.5° or 18°, which were under or above the threshold for conscious detection, respectively, and no correspondence between the actual and the seen movement (other's). After each movement subjects reported whether they felt like to be in control or out of control of the movement viewed and, in the former case, whether feedback was congruent or distorted with respect to their actual movement. As expected, a discrepancy was detected in 4 ± 3%, 23 ± 15%, 79 ± 11% and 100% of 0°d, 7.5°d, 18°d and other's movements, respectively. Time-frequency analysis computed on the activity of two clusters of ICs located in the mesial portion of precuneus and in the right angular gyrus demonstrated that movement-related α3 and β1 desynchronization was significantly higher in 18°d as compared to 0° and 7.5°d conditions. In case of altered sense of agency (other's), desynchronization in the same frequency bands was similar to that associated with 18°d in the first 500 ms since the exit from the starting point, then it partially recovered towards pre-movement values although movement was still ongoing. We speculate that during distortion the computational cost needed to incorporate/select afferent signals such as the incongruent visual and the veridical proprioceptive signals in the monitoring/matching process leads to an

increase of movement-related α3 and β1 desynchronization at the level of precuneus and right angular gyrus. According to this speculation, a reduced need of monitoring, which occurs when subjects became aware that visual feedback is not related to their own movement, is associated with a partial recover of α/β rhythms in these brain areas.