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ABSTRACTS

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Normal lateral inhibition mechanisms within the somatosensory cortex in patients with chronic migraine

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Objectives. In episodic migraine patients between attacks we previously found reduced lateral inhibition and habituation, but normal sensitization, mechanisms within the somatosensory cortex. During the attacks, after an initial transient sensitization, both delayed habituation and lateral inhibition normalized [1]. Here, we have studied lateral inhibition and habituation/sensitization in the somatosensory cortex of patients evolved from episodic to chronic migraine (CM), and we searched for possible correlations with clinical features.
Methods. Sixteen patients with CM without medication overuse, and 17 healthy volunteers (HV) underwent SSEPs elicited by electrical stimulation of the right median (M) and ulnar (U) nerve at the wrist separately and simultaneously (MU). We measured parietal N20-P25 amplitudes and we calculated the percentage of lateral inhibition by using the formula 100-(MU/(M+U)*100). Sensitization and habituation were calculated on the median nerve responses as the 1st N20-P25 amplitude block and as the slope of the linear regression between the 1st and the 2nd block of 100 averaged sweeps respectively.
Results. In CM patients, percentage of somatosensory lateral inhibition was comparable to that of HV. Patients had a generalized increase of SSEP amplitudes than HV and habituated normally. Percentage of lateral inhibition negatively correlated with monthly days with headache, and positively with severity of headache attacks.
Conclusions. In CM patients, we show a pattern of somatosensory response similar to that found in episodic migraine patients during a migraine attack. Moreover, in the transformation process between episodic and chronic migraine, lateral inhibition may contribute to clinical characteristics of CM.
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A new, micropatterned surface electrode for the assessment of nociceptive pathway function

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Backgroud. A new, interdigitated electrode was designed to provide selective stimulation of nociceptive system, activating electric field limited to intraepidermal free nerve endings. In this neurophysiological study, we aimed to verify the selectivity of this tool for the assessment of nociceptive pathway function in healthy humans and in patients with a selective nociceptive system involvement.
Methods. In experiment 1, the surface electrode was applied to the hairy skin of the hand dorsum in healthy subjects, to assess the subjective perception as a function of the stimulus intensity and to record superficial radial nerve sensory action potentials at increasing stimulation intensity in comparison with standard electrode. In experiment 2, pain related evoked potentials after face and hand stimulation were recorded using 32 Ag–AgCl scalp electrodes and were compared with laser evoked potentials. In experiment 3, pain related evoked potentials were recorded after simulation of three sites of the upper limb in order to calculate the conduction velocity. In experiment 4, a selective superficial radial nerve block involving nociceptive fibers was performed in order to test surface electrode selectivity. The new electrode was compared to laser in patients with selective nociceptive pathway damage.
Results. The micropatterned surface electrode elicited a clear pin-prick sensation in the majority of subjects with a stimulus intensity less than 10 mA and no sensory action potentials were recorded at this intensity. Scalp evoked potentials after microelectrode low intensity and laser stimulation were comparable. The calculated, mean conduction velocity was 14 +/- 6 m/s. After selective superficial radial nerve block, pain related evoked potentials were abolished.
Discussion. These data therefore suggest that the new micropatterned surface electrode after low intensity stimulation might be useful tool for a selective assessment of nociceptive system
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Fibromyalgia: neurophysiological and skin biopsy aspects in light of main comorbidities

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Background and objectives. *Fibromyalgia* (FM) is a chronic condition characterized by widespread pain, tenderness, fatigue, sleep disruption, cognitive dysfunction and other symptoms. It can be associated with psychiatric, neurological, rheumatic and autoimmune pathology. The pathophysiology is still unclear, but a dysfunction of pain modulation at central and peripheral level and a sympathetic dysfunction, attributed to the psychopathological traits, was described (1). Small fibers neuropathy is present in many cases (2). The aim of our study was to explore severity of FM patients in light of main comorbidities as central and peripheral nervous system, psychiatric and rheumatologic diseases.
Methods. We investigated a cohort of eighty-four FM patients. Comorbidity for migraine, according to current classification, psychiatric diseases, according to DSM V and non-active rheumatic and/or autoimmune disease was explored. All patients underwent skin biopsy from the right thigh and right ankle. All patients underwent the fibromyalgia impact questionnaire (FIQ-I). We also considered the Wide Pain Index (WPI), according to the recent ACR diagnostic criteria. The outcome of patients at 1 year follow up was considered.
Results. Skin biopsy showed epidermal density reduction at proximal site in the 83,3% of cases, at distal site in the 14,3 %. Migraine was present in the 43,6% of cases, psychiatric comorbidity in the 14,8%, autoimmune diseases in the 21,8%. Pain diffusion, as measured by WPI, prevailed in patients with associated migraine and psychiatric comorbidity (linear regression analysis: 10.74 p 0.0033). The severity of fibromyalgia, as measured by FIQ seemed reduced in patients with compromised distal epidermal fibers (linear regression analysis -2.12 p 0.040). The presence of auto-immune diseases and proximal neuropathy did not influence FM features.
Conclusions. Peripheral nerves involvement did not appear to be a factor influencing FM clinical phenotype. Migraine and psychiatric comorbidities could account for a more severe pain diffusion, confirming that FM phenotype is mainly explained by a disturbance of pain modulation at central level.
Key point: Fibromyalgia, small fibers neuropathy, migraine and psychiatric comorbidities
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Voice Analysis in Adductor-Type Spasmodic Dysphonia

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Objective. To investigate differences in voice parameters between patients affected by different variants of spasmodic dysphonia (SD) and healthy subjects (HS).
Background. SD is a task-specific focal dystonia manifesting with involuntary laryngeal muscle spasms leading to intermittent strained/strangled voice. The lack of diagnostic criteria and validated severity scales makes the diagnosis of SD rather challenging. In the present study, we examined voice instrumentally in SD patients by means of acoustic analysis and compared a number of voice parameters in SD patients and HS.
Materials and Methods. We investigated 50 right-handed non-demented, non-depressed native Italian speakers SD patients and 50 age and sex-matched healthy subjects. 25 SD patients were studied also during the effect of Botulinum Neurotoxin-A (BoNT-A) therapy. Phoniatric evaluation included laryngoscopy, voice spectrogram and voice cepstral analysis of a "standardized sentence repetition" and a "sustained vowel (A, E, IU, IAMM). We collected voice samples using a high-definition audio recorder. Cepstral peak prominence (CPP) together with other spectral features, such as CPPS (smoothed CPP), Hi/Low frequencies rate, harmonics-to-noise ratio, shimmer and jitter were extracted. Finally, in order to differentiate automatically voice in SD and HS, we used a classification procedure with Support Vector Machine (SVM), Naïve Bayes and Multilayer Perceptron Neural Network (ANN) using Weka software.
Results. Voice analysis discriminates HS and SD, with a sensitivity of 76% by using SVM, Naïve Bayes and ANN; and a specificity of 100%, 87% and 83% by using respectively SVM, Naïve Bayes and ANN. Positive predictive value is 100%, 84%, 80% by using respectively SVM, Naïve Bayes and ANN. Negative predictive value is 83%, 81%, 80% by using respectively SVM, Naïve Bayes and ANN. Accuracy increased significantly after Feature selection and Discretization. Good performances of the algorithm were obtained also in the differentiation of 25 SD patients examined under- and not-under BoNT-A therapy.
Discussion and Conclusions. Voice analysis discriminates SD patients from HS, representing a new helpful tool to better characterize voice abnormalities in SD. These results suggest the idea that voice features extraction and classification are important instruments to support clinicians in the correct diagnosis of SD, among different voice disorders.
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Painful legs and moving toes syndrome treated with botulinum toxin type A: a case report

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Background and objective. Painful legs and moving toes (PLMT) syndrome is a rare movement disorder, characterized by spontaneous pain in the lower limb and involuntary repetitive movements in the affected toes or feet (1). The etiology is still not fully understood, and an underlying lesion in the peripheral or central nervous system, such as neuropathy, radiculopathy or spinal cord lesion, may be identified in several cases (2). Although the pathophysiologic mechanism remains unclear, functional changes of the afferent inputs and subsequent central reorganization in the spinal cord or in the higher centers might play a role in the pathogenesis (2,3). Until recently, a wide spectrum of drugs have been used for the treatment, with overall low success rate (2). Herein, we describe one patient with characteristic pain and involuntary movements of PLMT syndrome, successfully treated with Botulinum toxin A.
Methods. A 55-years-old man with a history of mild chronic L5-S1 radiculopathy and previous psychiatric illness, referred to our department for 1-year history of burning pain in the left leg and continuous involuntary movements of toes. A previous ineffective attempt with different drugs was performed. The neurological examination was unremarkable except for continuous pseudo-rhythmic flexion and extension digit movements of the left foot. Brain and spinal MRI and blood tests were unremarkable. A comprehensive neurophysiological investigation, including

EMG, nerve conduction study, tibial nerve H-reflex, somatosensory evoked potentials and EEG with back-averaging have been performed. EMG recording showed spontaneous discharges of motor unit potentials in the extensor digitorum brevis (EBD) and flexor digitorum brevis (FDB) muscles, as pseudo-rhythmic phasic bursts of 50-300 ms, with a rate of 1-2 Hz and both synchronous and alternating pattern in antagonistic muscles. Incobotulinum toxin A was injected in the EBD (50 U) and FDB (50 U) under EMG guidance.

Results. The injections resulted in marked relief of leg pain and significant attenuation of toe movements in few days.

Conclusions. Treatment with botulinum toxin can cause significant pain relief and movements reduction in PLMT syndrome and should be considered in those patients who fail oral therapy.

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Blink rate analysis in Parkinson's disease as diagnostic tool

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Introduction. Decreased blink rate is a motor feature of idiopathic Parkinson's disease and other parkinsonism. This may results from nerve cell loss in the substantia nigra and from the reduction of striatal dopamine content[1]. It has been suggested that an objective evaluation of blink rate can be used as a diagnostic noninvasive biomarker for Parkinson's disease[2].

Objectives. The aim of the study was to compare blink rate in Parkinson disease patient in ON phase with healthy controls.

Methods. We enrolled 12 patients (68 ±6,5 yo) diagnosed with PD according to UK Parkinson's Disease Society Brain Bank diagnostic criteria, and 9 healthy subject as controls (55±9 yo). All subjects were filmed under three different test conditions for 1 min for each task. The three test conditions were: (1) rest, (2) conversation and (3) reading. Digitally recorded video images focusing on the eyes were collected. The observer reviewed the videotapes and measured the number of blinks for 1 min during each segment.

Results. A paired-samples t-test was conducted to compare the blink rate in PD patients and in healthy controls for each task. There was a significant difference in the blink rate during rest between PD patients (M 10.83; SD 12.15) and healthy controls (M 22.11; SD 6.25); $t(19)=-2.53$, $p = 0.020$. There was a significant difference also during conversation, between patients (M 17.42, SD 12.57) and controls (M 32, SD13.58); $t(19)=-2.54$, $p =0.020$. Otherwise, there was a non significant difference in the blink rate between cases (M 7.25, SD 10.21) and controls (M 16.56, SD 10.45); $t(19)=-2.04$ $p = 0.055$ during the reading task. Combining the two diagnostic predictors (blink rate during rest and conversation), the ROC AUC was 0.852.

Discussion and Conclusion. Combining the two diagnostic predictors (blink rate during rest and conversation), the diagnostic accuracy of PD vs healthy control discrimination is high. This study confirms the utility of an objective evaluation of the blink rate, as a quantitative tool for the diagnosis of Parkinson's disease.

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Abnormal α-synuclein deposits in skin nerves: inter and intra-laboratory reproducibility

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Objective. phosphorylated α-synuclein at serine 129 (p-syn) in skin nerves is a promising test for the in vivo diagnosis of synucleinopathies. Here we aimed to establish the intra and inter-laboratory reproducibility of intraneural p-syn positivity in two laboratories (Würzburg, Germany and Bologna, Italy) with a major expertise in this analysis.

Methods. we enrolled 42 patients (26 from Würzburg and 16 from Bologna) affected by Parkinson's disease (PD: 21 patients), REM sleep behavior disorder (RBD: 11), Multiple System Atrophy (MSA: 4) and small fiber neuropathy (SFN: 6). Skin biopsy was performed in C7 paravertebral spine region and distal leg. The analysis was standardized in both laboratories and made blinded on a single skin slide double stained with p-syn and PGP 9.5 (pan-neuronal marker). Fifty skin slides were analyzed. Slides differently classified were re-evaluated to understand the reasons of the discrepancy.

Results. The intra-laboratory analysis showed an excellent reproducibility both in Würzburg (concordance of classification 100% of slides; $K=1$; $p<0.001$) and Bologna (96% of slides; $K=0.92$; $p<0.001$). Inter-laboratory analysis showed a reproducibility in 45 slides (90%; $K=0.8$; $p<0.001$) and a different classification in 5 slides which was mainly due to fragmented skin samples or weak PGP 9.5 signal.

Conclusions. 1) p-syn analysis showed an excellent inter and intra-laboratory reproducibility supporting the reliability of this technique as in vivo biomarker for synucleinopathies; 2) the few ascertained discordances were important to further improve the standardization of this technique.

Palatal myoclonus as a possible onset of a motor neuron disease

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Introduction. Palatal myoclonus (PM) is a rhythmic involuntary jerking movement of the soft palate and tongue, often involving the muscles of the neck and the upper limbs, caused by a lesion in the triangle of Guillain and Mollaret. In case of an indemonstrable lesion, it's called essential PM and typically disappears during sleep. Symptomatic PM indeed can be associated to ocular and/or pharingeal myoclonus, ataxic syndrome and to an ear clicking, Moreover it persists during sleep. Electrophysiology helps to differentiate the two conditions by the Blink Reflex Study, in fact, in the essential myoclonus only the polysynaptic brainstem reflexes (R2) are abnormal, while, in the symptomatic one, the oligosynaptic (R1) and polysynaptic (R2) reflexes are both involved.

Material and Methods. A 69 years old man developed a palatal and tongue myoclonus that increased in stressful situations and disappeared during sleep. At first he ascribed this sign to dental malocclusion. In few months the symptomatology progressively worsened and a mild dysarthria, dysphagia and sialorrhoea appeared. In addition he started to loose weight. The patient came to our observation after 18 months from the onset. Neurological examination was normal, except for myoclonus and dysartria. He underwent a range of hematological investigations,

including serology for HIV, research of onconeural antibodies and tumor markers, autoimmunity test. A chest X-ray, an abdominal echography, an MRI of the brain, a lumbar puncture and an Electromyography (EMG) with motor and sensory nerve conduction and a Blink Reflex study were also conducted. After two months the neurological examination was unchanged but he had lost more weight.

Results. All the blood exams were unremarkable, except for isolated detectable ANA (1:160). MRI, Chest X-ray and abdominal echography were normal. EMG confirmed the palatal and tongue myoclonus, diffused to the upper limbs. Motor and sensory nerve conduction velocities were normal. Needle examination showed signs of acute denervation with complex repetitive discharges at the orbicularis oris and some fasciculations at the upper limbs; MAUPs were small and polyphasic with reduced recruitment in the bulbar region. Bilateral temporal dispersion of all the reflexes was found at the BR study.

Conclusions. Our patient showed features typical for an essential myoclonus, but the neurophysiological evaluation is more suggestive for a secondary form, associated with a second motor neuron souffrance.

We suggest that palatal myoclonus could be the first sign of a motor neuron disease but a longer clinical observation would be necessary to clarify the disease's etiology.

Impaired LTP-like plasticity in Parkinson's Disease can be restored by γ-transcranial alternating current stimulation

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Objective. Several transcranial magnetic stimulation studies have shown that intermittent theta burst stimulation (iTBS) fails to induce long-lasting changes in motor evoked potentials (MEPs) in Parkinson's Disease (PD), supporting the evidence of impaired long-term potentiation (LTP)-like plasticity in the primary motor cortex (M1). We have recently introduced a novel neurophysiological approach consisting in the combined stimulation of M1 by transcranial alternating current stimulation, delivered at the γ frequency (γ-tACS), and iTBS, which produced a significant boosting of the LTP-like plasticity in healthy young subjects. In this study we aimed to test whether the co-stimulation γ-tACS-iTBS is effective in improving the impaired LTP-like plasticity of M1 in patients with PD.

Material and methods. We designed a single-blinded placebo-controlled study in which patients ('OFF' dopaminergic therapy) underwent iTBS during 'real' γ-tACS and during 'sham' γ-tACS in two different randomized sessions. MEPs were recorded from the most affected side before (T0) and 5 (T1), 15 (T2) and 30 (T3) minutes after the intervention to measure the after-effects produced by the stimulation. A group of age- and sex-matched healthy subjects (HS) was also studied to compare the effect of γ-tACS-iTBS with that obtained in patients.

Results. In HS, 'sham' γ-tACS-iTBS produced a significant MEPs facilitation at T1 and T2. By contrast, the same stimulation did not induce long-lasting changes of MEPs in patients. When the effect of 'real' γ-tACS-iTBS was compared with that produced by 'sham' γ-tACS-iTBS, the analysis demonstrated an increased MEPs facilitation at all the time-points in the 'real' session in both groups. Importantly, in patients MEPs amplitude at T1, T2 and T3 was higher than those recorded at T0, and the amount of facilitation was comparable with that observed in HS. The effect produced by γ-tACS-iTBS was not related to the patient's age, most affected side, stage of the disease or severity of the motor symptoms, as assessed by the UPDRS-III scores.

Conclusions. iTBS-induced LTP-like plasticity is impaired in PD. However, by synchronizing the neuronal elements of M1 at the γ rhythm by using tACS, the mechanisms responsible for altered LTP-like plasticity can be restored. Thus, γ oscillations of M1 have an important pathophysiological role in LTP-like plasticity in PD.

MEG study on patients with essential tremor treated with magnetic resonance guided focused ultrasound (MRgFUS)

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Rational and Aims. Surgical treatments for medically refractory tremors are expanding and magnetic resonance guided focused ultrasound (MRgFUS) can be considered as a valuable option to treat essential tremor (ET) since it is a minimally invasive procedure without craniotomy and has almost no contraindications. To evaluate the neurophysiological correlates of its therapeutic effects, we recorded the MEG signal in patients with intractable essential tremor, in order to study event related activities and connectivity patterns in the sensorimotor cortex before and after sonication

Methods. MEG recording evaluation, including connectivity evaluation at rest and during motor activation, event related changes of the cortical oscillations in response to simple motor tasks, and the evaluation of somatosensory evoked fields (SEFs) are performed before, the day after treatment and after one month. The neurophysiological evaluation will be correlated with the clinical assessment using Essential Tremor Rating Assessment Scale.

Results. Preliminary data reveal substantially normal SEF at baseline, but a clear increased N20-P25 amplitude after MRgFUS treatment. The post-movement event related synchronization was present but moderately decreased after treatment.

Discussion. The observed increase of SEF suggest a relief from interfering tremor along the ascending somatosensory pathways. The reduced ERS amplitude suggest a change in balance between excitatory and inhibitory thalamo-cortical circuitries.

Conclusions. Preliminary results suggest that neurophysiological arrangement occurs in patients with ET treated with MRgFUS. Our study in a large cohort of ET is expected to clarify the circuitry changes and to detect markers predicting the outcome.

Balance Assessment by means of Wearable Sensors in Parkinson's disease

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Rationale and Objectives. Postural instability (PI) is a disabling motor symptom usually occurring in advanced stages of Parkinson's Disease (PD) and often leading to harmful falls. The clinical assessment of balance in PD is rather arbitrary and poorly sensitive in the recognition of early signs of balance disorders. Moreover, the pathophysiology of PI and its response to dopaminergic therapy remain largely unclear. Aims of the study are 1) to examine reactive postural responses during stance perturbations in patients with PD, without clinically overt PI, by using wearable sensors (inertial measurement units - IMUs), and 2) to assess the effect of dopaminergic therapy on such measures.

Material and methods. 10 Healthy Subjects (HS) and 10 age-matched patients with mild-to-moderate PD, without clinically overt PI, underwent unexpected stance (yaw) perturbations imposed by a mechatronic platform. The experimental trials were video-taped for off-line clinical evaluation and segmental joints kinematics were recorded by IMUs. We excluded PI clinically by means of UPDRS-III, BERG and PIGD scores. Additional clinical assessment included H&Y, MMSE, FAB, ABC, BAI

and BDI scales. Patients were assessed when under (ON) and not under (OFF) dopaminergic therapy. Reactive postural responses were evaluated through the ratio between excursion amplitudes of the distal with respect to the proximal segment of joints (G-Joint index) and the phase shift between them (Phi-Joint index). Finally, we examined the clinico-behavioral correlations.

Results. All patients completed the experimental trials without manifesting clinically overt balance disorders. However, when considering kinematic response, patients showed a lower excursion amplitude (altered G-joint index) and a lower excursion time delay (altered Phi-Joint index) than HS, in most of the joints examined (atlanto-occipital, elbow, lumbo-sacral and hip). L-Dopa left kinematic measures unchanged. Finally, the abnormal Phi-Joint index significantly correlated with the degree of patient's motor impairment (H&Y, UPDRS-III, BERG and PIGD scores) and subjective balance confidence (ABC scores).

Conclusions. Patients with PD, without clinically overt PI, present subclinical balance disorders detectable by means of IMUs. The lack of effect of L-Dopa on reactive postural responses suggests that PI arises from neurodegeneration in non-dopaminergic pathways. In conclusion, IMUs represent a valid tool to investigate reactive postural responses in patients with PD, opening to the long-term assessment of balance control in ecological environments. Finally, by disclosing subclinical balance disorders in patients with PD, without clinically overt PI, it would be possible to design early therapeutic strategies in order to prevent harmful falls.

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Multimodal assessment for predicting six-month outcome in prolonged disorders of consciousness: a multi-center longitudinal study

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Rationale and objectives. Management of patients with prolonged Disorders of Consciousness (DoC) requires challenging decision-making for planning appropriate care pathway.[1] In this process, reliable markers, easy to collect in the routine clinical practice, can help clinicians in accurately predicting clinical evolution of patients.[2] To date, most of prognostic studies evaluated clinical or neurophysiological predictors separately.[3] Additionally, previous investigations were conducted in single center, threatening the value of the evidence because of possible biases related to the case-mix. Here we present an international multicenter longitudinal observational study designed at identifying predictors for short-term clinical outcome in patients with prolonged DoC.

Methods. Twelve specialized medical institutions enrolled patients in prolonged vegetative state/unresponsive wakefulness syndrome (VS/UWS) or in prolonged minimally conscious state (MCS) within 3 months from brain injury. Demographic (i.e. age, sex), anamnestic (i.e. time post-injury, etiology), clinical (i.e. clinical diagnosis, level of consciousness and of functional disability measured by Coma Recovery Scale-Revised-CRS-R and Disability Rating Scale total score-DRS total scores respectively) and neurophysiological (i.e. EEG background activity and reactivity, somatosensory evoked potential and event related potentials-ERP) data were collected at study entry; then, patients were followed-up after 6 months post-injury. We classified as "improved" patient in MCS recovering full consciousness and patients in VS/UWS progressing to MCS or possibly full consciousness with respect to study entry, and as "not-improved" patients with clinical diagnosis worsened or unchanged with respect to baseline, or patient who died.

Results. One hundred-forty-eight patients were included (103 men; mean age: 49.3±19.8 years; VS/UWS =71, MCS=77; traumatic=55, vascular=57, anoxic=36; mean time post-injury=65.6±39.1 days). Out of 139 patients (VS/UWS=69; MCS=70) who reached the follow-up at 6 months post-injury, 70 improved (VS/UWS=26; MCS=44), whereas 69 did not (VS/UWS=43; MCS=26). We ran a logistic regression analysis showing that younger age, male sex, shorter time post-injury, higher CRS-R total score and presence of EEG reactivity to eye opening at study entry were significantly associated with a better outcome (all $p<.05$). Instead, etiology, clinical diagnosis, DRS, EEG background activity, acoustic reactivity and P300 on ERP were not associated with 6-month outcome.

Discussion and conclusions. The present longitudinal study suggested that multimodal clinical and neurophysiological assessment along to patients' demographic and anamnestic data can help clinicians in prognostication of patients with DoC. This multi-center project represents an international effort for standardization of prognostic procedures in the routine clinical management of patients with DoC.

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Cortical inhibitory dysfunction in epilepsia partialis continua: A high frequency oscillation somatosensory evoked potential study

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Objective. The pathophysiology of epilepsia partialis continua (EPC) is still unclear, a thalamo-cortical circuit dysfunction has been hypothesized. The aim of present study is the functional evaluation of the thalamo-cortical network in EPC by means of the study of low- and high- frequency somatosensory evoked potentials (LF-SEP and HF-SEP).
Material and methods. We present a case-control series study describing HF-SEP and LF-SEP recorded in 3 patients with EPC and in 2 cases of rolandic lesion without EPC (non-EPC). The SEPs were obtained by bilateral stimulation of median nerve. SEPs were simultaneously recorded by P3/P4, C3/C4, F3/F4 scalp electrodes. Off-line subtraction of P3-F3 and P4-F4 traces and 400-800 Hz filtering allowed us to study HF-SEP.
Results. In EPC patients, we recorded a significant reduction of post-synaptic HF-SEP burst and an amplitude reduction/absence of the LF-SEP P24 wave. Both these components are related to cortical inhibitory interneuron activity. HF-SEP and LF-SEP were normal in non-EPC patients.
Conclusions. The different results obtained in patients with a rolandic lesion with and and without EPC supports the hypothesis that EPC origins by a dysfunction of gabaergic interneurons of a cortical sensory-motor network activated by spared thalamo-cortical projections. Our results might contribute to the understanding of the physiological basis of the cortical dysfunction causing epilepsia partialis continua.
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Thalamo-cortical network dysfunction in temporal lobe epilepsy

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Objective. Imaging and intracranial recordings demonstrated that the cortical disfunction caused by focal epilepsy goes far beyond the epileptic focus, thus raising a new vision of focal epilepsy as a network disorder. The deep involvement of thalamo-cortical projections in temporal lobe epilepsy is a clear example. We aimed at demonstrating the interictal functional impairment of thalamo-cortical network in drug-naïve TLE patients by the study of high frequency oscillations of somatosensory evoked potentials (HF-SEP).
Material and methods. Twelve healthy controls (HC; 8 females, 4 men, 55.5±22.2 years-old) and 12 (8 females, 4 men) drug-naïve TLE patients (48.1±16.3 years-old) underwent bilateral median HF-SEP, recorded by scalp electrodes. Cp3'-Fz and Cp4'-Fz traces were 400-800 Hz filtered and allowed the HF-SEP evaluation.
Results. The affected hemisphere HF-SEP duration was significantly longer when compared to that of both the unaffected hemisphere and HC hemispheres. No significant inter-hemispheric differences were found in areas, powers, latencies of HF-SEP wavelets. No specific effects were found on the thalamocortical and intra-cortical HF-SEP components.
Conclusions. Our results demonstrate that TLE induces early interictal functional impairments of the thalamo-cortical transmission and intra-cortical processing of incoming stimuli. They strongly corroborate the vision of focal epilepsy as a network disorder and offer a possible neurophysiological bio-markers of TLE to support the diagnosis and to monitor pharmacological, surgical and neuromodulatory therapies.

Metronidazole-induced encephalopathy: a typical EEG pattern? Our experience and systematic review of literature

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Objective. Metronidazole-induced encephalopathy (MIE) is an iatrogenic condition that should be considered in metronidazole-treated patients presenting with encephalopathy, unexplained seizures and cerebellar signs. While typical MRI findings strongly support the clinical suspicion, EEG features have been rarely reported and poorly described. We studied and compared EEG pattern presentation and evolution in two patients with MIE. We discuss if this EEG pattern might represent a neurophysiological correlate of "cerebellar encephalopathy".
Material and methods. We reported a prospective longitudinal EEG study of two patients with MIE, a 64-year-old and a 75-years-old Caucasian men who were treated for a sepsis with Metronidazole at different dosage (126 g vs 22 g, respectively) and developed a fluctuating and progressive altered mental status. We analyzed and compared both EEGs pattern presentation and evolution and performed a literature search of MEDLINE, PubMed, and Google using the terms *metronidazole, intoxication, neurotoxicity, neurological, encephalopathy, seizures, epilepsy, EEG*, to compare the EEG results of other case reports of MIE using PROSPERO systematic review protocol with the aim of identifying every described EEG pattern of this encephalopathy.
Results. The EEGs of both patients showed a characteristic evolving pattern characterized by the initial appearance of sporadic sharp theta activity on anterior regions in the context of a diffuse background slowing which ultimately evolved to a rhythmic, quasi-continuous, medium voltage and monomorphic sharp theta activity progressively involving the whole brain in an anterior-posterior direction, without clinical or EEG changes after BDZ infusions.
Discussion and Conclusions. We propose these EEG findings might represent a peculiar EEG pattern related to the cerebellar dysfunction characteristic of MIE. Clinicians should be aware of this peculiar EEG pattern that, in addition to typical neuroradiological signs, suggest the diagnosis of this uncommon syndrome that requires promptly withdrawn of the metronidazole therapy, in order to prevent severe and permanent neurological sequelae.
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Localization of rapid eye movement sleep interictal epileptiform discharges and cortical tubers perfusion in tuberous sclerosis complex patients

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Objective. Drug-resistant epilepsy is a frequent neurological manifestation in tuberous sclerosis complex (TSC) patients.[1] Surgical approach has been described to lead to seizures control, assigning to a single tuberous the electrical source of crisis.[2] Therefore, non-invasive imaging methods could be useful to identify epileptogenic tuber. Interictal epileptiform discharges (IEDs) are lateralized during rapid eye movement (REM) sleep compared to those of non-REM sleep and wakefulness in children with intractable epilepsy secondary to TSC.[3] Lateralization of REM-IEDs corresponded with the hemisphere with ictal activity and larger tubers, and can be used to identify surgical candidacy in TSC children with intractable epilepsy.[3] Purpose of our study was to evaluate the possible association between Electrical Source Imaging (ESI) localization applied on REM sleep IEDs and cortical tubers perfusion (studied with pulsed Arterial Spin Labelling, pASL, MRI).
Material and methods. We prospectively evaluated twelve patients with Nocturnal Polysomnography and Anatomical and pASL brain MRI (1,5 /3 Tesla). Subjects were classified as "peri-ictal" in case a seizure occurred in the 24 h before MRI study, all the others were classified as "inter-ictal". We performed ESI on IEDs recorded in REM sleep and then compared ESI with pASL tubers perfusion.
Results. ESI was applicable in 11 of 12 (92%) patients (one subject had no spikes): a single focal IED in 9/11 (82%) patients, two independent focal IEDs in 2/11 (18%) patients.
Therefore, we located 13 Region of Interests (ROIs) among 11 patients: in 11/13 (85%) ROIs we identified tubers (in 2/11 (18%) two tubers, in 9/11 (82%) one tuber), in the other 2/13 (15%) ROIs we could not localize tubers inside. We identified 175 cortical hamartomas:162 (92,5%) hypoperfused, 13 (7,4%) hyperperfused relative to cerebellum CBF. Considering all patients, 14/175 tubers (8%) were localized inside ROIs, 161/175 (92%) outside.
Conclusions. ESI applied on REM interictal spikes seems to identify regions including tubers with fair precision. Tubers, located inside ROIs identified by ESI, seem not to show a peculiar perfusion rate (detected by ASL MRI) compared to others outside. Further studies (including video-EEG recorded seizures) are needed to assess the possible correspondence between a peculiar perfusion rate and localization of epileptogenic zone.
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The effect of Anti-Epileptic drugs on thalamo-cortical evoked fast oscillations

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Introduction. High Frequency Oscillations (HFOs) are evident when filtering N20 signal between 400-800 Hz. This fast oscillatory activity is the manifestation of sensory integration in the human primary sensory cortex 3b. Modulation of intra-cortical inhibition is known to effect HFOs and in particular late-HFO.
Objectives. Our aim is to evaluate if AEDs can influence HFOs produced by thalamo-cortical sensory signal integration. Furthermore we are interested in knowing if commonly prescribed AEDs have cumulative effect on HFOs.
Methods. We recorded bilateral SEP-HFOs from median nerve stimulation in 20 patients affected by focal epilepsy in treatment with 1, 2 or 3 AEDs. SEP were recorded with needle electrodes, impedance below 5 kΩ; stimulation was given at 3 times the sensory threshold; stimuli rate was 4,9Hz. 2000 SEP were averaged and then processed through a 400-800Hz band-pass filter. Number of waves (early, total, late), area (early, total, late), duration (early, total, late) and N20 amplitude were considered as variables. Variables were compared (ANOVA) among three groups, according to the number of AED (1, 2 or 3).
Results. One-way ANOVA showed a reduction in area of late and total HFO and late HFO burst duration over the Affected Hemisphere (AH) (p=.023, p=.032 and p=.014) between groups, according to number of AED taken by each patient. Difference were mostly significant between the group taking 1 AED and the group taking 3 AEDs; however our data shows a consistent trend towards reduction of late-HFO duration and area and total-HFO area according to the number of AEDs taken. We also evaluated HFOs in patients at T0 (drug NAÏVE) and at T1 after introduction of first-line AED therapy; the only significant difference evidenced in T1 group was the normalization of intra-hemispheric asymmetry, usually found in SEP-HFO of patients with focal epilepsy.
Conclusions. AEDs seem to have a direct influence on somatosensory HFOs that is specific to the AH and clearly evident when patients are in poly-therapy. Combination AED therapy has a consistent effect on thalamo-cortical fast oscillations, causing a reduction in area of total and late HFO and reduction in late HFO duration in the AH. These alterations are related to the number of drugs taken, possibly due to the cumulative effect of different pharmacodynamic mechanisms.
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Effects of MRI acoustic noise on brain activity and connectivity measured with magnetoencephalography (MEG)

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Background and aim. During the last decade there has been an increasing interest in tracking brain network fluctuations in health and disease by means of resting state functional MRI (rs-fMRI). Rs-fMRI, however, does not provide an ideal setting, as the participant is continuously exposed to the noise generated by MRI coils while performing an Echo Planar Imaging sequence (EPI). We focused on the effect of this acoustic noise on resting state connectivity using magnetoencephalography (MEG) recordings obtained while reproducing the rs-fMRI environment. As compared to fMRI, MEG has no sensitivity to brain activity generated in deep brain structures, but captures both the dynamic of cortical magnetic oscillations with high temporal resolution and the slow magnetic fluctuations highly correlated with BOLD signal.
Methods. Thirty healthy subjects were enrolled in a fully-randomized controlled design study including three conditions: a) silent resting state, b) resting state while delivering EPI noise, and c) resting state while delivering white noise. Amplitude envelope correlation (AEC) was estimated in alpha band over the entire duration of each condition (8 min) and in a dynamic fashion over 1-min long segments.

Results. fMRI and White acoustic noise consistently reduce the connectivity of cortical networks. The effects are widespread, but also noise and network specific. A progressive increase of slow theta-delta activity related to drowsiness was found in all conditions and significantly correlated with the variations of cortical connectivity.
Conclusion. rs-fMRI connectivity is biased by unavoidable environmental factors during scanning, which warrants more careful control and improved experimental designs. MEG is free from acoustic noise, allows a sensitive estimation of resting state connectivity and should be preferred over fMRI whenever the main interest is on cortical rather than subcortical networks.

An EEG-fMRI study of erps in an omitted stimulus paradigm

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Rationale and Objectives. Event-Related Potentials (ERPs) occurring independently from any stimulus are purely endogenous (emitted potentials) and their neural generators can be univocally linked with cognitive processes. In the present study, the subjects performed two similar visual counting tasks: a standard two-stimulus oddball, and an omitted-target oddball task, characterized by the physical absence of the target stimulus. Our investigation aimed at localizing the neural sources of the scalp-recorded endogenous/emitted ERPs.
Methods. To optimize the sources localization, the high temporal resolution of electrophysiology was combined with the fine spatial information provided by the simultaneous recording of functional magnetic resonance (fMRI). Thirteen healthy right-handed participants volunteered (5 females; mean age 26 years, range 22-29), recruited from an academic environment were enrolled.
Results. Both tasks identified two endogenous ERP components in the 300 to 520 ms interval. An earlier component, pP2, showed a bilateral generator in the anterior Insula. A later P3 component (P3b) was generated bilaterally in the temporal-parietal junction, the premotor and motor area and the anterior intraparietal sulcus (this last one only in the standard oddball). Anticipatory slow waves (i.e., beginning 900 to 500 ms pre-stimulus), also of endogenous nature, were produced by the inferior and middle frontal gyrus and the supplementary and cingulate motor areas.
Conclusions. Our protocol disentangled pre- from post-stimulus fMRI activations and provided original clues to the psychophysiological interpretation of emitted/endogenous ERPs.
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Lateralized rhythmic delta activity as an ictal pattern: a case investigated with a multimodal approach

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Objective. The ictal-interictal continuum (IIC) represents a diagnostic challenge even for expert electroencephalographers, often requiring additional multimodal diagnostic workup to understand its clinical significance. Lateralized rhythmic delta activity (LRDA) is an IIC pattern that only recently has been investigated and recognized potentially ictal and/or ictogenic. We describe the case of a patient with LRDA in whom such a multimodal approach was necessary to reach the correct diagnosis.
Material and methods. Advanced computed tomography imaging (direct, angiography and perfusion) was performed following our Institution protocol for stroke. Electroencephalogram (EEG) was then recorded with a standard 19 electrode montage according to the 10-20 SI. We describe the clinical features of the patient and his response to therapy.
Results. The patient presented acute onset aphasia, initially suspected for stroke. Advanced brain imaging with computed tomography perfusion showed features suggesting regional left temporo-parietal hyperflow and EEG revealed LRDA with fluctuations and intermixed sharp waves in the same areas. Treatment with lacosamide determined both clinical and EEG improvement after a few hours, supporting the hypothesis that the EEG pattern represented an ictal phenomenon.
Conclusions. In literature, a correlation between metabolic/perfusion imaging and IIC patterns is described regarding lateralized periodic discharges but, at the best of our knowledge, it has not been studied for LRDA. In our case, we adopted a multimodal approach integrating advanced imaging, EEG, clinical features and response to therapy, to confirm the ictal significance of LRDA.

Levetiracetam therapy effects on modulation of cerebral rhythms in temporal lobe epilepsy patients: a quantitative EEG study

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Objective. Electroencephalography (EEG) is the most important technique for the diagnosis and treatment follow-up in epilepsy patients and has been shown to be sensitive to the effect of various drugs, including anti-epileptic drugs (AED)s. The aim of our study was to evaluate the modifications induced by Levetiracetam (LEV) in the power spectrum of EEG frequencies in patients affected by temporal lobe epilepsy (TLE).
Material and methods. We retrospectively performed quantitative EEG resting state analysis in 20 patients affected by TLE before and after the beginning of therapy with LEV and 27 healthy controls. Power spectra were obtained using modern multitaper methods. The EEG was recorded for 15 min in resting-state conditions using Micromed Brain Quick System (21-channels scalp EEG). Statistical analyses were performed in Matlab R2016b. The results were thresholded for significance at $p<0.05$ and corrected for multiple comparisons.
Results. Relative power spectra were higher in TLE patients as compared to healthy subjects and these findings were more evident in the hemisphere with the epileptogenic focus (EF). AED therapy with LEV induced a significative reduction in global and frequency specific power spectra, with disappearance of the asymmetry between healthy hemisphere and hemisphere with EF in power frequency analysis.
Conclusions. LEV induced a decrease in EEG frequency power, more evident in the EF, of patients with TLE, leading to the recovery of the

EEG spectral power symmetry, coupled with a significant clinical control of seizures found in the majority of patients.

Safety and efficacy of treatment and re-treatment with botulinum toxin (BTX) injection into the cricopharyngeal muscle in neurogenic dysphagia due to insufficient of absent relaxation of the upper esophageal sphincter

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Aim. 1) To evaluate efficacy and safety of treatment with botulinum toxin (BTX) injection into the cricopharyngeal (CP) muscle in patients with different forms of neurogenic dysphagia linked to failed relaxation of the upper esophageal sphincter (UES); 2) To evaluate, in the same patients (both responders and not responders to the first treatment), the response to a second injection.
Subjects and Methods. 67 patients with neurogenic dysphagia associated with insufficient or absent opening of the UES as assessed by the electrokinesiographic/electromyographic study of swallowing (24 with brainstem or hemispheric stroke, 21 with extrapyramidal syndromes, 12 with multiple sclerosis, and 10 with spastic-dystonic syndromes secondary to post-traumatic encephalopathy) were treated with the injection of Incobotulinumtoxin A into the CP muscle (dose ranging from 15 to 20 U) under electromyographic guidance. The patients were assessed at baseline and after the first and second treatment by means of clinical evaluation and fiberoptic endoscopy of swallowing (FEES) performed by a otorhinolaryngologist. Dysphagia was quantified using the Dysphagia Outcome and Severity Scale (DOSS).
Results. Most patients responded to the first BTX treatment: 52.2% were high responders (>2 points increase in the DOSS score), while 28.4% were considered low responders (DOSS score increase of 1-2 points). The effect of the first treatment usually lasted longer than 4 months (67%), and in some cases up to a year. The treatment efficacy remained high also after the second injection, in particular a response to the second treatment was observed in 46.3% of patients qualified as high responders and in 32.8% of those showing a low response to the first injection. Only in the parkinsonian syndromes group we observed a reduction in the percentage of responders as compared with the first treatment. Side effects were mostly mild and reported in non-responders following the first injection. A severe side effect, consisting of ingestion pneumonia was observed following the second BTX injection in 2 patients who were non-responders to the first injection. Non-responders were characterized electromyographically by higher values of the oropharyngeal interval.
Conclusions. The present findings confirm that Incobotulinumtoxin A injection is effective and safe in the treatment of neurogenic dysphagia due to hyperactivity and/or relaxation deficit of the UES, even in the case of re-treatment over time. Utility of re-injection in non-responders to the first treatment should be carefully assessed.

Frequency spectral analysis of the electromyographic traces on the myotonic and neuromyotonic discharges

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Background and aims. Steinert myotonic dystrophy is a rare hereditary myopathy characterized by distal weakness and myotonic phenomenon, induced either by mechanical stimulation and voluntary contraction, which generate a delay in the muscle relaxation. This clinical phenomenon has the classical "wax and waning discharge" as electrophysiological correlate[1]. On the contrary, neuromyotonic discharges origin by the nerve and can be recorded in the muscle as an abrupt beginning and stopping discharge[2-3], The spectral analysis is an advanced technique to analyze a signal, generally used in EEG to obtain a spatial description of the frequencies in the different brain regions. It uses a Fourier transform to represent the frequencies of the different harmonics in which any periodic wave can be divided. Just a few papers in literature exploit this technique on needle-EMG traces.
Methods. 15 drug-free patients with a diagnosis of Steinert myotonic dystrophy genetically confirmed underwent an electromyographic exam. Three myotonic discharges per patient were recorded. The spectral analysis was performed in a sweep time of 100 ms of the EMG record. This minimum interval was chosen to include in the spectral analysis any harmonic wave with fundamental frequency greater than 10 Hz. Three neuromyotonic discharges per patient were also analyzed in 10 patients affected by Isaac's syndrome and radiculopathies. The "notch filter" was applied to exclude the alternating electrical current from the analysis.
Results. The analysis of all the myotonic discharges showed a fundamental frequency (minimum 30 Hz, maximum 70 Hz, average 43 Hz) and all the following harmonic frequencies. The neuromyotonic discharges showed only one or more frequencies (minimum 68 Hz, maximum 180 Hz, average 140 Hz), without a feature resembling an harmonic series.
Discussion and conclusions. This is the first study to perform a spectral analysis of the needle-EMG recorded paroxistic discharges. We demonstrated a different spectrum between discharges originated in the muscle and the ones originated by the nerve. The spectral analysis could be used to better characterize and classify paroxistic discharges and to solve the ambiguous cases.
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Electrophysiological assessment of the reproducibility of oropharyngeal swallowing in amyotrophic lateral sclerosis and extrapyramidal syndromes

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Aim. to investigate with an electrophysiological technique the reproducibility of oropharyngeal swallowing in patients with amyotrophic lateral sclerosis (ALS) and extrapyramidal syndromes, i.e. Parkinson's disease (PD) and atypical parkinsonisms (AP).
Subjects and methods. We enrolled 26 ALS patients and 40 patients with extrapyramidal syndromes (20 patients with PD and 20 patients with AT), both with and without clinical signs of dysphagia, and 20 age-matched controls. The reproducibility of the electrophysiological signals related to the oral phase (electromyographic activity of the submental/suprahyoid muscles) and the pharyngeal phase (laryngeal-pharyngeal mechanogram) of swallowing across repeated swallows was assessed. To do this we computed two similarity indexes (SI) by using customized mathematical algorithms.
Results. The reproducibility of oropharyngeal swallowing was significantly reduced in both patients with ALS or PD/AP suffering from

clinical signs of dysphagia. The SI of both phases of swallowing, oral and pharyngeal, correlated significantly with dysphagia severity and disease severity in all patients' groups. In ALS patients without clinical signs of dysphagia a significant decrease in the SI values relating both phases of swallowing (oral and pharyngeal) was found, whilst in the patients with extrapyramidal syndromes a significant decrease was observed only as regard reproducibility of the pharyngeal phase of swallowing.
Conclusions. In neurodegenerative disorders such as motoneuron disease and extrapyramidal syndromes different pathophysiological mechanisms can alter the stereotyped motor behaviors underlying normal swallowing, thus reducing the reproducibility and safety of the swallowing act. A decrease in swallowing reproducibility could be a preclinical sign of dysphagia and, beyond a certain threshold, a pathological hallmark of oropharyngeal dysphagia.

Methodological approach to the direct muscle stimulation in ICU

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Introduction and Objective. Critical Illness Polyneuropathy (CIP) and Critical Illness Myopathy (CIM) are the main cause of acute acquired weakness associated to a difficult weaning from the ventilator in Intensive Care Unit. CIP is a distal axonal sensory-motor polyneuropathy while CIM is a proximal necrotizing myopathy. The two conditions can coexist and share the same pathogenesis, an inactivation of sodium channels on cell membranes. These considerations support the hypothesis that CIM and CIP are different clinical manifestations of the same underlying disease process, the critical illness polyneuromyopathy (CIPNM). Recent studies show a worse outcome if nerve damage is predominant but either clinical examination or conventional neurophysiological exam may fail to differentiate between the two conditions. Amplitude reduction of compound muscle action potentials (CMAPs) and abnormal spontaneous EMG activity can be find indeed in both condition. The Gold Standard test is neuromuscular biopsy but it's expensive and invasive. In 1996 Rich et al. introduced direct muscle stimulation (DMS) exam to improve the reliability of neurophysiological diagnosis.
Material and methods. In literature the DMS is usually performed on Tibialis Anterior and Deltoid. Actually it can be done on almost all the accessible limb muscles. Generally, a monopolar needle electrode (cathode) and a subdermal needle electrode (anode) are used to stimulate while a concentric EMG needle is used to record the MAP. We preferred to stimulate with surface electrodes placed distally to a record concentric EMG needle to try different sites on the muscle belly and find the best orientation for the dipole. The cathode was placed on the muscular belly while the anode at 3 cm of distance. At first a muscle CMAP (dm-CMAP) was registered. Then the nerve was stimulated supramaximally using the same needle to record the nerve CMAP (ne-CMAP).
Discussion. If muscle excitability is preserved, the dm-CMAP is normal. If the muscle fibers lose their excitability, both dm-CMAP and ne-CMAP are reduced. It's usually calculated the ne-CMAP/dm-CMAP ratio. In CIP only the nerve potential is reduced, and the ratio is 0.5 or less. If the ratio is 0.9 the clinical picture is compatible with myopathy or normality depending on the amplitude values during standard electroneurography (ENG).
Conclusions. Direct muscle stimulation helps to predict the prognosis for the patient, defining a prevalence of muscular or nervous damage. It is easy to perform, not invasive and can be used also in comatose patients or when there isn't a spontaneous muscular activation.

Isolated peripheral neuropathy due to toluene exposure: a case report

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Objective. Toluene is used in organic solvents contained in many industrial and domestic products such as thinners, glues and spray paints and, due to its lipophylic attidude, is related to severe neurological disorders. The majority of literature describes multifocal central nervous system (CNS) disorders including:dementia, brainstem and cerebellar syndromes and optic neuropathy, in some case associated to peripheral neuropathy[1].We describe a case of isolated symptomatic peripheral neuropathy due to toluene exposure, with only subclinical CNS involvement.
Material and methods. A 52-years-old female came to our attention with a one-year history of tingling paresthesia and distal lower limbs dysesthesia, especially at night, with a strong urge to move her legs, worsening during the last 2 months. She did complain neither weakness nor muscle cramps. She had no history of chronic illness; family history revealed that both her husband and her son had been diagnosed with sensory-motor axonal neuropathy, with negativity of genetic tests for hereditary neuropathies. She had worked as a maid in a chrome plating industry for the last four years and sometimes she helped her relatives in agriculture. Personal history was negative for alcohol intake, tobacco smoking and drugs abuse. Neurological examination showed gait imbalance, absent ankle deep tendon reflex and Babinski sign bilaterally;muscle strength was preserved; sensory system examination showed sensory loss to light touch and pinprick;she was cognitively preserved. All laboratory testing (for vascular risk factors, peripheral neuropathies, paraneoplastic autoantibodies) resulted negative. Electromyography and nerve conduction velocity study showed axonal neuropathy with predominant involvement of sensory component. Brain MRI showed multiple T2–weighted abnormalities in the periventricular frontal and peritrigonal white matter regions. MRI of the spinal cord was normal. Carotid, vertebral and transcranial ultrasound examinations were normal, as well as somatosensory, pattern visual and brainstem evoked potentials; motor evoked potentials showed impaired central motor conduction to lower limbs. Because of the family history of neuropathy, toxicology tests were conducted: a markedly increase of urinary levels of toluene metabolites was detected.
Discussion. Central nervous system damage due to toluene has been first reported in glue and gasoline abusers[1]. At date, isolated neuropathy characterized by dominant motor signs has been already described in a young gasoline abuser[2].Our patient, suffering from isolated predominantly sensory neuropathy and restless syndrome, showed only subclinical signs of CNS involvement. We suspected that toluene poisoning was related to patient's working activity.
Conclusions. Toluene poisoning can be considered in patients suffering from peripheral neuropathy associated to restless syndrome when a work exposure is suspected.
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Radial nerve axonotmesis at the elbow may reveal somatotopic organization of motor and sensory fibers

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Objective. To demonstrate the importance of ENG/EMG together with nerve ultrasound in patients with peripheral nerve injury undergoing surgical intervention.
Material and methods. We describe the case of a 42-years-old male that has come to our attention for wrist drop after a cut-wound above the elbow crease caused by a steel plate penetration. After the trauma, he underwent hemostasis of muscular vessels without any vascular repair.
Results. ENG/EMG performed at 2 months from the trauma showed axonotmetic injury of the left radial nerve at the elbow with involvement only of the motor fibers (active denervation and poor ongoing reinnervation in brachioradialis, extensor radialis brevis, extensor digitorum communis, extensor indicis); intriguingly, SAP recorded from I digit stimulating radial nerve was normal.
Radial nerve ultrasound disclosed a partial interruption (nerve in continuity) of the radial nerve at the elbow associated to lateral neuroma compressing only the motor contingent of radial nerve; interestingly, sensory fibers, that pass more medially at the elbow, were spared.
Due to low clinical recovery, the patient was therefore candidate for surgical exploration.
Discussion. In radial nerve injuries at the elbow, we would expect the involvement of both the sensory and motor nerve fibers; we have demonstrated that partial damage of the nerve at this level can cause pure motor impairment. Our finding is due to the fact that a lateral damage of the radial nerve at the elbow may selectively compromise the lateral part of the nerve represented by motor fibers. This fact demonstrates that there is a somatotopic distribution of the motor and sensory fibers within the radial nerve and strengthens the importance of multidisciplinary approach, in particular EMG and nerve ultrasound, in the diagnosis, management and prognosis of traumatic peripheral nerve injury.

Nerve cross sectional area correlates to clinical severity in patients with Charcot Marie Tooth type 1A

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Background. Nerve cross sectional area (CSA) was reported to be on average larger than normal in Charcot-Marie-Tooth disease type 1A (CMT1A), although to a variable extent in single patients.
Aims. We explored whether CSA is correlated with clinical severity of CMT1A explored by CMT neuropathy score version 2 (CMTNS2) and its examination subscore (CMTES2).
Methods. We assessed 56 patients (mean age 46.5, SD 2.2; 28 men, 28 women; 42 families) with CMT1A. They underwent nerve conduction study (NCS), including left median and ulnar nerve CMAP amplitude and MNCV, and high-resolution ultrasound (HRUS) of the left median and ulnar nerves across their whole course and peroneal nerve at the fibular head.
Results. Univariate analysis showed NCS and HRUS variables to be significantly correlated to CMTNS2 and CMTES2 and to each other. Multivariate analysis showed that ulnar MNCV was significantly correlated with CMTNS2 only, while median nerve CSA at the forearm was significantly correlated with CMTNS2 and CMTES2.
Discussion. Nerve CSA explored with HRUS was significantly associated to clinical scores in patients with CMT1A. These data suggest that HRUS findings might represent a potential instrumental biomarker of CMT damage and progression. Future longitudinal studies should explore whether nerve CSA might be sensitive to change and potentially useful in clinical trials.

Neurophysiological evaluation in patients with multiple myeloma treated with bortezomib

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Background and Objectives. Bortezomib is a proteasome inhibitor that is frequently used for multiple myeloma and lymphoma. One of the main toxic effects of bortezomib is peripheral neuropathy, usually occurring in the form of a painful, sensory axonal neuropathy. The mechanisms of peripheral damage, however, are still unclear. We here evaluate a series of patients, treated with bortezomib, with two different neurophysiological assessments to evaluated sensitivity and specificity of electroneurography and sudoscan to detect a peripheral neuropathy.
Methods. Eighteen myeloma patients underwent electrophysiological examination and clinical testing before and 6 months after bortezomib treatment.
Results. Peripheral damage was characterized by demyelinating or mixed axonal-demyelinating neuropathy. Electroneurography and sudoscan showed similar sensitivity and specificity to detect a peripheral neuropathy.
Discussion. The peripheral damage, associated with bortezomib, seems to affect both the large and small fibers in similar way.
Conclusions. Bortezomib is part of a small list of agents that may cause a demyelinating polyneuropathy and axonal degeneration.

Electrodiagnostic accuracy in polyneuropathies: supervised learning algorithms versus electrophysiologists

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Introduction. Electrodiagnosis is a mainstay in the evaluation of polyneuropathies. However, up to 47% of chronic inflammatory demyelination polyneuropathy (CIDP) patients received an alternative diagnosis at reevaluation and the interpretation of nerve conduction studies was a major factor in misdiagnosis. Supervised learning algorithms (SLAs) can predict the electrodiagnostic classification of a subject on the basis of a training data set based on the leave out one cross validation method.
Methods. In this study we investigated the diagnostic accuracy of four SLAs, shrinkage discriminant analysis, multinomial logistic regression, classification and regression trees, support vector machine (SVM), and of three expert and three trainee electrophysiologists. Three academic tertiary neuromuscular centers participated in the study and 434 subjects were enrolled with the following reference diagnoses: CIDP (99), Charcot-Marie-Tooth disease type 1(124), hereditary neuropathy with liability to pressure palsy (46), diabetic polyneuropathy (67), and controls (98). The final data set contained, for each subject, three motor and three sensory nerves with 27 electrophysiological parameters.

Results. SVM showed the highest (91%) diagnostic accuracy for all five diagnostic classes when compared with other SLAs (76.3-86.6%), expert neurophysiologists (74.9-82%), and trainees (54.6-77%). SVM demonstrated also the best balance between sensitivity and specificity. In particular, regarding CIDP, SVM had sensitivity of 80.8% and specificity of 95.2% compared with other SLAs (52.5-75.8%; 89.2-98.8%), expert neurophysiologists (51.5-77.8%; 80.9-96.4%) and trainees (36.4-52.5%; 68.4-98.5%).
Conclusions. Overall SVM exhibits the best diagnostic performances compared with other SLAs and neurophysiologists. Moreover SVM, as other SLAs, has the advantage of assigning to a subject the probability of belonging to each of the five diagnostic classes. SLAs are already available in statistical packages and electromyographic machines could be easily equipped with a software to introduce this robust diagnostic support system in clinical practice to reduce misdiagnoses of polyneuropathies**.**

Intraoperative Optimization of Posterior Tibial Nerve Somatosensory Evoked Potential P40-N50 Complex

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Objectives. Intraoperative posterior tibial nerve Somatosensory Evoked Potentials (ptn-SEPs) cortical P40 is routinely used in spine surgery in order to detect an impending neurologic damage to posterior columns. In order to gain this goal, multiple channels recordings are recommended. The aim of our study was to identify the best derivation to display the best P40.
Methods. In this retrospective study we reviewed the ptn-SEPs recorded during Propofol + Remifentanyl TIVA/TCI anesthesia in 99 surgeries (33 idiopatic scoliosis, 66 lumbar stabilization) from centroparietal ipsilateral to frontopolar midline (CPi-Fpz), centroparietal midline to frontopolar midline (CPz)-Fpz and centroparietal ipsilater to centroparietal contralateral derivations (CPi-CPc). The amplitude of the P40 was measured from the onset of the P40 waveform to the peak of the subsequent N50. Baseline P40 amplitude was set after optimization of stimulation intensity, pulse width, and stimulation rate.
Results. The highest P40 amplitude was recorded from CPz-Fpz (88 limbs - 44,44 %) and from CPi-CPc (86 limbs, 43.43%). The CPi-Fpz showed the high-voltage P40 in 24 (12.12%) surgeries. Mean amplitude of P40-N50 cortical complex was 1.67 ± 1.22 □V, 1.43 ± 0.93 □V and 1.29 ± 0.78 □V in the CPz-Fpz, CPi-CPc and CPi-Fpz derivation respectively.
Conclusions. A multiple channels setting, including at least Cpz-Fpz and CPi-CPc derivations are recommended in order to intraoperatively record a robust ptn-SEPs cortical P40-N50 complex.

Association between delirium, ICU acquired weakness and critical illness polyneuropathy

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Rationale and Objectives. Acquired weakness and delirium are frequent in patients admitted to ICU and are prognostically unfavorable factors. The aim of this study was to evaluate its concomitance and association with neurophysiological parameters of functionality of the central and peripheral nervous system
Methods. We studied 31 patients admitted to local intensive care (general, neurosurgery, cardiac surgery) emerging from pharmacological sedation for various causes (surgical interventions, brain injuries, brain infections, etc), for at least 24 h. They were evaluated according to the "Confusion assessment method (CAM-ICU)", the "Intensive care delirium screening checklist" (ICDSC), and subdivided according to the presence or absence of delirium. They were subjected to a peripheral neurophysiological evaluation, EEG and somatosensory evoked potentials.
Results. 8 patients had hypoactive delirium, 9 mixed, 14 no delirium. Subjects with delirium had an average amplitude of sensory action potentials (p 0.012) and motor (p 0.001) less than controls, while there were no significant differences with respect to reflex responses, somatosensory evoked potentials, and EEG.
Discussion. The results of this study confirmed the presence of an association between delirium and weakness acquired in resuscitation. This multifactorial syndromic progression derives from the complex interaction between the basal vulnerability of the individual (predisposing factors) and the factors connected to hospitalization (precipitating factors). The hypothesis that in the hypoactive delirium there is also a pathological involvement of the peripheral nervous system, whose etiology probably involves the same mechanisms of encephalopathy underlying the delirium, is reinforced. The limited number of the enlisted population certainly makes further studies desirable to confirm the results obtained.
Conclusions. The neurophysiological evaluation provides useful information on the involvement of the peripheral nervous system which, especially in patients with hypoactive delirium, reflects motor and sensory somatic axonopathic damage

Placement of "epidural" D wave electrodes at the spinal level: above or below the dura?

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Rationale and Objectives. To evaluate the best electrode placement for D wave recording at the spinal level above or below the dura mater.
Methods. In 12 patients who underwent spinal surgery, we placed the electrode to record the D wave both epidural and subdural, at the beginning of the surgical procedure, maintaining the same stimulation parameters. In three of these patients the D wave was also recorded proximal to the lesion, always with double registration above and below the dura
Results. On 9 subjects it was possible to record the D wave distally to the lesion, in one case only with the subdural positioning. The differences in amplitude between epidural and subdural registration were between 11 and 67% in favor of subdural registration. There were no differences in appearance latency of the D wave. In no case were there any periprocedural complications.
Discussion. The increase in the signal amplitude of the D wave with placement of the electrode in the subdural space, is due to the reduction of impedance from the dura. From a surgical point of view, there are no absolute contraindications to this positioning
Conclusions. If the intervention foresees the opening of the dura mater, the subdural positioning of the electrode to record the D wave appears safe and allows in most cases to improve the amplitude and thus the monitoring of the D wave.

Detethering of ventral and dorsal fibrous bands of the spinal cord during a hemivertebrae resection using a three-step approach: a case report

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Rational and Objectives. Simultaneous ventral and dorsal spinal cord tethering (*i.e.* double tethering) in association with congenital kyphosis of the thoracolumbar spine is rare. We report the first case of simultaneous double detethering surgery of the cord with hemivertebrae resection and deformity correction.
Methods. A 4-years-old male patient was referred to our hospital because of a progressive kyphosis at the thoracolumbar junction diagnosed before birth.
Patient complained of occasional pain in the lumbar spine and low exercise tolerance. On neurological examination, patient had some difficult only when walking on his heels.
A spine X-ray demonstrated a partial agenesis of the L2 vertebral body and hemivertebra of the L1 with a segmental kyphosis of 35°. MRI showed a posterior displacement of the L1 hemivertebra causing an impingement on the spinal cord. The conus was displaced at L3 level due to a tethered filum terminale. Furthermore, a fibrous band originating from the ventral surface of the spinal cord at T11-T12 level caused ventral tethering. Pre-operative SEP from posterior tibial nerve stimulation showed increased bilateral cortical latencies and a reduced amplitude on the left side. Six months later, pain, segmental kyphosis (40°) and posterior displacement of the L1 hemivertebra had worsened. Following a multidisciplinary team discussion, decision was made to proceed with single surgery but multiple different steps. Firstly, filum terminale was resected, then spine from T11 to L3 was exposed, pedicle screws were placed in T11, T12, and L3 and a temporary rod was used to stabilize the spine, the L1-L2 hemivertebrae were resected. The ventral aspect of the cord at T11-T12 was approached and the ventral tether was resected. Finally, the kyphosis was corrected through compression manouvers. Multimodality intraoperative neurophysiology (IN) with monitoring (SEPs, Tc-MEP, EMG free run) and mapping was performed. During surgery, oscillations in amplitude of bilateral lower limbs Tc-MEPs were recorded. At the end reduction in amplitude of left abductor hallucis MEP, without SEP changes, was noted.
Results. Postoperatively, patient presented some mild inflammation symptoms (pain on knee extension) which resolved with steroids. At discharged patient was neurologically intact. Kyphosis had been corrected from 40° to 2,5°.
Conclusion. To the best of our knowledge, there is only one previous case report describing ventral and dorsal bands detethering surgery in literature. In this case, we were able to perform double detethering surgery but also hemivertebrae resection and deformity correction at the same time with multidisciplinary approach and IN.
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Intraoperative neurophysiological study of segmental spinal myoclonus during removal of cervical intramedullary tumor

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Rational and Objectives. A 13-year-old right-handed girl had a 2-months history of continuous involuntary jerking of the right hand, persisting during sleep. Arm and hand function was undisturbed. On examination, there was continuous focal rhythmic jerking of the flexors of all fingers and thumb of the right hand, not suppressed by passive or active movement, posture, distraction, or other stimuli (frequency 1 Hz). No other neurological signs were present.
Methods. Magnetic resonance imaging (MRI) of the brain was normal, while MRI of the spine revealed an intramedullary cord tumor at the level of C7. Video-electroencephalogram (EEG) recordings showed a normal awake activity with no epileptic abnormalities. The simultaneous surface electromyogram (EMG) of the right flexor radialis carpis, extensor radialis carpis, and abductor pollicis brevis showed myoclonic activity, that was rhythmic (1Hz) and synchronous in all the examined muscles. The girl underwent a surgical removal of the intramedullary tumor, under intraoperative neurophysiologic monitoring (IOM) with Somatosensory Evoked potentials (SEPs) and transcranic electric stimulation Motor Evoked potentials (tce-MEPs) at four limbs under total venous anesthesia. Spontaneous electromiographic activity was recorded from Deltoid, Biceps brachii, Triceps brachii, Flexor radialis carpis, Extensor Radialis carpis and Abductor pollicis brevis muscles bilaterally. A macroscopically complete removal of the tumor was obtained.
The myoclonus was recorded from the right Flexor Carpis Radialis (FCR) and Abductor Pollicis Brevis (ABP) muscles with the same features as it was described preoperatively. During myelotomy, even minimal traction of the spinal cord lead to a rise of the jerk frequency, which returned to baseline when the mechanical stimulation of the spinal cord was stopped. Progressive changes of the pattern of myoclonic jerks were recorded during the removal of the tumor. At the end of the removal of the lesion, no spontaneous activity was recordable from muscles of the upper limbs.
Results. Postoperatively the myoclonus was completely disappeared. However, one month later myoclonic jerks of the hand appeared again. MRI showed no relapse of the tumor.
Conclusion. There are few reports of segmental spinal myoclonus (SSM) as the presenting symptom of a spinal cord tumor (1,2). Some changes over the time of SSM, such as the shift from a nonrhythmic to a rhythmic activity, or variations of frequency have been also described as symptomatic progression of le spinal lesion (3). To our knowledge, this is the first description of intraoperative rapid change of SSM during suprasegmental lesion removal.
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Usefulness of Somatosensory Evoked Potentials to detect myelopathy and document functional improvement after surgical decompression in very young children with achondroplasia

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Rationale and Objectives. To evaluate the role of SEPs in detection of myelopathy due to foramen magnum stenosis and in documentation of early functional improvement of somatosensory central pathways after surgical decompression in very young children with achondroplasia.
Method. We perform SEPs, neurological evaluation comprehensive of MN and PTN nerves stimulation, brain and spinal cord MRI and clinical evaluation in 17 very young patients with achondroplasia (9 M, 8 F; mean age at first evaluation 1 year and 6 months, min 2 months, max 3 years) at

birth or at first evaluation at our center. We considered and analyzed latency and amplitude of cortical responses. Patients with normal findings at baseline underwent neurophysiological follow up every six months. 8/17 Patients with pathological SEPs and signs of myelopathy at MRI are evaluated worthy for surgical intervention and underwent neurosurgical spinal cord decompression for foramen magnum stenosis. Three months after intervention neurophysiological evaluation was repeated.

Results. As shown in literature our results confirm that increase in PTN-SEPs latency was the most sensitive and earlier parameter suggestive for myelopathy due to foramen magnum stenosis in children with achondroplasia, even if clinically asymptomatic. SEPs performed three months after neurosurgical decompression show improvement of neurophysiological parameters in all operated patients. Also cortical latency of MN-SEPs and amplitude of both PTN and MN SEPs showed improvement after surgery. Some patients even if judged preoperative non symptomatic improved clinically after surgery.

Discussion and Conclusions. In achondroplasic children suffering from myelopathy due to foramen magnum stenosis SEPs could be used as an early, non-invasive and repeatable indicator of myelopathy, as a guide for neurosurgical indications. SEPs are useful in early detection of cervical spinal cord neurofunctional improvement after surgical decompression.

EEG monitoring and Somatosensory Evoked Potentials as Prognostic Bedside Tools in Pediatric Cardiac Intensive Care Children

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Introduction. One of the main reasons for neurological consultation in the cardiac pediatric intensive care unit (CICU) involves providing prognostic information for children with suspected brain injury. Multimodal neurophysiological monitoring in the CICU will be more predictive of outcome than one exam. Somatosensory evoked potentials (SEPs) are of particular interest in critical care. Bilateral absent short latency peaks (N20) have 100% predictive value for poor outcome (death or severe disability). EEG monitoring also plays a role in predicting outcomes and can be especially useful in sedated children to detect subclinical seizures.

Materials and Methods. We performed combined EEG monitoring and SEPs in 23 patients affected by complex congenital heart disease. A standardized procedure was used: neurological evaluation, EEG and brain-CT scan within 12-24 h, followed by SEPs within 3-7 days. Follow-up period was 6 months. Patients were divided into three groups according to their symptoms: 1) Coma; 2) Hemiparesis; 3) Movement disorders.

EEG was classified as: low-voltage (LV-EEG), focal slow (FS-EEG), diffuse slow (DS-EEG). SEPs were classified as N/N (bilaterally normal), N/A (monolaterally absent), A/A (bilaterally absent).

Results. Group-1 Coma was identified in 16 patients (56.5%): all of them presented SEP-A/A, 11 patients had low-voltage EEG patterns while the other 5 children showed diffuse slow-EEG patterns. All patients with LV-EEG and SEP-A/A either died during hospitalization (nine) or evolved in a vegetative state (two). Subclinical seizures were identified in 4 patients.

Group-2 Hemiparesis was identified in 5 children (31%): all of them showed FS-EEG and SEP-N/A. 1 child died during hospitalization while the other 4 showed hemiparesis at 6 months.

Group-3 Movement disorders were identified in 2 patients (12.5%): both patients with DS-EEG and SEP-N/N presented transitory post-pump-chorea with a normal neurological exam at 6 months follow-up.

Discussion and Conclusions. Discussion is conducted regarding the prognosis in respect to the evidence of SEP and EEG but considering also the cardiac condition of the patients.

We believe that the use of EEG and SEPs at the bedside in pediatric cardiac patients affected with acute brain injury can aid physicians in diagnosis of the severity of the case and predicting long term outcomes.

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EEG spectral analysis in neonatal encephalopathy: insight from a 0,5 Hz frequency steps analysis

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Background. At present, no optimal frequency range has been defined for use in quantitative analysis of the neonatal EEG, particularly in encephalopathy. Our aim was to analyze the full EEG spectrum in 0,5 Hz steps in a cohort of neonates affected by post asphyxia encephalopathy with and without seizures

Methods. The study group consisted of 36 term neonates affected by hypoxic ischemic encephalopathy undergoing hypothermia; 6/36 (16,6%) had seizures. We analyzed the interictal background EEG activity of multichannel (10-20 System modified for neonates) EEG traces, recorded for at least 30 min at around 12 h of life (mean 13 h of life, range 8-24). We measured 30 epochs of 2 s for each patient's trace and analyzed the Relative Power Percent (RPP) of all spectral frequencies from 0 to 30 Hz in steps of 0,5 Hz.

Results. The maximal RPP was in the range of the frequencies from 1 to 2,5Hz. In that range a significant difference between patients with and without seizures was found ($p< 0,001$) for each channel except for occipital leads.

Conclusion. By using step by step analysis of neonatal EEG frequencies we found that the more represented frequency band of encephalopatic patients is 1-2.5 Hz. Therefore, the use of predefined frequency bands, as generally performed in neonatal EEG analysis, may miss important EEG information. Using this methodology we were able to detect abnormal spectral changes in the interictal EEG background activity associated with seizures. The follow up in progress for our patients will clarify in the future the possible prognostic significance of this finding.

AVXS-101 Gene-Replacement Therapy for Spinal Muscular Atrophy Type 1: Pivotal Phase 3 Study (STR1VE) Update

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Rationale and Objectives. Spinal muscular atrophy type 1 (SMA1) is a rapidly progressing neurodegenerative disease caused by biallelic survival motor neuron 1 gene (*SMN1*) deletion/mutation. Onasemnogene abeparvovec (AVXS-101) is a gene-replacement therapy treating the genetic root cause of SMA1. In the phase 1/2a study, AVXS-101 dramatically improved outcomes in SMA1 patients. We report study design and preliminary data of STR1VE, a pivotal phase 3 study (NCT03306277) of AVXS-101.
Methods. STR1VE is a phase 3, open-label, one-time–infusion study in SMA1 patients <6 months old (biallelic SMN1 mutation/deletion, 2x*SMN2*). Primary outcomes are independent sitting for ≥30 s at 18 months old, and survival (avoidance of death/permanent ventilation) at 14 months. Secondary outcomes include ability to thrive and ventilatory support at 18 months. Exploratory outcomes include CHOP INTEND and Bayley score.
Results. Enrollment is complete (22 patients dosed). Mean age at symptom onset, genetic diagnosis, and enrollment was 1.9 (0–4.0), 2.1 (0.5–4.0), and 3.7 (0.5–5.9) months. At baseline, no patient required ventilatory/nutritional support; all exclusively fed by mouth. Mean baseline CHOP INTEND score was 32.6 (17.0–52.0). As of June 29, 2018, mean CHOP-INTEND increase from baseline was 6.9 (-4.0–16.0, n=20), 10.4 (2.0–18.0, n=12), and 11.6 (-3.0–23.0, n=9) points at 1, 2, and 3 months.
Discussions and Conclusions. Data from STR1VE show rapid motor function improvements (CHOP INTEND) in patients with SMA1 that parallel phase 1/2a study findings and may correlate with survival benefit, motor milestone achievement, and bulbar function improvements. Updated data will be presented.
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AVXS-101 Gene-Replacement Therapy in Spinal Muscular Atrophy Type 1: Long-Term Follow-Up From the Phase 1 Clinical Trial

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Rationale and Objectives. Spinal muscular atrophy type 1 (SMA1) is a rapidly progressing neurodegenerative disease caused by biallelic survival motor neuron 1 gene (SMN1) deletion/mutation. Onasemnogene abeparvovec (AVXS-101), a one-time gene-replacement therapy, treats the genetic root cause of SMA, and is designed for immediate, sustained expression of SMN protein, allowing rapid onset and durable effect. In the phase 1/2a trial (NCT02122952), 15 SMA1 patients received a one-time intravenous dose of AVXS-101 (lower dose [cohort 1]: n=3; proposed therapeutic dose [cohort 2]: n=12). There was dramatic event-free survival and developmental motor milestones.[1] Here we report long-term follow-up study design and data.
Methods. Patients in the phase 1/2a study could rollover into a long-term follow-up study (NCT03421977). The primary objective is long-term safety (incidence of serious adverse events, hospitalizations, adverse events of special interest). Patients will have annual visits for 5 years followed by annual phone contact for 10 years. Additionally, patient record transfers from their local physician and/or neurologist will be requested. Safety assessments include medical history and record review, physical examination, clinical laboratory evaluation, and pulmonary assessments. Efficacy assessments include developmental milestones (physical examination).
Results. As of September 27, 2018, the oldest patients in cohort 1 and 2 were 59.2 and 52.1 months old, respectively, and free of permanent ventilation. Preliminary data (survival, developmental milestones) will be presented.
Discussions and Conclusions. Patients treated with a one-time dose of AVXS-101 continue to gain strength, develop, and achieve new milestones, demonstrating a long-term, durable response.
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Maturation effects on properties of motor unit action potentials: quantitative anterior tibial muscle electromyography in children under six years old

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Objective. The shape properties (amplitude, duration, phases, turns and firing rates) of motor unit action potentials (MUAPs) reflect the spatial and temporal organization of the motor units in a muscle and are assessed clinically in the electrophysiological evaluation of patients with neuromuscular disorders.
Special reference values on MUAPs data for children are not collected. This study's objective was to evaluate quantitative electromyography (QEMG) using multiple-motor-unit (multi-MUP) analysis of tibial anterior muscle (TA) in normal children, rather easy to get voluntary and involuntary activated, to investigate the influence of maturation and age.
Material and methods. EMG recordings were taken from the anterior tibial muscles of 32 normal unsedated children from 0 to 74 months for a total of 1100 MUAP analysis between October 2016 and February 2019. Neurologic histories were reviewed to ensure that no subject had a history or symptoms of known or suspected neurologic or neuromuscular disorder.
Recordings were made using standard CNEs inserted into the midportion of the muscle. The EMG signal from each 10-s epoch of involuntary contraction induced by foot stimulation was collected.
Results. Specific data MUAPs at time 0, 1, 2, 3, 6, 9, 12, 15, 18, 21, 36, 60, 74 months are collected.
From birth to six years old MUAP amplitude and duration showed increase with age reaching the values of adult by 9 months and 1 year, respectively (in newborns amplitude is 500 uV and duration 9 ms on average). In children until six years old number of turns per MUAP is always higher than adults (3 to 5 vs 2-3). Firing rate is 7 to 8 on average, very similar to young adult compatible with data of a significant fall in firing rate with age (from young to elderly). We recorded a large variability of MUAPs data for each properties but a slight difference due to maturation of motor unit is well definable.
Discussion/Conclusions. Quantitative analysis of a limited electromyography protocol performed in unsedated children is a very valuable diagnostic tool as screening for with suspected neuromuscular diseases. QEMG allows a rapid characterization of the properties of MUAPs and

the degree of maturation. Sedation is not required for a successful EMG recording in children at all ages.

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Efficacy of isometric strengthening of the lower limb muscles in improving hyperactive bladder symptoms in multiple sclerosis patients

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Introduction. Multiple sclerosis (MS) is a chronic inflammatory disease that affects mainly young people. The urinary dysfunction prevalence in MS patients is between 80 and 100 % during the disease course. The overactive bladder (OB) symptoms are the most frequently reported and have a negative impact on quality of life, mainly in young patients. It's known that the electric stimulation of the Posterior Tibial nerve (which partially share the same radicular innervation with bladder) induces an improvement of OB symptoms through a modulation of spinal circuitry.. Our hypothesis is that the voluntary muscular activation of hamstrings and planti-flexor muscles may induce a modulation of the sacral root as long as the electric stimulation. The objective of our study is to verify if the isometric contraction of these muscles induces a significant reduction of OB symptoms in patients with MS.

Methods. this is a monocentric randomized study. The expected sample size is 30 patients with MS, admitted to the Neurorehabilitation Unit of the San Raffaele Hospital. The experimental group performs for 10 days a daily physiotherapy session of isometric reinforcement of plantar flexors and hamstrings. All patients perform H-reflex, H/M ratio and post-activation depression of H-wave before and after the experimental training. The primary outcomes are: the reduction of the frequency and urinary urgency, measured through the diary and the reduction of the impact of bladder symptoms on patient's quality of life, measured through the OAB-q questionnaire. Secondary outcomes are: sensation of symptoms' change, assessed through PGI, the bladder volumes extrapolated from the bladder diary, Pad-test 24-H and the modification of post-activation depression of H-wave.

Results. We recruited 8 patients. Half were in the experimental group. Preliminary results evidence in experimental group a reduction of urgency, and of urinary leak measured by PAD-test-24H. Urinary frequency did not change significantly. Both groups had an improvement of the sensation of symptoms' change, assessed through PGI, which was prevalent in experimental group. We registered an improvement of post-activation depression of H-wave after rehabilitation training in both groups.

Discussion. The study is still ongoing. Four out of eight recruited patients were in the experimental group. These preliminary results show that isometric reinforcement of plantar flexors and hamstrings would have a positive effect on OB symptoms in MS patients, in term of reduction of urgency and urinary leaks. The improvement of post-activation depression of H-wave in both groups of patients could be related to the rehabilitation program meant for spastic paraparesis, often coexisting in MS patients with OB. The completion of recruitment will allow confirming these preliminary data.

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Pattern-reversal electroretinography discloses retinal pathology in patients suspected for optic neuritis due to normal ophthalmologic examination and abnormal pattern-reversal visual evoked potential

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Objective. Pattern-reversal Visual Evoked Potentials (VEPs) are useful diagnostic tool to assess the function of the anterior visual pathway, especially when optic neuritis is suspected. However, alteration of VEPs often can only localize the lesion in the anterior visual pathway without distinction between nerve lesions and ocular pathologies. From 2016 we perform a whole neurophysiological assessment of the visual system, including pattern-reversal electroretinography (PERG)[1,2], and we report two cases in which we found this method useful in distinction between ocular diseases and optic nerve damage.

Material and methods. We report two cases in which PERG disclosed a retinal pathology in patients in whom an optic nerve dysfunction had been initially suspected relying only to VEPs.

Case 1. A 45 yo woman noticed bilateral blurred vision, few days after symptoms onset an ophthalmological examination was normal as it was a brain CT scan, but computed visual field disclosed a diffuse attenuation of stimulus perception. Basal VEPs showed bilateral increase of P100 latency (119 ms and 117 ms respectively, normal <110) and bilateral optic neuritis was suspected. Case 2. A 48 yo woman developed progressive impaired vision in the right eye for about two years and since the ophthalmological examination was normal she was referred for a suspected optic nerve disease. VEPs showed a slight increase of P100 latency for the right eye (119 ms, normal <110) with slight amplitude reduction.

Results. Case 1. PERG disclosed ad increased latency of all components, P50 included (58 ms bilaterally, normal <55) so a retinal disease was suspected. The subsequent ophthalmologic work-up disclosed s subtle glaucoma and after an initial treatment pattern-reversal VEPs improved. Case 2. PERG disclosed a striking increase of the latency of P50 (66 ms, normal value <55) for the right eye, addressing the problem towards an ocular pathology. An experienced ophthalmologist revised the whole data and history founding a relevant myopia in the right eye and concluding for myopic retinopathy.

Discussion/Conclusions. Patient with visual loss can seldom present a normal o near-to-normal baseline ophthalmological examination even in the presence of a retinal pathology, and in these cases it can be difficult to ascribe the problem to an ocular disease. In these cases sometimes VEPs can be abnormal, misleading the diagnosis towards an optic nerve disease. Performing PERG in uncertain or complex cases may help in distinguish between ocular or optic nerve pathology in patient with visual loss.

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Effects of concurrent visual and somatosensory stimulation on somatosensory evoked potentials habituation in healthy humans

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Background. Merging of sensory information is an important process towards the production of learning and memory. In animal models, co-application of tactile and visual stimulations enhances the magnitude of responses to somatosensory stimulations. This multisensory integration process takes place at a thalamic level, under cortical control. Here, we have sought evidence for the existence of the same process of multisensory integration in humans, by evaluating the potential ability of concurrent visual and somatosensory stimulations to affect the mechanisms of habituation, a basic form of learning.
Methods. We recorded somatosensory evoked potentials (SSEPs) in ten healthy volunteers (HVs) before (T0), during, and 5 min (T1) after simultaneous visual stimulation with a black-and-white checkerboard pattern-reversal (15 min of arc cheques, 3.1 reversal per second). Six-hundred sweeps were acquired for each condition and partitioned off-line in 2 blocks of 100 sweeps for the calculation of habituation as the slope of the regression line between the 1st and the 2nd block of averaged N20-P25 SSEP amplitude response.
Results. SSEP N20-P25 habituation, i.e. amplitude decrement between 1st and 2nd block, which was obvious in most HVs during the T0 recording session, was deficient (amplitude increment) during the visuo-somaesthetic stimulation. During the T1 recording session, the SSEP amplitude linear trend was not different from that observed at T0.
Conclusion. Our study is the first to report the existence in healthy humans of the same cross-modal interaction previously observed in animal model, which manifests as an augmenting response to somatosensory stimuli. We suggest therefore that multisensory integration may enhance short-term memory mechanisms. Extending our study from HVs to patients with migraine between attacks would offer a unique opportunity to investigate defensive strategies against multisensory overload under conditions when baseline habituation is already absent.

Different contribution of muscular and cutaneous afferents to the scalp SEPs

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Background and objective. Although somatosensory evoked potentials (SEPs) represent a largely diffused neurophysiological technique, the pathways generating the short-latency scalp components are not fully known. We aimed to investigate the SEPs recorded from the scalp and deep brain stimulation (DBS) leads to selective electrical stimulation of either muscular or cutaneous afferents.
Methods. SEPs were recorded in 6 patients suffering from advanced Parkinson's disease who underwent electrode implantation in the pedunculopontine (PPTg) nucleus area. We compared SEPs recorded from the scalp and DBS electrode contacts to electrical stimulation of: a) the median nerve at the wrist (mixed stimulation), b) the abductor pollicis brevis motor point (pure stimulation of the muscle afferents), and c) the distal phalanx of the thumb (pure cutaneous stimulation). High-frequency oscillations (HFOs) subtending the low-frequency SEPs were also analyzed.
Results. The macroelectrode contacts recorded a triphasic (P1-N1-P2) potential and the scalp electrodes recorded all the classical SEP components, including the widespread N18 response, after both median nerve and pure cutaneous stimulation. After motor point stimulation, the scalp N18 component and the PPTg N1 response were not recorded. No difference in the HFOs between the stimulation modalities was found. The scalp N20 component was recorded to stimulation of any modality, even if with different latency and amplitude.
Discussion. Considering that both the scalp N18 response and PPTg N1 component reflect the activity of a pre-postsynaptic neural network in the cuneatus nucleus, our data suggest that the cuneate response is specifically evoked by cutaneous inputs, while muscle afferents are processed elsewhere.
Conclusions. Our results are important for understanding the physiological mechanism of the proprioceptive and cutaneous sensory processing.

Conduction velocity of the human spinothalamic tract as assessed by cold evoked potentials

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Objectives. To investigate the central conduction velocity of the spinothalamic tract after cold stimulation in the human spinal cord.
Methods. In 15 healthy subjects we recorded evoked potentials from cold stimulation and from warm and noxious stimulation as control (CEPs, C-LEPs and Aδ LEPs) of the dorsal midline at C5, T2, T6, and T10 vertebral levels. This method allowed us to calculate the spinal conduction velocity (CV) in two different ways: (1) the reciprocal of the slope of the regression line obtained from the latencies of the different EP components, and (2) the distance between C5 and T10 divided by the latency difference of the responses at the two sites.
Results. We were able to record large-amplitude vertex potentials (N2P2) from all stimulation sites with all three modalities. The two methods to calculate CV yielded overlapping results: the mean conduction velocity of the STT was 2.1 m/s for warm stimulation, 10.4 m/s for noxious stimulation and 11.9 m/s for cold stimulation (R square 0,5671; 0,2484; 0,1926. P>0.001).
Discussion. It is the first report about the central conduction velocity of the human spinothalamic tract after cold stimulation.
Since dorsal stimulation readily yielded reproducible Cold Evoked Potentials, we expect this technique to be useful as a diagnostic tool for assessing the level of spinal cord lesions.
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Electroretinogram (ERG) abnormalities in adult-onset leukodystrophy with vanishing white matter (LVWM)

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Objective. LVWM is a rare autosomal-recessive disease that typically (but not always) appears in childhood. Its clinical symptoms include cerebellar ataxia, limb spasticity, cognitive impairment and bladder dysfunction, and brain MRI findings are characterized by typical WM changes, including rarefaction. Retinal involvement related to Müller glia

disease is frequent. The aim of this study was to investigate ERG retinal abnormalities in patients with adult-onset LVWM.

Materials and Methods. Nine patients with genetically confirmed adult-onset LVWM (M:F ratio 3:6; mean age 43.9) underwent flash-ERG recordings under photopic and scotopic conditions to allow the analysis of a- and b-wave and oscillatory potential (OP) latency and amplitude, and mean 30 Hz flicker amplitude. Pattern-ERGs (pattern reversal check size 30', contrast 60%) were recorded in six patients.

Results. Three patients had normal flash-ERGs; six were characterized by b-wave amplitude attenuation and increased latency (particularly the white flash maximal, and dim blue scotopic ERGs). Flicker and OPs were less affected, but two patients showed severe involvement, with preserved a-wave activity suggesting mixed rod-cone dysfunction. Pattern-ERGs were normal in two patients, and showed changes ranging from reduced amplitude to marked deterioration in four.

Conclusions. Our findings confirm frequent ERG changes in patients with adult-onset LVWM mainly involving maximal and dim blue scotopic ERG b-waves, and primarily supporting Müller cell dysfunction. However, electrophysiological signs of deeper retinal layer involvement (OP and flicker changes), and pattern-ERG changes suggesting ganglionic cell dysfunction possibly due to secondary visual pathway axonal degeneration, indicate greater retinal involvement than previously thought.

Study of the variables influencing the Electroretinogram setting of non-compliant patients as infants

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Objective. The full-field electroretinogram (ERG) is an electrophysiological test that examines the functional integrity of the retina. The use of surface electrodes produces good results in comparison with the corneal and conjunctival electrodes[1]. In non-compliant patients this test according to ISCEV standards is difficult to perform and responses are influenced by many variables (eye position, eye closed, stimulator position). In the awake infants this examination is often influenced by this variables. The objective of our study is to define and quantify the principle variables that can affect the ERG response in non-compliant patients (i.e. pediatric or other not compliant patient).

Material and methods. Twenty healthy volunteers (2 male and 28 female, aged 26,2±6,9) with no ocular or systemic disorders were studied. Silver surface electrodes were used. Standard Flash Photic Response (PR), Flicker Response (FR), Maximal Combined Response (MCR) and Scotopic response (SR) were recorded using three different recording channels: (1) middle third of the lower eyelid – orbital rim2, (2) above brow line – Nasion, (3) Nasion – Cz in different conditions: (a) eyes position (medial, lateral, up and down), (b) stimulator position (45° right, 45° left), (c) eyes open/eyes close (d) absence/presence of mydriasis. We analyzed changes in amplitude and latency of component "a" and "b" of the ERG PR and FR for all condition above mentioned.

Results. Channel 2 compared to channel 1 showed a significant decrease in amplitude of a wave and b wave ($a\Delta=79$, $b\Delta=84$ $p>0{,}001$). Eyes position (medial, lateral, up and down) caused a significant change in PR of the a wave and the b wave amplitude with a greater decrease when the eyes were in lateral position ($a\Delta=61$, $b\Delta=63$, $p<0{,}001$). We found a significant decrease in the amplitude of b component of PR for both directions of stimulation (45°right $\Delta=35$, and 45° left $\Delta=45$, $p< 0{,}001$) compared to the frontal position; as shown in previous studies (REF), there is a significant decrease of b component amplitude in the eyes closed condition ($\Delta = 41$, $p<0{,}0001$). Pharmacological mydriasis showed a significant increase of amplitude in FR ($p<0{,}001$).

Discussion/Conclusions. Our results show that different technical conditions influence the amplitude of ERG responses. Further studies with larger number of patients of different age groups are needed to better quantify the magnitude of each variable's effect, in order to avoid misinterpretation of results in non-compliant patients.

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Grade of achievement of patient-tailored goals in ms patients with focal spasticity, treated with botulinum toxin A and physiotherapy

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Rationale and Objective. botulinum toxin type A (BT-A) is effective in reducing spastic hypertonia, both in lower and upper limb. A few evidences, instead, are available on BT-A effect in modifying active or passive function, and quality of life, mostly in Multiple Sclerosis (MS) patients. MS patients have a wide spectrum of disability depending on disease evolution and duration; so the final clinical objective of reducing MS patient disability has to go through a correct assessment of the residual function of each patient and an adequate individuation of the goal of the BT-A and physiotherapy treatment. The aim of our study is to evaluate the grade of achievement of the predefined and individualized goals through the treatment of focal spasticity in MS patients, with BT-A and physiotherapy.

Methods. consecutive hospitalized patients presenting with focal spasticity and Multiple Sclerosis, were evaluated. After a multidisciplinary examination of residual functional and disability state, it was identified a realistic and specific objective for each patient; a rehabilitative program was drawn and BT-A was administered depending on spasticity pattern. The grade of achievement of the predefined target was assessed at week 4 using the Goal Attainment Scale (GAS). Moreover, specific quantitative or semi-quantitative scales were administered for every goal, depending on the function or disability domain involved.

Results. we treated 23 patients. 20 out of 23 reached the goal. The most frequent selected goal was gait improvement (17 out of 23) and in particular for 11 patients improving gait resistance and for 6 patients improving home mobility. Respectively the 6 min Walking test (6-WT) and the Time Up and Go (TUG) improved in all patients who reached the target. The 3 patients with the failure in reaching the target did not demonstrate an improvement in all associated scales.

Discussion and Conclusion. these data show that an integrated and multidisciplinary approach in treating focal spasticity in MS patients is effective for reaching the individualized objective, even when the goal is an active function; to target the intervention on actual needs of every patient focusing on realistic measurable and specific goal is necessary. GAS in an adequate scale for evaluating the response to planned intervention, since the concordance between GAS score and the improvement of specific quantitative or semi-quantitative scale for single goal. This is the first step for a subsequent evaluation of a real impact of our intervention in reducing global disability of patients.

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Subthalamic circuit disruption as a cause of hyperventilation triggered paroxysmal hemidystonia

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Objectives. Paroxysmal dystonia is a possible manifestation of focal lesions and has been related to the pathologic involvement of various area into thalamic and subthalamic areas1. Paroxysmal dystonias consist of involuntary, accessual, brief muscle contractions causing posture, movements or both; the episodes are usually self-limited and trigger-induced. Among trigger movements, sensory stimulation and hyperventilation (HV) are the most frequent 2. They can be preceded by a sensory aura and can be painful in some occasions1,3. Among the possible etiologies, in young people, multiple sclerosis (MS) is a diagnosis that need to be taken in consideration1. Other causes of symptomatic hemidystonia have been described, such as stroke, infections, metabolic diseases, head trauma, Wilson's disease and hyperthyroidism2. We present a case of a male patient with paroxysmal hemidystonia, occurring spontaneously and triggered by hyperventilation, caused by controlateral demyelinating subthalamic and midbrain lesion.
Methods. A 54 years old Caucasian man presented a five-day history of sudden, transient, involuntary movements, including painful dystonic postures of right leg and arm, triggered by hyperventilation (HV). The episodes were very intense and preceded by rising epigastric feeling. Facial muscles were not involved; the patient was fully conscious during the episodes and had no speech disturbance and the episodes were self-limiting without sequelae. The patient showed 5-6 spontaneous episodes per day, which lasted for about 30 s.
Results. MRI brain scan showed the presence of a T2 hyperintense lesion in the subthalamic region, involving the posterior arm of the internal capsule and extending to the subthalamic nucleus and mesencephalon and in the periventricular white matter. The Cerebrospinal fluid (CSF) analysis showed marked increased proteins, lymphocytic hypercellularity and the presence of oligoclonal bands.
Discussion and Conclusion. The CSF analysis results with marked increased proteins, lymphocytic hypercellularity and the presence of oligoclonal bands in addition to MRI findings of periventricular lesions suggests primary or post-infectious inflammatory demyelinating diseases as their probable cause. In conclusion, multiple sclerosis-related paroxysmal hemidystonia was diagnosed because of a clinical episode and the presence of both dissemination in space (periventricular lesions on T2 MRI) and dissemination in time (specific oligoclonal bands in CSF) criteria.
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Functional and Structural Evaluation of the Visual Pathway in Progressive Multiple Sclerosis

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Background and Aims. The visual pathway is an elective platform to study demyelination-neurodegeneration interaction in multiple sclerosis (MS). We applied functional (visual evoked potentials-VEPs) and structural (optical coherence tomography-OCT) assessment of the visual system to primary (PPMS) and secondary (SPMS) progressive MS.
Methods. 300 patients (188 SPMS-112 PPMS) underwent a cross-sectional evaluation with EDSS, high (HCVA)- and low-contrast (LCLA) visual acuity, full-field (ff-VEPs) and multifocal (mf-VEPs) VEPs, and OCT. We collected follow-up (mean 2.05±1.13 years) data of 120 patients (40 PPMS and 80 SPMS).
Results. we found PPMS to have better LCLA than SPMS patients (median 0.32 vs 0.25 decimals, p=0.005). VEPs latency was higher among SPMS patients than PPMS (ff-VEP: mean 143.6 vs 135.56 ms, p=0.001; similar results for mf-VEPs). Retinal Nerve Fiber Layer (RNFL) was thinner in SPMS vs PPMS (mean 81.48 vs 88.81 μm, p<0.001) with similar results for Ganglion Cell-Inner Plexiform Layer (GCIPL). Considering the evolution of functional and structural parameters we found no significant difference comparing PPMS and SPMS; classifying our cohort according to EDSS status (stability n.77 vs worsening n.43) we found a difference in terms of RNFL evolution (mean ΔRNFL -0.23 μm vs -0.75 μm for stable and progressing patients respectively, p=0.0239) with a correlation between EDSS and RNFL change (ρ=-0.299, p=0.003); similar results were obtained for GCIPL.
Conclusions. our results suggest a greater functional and structural involvement of the visual system in SPMS compared to PPMS. Follow-up data suggest however neurodegeneration to occur with no difference between SPMS and PPMS, with OCT representing a useful tool to monitor disease progression.
Disclosures: part of this work was supported by Merck, Geneva, Switzerland. Merck is the biopharmaceutical division of Merck KGaA, Darmstadt, Germany.

High frequency oscillations (HFOs) as neurophysiological biomarker of fatigue in Multiple Sclerosis

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Objective. Fatigue is the most frequent symptom reported by patients affected by Multiple Sclerosis (MS) and it begets a severe detrimental effect on patient's quality of life. At present, there are no neurophysiological tests to measure fatigue. Recordings of somatosensory evoked potentials (SEPs) are an effective method to evaluate the somatosensory conduction pathways and are widely used as a diagnostic tool in MS. Through the application of a high-pass filter, it is possible to isolate a burst of fast oscillations superimposed on the parietal N20 response, called High-Frequency oscillations (HFOs). The early part of HFOs is thought to reflect thalamo-cortical network activity, a critical neural circuit involved in generation of fatigue in MS. In this experimental study we compared how HFOs behave after a fatigue-inducing exercise in patients who self-report fatigue and in healthy controls.
Material and methods. Seventeen patients with a clinically definite MS in according to 2017 McDonald Criteria and eleven healthy controls participated in this study. Two different questionnaires (Modified Fatigue Impact Scale or MFIS and Fatigue Severity Scale or FSS) exploring the impact of fatigue in everyday life were administer to MS patients. Both patients and healthy controls, underwent three separate recordings of SEPs (baseline, post1, post2) after median nerve electrical stimulation. Before the second and the third set of SEPs, subjects were asked to perform a fatigue inducing exercise (*ie* pushing a button for 4 min). We then compared mean HFOs amplitude of baseline, post1 and post2 in MS patients and healthy subjects.
Results. Our data showed a progressive increase of HFOs amplitude after fatigue-inducing exercise in healthy subjects, while in MS patients, especially in the third recording, there is a decreasing trend. This tendency is

particularly evident for the early part of HFOs. In patients without clinically relevant fatigue (FSS < 4) HFOs behave in a similar way to the healthy subjects, but with lower amplitude.
Discussion. Our findings indicated that HFOs are a promising tool for evaluating fatigue in patients with MS. In particular, the different behaviors of HFOs in patients with fatigue (FSS > 4) compared to patients without fatigue and healthy subjects suggest that a disruption of thalamo-cortical network could actually play a key role in the pathophysiology of fatigue.
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Homeostatic-like plasticity is impaired in Multiple Sclerosis

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Background and Objectives. Acute and chronic brain damage disrupts brain connectivity producing neurological signs and/or symptoms. In several neurological diseases, particularly in Multiple Sclerosis (MS), structural imaging studies cannot always demonstrate a clear association between lesion site and clinical disability, originating the "clinico-radiological paradox." The discrepancy between structural damage and disability can be explained by a complex network perspective. Both brain networks architecture and synaptic plasticity may play important roles in modulating brain networks efficiency after brain damage. In this study, we evaluate homeostatic plasticity mechanism in naïve patients with Multiple Sclerosis (MS)
Methods. We enrolled 10 naïve MS patients. We explored the effect of transcranial direct current stimulation (tDCS) priming on the conditioning effect of 1 Hz repetitive transcranial magnetic stimulation (rTMS) on motor cortex excitability. All participants received 15 min of subthreshold 1 Hz rTMS to the left primary motor cortex (M1), this was preceded either by a 10 min period of effective TDCS to the left motor cortex using anodal (excitatory) or cathodal (inhibitory) polarity.
Results. Our data showed that homeostatic plasticity mechanism are impaired.
Discussion. Homeostatic mechanisms that stabilize excitability levels within a useful dynamic range are impaired in naïve patients with MS.
Conclusions. Modulation of plasticity with different non-invasive brain stimulation (NIBS) techniques has been used to promote recovery of MS symptoms. Better knowledge of features inducing brain disconnection in MS is crucial to design specific strategies to promote recovery and use NIBS with an increasingly tailored approach.

How to improve the cardiovascular autonomic tests in diagnosis of Parkinson's diseases and parkinsonisms?

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Objective. Parkinson's disease (PD) and multiple system atrophy with predominant parkinsonism (MSA-P) in the early and medium stages could be difficult to differentiate. The aim of study was to evaluate whether using different sympathetic indexes (SI) and power spectral analysis of the heart rate and blood pressure (BP) short-term variability is useful in differentiating MSA-P and PD.
Methods. We prospectively evaluate patients with a parkinsonian syndrome and dysautomic symptoms referred to our Institute. We included only patients with a Hoehn & Yahr scale <2.5 with symptoms of urinary or cardiovascular or gastrointestinal dysautonomia. Patients performed a standardized evaluation including the Compass 31 questionnaire, neurological examination, UPDRS III. Part of patients underwent also myocardial scintigraphy with [123I] metaiodobenzylguanidine (MIBG). The final diagnosis of probable MSA and PD was performed after a mean period of follow-up of 6 months. A population of 25 controls matched for age and sex were included. All performed a battery of cardiovascular Ewings test including deep breathing, head-up tilt test (HUTT), Valsalva maneuver (VM), and sustained handgrip. We analyzed also six Sis during the VM introduced by Novak and the power spectral analysis of the R-R interval and blood pressure (BP) short-term variability.
Results. We enrolled 21 PD and 30 MSA patients that completed all the tests and clinical evaluation. Other 41 PD and 25 MSA not fulfilled the inclusion criteria. Cardiovascular reflexes indices were significantly more affected in MSA-P compared to PD and controls. Orthostatic hypotension was found in 22 MSA-P and 12 PD patients. SI 3 (difference between baseline and the end of phase 2) and SI 5 (BP recovery time after phase 2b) were significant affected in MSA-P then in PD and control subjects. At rest, total power spectral analysis showed lower LF/HF ratio in PD and MSA-P than in controls, however, during 10-min HUTT the LF/HF ratio and variation was considerable lower in MSA-P than in PD.
Conclusions. Our results suggest that using few sympathetic indexes and power spectral analysis of HR and BP could improve the classical Ewing tests in diagnosis of cardiovascular dysautonomia in early stages of PD and MSA-P.

Sympathetic overactivation associated with Hypertension after Sodium Oxybate overuse: a Microneurographic study in a patient with Narcolepsy type I.

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Background and aim. Sodium Oxybate (SO) has shown benefit in both cataplexy and excessive daytime sleepiness in Narcolepsy tipe I (NT1). Although not so commonly, hypertension has been reported as side effect of SO but it is unknown whether is neurally mediated or not.
Herein we describe a patient affected by NT1 performing serial microneurographic recording of muscle sympathetic nerve activity (MSNA) and blood pressure (BP) at baseline evaluation and through disease course under SO stable treatment and overuse.
Methods. Microneurography recordings were performed from the peroneal nerve in the left limb. Multiunit recordings of efferent muscle sympathetic nerve activity (MSNA) with the corresponding organ effector responses (skin vasomotor response-SVR) were recorded. [1,2] MSNA was considered acceptable when it revealed spontaneous, pulse-synchronous bursts of neural activity modulated by respiration and variations in blood pressure or intra-thoracic pressure
Results. At 44 years old the patient received a diagnosis of NT1: his orexin CSF levels were undetectable and he showed pathological results on Multiple Sleep Latencies Test (sleep onset latency of 3'36" and 5 sleep onset REM periods). At baseline MSNA was 77 burst/100 heart beat(HB) and BP 120/85 mmHg. On discharge he started SO progressively increased up to 8 g/day. At 6 month follow-up he reported resolution of cataplexy and of excessive daytime sleepiness. A second microneurographic recording disclosed a slight increase of MSNA and BP: 88 burst/100 HB and BP 130/90 mmHg. At long term follow-up (6

years) the patient was admitted for re-evaluation: a third microneurographic recording revealed relevant sympathetic overactivity (100 burst/100 HB) and BP 170/120 mmHg. He was still asymptomatic for cataplectic attacks and diurnal sleepiness. The patient admitted SO overuse (approximately 16 g/day) in the month foregoing the admittance because of depressive symptoms due to familiar problems. Other possible causes of secondary hypertension. The patient introduced antihypertensive medications, SO dosage was reduced and then discontinued.

Discussion. The over activation of sympathetic activity we found at microneurographic recording during SO abuse, is consistent with the hypothesis that hypertension caused by SO is neurally mediated. The underlying mechanism is likely dependent on biological activity of the molecule on GABA B receptor. [3]

Conclusion. Our data support that hypertension related to SO could be neurally mediated. Vigilance of dose assumption is recommended considering the potential risk of abuse the substance has.

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Sudomotor dysfunction scales with Amyotrophic Lateral Sclerosis progression

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Objective. Autonomic dysfunction can occur in Amyotrophic lateral sclerosis (ALS) patients, mostly involving cardiovagal and sudomotor functions[1]. Specifically, regarding the latter aspect, morphological data from skin biopsies have demonstrated severe derangement of sweat gland structure. Importantly, autonomic denervation appeared to be linked to disease progression rate[2]. To better delineate the role of sudomotor function in ALS progression, we used a device that has been recently introduced by our group: the dynamic sweat test (DST)[3]. DST allows measuring at the same time sweat gland density, distribution of active glands, and sweat rate.

Material and methods. The DST was used to evaluate sweating in the distal leg of 25 ALS patients (14 males and 11 females; age 60.7 ± 7.3). The formation of the imprint of pilocarpine-induced sweating was recorded by a digital video camera through a starch-powdered transparent tape used as a contrast-enhancing device. Mean sweat output per gland and per skin area and sweat gland density per cm^2 were evaluated. Disease severity and sensory and autonomic symptoms were scored using dedicated rating scales.

Results. We observed a significant reduction of sweating in 26 ALS patients compared to controls. Sweat gland density per cm^2 (40.4 ± 17.3 vs 83.7 ± 17.3; $p < 0.05$) and mean sweat output (nL/min) per gland (5.8 +/- 2.8 vs 8.3 ± 2.7; $p < 0.05$) and per skin area (214 ± 107.4 vs 645 ± 296; $p < 0.05$) were reduced in the lower limb. Importantly, sweat gland density scaled with disease progression rate (r= -0.665, p= 0.009) and muscular strength at lower limbs (r= 0.500, p= 0.032). Surprisingly, regarding the mean sweat output per gland, we found a positive correlation with disease progression rate (r= 0.690, p= 0.006).

Discussion/Conclusions. Sudomotor function, expressed as sweat gland density, is impaired in patients with ALS with faster disease progression. Interestingly the higher sweating production in the more severe cases may suggest compensatory processes that need further insights in future studies.

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Neuromuscular magnetic stimulation counteracts muscle decline in ALS patients: results of a randomized, double-blind, controlled study

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Objective. The aim of the study was to verify whether neuromuscular magnetic stimulation (NMMS) improves muscle function in spinal-onset amyotrophic lateral sclerosis (ALS) patients.

Material and methods. Twenty-two ALS patients were randomized in two groups to receive, daily for two weeks, NMMS in right or left arm (referred to as real-NMMS, rNMMS), and sham NMMS (sNMMS) in the opposite arm. All the patients underwent a median nerve conduction (compound muscle action potential, CMAP) study and a clinical examination that included a handgrip strength test and an evaluation of upper limb muscle strength by means of the Medical Research Council Muscle Scale (MRC). Muscle biopsy was then performed bilaterally on the flexor carpi radialis muscle to monitor morpho-functional parameters and molecular changes. Patients and physicians who performed examinations were blinded to the side of real intervention. The primary outcome was the change in the muscle strength in upper arms. The secondary outcomes were the change from baseline in the CMAP amplitudes, in the nicotinic ACh currents, in the expression levels of a selected panel of genes involved in muscle growth and atrophy, and in histomorphometric parameters of ALS muscle fibers.

Results. The Repeated Measures (RM) ANOVA with a Greenhouse-Geisser correction (sphericity not assumed) showed a significant effect [$F(3, 63) = 5.907$, $p < 0.01$] of rNMMS on MRC scale at the flexor carpi radialis muscle. Secondary outcomes showed that the improvement observed in rNMMS-treated muscles was associated to counteracting muscle atrophy, down-modulating the proteolysis, and increasing the efficacy of nicotinic ACh receptors (AChRs). We did not observe any significant difference in pre- and post-stimulation CMAP amplitudes, evoked by median nerve stimulation.

Discussion/Conclusions. The real and sham treatments were well tolerated without evident side effects. Our results demonstrate that the rNMMS significantly improves muscle strength in flexor muscles in the forearm. The lack of increase in CMAP amplitude suggests that the improvement in muscle strength observed in the stimulated arm is unlikely related to reinnervation. Although promising, this is a proof of concept study, with limited immediate clinical translation, that requires further clinical validation.

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Safety and tolerability of extremely low frequency magnetic fields in acute ischemic stroke: an open-label, one-arm, dose-escalation study

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Objective. Extremely low frequency magnetic fields (ELF-MF) could be an alternative neuroprotective approach for ischemic stroke because preclinical studies have demonstrated their effects on the mechanisms underlying ischemic damage. The purpose of this open-label, one arm, dose-escalation, exploratory study is to evaluate the safety and tolerability of ELF-MF in patients with acute ischemic stroke.
Material and methods. Within 48 h from the stroke onset, patients started ELF-MF treatment, daily for 5 consecutive days. Clinical follow-up lasted 12 months. Brain MRI was performed before and 1 month after the treatment. The distribution of ELF-MF in the ischemic lesion was estimated by dosimetry. The system for delivering ELF-MF consisted of a custom-made rectangular, flexible coil kept in place by a Velcro strap, upon the ischemic hemisphere. The magnetic pulse generator (B-01; IGEA, Carpi, Italy) supplied the coil with a single-pulsed signal at 75±2 Hz, with a pulse duration of 1.3 ms. The peak intensity of the magnetic field was 1.8±0.2 mT.
Results. Six patients were stimulated, three for 45 min/day and three for 120 min/day. None of them reported adverse events. Clinical conditions improved in all the patients. Lesion size was reduced in one patient stimulated for 45 min and in all the patients stimulated for 120 min. Magnetic field intensity within the ischemic lesion was above 1 mT, the minimum value able to trigger a biological effect in preclinical studies.
Discussion/Conclusions. To our knowledge, this is the first study that explored the feasibility of ELF-MF stimulation in acute ischemic stroke patients. In a previous study on healthy volunteers, we have demonstrated that ELF-MF do not produce any side effect in humans. In this pilot trial, we confirmed that such stimulation is safe and tolerable, also in stroke patients. Dosimetry study shows that, in all patients, the peak intensity of the magnetic field induced in the ischemic lesion was never below 1 mT, the minimum value able to trigger the upregulation of A2A receptors in preclinical studies. In addition to the possible effects mediated by adenosine receptors, at these intensities, ELF-MF exposure can also exert a direct protective action towards hypoxic insult by reducing ROS generation and proinflammatory cytokine release, crucial events in the exacerbation of ischemic condition. Our pilot study demonstrates that ELF-MF are safe and tolerable in acute stroke patients. A prospective, randomized, placebo-controlled, double-blind study will clarify whether ELF-MFs could represent a potential therapeutic approach.
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The effects of rTMS of the motor cortex on disease progression and on glutamate and GABA levels in ALS: a proof of principle study

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Objective. Previous studies suggest that rTMS (cTBS) might slightly reduce disease progression in ALS. rTMS has been usually delivered for five consecutive days/month. Here we doubled the duration of rTMS treatment, giving bilateral motor cortex cTBS for five days/week for two consecutive weeks, every month, for up to 12 months. We focused on: a) the difference between the actual disease progression and the expected clinical decline without cTBS, b) the effect of one week of cTBS on glutamate and GABA levels by means of MRI spectroscopy (MRS), c) comparison of the new cTBS schedule vs the one used in the previous studies by means of a pooled analysis.
Material and methods. Five male patients with a diagnosis of definite ALS were enrolled. Four patients were treated for 12 months, one for 6 months. The ALSFRS-R was measured starting 3 months before cTBS and every month until the end of the study. We computed the slope of the ALSFRS-R change over the period of three months before the treatment and estimated the expected ALSFRS-R without stimulation over a period of 12 months. MRS analysis was restricted to three patients and performed before and after a cycle of stimulation. GABA level was estimated within the left motor cortex and glutamate level in left motor cortex, left white matter, and pons. We also compared the disease progression of the cohort of this study with the data previously published by our group.
Results. The comparison of ALSFRS vs Expected_ALSFRS-R showed higher ALSFRS at 1 month after the beginning of cTBS. The difference was more pronounced after 6 months, but did not reach the statistical significance. cTBS did not affect metabolite concentration, however the variation of clinical status, showed a significant negative relationship with the change of GABA. No relationship was found for glutamate. The comparison of the disease progression across different studies, focused on three groups homogeneous for type of stimulation: bilateral cTBS 2weeks/month, bilateral cTBS 1week/month, sham stimulation. Statistical analysis showed that both the 2weeks/month and the 1week/month groups had a significantly milder worsening than Sham. A trend towards a better performance of the 2 weeks/month group vs the 1 week/month group was also found.
Discussion/Conclusions. This proof-of-principle study is insufficient to draw conclusions about the efficacy of rTMS in the treatment of ALS, but provides some support to the potential efficacy of rTMS and suggests that prolonged periods of stimulation might be more effective.
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Neural response induced by transcranial magnetic stimulation: a TMS-EEG study

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Introduction. The effect of Transcranial magnetic stimulation (TMS) can be assessed by measuring direct cortical responses to magnetic pulses, named TMS-evoked potentials (TEPs). In addition to TEP, the TMS pulse might produce auditory (AEP) and somatosensory evoked potentials (SEP). Recent studies have investigated the extent to which the latter can influence TEP waveform, but results are conflicting [1, 2]. The aim of this study is to further investigate how AEP and SEP may influence TEP.
Materials and methods. We collected 64-channel TEPs in nine healthy subjects using 5 different protocols. TMS pulses (90% resting motor threshold; fig. 8 coil) were applied over the left primary motor cortex with and without noise masking (NM). The influence of AEP on TEP was investigated by placing a plastic cylinder between a sham TMS coil and scalp, again with and without NM. Finally, we electrically stimulated the scalp at the target site to investigate a possible contribution of SEP to TEP.
Results. Standard TMS elicited the highest amplitude responses. In particular, early responses (<50ms) after stimulation were similar regardless of the noise masking, whereas late waves were larger without NM. Auditory stimulation without NM induced clear late components, which disappeared with NM. The other conditions did not elicit clear EEG responses.
Conclusion. When properly controlled with NM, TEPs over M1 mostly represent responses due to direct cortical activation.
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Transcranial Alternating Current Stimulation Has Frequency-Dependent Effects on Motor Learning in Healthy Humans

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Objective. It is well established that the primary motor cortex (M1) plays a significant role in motor learning in healthy humans. It is unclear, however, whether mechanisms of motor learning include M1 oscillatory activity. In this study, we aimed to test whether M1 oscillations, entrained by Transcranial Alternating Current Stimulation (tACS) at motor resonant frequencies, have any effect on motor acquisition and retention during a rapid learning task, as assessed by kinematic analysis. We also tested whether the stimulation influenced the M1 excitability changes after motor learning.
Material and methods. Sixteen healthy subjects were enrolled in the study. Participants performed the motor learning task in three experimental conditions: sham-tACS (baseline), β-tACS and γ-tACS. M1 excitability was assessed with single-pulse TMS before the motor learning task and 5, 15, and 30 min thereafter. Motor retention was tested 30 min after the motor learning task.
Results. During training, acceleration of the practiced movement improved in the baseline condition and the enhanced performance was retained when tested 30 min later. The β-tACS delivered during training inhibited the acquisition of motor learning task. Conversely, the γ-tACS slightly improved the acceleration of the practiced movement during training but it reduced motor retention. At the end of training, M1 excitability had similarly increased in the three sessions.
Discussion/Conclusions. The results are compatible with the hypothesis that entrainment of the two major motor resonant rhythms through tACS over M1 has different effects on motor learning in healthy humans. The effects, however, were unrelated to M1 excitability changes.

Assessment of cholinergic cortical circuits after Transcutaneous Nerve Stimulation (tVNS) in healthy humans

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Objective. Transcutaneous vagus nerve stimulation (tVNS) is a safe and effective way to stimulate vagus nerve non-invasively. Previous studies have explored the potential effects of tVNS on cortical excitability and evidence suggests the possible increase of GABA-A activity in microcircuits of cerebral cortex after 60 min exposure to tVNS. Herein we tested the hypothesis that short-afferent inhibition (SAI), a paradigm in which a sensory afferent volley (i.e. electrical stimulation of the median nerve) inhibits the motor response evoked by Transcranial Magnetic Stimulation (TMS) in a given muscle, could be modified by tVNS.
Material and methods. This study is a randomized placebo-controlled double-blind study. Each subject underwent two different sessions (real tVNS and sham tVNS), separated by at least 48 h. Real tVNS was performed at the left external acoustic meatus and sham stimulation at the left ear lobe. tVNS was delivered as trains of 600 pulses at 20 Hz repeated every 5 min for 1 h. SAI was studied using the technique originally described by Tokimura et al. in 2000. Conditioning stimulus to the median nerve was given at the wrist through an electrical stimulator using a bipolar electrode (cathode proximal) and an intensity inducing a painless thumb twitch. The intensity of the conditioning stimulus (CS) was set over the motor threshold for evoking a visible twitch in the thenar muscles; the CS preceded the magnetic test stimulus (TS) by different interstimulus intervals (ISIs). ISIs were calculated on the basis of the individual N20 response of somatosensory evoked potentials (SEPs) induced by the stimulation of the right and left median nerve. We recorded 30 sweeps at three different ISIs (N20 + 2, N20 + 3, N20 + 4 ms). These recordings were performed before and after tVNS exposure for each subject.
Results. Mean MEP amplitude decreased after SAI, both in sham and real tVNS session. No significative statistical effect of tVNS could be noticed on MEP amplitude.
Discussion/Conclusions. SAI is supposed to be a phenomenon related to the intracortical activity of cholinergic neurons, while tVNS seems to elicit effects mostly on GABA-A circuitry. Our findings seem to confirm these hypotheses and provide new evidence on tVNS mechanisms of action at the cortical level. More studies are required to better understand cerebral microcircuits and the potential clinical application of tVNS.
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Comparison among tonic, high frequency and burst spinal cord stimulation in the treatment of neuropathic pain

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Objective and aims. Spinal cord Stimulation (SCS) is an effective option for neuropathic pain treatment. New technological developments, as high frequency (HF) and Theta Burst Stimulation (TBS), have shown promising results, although putative mechanisms of action are still debated.
Methods. Twenty-five patients with lower back pain were enrolled and underwent LF, HF and TBS. LEPs were recorded by using a Nd:YAG laser: amplitudes and latencies of the main two components (N1, N2/P2) were compared among different experimental conditions. Similarly, changes in Resting Motor Threshold (RMT), cortical Silent Period (cSP), Short Intracortical Inhibition (SICI) and Intracortical Facilitation (ICF) were evaluated.
Results. TBS dampened LEP amplitudes compared with LF (N1: $p = 0.016$; N2/P2: $p = 0.02$) and HF stimulation ($p = 0.015$; $p = 0.031$); while RMT and SICI did not change among experimental conditions, TBS significantly prolonged cSP duration compared with baseline ($p = 0.002$), LF ($p = 0.048$) and HF-SCS ($p = 0.016$); both HF ($p = 0.004$) and TBS ($p = 0.0039$) increased ICF.
Discussion and Conclusions. TBS modulates the sensory-discriminative and the affective-emotional dimension of pain through distinct mechanisms, thus involving intracortical GABAergic and Glutamatergic networks. These results have implications for therapy and for the choice of the stimulation protocol.
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The usefulness of evoked potentials in the follow-up of X-linked adrenoleukodystrophy children.

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Objective. in children with X-linked adrenoleukodystrophy (X-ALD) the evoked potentials (EPs) are considered as a useful electrophysiological diagnostic tool, with a classical pattern of normal visual EP (VEPs) and abnormal motor EPs, somatosensory EP (SEPs), and BAEP[1]. The objective of this work was to evaluate modifications of the multimodal EPs (VEPs, BAEPs and SEPs) in a sample of pediatric X-ALD patients in a long-term follow-up, in order to verify how the EPs abnormalities correlate with the clinical course of the disease and if they modify after Hematopoietic Stem Cell Transplantation (HSCT), the main therapeutic option in these patients.
Material and methods. VEPs, SEPs and BAEPs were analyzed in 15 X-ALD patients with a genetically confirmed diagnosis (age 4-13 years, mean 7,4) for 3 or more years, with EPs performed at least once per year. The mean latency of the P100 components of the VEPs, the mean duration of the I-V inter-peak interval of the BAEPs and the mean central conduction times of the SEPs were analyzed both for the asymptomatic patients (5) and for the patients who developed neurological signs (10). Moreover, in a subgroup of 7 symptomatic patients who underwent HSCT, we verified the evolution of the EPs after the HSCT.
Results. we observed that there was a difference of the EPs parameters considered among the clinically asymptomatic and symptomatic patients; in the latter there was an increase of the duration of central conduction times higher than the average + 3 SD of the reference norm of our laboratory for the SEPs, of the latency of P100 for the VEPs and of the duration of I-V interval for the BAEPs in 9/10, 2/10 and 4/10 patients, respectively. In 5/7 patients of the subgroup who underwent HSCT, EPs parameters stabilized (I.e. there was not a further worsening) in the range of 6 months-one year after HSCT.
Discussion/Conclusions: we demonstrated that a long-term follow-up of the EPs may underline differences among symptomatic and asymptomatic X-ALD children; in symptomatic X-ALD EPs could help in the early diagnosis and in the management of therapeutic strategy, probably for the determination of the correct timing of the HSCT[2]. Our data suggest that treatment with HSCT may stop the progression of the neurophysiological signs of the disease, unlike other therapies[3].
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Utility of pre-operative electroneuromyography and nerve ultrasound study in a complex case of neurofibromatosis type I

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Background. A 49 year old woman affected by Neurofibromatosis type I, who underwent a first surgery in 2011 for partial resection of a left cervico-thoracic C7-T1 neurofibroma, was admitted to our Neurosurgery Department in 2018. Clinical examination evidenced left arm mild weakness and progressive atrophy associated to paresthesia in left hand, with impairment of C8 root-innervated muscles. MRI showed a volumetric increase of the previous lesion.
Methods. In order to reduce C8 root compression, in January 2019 the patient underwent a C7-T1 laminectomy aided by Intraoperative Neurophysiological Monitoring (IONM) and mapping. ENG/EMG was performed two days after surgery and one month later follow up examination was completed with brachial plexus and nerve high resolution ultrasound (HRSU) study.
Results. No MEPs and SSEPs changes were detected throughout the surgery and no spontaneous activity or others pathological patterns on free-running EMG recording were observed. Mapping of C8 root in the intra- and extra-foraminal portion did not evoke any muscle response, despite the use of high stimulation intensities (up to 10 mA) and the combination of both monopolar and bipolar concentric probes. ENG/EMG findings demonstrated chronic denervation of C7-C8-T1 roots, a slight left carpal tunnel syndrome (CTS), associated ulnar neuropathy

with partial motor block at the elbow and reduction of V digit sensory action potentials (SAP) amplitude.
Nerve HRSU study confirmed the suspect of CTS. Moreover, it showed the presence of multiple neurofibromas along the nerves: one on median nerve at the distal third of the forearm, one on radial nerve at the distal third of the arm and the biggest one (4-5 cm) along ulnar nerve at the medial-distal third of the arm, proximal to the elbow. Plexus HRSU study evidenced an upper dislocation of C5-C6-C7 roots, while C8 root was not recognizable.
Discussion. IONM data suggested that C8 root functional integrity may have been compromised after the first surgery. Accordingly, left hand atrophy may have been caused by the presence of median and ulnar neurofibromas as evidenced by nerve HRSU study.
Conclusions. In complex clinical conditions (as Neurofibromatosis type I), motor impairment may occur after damage of root, plexus or peripheral nerve. As MRI and clinical presentation alone may be insufficient to disentangle the underlying pathophysiology, ENG/EMG combined with nerve and plexus HRSU study should be indicated to tailor the best surgical treatment.

Effect of Painful Invasive Procedures in Neonatal Intensive Care on the Maturation of Evoked Potentials, EEG and SSR on Preterm Infants: Preliminary Data

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Backgroud. Highly premature infants require invasive procedures for diagnostic and / or therapeutic purposes during their stay in Neonatal Intensive Care Unit (NICU). This contrasts greatly with the calm and protective environment of the womb, thus exposing these newborns to repeated experiences that are highly stressful and potentially painful (1).
Objective. To find a correlation between invasive pain procedures (frequency and /or type) and Somatosensitive Evident Potentials (PES), Visual (PEV), EEG and Sympathetic-Cutaneous Response (SSR) in strongly preterm infants registered at achievement of the term age.
Methods. To date, we have studied 7 newborns with EG <32 weeks, without neurological damage admitted to the NICU of AOU Careggi (Florence) with the approval of the Ethics Committee.
The protocol provides for the quantification of pain exposure obtained from medical and nursing records, reported in the table as the number and type of invasive procedures (heel / arterial / venous sampling, central / peripheral venous catheter and / or thoracic drainage, intubation, extubation, naso-gastric tube, lumbar puncture, bladder catheter, ocular examination). The duration of the study will be 36 months with evaluation of about 85 newborns and neuro-evolutionary follow-up at 6-12 months. Neurophysiological examinations are recorded at the term age of a multi-modal system: polygraphic VEEG and PESS simultaneously, SSR with electrical stimulation and light-stimulated PEV with goggles-LED.
Results. the preliminary data collected from the 7 registered preterm infants showed the EEG cycle of sleep-wake rhythm not respected, evoked PES with increased latency and reduced amplitude, PEV with immature morphology, SSR response present and persistent, compared to healthy term control group (20 newborns).
Discussion and Conclusions. recent studies have shown that greater exposure to pain in preterm newborns is associated with reduction in the volume of frontal and parietal lobes, altered diffusion and functional connectivity in temporal lobes, abnormal pattern of movements and reduced maturation of White and Gray Subcortical Matter at the term age (2.3).
At the moment our preliminary data do not allow a conclusion for the small number of subjects studied, but a first observation seems to agree with the hypothesis of literature.

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Electrical and acoustic SSR in pediatric age: preliminary data in a healthy population

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Background. The sympathetic skin response (SSR: sympathetic skin response) is a specific neurophysiological tool for clinical assessment of sudomotor function of the sympathetic branch of the autonomic nervous system[1,2]. In some pediatric diseases, SNA can be implicated and altered and the SSR can be a valuable tool for its assessment, as it is easy for children to perform. The literature is lacking of normative data concerning SSR in pediatric age. Toyokura (2012)[3] showed a congruence between the various SSR responses in adult individuals subjected to three different stimuli: acoustic, electrical, and magnetic, and hypothesized that, in an individual, endogenous factors strongly conditioned the development of the SSR.
Objective. The study collects preliminary normative data of the SSR in a healthy pediatric population (14 children, 6 m average age 10aa, 6 infants, average age 2 months) applying two types of stimulation, one electric and one acoustic, evaluating the latency and amplitude of the obtained responses. Verify the existence of a consistency of the responses evoked by different intra-subject stimulation.
Method. Recording performed from monolateral palm hand-plant foot, applying first the electrical stimulus to the median nerve distally at an intensity between 10-25 mA and then the acoustic one at 110 dBL, through the cap,both delivered by surprise. Descriptive statistical analysis with measurement of mean, minimum, maximum, standard deviation, lower and upper reference limit for amplitude and latency parameters. Parametric statistics, through the parametric T-student test for paired data.
Results. The results confirm a replicability of the intra-subject response. The values of children were: by electrical stimulation 4.3±2,5uV-1311.3±214.5ms (hand), 2.1±1.3uV-1803.3±200.7ms(foot); by acoustic stimulation 4.2 ±2.5uV-1169.1±220.2ms (hand), 1.6±1.0uV-1616.3± 248.4(foot). The values of neonates were:4.4±6.4uV-876.6±130.5ms(hand), 3.4±3.8uV-1353.3 ±136.5ms(foot) by electrical stimulation;1.4±2,8uV-717±258ms (hand), 1.2 ±2,0uV-999.7±50ms (foot) by acoustic stimulation. The appearance, the morphology of the response (amplitude /latency) and the comparisons that were made in the same subject responding to two different stimulations did not reveal discrepancies /divergences.
Discussion/conclusion. It is possible to conclude that there is a coherence in the SSR intra-subject response obtained with different types of stimulation. Our study is probably among the firsts to analyze the SSR and its responses to different stimulations in the pediatric field. We also considered the endogenous factors that affect the variability that characterizes this response to further complicating the result, however, our preliminary data (small number of subjects) for the obtainable replicability of the answers can be useful from the clinical point of view.

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Multimodal evoked potentials (EPs) in adult hypomyelinating leukodystrophies (HLDs)

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Rationale. Adult HLDs are characterized by defective central nervous system (CNS) myelin formation, and evoked potentials (EPs) are useful for studying the central pathway conduction (CC). The aim of this study was to characterize CNS involvement in adult HLDs by evaluating multimodal EPs.
Methods and Patients. The study involved 22 patients (M:F ratio 10:12; mean age 38, range 19-55) whose brain MRI findings (mild diffuse T2 hyperintensity and a near-normal T1 signal) were consistent with central hypomyelination. All were affected by lower limb spasticity and mild cognitive impairment; the causative gene was known in 19 cases. Pattern reversal visual (VEPs), auditory brainstem (BAEPs), median nerve (mSEP) and tibialis posterior somatosensory EPs (tpSEPs) were assessed using standard methods, and electroretinograms (ERGs) were recorded. EP latencies, amplitudes and CC times (CCTs) were parametrically analyzed, and scored on the basis of the severity of the neurophysiological alterations.
Results. The patients all had moderately or severely altered mSEPs, BAEPs and tpSEPs characterized by increased latency, reduced amplitude, and increased CCTs. BAEPs and tpSEPs were the most severely altered (no cortical responses in four patients) and had the highest CNS involvement scores. VEPs were normal in two patients, slightly abnormal in one, and markedly altered (increased latency and reduced amplitude) in 19. ERGs were abnormal in three cases.
Conclusions. EPs sensitively detect abnormal CC in adult HLD patients, with particularly lower limb SEPs and BAEPs revealing slowed multisystem, systemic conduction. This highly suggests central hypomyelination and can support the timely identification of currently under-detected HLDs.

Different cortical excitability profile in hereditary brain iron and copper accumulation

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Objective. Neurodegeneration with brain iron accumulation (NBI) and Wilson's disease (WD) are considered the prototype of neurodegenerative disorders characterized by the overloading of iron and copper in the central nervous system. Growing evidence has unveiled the involvement of these metals in brain cortical neurotransmission.[1] Aim of this study was to assess cortical excitability profile due to copper and iron overload.
Material and methods. Three patients affected by NBI, namely two patients with a recessive hereditary parkinsonism (PARK9) and one patient with aceruloplasminemia and 10 patients with neurological WD underwent transcranial magnetic stimulation (TMS) protocols to assess cortical excitability[2]. Specifically, we evaluated the motor thresholds that represents the ease of activation of motor cortex via glutamaergic networks, and ad hoc TMS protocols to probe inhibitory-GABAergic (short interval intracortical inhibition, SICI; short-latency afferent inhibition, SAI; cortical silent period, CSP) and excitatory intracortical circuitry (intracortical facilitation, ICF).
Results. Patients with NBI exhibited an abnormal prolongation of CSP respect to HC and WD patients. On the contrary neurological WD displayed higher motor thresholds and reduced CSP and SICI.
Discussion. hereditary conditions due to overload of copper and iron exhibited peculiar cortical excitability profile that can help during differential diagnosis between these two conditions. Moreover, such results can give us more clues about the role of metals in acquired neurodegenerative disorders, such as Parkinson disease, Alzheimer disease and multiple sclerosis.
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Neurocognitive impairment in patients with chronic hepatitis C: qEEG changes after direct antiviral agents therapy

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Objective. Neurocognitive impairment in patients with Hepatis C virus (HCV) infection maybe related to the infection per se or to the liver disease and hepatic encephalopathy. Neuropsychological tests and quantitative EEG (qEEG) are sensitive measures of early cognitive impairment. To test the hypothesis that the infection may cause some degree of cognitive impairment, we assessed the neurocognitive profile and qEEG changes in patients with chronic HCV before and 3 months after the novel eradicating therapy with direct-acting antiviral agents (DAA), with no evidence of progression of liver disease.
Material and methods. We studied 10 adults with chronic HCV undergoing DAA therapy. Ten normal subjects of similar age and sex acted as controls (HC). EEG and neurocognitive tests were performed at baseline and 3 months after the end of the treatment. EEG data were analyzed offline and the Fast Fourier Transform was used to compute the relative power of delta, theta, alfa and beta frequencies. Repeated measures ANOVA was applied for statistical analysis.
Results. A significant improvement was observed in several cognitive fields, including logic thinking ($p<0.001$) and executive functions ($p=0.001$). Delta relative power in frontal electrodes was significantly lower after DAA therapy in patients compared to HC ($p<0.05$).
Conclusions. The novel eradicating therapy appears to induce early improvement of various cognitive domains and reduce the frontal delta frequency. QEEG can be an objective tool for assessing early cognitive changes in patients with HCV after virus eradication.

Neurophysiological intraoperative modifications in "Concorde" prone position during spine surgery

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Objective. The prone position in spine surgery is very often pivotal for optimal operating surgery conditions and operative-site exposure but patients are placed in positions that may lead to complications. Prevention of peripheral neuropathies is part of the larger process of perioperative care in spine surgery patient. Brachial plexus hyperextension is a

complication which may be related to patient's prone position during spine surgery with the result of a functional loss and disability.
Material and methods. In the last 2 years 59 patients underwent spine procedures with IOM to avoid neurosurgical injury: SEPs (Median and Tibial nerves), MEPs (ADM, ECD, deltoid, TA and AH muscles), EEG and EMG activity were attempted in all patients. TIVA-TCI anesthesia was used. Usually, for cervical spine surgery, the patient is in the "Concorde" position, a variation of the prone one where arms are placed and fixed alongside to the trunk.
Results. In three cases we recorded significant transient alterations of IOM due to the position of the patient: in two cases of posterior arthrodesis C4-C6 with an important decrease in amplitude of cortical SEPs only from both upper limbs (and MEP from ADM in one case) that slowly returned at normality after modifying patients shoulder position, and in a case of D2-D3 neurinoma we attended a rapid decrease of cortical SEPs from right Median nerve which solved changing arm position.
Discussion/Conclusions. It is important for spine surgeon to be aware of arm and shoulder position, especially when the Concorde position is used, to avoid the occurrence of brachial plexus injury.

Nerves conduction study in pediatric patients with Chemotherapy induced peripheral neuropathy

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Objective. Chemotherapy induced peripheral neuropathy (CIPN) is a very common Chemotherapy side effect and sometimes it can compromises treatment efficacy, due to request of dose reduction or discontinuation. Neurophysiologic tests can enable early detection of neurotoxic chemotherapy agents. A relevant aim is to compare new drugs side effects with those caused by old meds (such as Vincristine), studying in particular the CIPN type and its incidence.
Material and methods. We used Nerves conduction study (NCS) techniques to monitor and detect neuropathy during and after Chemotherapy. Children hospitalized in Oncology ward in the last 2 years, were sent to Neurophysiology Department because they reported peripheral motor or sensory disorders. We calculated how many of those cancer patients had diagnosis of CIPN, and we analyzed which Neuropathy type they referred and their incidence.
Results. Most of cancer patients reporting peripheral symptoms, had diagnosis of CIPN. Manifestation of neuropathy can be motor, sensory or autonomic and this is associated also with chemotherapy drug type. Lower limbs seem to be more affected than upper limbs.
Discussion/Conclusions. Unfortunately, new Chemotherapy drugs caused CIPN anyway, equally to the old ones; sometimes they give patients even worse symptoms. However, children with CIPN have a favorable outcome with most showing electrophysiological improvement after chemotherapy completion, but it is still very important to monitor their peripheral nerves conduction to understand, through the test results severity consideration, if they can have an amelioration in the future.

Effects of prolonged anodal transcranial direct current stimulation on motor cortex excitability

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Background and objective. Transcranial direct current stimulation (tDCS) is a promising tool for neuromodulation. Anodal tDCS has shown differential effects on motor cortex excitability depending on stimulation parameters. Furthermore, the safety of repeated stimulations has not been systematically studied. The aim of this study was to evaluate the safety (assessed by clinical evaluation and brain MRI) and the effects on motor cortex excitability (assessed by motor evoked potentials (MEPs) amplitude) of an intensive protocol of anodal- tDCS.
Methods. 26 healthy subjects (14 females, age 25.7 ± 6.1 years) were recruited. 5 anodal-tDCS sessions, of 15 min each, were performed in 24 h with a constant-current. Stimulation parameters: intensity 2mA, electrodes size: 7x10cm; electrodes location: anode over first dorsal interosseous (FDI) hotspot of the dominant hemisphere; cathode on the ipsilateral shoulder. 20 MEPs were recorded from the FDI contralateral to the stimulated hemisphere at 8 time points and MEP amplitude over time analyzed by ANOVA (groups: responders, non/inverse responders). Brain MRI (FLAIR, SWI and DWI sequences) were acquired using a 3 Tesla scanner (8 subjects, 3 time points) and examined by visual inspection.
Results. Safety: No serious adverse effects occurred. Tingling or burning sensation were reported by all subjects under the cephalic electrode. MRI visual inspection did not reveal signal abnormalities. EFFECTS on motor cortex excitability: the amplitude of the MEPs evoked from the stimulated hemisphere, evaluated at 1h after the first stimulation session, increased in 50% of the subjects ("responders"), decreased in 15% ("inverse responders") and did not change significantly in 35% of the subjects ("non-responders").
Discussion and conclusion. The intensive protocol of anodal tDCS resulted safe. Its effects on cortical excitability were highly variable across subjects, while intra-individual effects were more consistent, suggesting that a single tDCS session might be used to assess individual response.

The effect of painful laser stimuli on gamma-band activity in migraine patients and healthy controls

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Background. Several study have demonstrated that brief painful stimuli induce gamma-band oscillations (GBO) in somatosensory cortex, which likely reflect the local processing of sensory information and subjective pain perception. However, there is still debate about the relevance of GBO in pain processing.
Objective. In this study we investigated whether and when increased GBO can be found after painful laser stimulation and whether this differs between migraine patients and healthy subjects.
Matherial and Methods. We recorded laser evoked potentials (LEPs) in 62 migraine patients without aura and 39 healthy controls by stimulating the right handback and the right forehead. Subjective pain was rated on a visual pain analogue scale (VAS). Time-frequency analysis was performed with both the complex Morlet wavelet convolution method (MW) and the Multitaper method (MT). The data were converted to decibel change from baseline after averaging trials. As baseline we considered the time between 2 and 1s before laser onset to avoid expectation reactions.
Results. Relevant perturbations on fronto-central regions were found on the midline in migraine. In controls subjects, the GBO perturbation seems reduced with all methods. We have found similar but attenuated pattern of GBO activation for the hand stimulation in migraine and in controls. We did not found significant differences in GBO between migraine and controls for both the hand and forehead stimulation. The GBO perturbation seems to have a spatial distribution coherent with a cortical not muscular source. We found a correlation between GBO and the subjective pain

intensities for both the hand and forehead stimulation only in controls. In migraine, GBO by hand stimulation was a correlate of anxiety, depression and allodynia, but not of attack frequency, while GBO by forehead stimulation was a correlate of pain catastrophizing.
Discussion/Conclusions. The definition that GBO reflects the activity of cortical regions subtending cognitive aspects of pain sounds good in light of present results. The methodological approach with multitaper not laplacian filter seems reliable to detect GBO perturbation. In migraine, cortical generators of GBO may be involved in mechanisms of central sensitization, as suggested by the correlation between GBO perturbation and anxiety, depression and allodynia. This would be an intrinsic pattern of allodynic migraine, possibly predisposing to chronic evolution. Laser induced GBOs in migraine are a reliable measure of aspects of pain processing. They are not a simple correlate of laser pain perception. They could explain something more about electrophysiological correlates of central sensitization and facilitating factors.

Intraoperative neurophysiological monitoring in spine surgery: our experience

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Background and Objectives. Although there is recent evidence for the role of intraoperative neurophysiological monitoring (IONM) in spine surgery, there are no uniform opinions on the optimal combination of the different tools. We analyzed the impact of the mIONM on the preservation of neuronal structures and on functional restoration in a prospective series of our patients who underwent spine surgery.
Methods. Multimodal IONM (mIONM) approach in spine surgery involves the evaluation of somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs) with electrical transcranial stimulation, including the use of a multipulse technique with multiple myomeric registration of responses from limbs, and a single-pulse technique with D-wave registration through epi- and intradural recording, and free running and evoked electromyography.
Results. We observed an improvement of neurological status in 50% of the patients. The D-wave registration was the most useful intraoperative tool, especially when MEP and SEP responses were absent or poorly recordable.
Conclusions. Our data confirm that mIONM plays a fundamental role in the identification and functional preservation of the spinal cord and nerve roots. It is highly sensitive and specific for detecting and avoiding neurological injury during spine surgery and represents a helpful tool for achieving optimal postoperative functional outcome.
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Monitoring Neuronal Damages in Multiple Sclerosis with Multi-focal Visual-Evoked Potential and Optical Coherence Tomography: a Case Report

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Background. Multiple sclerosis(MS) is a chronic inflammation disease, which often affects the visual system. Due to its highly topological arrangement, any insult within it can lead to neurodegeneration of the pathway in corresponding areas. The damages can be detected with non-invasive techniques such as multi-focal visual evoked potential(mfVEP) and optical coherence tomography(OCT). Demyelination resulted in delayed latency in mfVEP, while neurodegeneration causes reduced amplitude of mfVEP, also atrophy of retinal nerve fiber layer(RNFL) and ganglion cell layer(GCL) of OCT. Here we present a clinical case with a retrochiasmatic lesion to demonstrate the diagnosis potential of this combination.
Methods. A 21-years-old female with MS suffered with right homonymous hemianopia(HH), 3 months after steroid treatment the symptoms ceased and she underwent mfVEP and OCT in our institute. The mfVEP was employed with Visionsearch1 system with four electrodes placed around Inion and a reference electrode on forehead. The recorded signals then assorted with Fourier transform and the signal of each sector was extracted, resulted in 56 sectors with its unique VEP waveform. Amplitude and latency of P100 of each VEP was quantified for further comparison. The OCT scan was performed with Heidelberg Spectralis, the protocol consisted with 20 degree macula volume scan and 12 degree peripapillary circular scan. The images were further segmented and quantified as the thickness of RNFL and GCL.
Results. Multi-focal VEP showed prolonged latency and reduced amplitude of the temporal field of the right eye and of the nasal field of the left eye(especially the upper visual field), which consistent with the right HH. Furthermore, these area showed corresponding atrophy of GCL in Macula OCT. Interestingly, owing the projection pattern of the ganglion cell from macula to optic nerve head, only right temporal RNFL showed significant atrophy, while left temporal RNFL only revealed a borderline atrophy. Combining mfVEP and OCT results suggested retrochiasmatic lesion on left side, possibly on optic radiation.
Discussion and Conclusion. The patient later underwent magnetic resonance imaging(MRI) and confirmed an inflammatory lesion on left temporal-hippocampal area with ring-enhancement, which may result in the trans-synaptic atrophy of GCL under OCT, and the reduced amplitude of hemi-upper visual field in mfVEP. Further, the latency delay in mfVEP suggests inflammatory demyelination. Noteworthy, unlike mfVEP, the latency of traditional full-field VEP was normal since it was unable to detect sub-field deficits. Our results demonstrate the diagnostic potential of combining mfVEP and OCT in monitoring neuronal damage in MS.

Motor evoked potential: normal values of the central motor conduction time (CMCT) calculated with direct and indirect method

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Objective. The purposes of this study were to obtain reference values for CMCT calculated using both a direct ($CMCT^d$) as well as an indirect ($CMCT^i$) method.

Material and methods. Normative data were obtained from 29 healthy young volunteers, aged 20 to 55 years. MEPs were elicited with a MagPro Compact stimulating circular coil positioned over the primary motor cortex. Evoked responses were recorded by surface EMG electrodes from the abductor digiti minimi (ADM), tibialis anterior (TA) and abductor halluces (AH) muscles contralateral to the site of TMS. In all the subjects motor responses to magnetic cortical stimulation were always obtained with slight voluntary contraction of the target muscles. Limits of norm were calculated both by mean + 2.5 SD and 95° percentiles.

Results. In the ADM muscle the upper limit of norm of $CMCT^d$ and $CMCT^i$ as defined by the 95° percentile is: $CMCT^d$ - 6.7 ms, $CMCT^i$ - 6.2 ms; in the TA muscle the upper limit of norm of $CMCT^d$ is 15.4 ms, while $CMCT^i$ is 13.3 ms; in the AH muscle the upper limit of norm of $CMCT^d$ is 17.3 ms, while $CMCT^i$ is 15.2 ms.

Conclusions. When the motor cortex is activated with transcranial magnetic stimulation (TMS), the time taken for stimuli to reach the spinal motor-neurons (Central motor conduction time; CMCT) can be calculated by subtracting the latency obtained by cervical or lumbar stimulation from the latency obtained by transcranial stimulation, but this method includes the synaptic delay in the spinal cord and the conduction time of the stimulus from the proximal root to the intervertebral foramen. It is therefore more accurate to derive CMCT from F-wave latency, using the formula CMCT = MEP latency – (F + M – 1/2). We have provided clinically useful reference values for CMCT in healthy subjects. The CMCT is the most important MEP parameter in clinical practice. However, each laboratory needs to establish its own normative data set for reliable diagnostic testing in clinical practice. We prefer to use the direct method because it is less painful and requires less time than the F-wave method. In addition, the F-wave method is only applicable for certain muscles in which F-waves is recordable, such as for distal muscles in hand and foot. However, the indirect method would be useful in patients where magnetic spinal root stimulation cannot be applied.

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