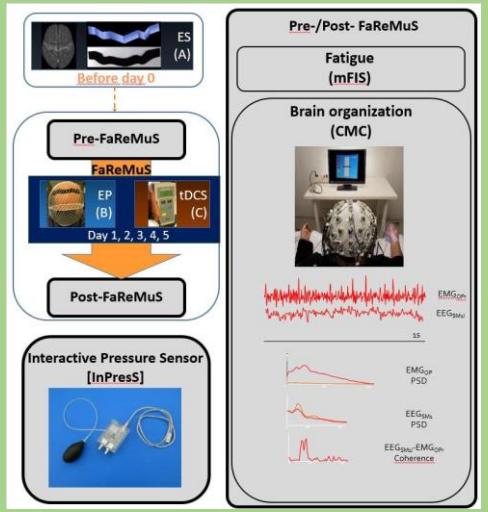
Effects on motor control of personalized neuromodulation against multiple sclerosis fatigue

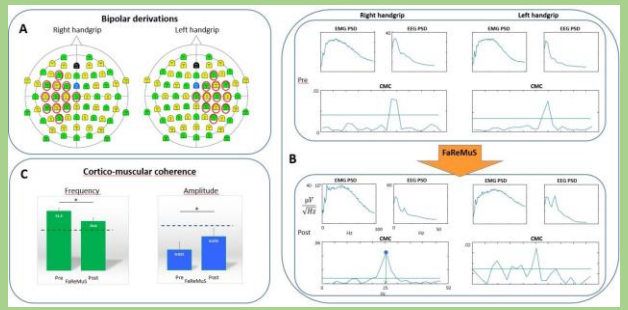
Matteo Padalino, Carla Scardino, Giancarlo Zito, Andrea Cancelli, Carlo Cottone, Massimo Bertoli, Eugenia Gianni, Teresa L'Abbate, Elisabetta Trombetta, Camillo Porcaro, Fabiano Bini, Franco Marinozzi, Maria Maddalena Filippi, Franca Tecchio

Background: Two randomized controlled trials (RCTs) showed that the personalized neuromodulation called Fatigue Relief in Multiple Sclerosis (FaReMuS) efficaciously fights multiple sclerosis (MS) fatigue. By this Proof of Concept study, we tested whether FaReMuS reverts the alteration of the central-peripheral synchronization previously observed occurring with fatigue.

Methods: The cortico-muscular coherence (CMC) was studied in 11 patients before and after FaReMuS, a 5-day anodal transcranial direct current stimulation (1.5 mA, 15 min per day) over the whole body somatosensory representation (S1) via a personalized MRI-based electrode (35 cm2) with occipital cathode (70 cm2).



Study design and electrophysiological exam and variables
Experimental procedure in each person with MS undergoing FaReMuS. **Left Top**: Individual brain MRI-based personalized electrode shaping (ES, A) performed once for each person with MS. After the data collection (Pre-FaReMuS), the electrode positioning (EP, B) is executed for each tDCS stimulation (C) repeated for 5 days of treatment. In the day of the last tDCS, we performed the data collection (Post-FaReMuS). **Right from top**: The data collection (Pre- and Post-FaReMuS) includes the fatigue level assessment via mFIS and the EEG, EMG for the brain effects. The *in-house* developed Interactive Pressure Sensor (InPresS, **Left bottom**) provided the visual feedback on the exerted pressure. One second windowed signal of EMG from right opponens pollicis muscle (EMGOPr) and from bipolar derivation selected as maximally coherent with contralateral EMG activity (EEGSM1) during contraction. In the successive rows, power spectral density (PSD) function of frequency in resting periods (orange) and during movement (red) in the [1-100] Hz frequency range for EMGOP and [1-50] Hz for EEGSM1 (ordinate scales are fixed across the two conditions) and the coherence function between EEGSM1 and EMGOPr.



Cortical and muscular activities and their coherence with FaReMuS
A: indication of the channels considered to identify the bipolar derivation with maximal corticomuscularcoherence (CMC). **B**: For a representative patient, before and after FaReMuS, the power spectral density function (PSD) of opponens pollicis EMG and of the EEG bipolar derivation with maximal CMC and the CMC (horizontal line indicating significance level) when moving the right and left hand. Each variable is represented as function of frequency. Scales are fixed across hemi-body for corresponding variable unless differently indicated. CMC is a dimensionless number. Note the different scales in frequency (EMG PSD 0-300 Hz, EEG PSD and CMC 0-50 Hz) and amplitude (40 mV/sqrt(Hz) for EMG PSD, 40 μV/sqrt(Hz) for EEG PSD. In the left bottom CMC (Post-FaReMuS, right handgrip), we represented the amplitude (blue dot) and frequency (green arrow) parameters, that is frequency and amplitude of the maximum CMC, submitted to population analysis. **C**: Population results of CMC frequency and amplitude Pre and Post-FaReMuS, the horizontal dashed line is the value in healthy controls: CMC features altered before FaReMuS normalized after the treatment.

Results: Before FaReMuS, the CMC was observed at a mean frequency of 31.5 ± 1.6 Hz (gammaband) and positively correlated with the level of fatigue ($p = .027$). After FaReMuS the rate of fatigue reduction was 28% ± 33% estimated as (post-pre) / pre modified Fatigue Impact scale (mFIS) score and the CMC frequency reduced to 26.6 ± 1.5 Hz ($p = .022$), thus forthcoming the physiological beta band as observed in healthy people.

Conclusions: The personalized neuromodulation treatment targeting S1 was able to ameliorate the central-peripheral communication, which subtends simple everyday movements. The sensorimotor feedback ameliorated by targeting S1 strengthens the appropriateness of neuromodulations aiming at increasing the parietal excitability in fighting MS fatigue.