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# Simple index of functional connectivity at rest in Multiple Sclerosis fatigue

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## HIGHLIGHTS

- EEG-based functional connectivity at rest (FCR) was tested in Multiple Sclerosis (MS) patients with fatigue.
- Beta temporo-parietal FCR was higher in fatigued MS patients than controls.
- MS fatigue severity correlated directly with beta temporo-parietal FCR.

## ABSTRACT

*Objective:* To investigate the EEG-derived functional connectivity at rest (FCR) patterns of fatigued Multiple Sclerosis (MS) patients in order to find good parameters for a future EEG-Neurofeedback intervention to reduce their fatigue symptoms.
*Methods:* We evaluated FCR between hemispheric homologous areas, via spectral coherence between pairs of corresponding left and right bipolar derivations, in the Theta, Alpha and Beta bands. We estimated FCR in 18 MS patients with different levels of fatigue and minimal clinical severity and in 11 age and gender matched healthy controls. We used correlation analysis to assess the relationship between the fatigue scores and the FCR values differing between fatigued MS patients and controls.
*Results:* Among FCR values differing between fatigued MS patients and controls, fatigue symptoms increased with higher Beta temporo-parietal FCR ($p = 0.00004$). Also, positive correlations were found between the fatigue levels and the fronto-frontal FCR in Beta and Theta bands ($p = 0.0002$ and $p = 0.001$ respectively).
*Conclusion:* We propose that a future EEG-Neurofeedback system against MS fatigue would train patients to decrease voluntarily the beta coherence between the homologous temporo-parietal areas.
*Significance:* We extracted a feature for building an EEG-Neurofeedback system against fatigue in MS.

## 1. Introduction

Primary fatigue is among the most common and debilitating symptoms of Multiple Sclerosis (MS), reported by up to 90% of the patients at some point in the disease course and considered to be one of the main causes of impaired quality of life (Braley and Chervin, 2010; Strober, 2015). Fatigue is defined as either lack of physical and/or mental energy that is experienced by the individual to interfere with usual or desired activities (Tur, 2016). Primary fatigue is not directly related with the physical activity and may be present even after a restful night's sleep (Shen et al., 2006).

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Although the etiology of primary fatigue in MS is not yet fully understood, there is growing evidence that alterations of the sensorimotor system at cortical and subcortical levels might be contributing to its development (Kos et al., 2008; Tomasevic et al., 2013; Zito et al., 2014; Cogliati Dezza et al., 2015).

With the final aim to modify such alterations, we considered brain–computer interfaces (BCIs) as systems enabling the interaction with the brain activity organization (Birbaumer and Cohen, 2007; Tecchio et al., 2007). The variation of BCI called BCI-Neurofeedback translates neuronal signals into proper sensory inputs provided to the user. BCI-Neurofeedback may contribute to patients' experience of self-efficacy, defined as the extent or strength of one's belief in one's own ability to complete tasks and reach goals. Self-efficacy *per se* is an important therapeutic factor (Linden, 2014) and may improve everyday life conditions thank to the generalizability of the gained brain regulation ability.

The most common neuroimaging method used for the neurofeedback is electroencephalography (EEG) (Rogala et al., 2016) due to its high temporal resolution ($\sim$1 ms) that is useful to provide continuous feedback to the subjects, its favorable cost/efficiency ratio and its mobility that makes the system accessible for home treatments.

To date, several EEG features (e.g. mu rhythm, slow cortical potentials, spectral power ratios between different frequencies) have been used as a target for EEG-Neurofeedback (Huster et al., 2014). More recently, coherence that estimates the degree of similarity between two signals in the frequency domain (Guevara et al., 2011) and considered as an indicator of neuronal functional connectivity (Montplaisir et al., 1990; Koeda et al., 1995; Cantero et al., 1999; Nolte et al., 2004; Leocani et al., 2007; Srinivasan et al., 2007; Di Pino et al., 2012; Dubovik et al., 2012; Pellegrino et al., 2012; Tombini et al., 2012; Van Schependom et al., 2014) has been proposed as a target for neurofeedback (Sacchet et al., 2012; Hassan et al., 2015; Mottaz et al., 2015; von Carlowitz-Ghori et al., 2015).

Patients with MS show altered functional intra- and inter-hemispheric connectivity at rest as measured by functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and EEG (Leocani et al., 2000; Lowe et al., 2002; Cover et al., 2006; Sekihara et al., 2011; Hardmeier et al., 2012; Cruz Gomez et al., 2013; Lenne et al., 2013; Tomasevic et al., 2013; Leavitt et al., 2014; Schoonheim et al., 2014; Tecchio et al., 2014; Zito et al., 2014; Cogliati Dezza et al., 2015; Tewarie et al., 2015). In agreement with EEG-Neurofeedback ability to change the functional connectivity and consequent behavior (Sacchet et al., 2012; Ros et al., 2013; Bonavita et al., 2015; Mottaz et al., 2015; Rasova et al., 2015; von Carlowitz-Ghori et al., 2015), our perspective aim is to build an EEG-Neurofeedback system to reduce fatigue by promoting changes in functional connectivity. In previous studies, the cortico-muscular (Tomasevic et al., 2013) and the cortico-cortical (Cogliati Dezza et al., 2015) coherence within the primary somatosensory network was altered in proportion of the fatigue symptoms increase. The aim of the present study is to identify the regions across the whole brain, possibly outside the primary sensorimotor system, whose functional connectivity is mostly involved in MS fatigue. We considered that the dynamic interplay between homologous cortical areas is a critical element for a proper brain functioning either during task execution or even at rest, in which the behavioral performance associates to the functional connectivity across the nodes of the devoted networks (Deco and Corbetta, 2011; Pellegrino et al., 2012; Cogliati Dezza et al., 2015). Thus, here we focused on the functional connectivity at rest (FCR) between homologous brain cortices.

To understand further the degree of impairment of the system functional connectivity in MS fatigue, we will compare patient data with those of age and gender matched healthy controls. Considering the chronic nature of MS fatigue, we are especially interested in characterizing the EEG-derived functional connectivity at rest (Nolte et al., 2004; Sekihara et al., 2011; Van Schependom et al., 2014; Hassan et al., 2015; Mottaz et al., 2015).

## 2. Methods

### 2.1. Participants

The Ethics Committee of the Fatebenefratelli Hospital approved the present study, performed in accordance with the ethical standards noted in the 1964 Declaration of Helsinki. All subjects signed informed consents prior to their inclusion in the study.

Neurologists collected a detailed clinical history, inclusive of ongoing Disease-Modifying Therapy, disease duration and annual relapse rate, Beck Depression Inventory (BDI, (Beck et al., 1996)) and Extended Disability Status Scale (EDSS, (Kurtzke, 1983)).

Fatigue levels were scored using the modified Fatigue Impact Scale (mFIS, (Fisk et al., 1994)). mFIS identifies the physical, cognitive and psychosocial components of fatigue. Inclusion criteria were as follows: minimal to mild clinical severity (EDSS $\leq$ 2); absence of clinical relapse or radiological evidence of disease activity over the last three months. The exclusion criteria were: i. Clinically relevant depression (use of antidepressant) within the past three months; ii. Assumption of symptomatic drugs affecting the fatigue; iii. Epilepsy or other central/peripheral nervous system comorbidities; iv. Any systemic conditions that may cause fatigue (e.g., anemia or pregnancy).

According to Lublin's categories (Lublin et al., 2014), 18 relapsing-remitting (RR) MS patients (12 females; age range 24–47 years, mean = 37, Table 1) were recruited at the MS center of 'San Giovanni Calibita' Fatebenefratelli Hospital (Rome, Italy). A special care was given to enroll patients to have a high variability of fatigue based on the mFIS scores, which ranged between 5 and 52 score. As a control group, 11 healthy people (9 females; age range 28–49 years, mean = 36) were involved. No age and sex difference between the patient and control groups were found (independent samples 2-tailes $t$-test $p = 0.711$ for the age and $p = 0.867$ for the sex).

### 2.2. Electrophysiological recordings

EEG data were recorded by Ag/AgCl electrodes from the standard 19 channels of the 10–20 International system (Fig. 1A). Other Ag–AgCl cup electrodes were used for recording electrooculogram (EOG) and electrocardiogram (ECG) to control eye blinking and cardiac interferences. All signals were recorded using a Micromed System Plus equipped with SAM32 headbox (Micromed s.p.a., Mogliano Veneto, Italy), with a mid-frontal reference and an occipital ground. Electrode impedances were maintained below 5 k$\Omega$. Sampling frequency was set at 1024 Hz (band pass filter 0.48–256 Hz) and data were stored on a computer for off-line processing.

All subjects sat comfortably on a chair in front of a screen with a fixation point. For each subject, at least 4 min eyes-open resting state data were collected.

### 2.3. EEG data pre-processing

EEG data were analyzed offline using BrainVision Analyzer2 software (Brain Products GmbH, Munich, Germany) and with in-house written Matlab scripts (The MathWorks, Natick, MA).

After saturated epoch exclusion by visual inspection, a semiautomatic independent component analysis (ICA)-based procedure was used to identify and remove cardiac and ocular artifacts