Clinical Neurophysiology 128 (2017) 807–813

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Simple index of functional connectivity at rest in Multiple Sclerosis fatigue

Korhan Buyukturkoglu [a,*], Camillo Porcaro [d,e,f], Carlo Cottone [d], Andrea Cancelli [d,g], Matilde Inglese [a,b,c,h], Franca Tecchio [d]

[a] Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[b] Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[c] Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, United States
[d] Laboratory of Electrophysiology for Translational Neuroscience (LET'S)-ISTC, CNR, Rome, Italy
[e] Movement Control and Neuroplasticity Research Group, Department of Kinesiology, KU Leuven, Leuven, Belgium
[f] Department of Information Engineering, Università Politecnica delle Marche, Ancona, Italy
[g] Institute of Neurology, Catholic University of the Sacred Hearth, Rome, Italy
[h] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy

ARTICLE INFO

Article history:
Accepted 14 February 2017
Available online 28 February 2017

Keywords:
Brain computer interfaces (BCI)
Electroencephalography (EEG)
EEG functional connectivity at rest (FCR)
Multiple Sclerosis
MS fatigue
Coherence
Neurofeedback

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).

* Corresponding author at: Hess Building for Science and Medicine, 1470 Madison Avenue 10th Floor, Room 109, New York, NY 10029, United States.
E-mail address: korhan.buyukturkoglu@mssm.edu (K. Buyukturkoglu).

http://dx.doi.org/10.1016/j.clinph.2017.02.010
1388-2457/

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 (~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 ≤ 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 kΩ. 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

Table 1
Multiple sclerosis patient demographic and clinical profile.

	Sex	Age	DMT	Disease duration	Rel	EDSS	mFIS	BDI
Lower fatigue	8F/5M	37.2	9 IFN	5.0	0.6	1	18.6	7
		6.6		*4.0*	*0.8*	*[0.2]*	*8.9*	*[0.11]*
Higher fatigue	4F/1M	37.0	4 IFN	6.1	0.2	1.5	44.4	8
		4.6		*4.3*	*0.4*	*[0.2]*	*4.7*	*[1.12]*
p		0.963		0.652	0.277	0.920	< 0.001	0.611
Whole group	12F/6M	37.1	13 IFN	5.2	0.5	1	25.8	7.5
		5.9		*3.9*	*0.7*	*[0.2]*	*14.2*	*[0.12]*

Abbreviations: DMT, disease-modifying therapy; IFN, Interferon beta; Rel, annual relapse rate; EDSS, Extended Disability Status Scale; mFIS: modified Fatigue Impact Scale; BDI, Beck Depression Inventory; F, female; M, male.
Mean and standard deviations (in *italics*) or median and range (in squared brackets) separately for the patients who complained less (Lower Fatigue, mFIS < 35) or more (Higher Fatigue, mFIS > 35) fatigue and for the whole (last rows). In row "*p*," the significance of intergroup differences in the means or nonparametric test (EDSS, BDI). Notably, the 2 groups differed only on fatigue.

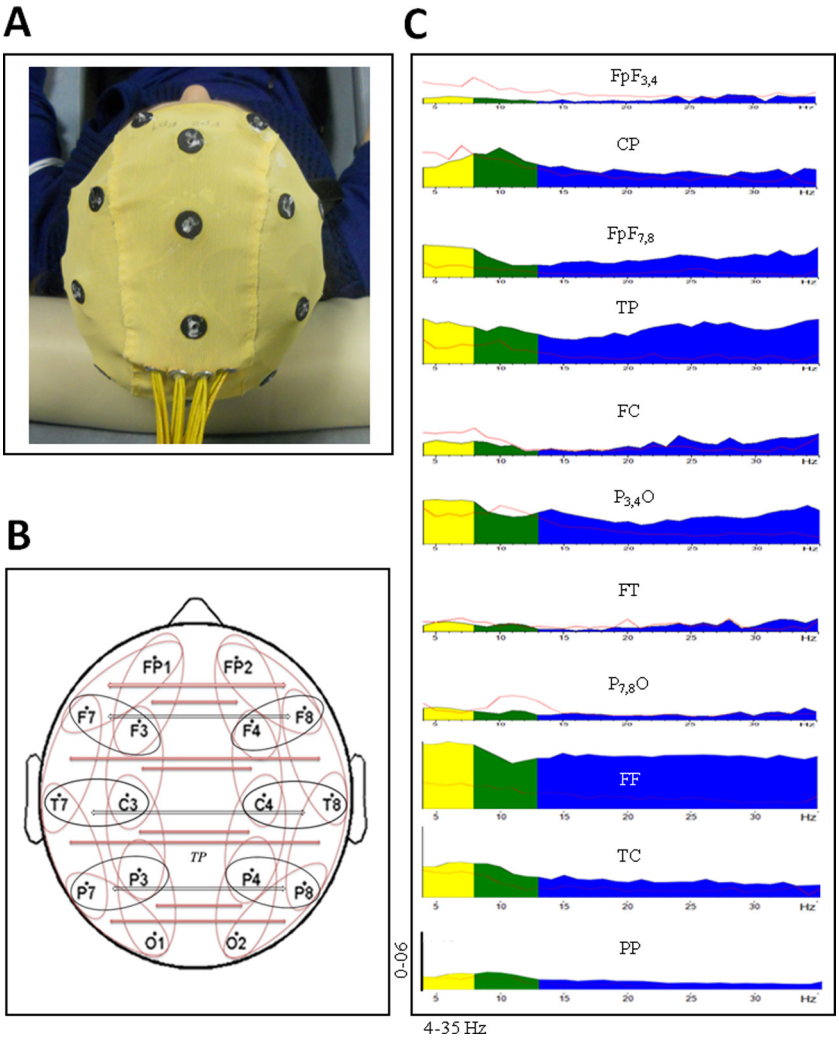

Fig. 1. (A) Electroencephalography (EEG) cap for the 19-channel recordings. (B) Schematic representation of the bipolar derivations used in this study, with double-arrow segments showing the coherence estimated between the 11 homologous cortical areas (8 anterior-posterior, 3 medio-lateral derivations). (C) Coherence values with the indication of the frequency ranges where the coherence is averaged to obtain the band value. Colored areas represent the coherence values averaged across the MS patients for the each frequency band. The red-lines represent the coherence values of the HC. Nomenclature of homologous areas coherence corresponds to section B: for example CP refers to the coherence between the two bipolar derivations C3-P3 in the left hemisphere and the C4-P4 in the right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

without rejecting the contaminated epochs (Barbati et al., 2004; Porcaro et al., 2015).

We fixed the length of the artefact-free signals (3 min) across subjects since coherence estimates depend on the number of averaged epochs.

Since EEG recordings were performed to assess interhemispheric connectivity between the homologous cortical areas, central electrodes (Fz, Cz and PZ) were excluded from the analysis. Bipolar derivations were obtained by subtracting one measured potential from the other.

2.4. Coherence analysis

Considering that EEG-Neurofeedback mostly uses brain activity in frequency bands modulated by active intention, we focused our analysis on the following three frequency bands: Theta (4–8 Hz), Alpha (8–13 Hz) and Beta (13–35 Hz).

BrainVision Analyzer2 was used to compute the coherence using the following equation:

$$Coh_i^{xy} = |PCD_f^{xy}|^2 / PSD_f^x \times PSD_f^y$$

where f is the frequency bin, PCD the power cross spectrum estimated accordingly to the power spectral density (PSD) of the two electrodes (an electrode pair, x and y). The PSD was calculated through a standard Fast Fourier Transform (FFT) approach using Welch technique and a Hanning windowing function (window 1024 ms, no overlap). The Coh_i^{xy} was calculated using a fixed number of 180 averaged trails.

Coherence values between hemispheric homologous areas were calculated via the 11 electrode pairs: Fp1-F3/Fp2-F4, F3-C3/F4-C4, C3-P3/P4-C4, P3-O1/P4-O2, Fp1-F7/Fp2-F8, F7-T7/F8-T8, T7-P7/T8-P8, P7-O1/P8-O2, F7-F3/F8-F4; T7-C3/T8-C4 and P7-P3/P8-P4 (Fig. 1B and C).

2.5. Statistical analysis

The Statistical Package for Social Studies (SPSS v19) was used for statistical analysis (IBM, Armonk, NY).

As the core of our analysis, we studied the relationship between the fatigue scores and the FCR in patients.

Preliminarily, to reduce the number of variables for the correlation analysis and to relate the fatigued MS patients' data with healthy controls' ones, we tested whether some FCR differed from controls, in dependence of the level of fatigue. To this aim, to be more sensitive to fatigue effects, we subdivided in two groups the MS patients using mFIS = 35 as cutoff (Table 1).

Since data distributions differed from a Gaussian, FCR values were analyzed by an analysis of variance on ranks (Kruskal-Wallis H Test) to examine the difference among the healthy control and MS patients suffering for less or more fatigue. We investigated the *Group* (HC, HF, LF) between-subject factor of each brain regions' FRC ($FpF_{3,4}$, CP, $FpF_{7,8}$, TP, FC, $P_{3,4}O$, FT, FF, TC, PP), in the three frequency bands (Theta, Alpha, Beta). Proper post-hoc non-parametric tests (Mann-Whitney U test) were used for comparing single groups when Kruskal-Wallis H test analysis revealed a significant *Group* effect. Because we have 11 comparisons for each band (listed above), we used Bonferroni adjusted alpha significance level at 0.005 per test (0.05/11) for the Kruskal-Wallis H and Mann-Whitney U tests.

Finally, we executed the non-parametric correlation analysis (Spearman's rho) for those FCR values, which the Kruskal–Wallis H Test had indicated different among the groups.

3. Results

Kruskal-Wallis H Test showed significant *Group* effect for FCR between the following pairs of bipolar derivations:

In anterior-posterior direction F7-T7/F8-T8 in Alpha band (Alpha TP; H = 9.049, 2 df., $p = 0.011$ with the mean rank coherence score of 10.18 for HC, 20.23 for LF and 12 for HF), T7-P7/T8-P8 in Beta band (Beta TP; H = 16.379, 2 df., $p = 0.0002$ with the mean rank coherence score of 6.82 for HC, 19.85 for LF and 20.40 for HF) and C3-P3/C4-P4 in Theta band (Theta CP, H = 10.040, 2 df, $p = 0.007$, with the mean rank coherence score of 18.50 for HC, 16.15 for LF and 4.30 for HF). In the medio-lateral bipolar derivations, the *Group* effect was found in the F7-F3/F8-F4 in Beta (H = 20.096, 2 df, $p = 0.00004$ with the mean rank coherence score of 6.27 for HC, 21.85 for LF and 16.40 for HF) and Theta (H = 19.464, 2 df, $p = 0.00005$ with the mean rank coherence score of 6.55 for HC, 21.92 for LF and 15.60 for HF). We represent the data by parametric values in Fig. 2, where the asterisks correspond to the rank analysis *Group* effect.

Post-hoc Mann-Whitney U tests revealed that for anterio-posterior derivations in Beta band between temporo-parietal areas both LF MS ($U = 5$, $p = 0.0001$) and HF MS patients ($U = 4$, $p = 0.005$) had higher coherence than the HC. In Theta band between centro-parietal areas only HF patients showed lower coherence than the HC ($U = 0$, $p = 0.0004$). In medio-lateral direction, post-hoc Mann-Whitney U tests revealed that both LF and HF MS patients have higher coherence values as compared with the HC in all frequency bands between the fronto-frontal electrode pairs (F7-F3/F8-F4, $U = 13$, $p = 0.0002$ in Alpha for the LF vs HC, $U = 2$, $p = 0.000003$ in Beta for the LF vs HC, $U = 1$, $p = 0.001$ for the HF vs HC, $U = 3$, $p = 0.0007$ in Theta for the LF vs HC and $U = 3$, $p = 0.003$ for the HF vs HC).

Considering the coherences differing among groups for the anterior-posterior derivations (Beta TP and Theta CP) in correlation with mFIS scores, a positive correlation was found with the Beta TP ($r(29) = 0.647$, $p = 0.0001$). Since we observed that one patient was an outlier, expressing coherence 0.8, we repeated the correlation analysis excluding that patient and found a correlation with mFIS ($r(28) = 0.620$, $p = 0.00004$, Fig. 3). For the medio-lateral fronto-frontal coherence in Alpha, Beta and Theta, we found a positive correlations with the mFIS scores in Beta and Theta bands (Beta $r(28) = 0.635$, $p = 0.0002$ and Theta $r(28) = 0.573$, $p = 0.001$). We decided to focus the result on the Beta band temporo-parietal FCR not only because the correlation is stronger, but for the reasons detailed in discussion.

4. Discussion

Our main finding is that a future EEG-Neurofeedback system against MS fatigue would train patients to voluntarily decrease beta band coherence between the homologous temporo-parietal cortices. We don't think that we are removing a cause of fatigue; instead we believe that contrasting a brain organization feature, which alters more as the symptom became severer, we can ameliorate this symptom.

Among the EEG-Neurofeedback features that might be selected to be voluntary regulated (Huster et al., 2014), we focused the dynamic interplay between homologous cortical areas because it is critical for the brain networks effective functioning. Rather than the activity in the slow Delta and high Gamma frequency bands, training the subjects to regulate the activity at the Alpha and/or Beta bands might provide better results since these bands are mainly involved in motor processing and might be related more with the fatigue sensation (Cao et al., 2014). Furthermore, during the EEG-Neurofeedback use, the Delta band activity can increase for eye-artifacts, which are especially frequent when the training requires object tracking by eye (e.g., tracking a moving ball image or a graphical thermometer on a screen as a representative of the ongoing brain activity and related neurofeedback).

Our results also revealed that, MS patients show higher FCR between fronto-frontal areas in all frequency bands. However, since the primary aim of this study was extracting EEG features for a future EEG-Neurofeedback study and since frontal EEG activity might be effected by the eye movements during a visual task (e.g. following a digital ball on the screen during a neurofeedback session) we didn't emphasize the activity difference in that area as a neurofeedback system target.

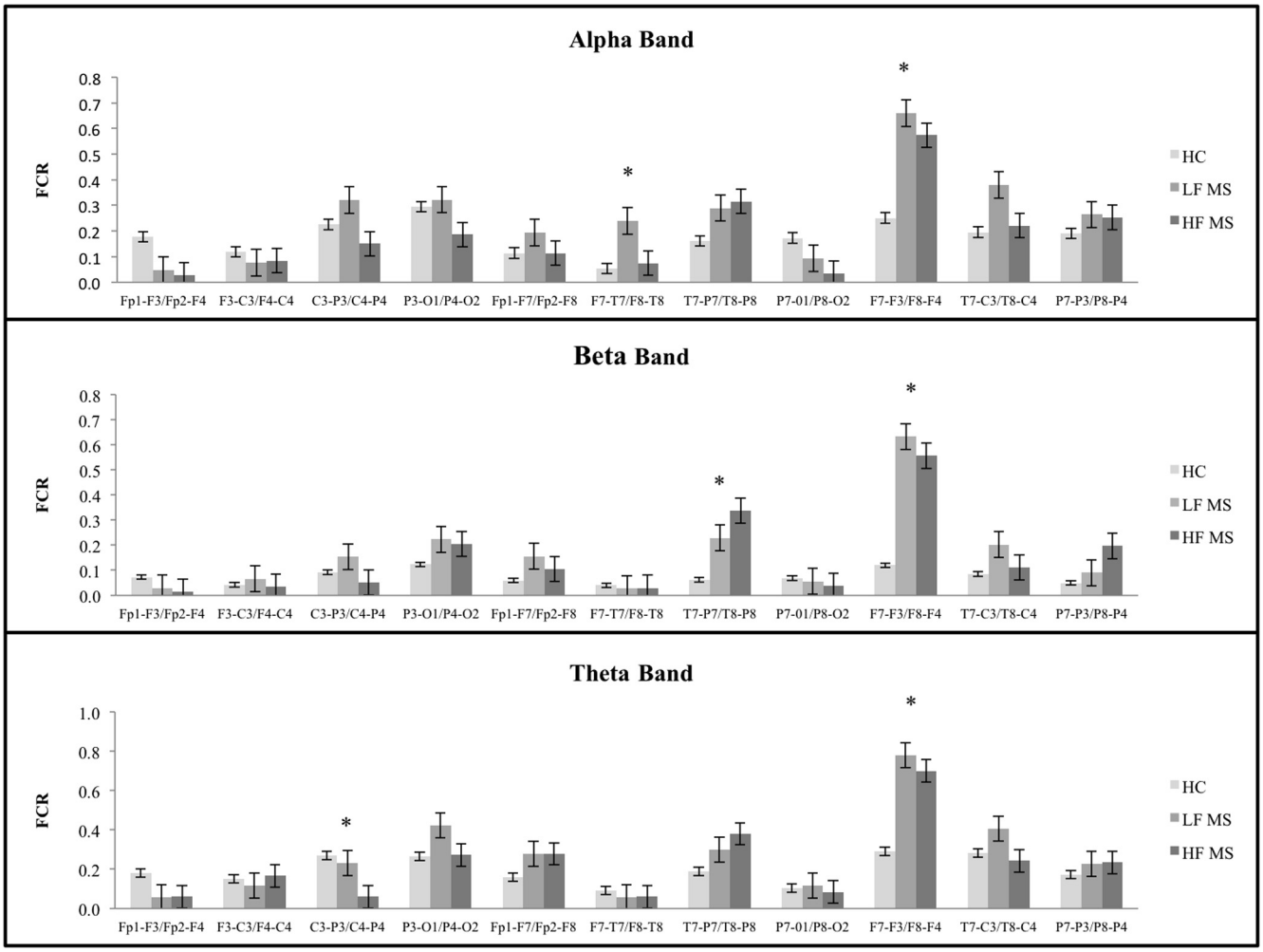

Fig. 2. Functional connectivity at rest (FCR) in Alpha, Beta and Theta bands averaged across the healthy controls (HC) and MS patients with low (LFMS) and high fatigue (HFMS). Group variability is reported (vertical segments) as standard error. The asterisks indicate a significant difference between the groups as estimated by analysis of variance on ranks (*Group* effect at Kruskal-Wallis H Test).

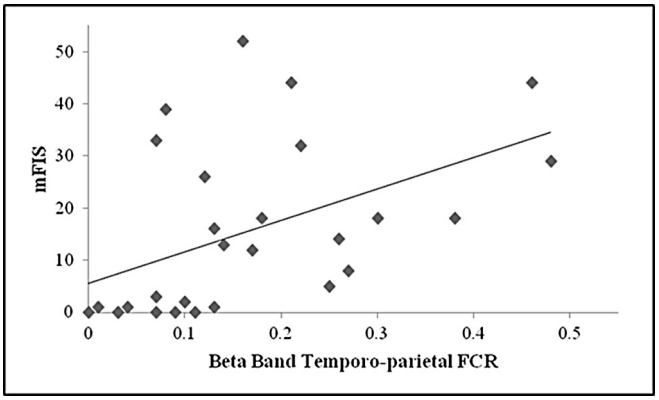

Fig. 3. Relationship between Temporo-parietal Beta coherence and mFIS scores in MS patients. Data from one patient was excluded from the analysis as an outlier.

It has been suggested that MS fatigue might be related to the compensatory reorganization of the brain to adapt to demyelination and/or axonal loss (Braley and Chervin, 2010). This compensatory process could facilitate normal functioning, but also result in a feeling of fatigue (Wilting et al., 2016). Another independent not-mutually exclusive mechanism is that inflammatory processes might be more prominent and contribute to the feeling of fatigue (Dettmers and DeLuca, 2015).

In our study, the functional connectivity at rest between hemispheric post-central sensory networks was altered in parallel with fatigue symptoms, strengthening the idea that region-specific and homologous region asymmetric dysfunctions parallel MS fatigue. Notably, in another fMRI study (Engstrom et al., 2013), the only brain activation positively correlated to experienced fatigue was the left posterior parietal cortex. In yet another study (Cogliati Dezza et al., 2015), it was found that fatigue increased along with the functional inter-hemispheric imbalance of sensorimotor homologous areas EEG activities, both at rest and during movement. The increasing temporo-parietal prevalence of the connectivity alteration in parallel with increasing fatigue strengthens the notion that perception plays a pivotal role in fatigue. In particular, this finding supports the hypothesis that prolonged perception of fatigue reduces motivation, and opposes the competing hypothesis in which decreasing motivational drive increases the perception of fatigue (de Lange et al., 2004).

A limitation of our study is that fatigue symptoms were assessed using the mFIS self-report questionnaire. All of our patients completed the questionnaire by themselves, scoring how much fatigue impacts their lives in terms of physical, cognitive, and psychosocial functioning. Tecchio and colleagues reported mFIS collected twice in stable conditions for 10 patients and

observed a small mFIS divergence in the two scorings (mean difference 0.1 ± 1.9, Intra-Class Correlation 0.96) (Tecchio et al., 2014). Nevertheless, all studies investigating these symptoms are subject to a lack of the ability to quantify patients' suffering via entirely objective measures.

5. Conclusion

We document that MS fatigued patients show increased beta band functional connectivity at rest between left and right temporo-parietal regions in proportion with fatigue symptoms increase. In the light of these results, we suggest that an EEG-Neurofeedback intervention against MS fatigue would train patients to decrease voluntarily the beta coherence between the homologous temporo-parietal areas.

Acknowledgments

The authors are sincerely grateful to all involved for the time and cooperation dedicated to participation. This work was supported by: (1) FISM–Fondazione Italiana Sclerosi Multipla– Cod. 2014/R/22 [FaReMuS CuNeH], (2) PNR-CNR Aging Program 2012-2018.

Conflict of interest statement: None of the authors have potential conflicts of interest to be disclosed.

References

Barbati G, Porcaro C, Zappasodi F, Rossini PM, Tecchio F. Optimization of an independent component analysis approach for artifact identification and removal in magnetoencephalographic signals. Clin Neurophysiol 2004;115:1220–32.

Beck AT, Steer RA, Brown GK, editors. Manual for beck depression inventory-second edition. 1996.

Birbaumer N, Cohen LG. Brain-computer interfaces: communication and restoration of movement in paralysis. J Physiol 2007;579:621–36.

Bonavita S, Sacco R, Della Corte M, Esposito S, Sparaco M, d'Ambrosio A, et al. Computer-aided cognitive rehabilitation improves cognitive performances and induces brain functional connectivity changes in relapsing remitting multiple sclerosis patients: an exploratory study. J Neurol 2015;262:91–100.

Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep 2010;33:1061–7.

Cantero JL, Atienza M, Salas RM, Gomez CM. Alpha EEG coherence in different brain states: an electrophysiological index of the arousal level in human subjects. Neurosci Lett 1999;271:167–70.

Cao T, Wan F, Wong CM, da Cruz JN, Hu Y. Objective evaluation of fatigue by EEG spectral analysis in steady-state visual evoked potential-based brain-computer interfaces. Biomed Eng Online 2014;13:28.

Cogliati Dezza I, Zito G, Tomasevic L, Filippi MM, Ghazaryan A, Porcaro C, et al. Functional and structural balances of homologous sensorimotor regions in multiple sclerosis fatigue. J Neurol 2015;262:614–22.

Cover KS, Vrenken H, Geurts JJG, van Oosten BW, Jelles B, Polman CH, et al. Multiple sclerosis patients show a highly significant decrease in alpha band interhemispheric synchronization measured using MEG. NeuroImage 2006;29:783–8.

Cruz Gomez AJ, Ventura Campos N, Belenguer A, Avila C, Forn C. Regional brain atrophy and functional connectivity changes related to fatigue in multiple sclerosis. PLoS ONE 2013;8:e77914.

de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Werf SP, van der Meer JW, et al. Neural correlates of the chronic fatigue syndrome–an fMRI study. Brain 2004;127:1948–57.

Deco G, Corbetta M. The dynamical balance of the brain at rest. Neuroscientist 2011;17:107–23.

Dettmers C, DeLuca J. Editorial: fatigue in multiple sclerosis. Front Neurol 2015;6:266.

Di Pino G, Porcaro C, Tombini M, Assenza G, Pellegrino G, Tecchio F, et al. A neurally-interfaced hand prosthesis tuned inter-hemispheric communication. Restor Neurol Neurosci 2012;30:407–18.

Dubovik S, Pignat JM, Ptak R, Aboulafia T, Allet L, Gillabert N, et al. The behavioral significance of coherent resting-state oscillations after stroke. NeuroImage 2012;61:249–57.

Engstrom M, Flensner G, Landtblom AM, Ek AC, Karlsson T. Thalamo-striato-cortical determinants to fatigue in multiple sclerosis. Brain Behav 2013;3:715–28.

Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. Can J Neurol Sci 1994;21:9–14.

Guevara MA, Hernández-González M, Sanz-Martin A, Amezcua C. EEGcorco: a computer program to simultaneously calculate and statistically analyze EEG coherence and correlation. J Biomed Sci Eng 2011;4:774–87.

Hardmeier M, Schoonheim MM, Geurts JJG, Hillebrand A, Polman CH, Barkhof F, et al. Cognitive dysfunction in early multiple sclerosis: altered centrality derived from resting-state functional connectivity using magneto-encephalography. PLoS ONE 2012;7:e42087.

Hassan MA, Fraser M, Conway BA, Allan DB, Vuckovic A. The mechanism of neurofeedback training for treatment of central neuropathic pain in paraplegia: a pilot study. BMC Neurol 2015;15:200.

Huster RJ, Mokom ZN, Enriquez-Geppert S, Herrmann CS. Brain-computer interfaces for EEG neurofeedback: peculiarities and solutions. Int J Psychophysiol 2014;91:36–45.

Koeda T, Knyazeva M, Njiokiktjien C, Jonkman EJ, De Sonneville L, Vildavsky V. The EEG in acallosal children. Coherence values in the resting state: left hemisphere compensatory mechanism? Electroencephalogr Clin Neurophysiol 1995;95:397–407.

Kos D, Kerckhofs E, Nagels G, D'Hooghe MB, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. Neurorehabil Neural Repair 2008;22:91–100.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–52.

Leavitt VM, Wylie GR, Girgis PA, DeLuca J, Chiaravalloti ND. Increased functional connectivity within memory networks following memory rehabilitation in multiple sclerosis. Brain Imaging Behav 2014;8:394–402.

Lenne B, Blanc J-L, Nandrino J-L, Gallois P, Hautecaur P, Pezard L. Decrease of mutual information in brain electrical activity of patients with relapsing-remitting multiple sclerosis. Behav Neurol 2013;27:201–12.

Leocani L, Comi E, Annovazzi P, Rovaris M, Rossi P, Cursi M, et al. Impaired short-term motor learning in multiple sclerosis: evidence from virtual reality. Neurorehabil Neural Repair 2007;21:273–8.

Leocani L, Locatelli T, Martinelli V, Rovaris M, Falautano M, Filippi M, et al. Electroencephalographic coherence analysis in multiple sclerosis: correlation with clinical, neuropsychological, and MRI findings. J Neurol Neurosurg Psychiatry 2000;69:192–8.

Linden DE. Neurofeedback and networks of depression. Dialogues Clin Neurosci 2014;16:103–12.

Lowe MJ, Phillips MD, Lurito JT, Mattson D, Dzemidzic M, Mathews VP. Multiple sclerosis: low-frequency temporal blood oxygen level-dependent fluctuations indicate reduced functional connectivity initial results. Radiology 2002;224:184–92.

Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83:278–86.

Montplaisir J, Nielsen T, Cote J, Boivin D, Rouleau I, Lapierre G. Interhemispheric EEG coherence before and after partial callosotomy. Clin Electroencephalogr 1990;21:42–7.

Mottaz A, Solca M, Magnin C, Corbet T, Schnider A, Guggisberg AG. Neurofeedback training of alpha-band coherence enhances motor performance. Clin Neurophysiol 2015;126:1754–60.

Nolte G, Bai O, Wheaton L, Mari Z, Vorbach S, Hallett M. Identifying true brain interaction from EEG data using the imaginary part of coherency. Clin Neurophysiol 2004;115:2292–307.

Pellegrino G, Tomasevic L, Tombini M, Assenza G, Bravi M, Sterzi S, et al. Inter-hemispheric coupling changes associate with motor improvements after robotic stroke rehabilitation. Restor Neurol Neurosci 2012;30:497–510.

Porcaro C, Medaglia MT, Krott A. Removing speech artifacts from electroencephalographic recordings during overt picture naming. Neuroimage 2015;105:171–80.

Rasova K, Prochazkova M, Tintera J, Ibrahim I, Zimova D, Stetkarova I. Motor programme activating therapy influences adaptive brain functions in multiple sclerosis: clinical and MRI study. Int J Rehabil Res 2015;38:49–54.

Rogala J, Jurewicz K, Paluch K, Kublik E, Cetnarski R, Wrobel A. The Do's and Don'ts of neurofeedback training: a review of the controlled studies using healthy adults. Front Hum Neurosci 2016;10:301.

Ros T, Theberge J, Frewen PA, Kluetsch R, Densmore M, Calhoun VD, et al. Mind over chatter: plastic up-regulation of the fMRI salience network directly after EEG neurofeedback. NeuroImage 2013;65:324–35.

Sacchet MD, Mellinger J, Sitaram R, Braun C, Birbaumer N, Fetz E. Volitional control of neuromagnetic coherence. Front Neurosci 2012;6:189.

Schoonheim MM, Geurts J, Wiebenga OT, De Munck JC, Polman CH, Stam CJ, et al. Changes in functional network centrality underlie cognitive dysfunction and physical disability in multiple sclerosis. Mult Scler 2014;20:1058–65.

Sekihara K, Owen JP, Trisno S, Nagarajan SS. Removal of spurious coherence in MEG source-space coherence analysis. IEEE Trans Biomed Eng 2011;58:3121–9.

Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. Sleep Med Rev 2006;10:63–76.

Srinivasan R, Winter WR, Ding J, Nunez PL. EEG and MEG coherence: measures of functional connectivity at distinct spatial scales of neocortical dynamics. J Neurosci Methods 2007;166:41–52.

Strober LB. Fatigue in multiple sclerosis: a look at the role of poor sleep. Front Neurol 2015;6:21.

Tecchio F, Cancelli A, Cottone C, Zito G, Pasqualetti P, Ghazaryan A, et al. Multiple sclerosis fatigue relief by bilateral somatosensory cortex neuromodulation. J Neurol 2014;261:1552–8.

Tecchio F, Porcaro C, Barbati G, Zappasodi F. Functional source separation and hand cortical representation for a brain-computer interface feature extraction. J Physiol 2007;580:703–21.

Tewarie P, Schoonheim MM, Schouten DI, Polman CH, Balk LJ, Uitdehaag BMJ, et al. Functional brain networks: linking thalamic atrophy to clinical disability in multiple sclerosis, a multimodal fMRI and MEG study. Human Brain Mapp 2015;36:603–18.

Tomasevic L, Zito G, Pasqualetti P, Filippi M, Landi D, Ghazaryan A, et al. Cortico-muscular coherence as an index of fatigue in multiple sclerosis. Mult Scler 2013;19:334–43.

Tombini M, Rigosa J, Zappasodi F, Porcaro C, Citi L, Carpaneto J, et al. Combined analysis of cortical (EEG) and nerve stump signals improves robotic hand control. Neurorehabil Neural Repair 2012;26:275–81.

Tur C. Fatigue management in multiple sclerosis. Curr Treat Options Neurol 2016;18:26.

Van Schependom J, Gielen J, Laton J, D'Hooghe MB, De Keyser J, Nagels G. Graph theoretical analysis indicates cognitive impairment in MS stems from neural disconnection. NeuroImage Clinical 2014;4:403–10.

von Carlowitz-Ghori K, Bayraktaroglu Z, Waterstraat G, Curio G, Nikulin VV. Voluntary control of corticomuscular coherence through neurofeedback: a proof-of-principle study in healthy subjects. Neuroscience 2015;290:243–54.

Wilting J, Rolfsnes HO, Zimmermann H, Behrens M, Fleischer V, Zipp F, et al. Structural correlates for fatigue in early relapsing remitting multiple sclerosis. Eur Radiol 2016;26:515–23.

Zito G, Luders E, Tomasevic L, Lupoi D, Toga AW, Thompson PM, et al. Inter-hemispheric functional connectivity changes with corpus callosum morphology in multiple sclerosis. Neuroscience 2014;266:47–55.