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Cortical sources of resting state electroencephalographic rhythms differ in relapsing–remitting and secondary progressive multiple sclerosis

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HIGHLIGHTS

- Resting state eyes-closed EEG activity was recorded in subjects with multiple sclerosis (MS) sub-types (phenotypes) such as relapsing–remitting (RR) and secondary progressive (SP).
- Cortical sources of resting state EEG rhythms differ between RR and SP subjects.
- Future studies should test the utility of these EEG markers in diagnostic and management of RR and SP subjects and in the therapy evaluation.

ABSTRACT

Objective: Resting state electroencephalographic (EEG) rhythms are abnormal in multiple sclerosis (MS) patients, but it is unclear if they can reflect different neurophysiologic abnormalities in MS sub-types (phenotypes) such as relapsing–remitting (RR) and secondary progressive (SP).
Methods: We tested whether cortical sources of resting state EEG rhythms are abnormal in MS patients and differ between MS phenotypes. Resting state eyes-closed EEG activity was recorded in 36 RR, 23 SP, and 41 matched healthy subjects. EEG bands of interest were individually identified based on Transition frequency (TF), Individual alpha frequency (IAF), and Individual beta frequency (IBF). LORETA freeware estimated cortical EEG sources.
Results: Widespread TF −4 Hz (delta) and IAF (alpha) cortical sources were abnormal in the MS sub-groups compared to the control group. Furthermore, TF −4 Hz sources in central, parietal, and limbic regions were higher in amplitude in the SP compared to the RR sub-group.
Conclusion: Cortical sources of resting state EEG rhythms are abnormal in MS patients at group level and differ between RR and SP sub-groups.
Significance: Future studies should test the utility of these EEG markers in the diagnosis and management of MS clinical phenotypes and in the therapy evaluation.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS) with a progressive course. It clinically manifests signs of multiple neurological dysfunctions. There are two major forms of

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MS. Most people with MS (85–90%) have the relapsing–remitting (RR) phenotype, which is characterize by clearly defined attacks of worsening neurologic function. These attacks (i.e. relapses) are followed by partial or complete recovery periods (i.e. remissions), during which symptoms improve partially or completely. After living with RR for many years, the majority of MS patients later develop secondary progressive (SP) phenotype (Lublin et al., 1996). While RR is defined by attacks of inflammation (i.e. relapses) in the brain, progressive forms of MS involve much less this type of inflammation. Specifically, people with RR tend to have more brain lesions, while people with SP tend to have more spinal cord lesions, which contain fewer inflammatory cells. To date, it is unclear why the disease makes the transformation from RR to SP due to a poor knowledge of its neural substrate.

Neural substrate of MS and its more common two sub-types (i.e. RR, SP) have been investigated by neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET). On one hand, structural and functional MRI studies showed vascular lesions and abnormal BOLD activity in MS patients compared to healthy control (HC) subjects, as a function of disease onset and cognitive impairment (Swirsky-Sacchetti et al., 1992; Arnett et al., 1994; Morgen et al., 2006; Calabrese et al., 2010). Other MRI evidence unveiled differences between RR and SP sub-groups of MS patients by anatomical connectivity mapping (Lyksborg et al., 2014). Furthermore, there were differences as revealed by functional connectivity mapping in sensory-motor network (SMN) and default-mode network (DMN) in MS patients compared to HC subjects (Basile et al., 2013). On the other hand, PET studies with ligands of pro-inflammatory proteins showed abnormal neuroimaging markers in MS patients (Politis et al., 2012), related to their clinical status as indexed by the score of Expanded Disability Status Scale (EDSS; Kurtzke, 1983). However, no MRI and PET marker allows a clear-cut diagnosis of MS or prediction of the disease progression. Furthermore, they are invasive and/or expensive for serial recordings aimed at monitoring disease progression or therapy effects along years.

Keeping in mind the above premises, field researchers have been testing new non-invasive and cost effective procedures to enrich the clinical decision making processes in the assessment of MS patients. Among other candidates, electroencephalographic (EEG) markers fit these ideal features, as its recording is cost effective and largely available. EEG activity has been investigated in MS patients during sensory stimulations and cognitive tasks. Compared to healthy subjects, MS patients showed increased power of higher EEG frequencies (i.e. gamma band) during cognitive tasks (Vazquez-Marrufo et al., 2008). Furthermore, MS patients showed abnormalities of EEG activity related to visual and auditory stimuli (i.e. negative and positive components of event-related potentials, ERPs; Newton et al., 1989; Piras et al., 2003; Whelan et al., 2010). Of note, Ellger and colleagues observed difference of ERPs between RR and SP phenotypes, thus suggesting that ERP abnormalities may reflect the course of the disease (Ellger et al., 2002).

Another typical EEG procedure in clinical environment is the recording of EEG activity in resting state eyes-closed condition, which is largely available in all countries and not affected by learning or repetition effects. It allows the evaluation of resting state EEG rhythms, which probes general neurophysiologic mechanisms of cortical neural synchronization and desynchronization during fluctuation of cortical arousal and tonic alertness (Babiloni et al., 2011a). Spectral analysis of these EEG rhythms unveiled that 40–80% of MS patients show abnormalities in EEG power density (Leocani and Comi, 2000). Specifically, there was a pathological increase of EEG power density at low frequencies (delta, 2–4 Hz) and a decrease of EEG power density at higher frequencies (alpha, 8–12 Hz), which is a spectral pattern typically related to cognitive dysfunctions in humans (Leocani and Comi, 2000). Compared to healthy subjects, MS patients pointed to an increase of EEG power density at slow frequency in frontotemporal-central scalp regions, as well as decreased coherence/mutual information of EEG rhythms between electrode pairs (Leocani et al., 2000, 2010; Lenne et al., 2013). A similar reduction of coherence between electrodes placed in the two hemispheres (i.e. inter-hemispheric coherence) was also observed by resting state magneto-electroencephalography (MEG; Cover et al., 2006). Noteworthy, there is no evidence that resting state EEG markers are able to distinguish diverse clinical MS phenotypes such as RR and SP.

It should be noted that previous EEG studies did not explore cortical sources of resting state EEG rhythms in MS patients, although it is well known that estimation of cortical sources of these rhythms enhances spatial information content of scalp EEG activity in neurologic patients such as subjects with mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease (PD), human immunodeficiency virus (HIV), covert encephalopathy du e to liver cirrhosis (LC), and down syndrome (Babiloni et al., 2004a,b, 2006a,b, 2007, 2008a,b, 2009a,b, 2010, 2011a,b, 2012, 2013a,b, 2014). To fill this gap, here we explored cortical sources of resting state EEG rhythms in MS patients. The main study aim was to test whether these sources are abnormal and distinguish at group level common MS phenotypes such as RR and SP.

2. Methods

2.1. Subjects and diagnostic criteria

Fifty-nine MS patients were evaluated by EDSS to measure MS severity (Kurtzke, 1983). Concerning the clinical phenotype, 36 MS patients were diagnosed as RR (mean EDSS = 3.9 ± 0.3 standard error, SE; mean age = 48.8 ± 1.4 SE), while 23 MS patients were diagnosed as SP (EDSS = 5.4 ± 0.3 SE; mean age = 52.8 ± 1.6 SE). In addition, 41 healthy subjects matched for age and gender (HC; mean age = 51.9 ± 1.8 SE) were used as a control group. Local institutional Ethics Committee approved the study. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board.

The recruited MS patients underwent general medical, neurological, and psychiatric assessments. These patients were also rated with a number of standardized diagnostic instruments that included mini mental state evaluation (MMSE; Folstein et al., 1975) and EDSS for the assessment of global cognition and disease symptoms, respectively. An accurate clinical exam was performed to exclude causes of progressive or reversible dementias.

Inclusion criteria of the MS subjects were as follows: (1) MS defined according to McDonald's criteria (Polman et al., 2005) with RR or SP course; (2) patients who have received care for at least 2 years; (3) at least one relapse in the 2 years before the inclusion in the present study as RR patient; (4) disease duration from diagnosis to study inclusion $\leqslant$10 years for RR and $\leqslant$15 years for SP; (5) stable neurological condition without relapse for at least 30 days; (6) patient not undergoing cortisone therapy, or undergoing disease modifying therapies without modification for at least 6 months (i.e., all RR patients were in the remitting phase at the time of the present EEG experiment).

Exclusion criteria of the enrolled MS subjects were as follows: (1) chronic systemic illnesses (e.g. diabetes mellitus); (2) use of psychoactive drugs; and (3) other neurological or psychiatric diseases.

The healthy control (HC) subjects matched age, gender, and education of recruited MS subjects. All subjects underwent physical and neurological examinations as well as cognitive screening (including MMSE).

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