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Cognition in MS correlates with resting-state oscillatory brain activity: An explorative MEG source-space study

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ABSTRACT

Clinical and cognitive dysfunction in Multiple Sclerosis (MS) is insufficiently explained by structural damage as identified by traditional magnetic resonance imaging (MRI) of the brain, indicating the need for reliable functional measures in MS. We investigated whether altered resting-state oscillatory power could be related to clinical and cognitive dysfunction in MS. MEG recordings were acquired using a 151-channel whole-head MEG system from 21 relapsing remitting MS patients and 17 healthy age-, gender-, and education-matched controls, using an eyes-closed no-task condition. Relative spectral power was estimated for 78 regions of interest, using an atlas-based beamforming approach, for classical frequency bands; delta, theta, alpha1, alpha2, beta and gamma. These cortical power estimates were compared between groups by means of permutation analysis and correlated with clinical disability (Expanded Disability Status Scale: EDSS), cognitive performance and MRI measures of atrophy and lesion load. Patients showed increased power in the alpha1 band and decreased power in the alpha2 band, compared to controls, mainly in occipital, parietal and temporal areas, confirmed by a lower alpha peak-frequency. Increased power in the alpha1 band was associated with worse overall cognition and especially with information processing speed. Our quantitative relative power analysis of MEG recordings showed abnormalities in oscillatory brain dynamics in MS patients in the alpha band. By applying source-space analyses, this study provides a detailed topographical view of abnormal brain activity in MS patients, especially localized to occipital areas. Interestingly, poor cognitive performance was related to high resting-state alpha1 power indicating that changes in oscillatory activity might be of value as an objective measure of disease burden in MS patients.

1. Introduction

Multiple Sclerosis (MS) is an acquired progressive neurological disease with a highly variable course, leading to both physical symptoms and cognitive impairment. Clinical and cognitive decline in MS is insufficiently explained by classical MRI measures such as lesion load or atrophy of the white matter (Barkhof, 2002). However axonal damage and demyelination in the gray matter seem to correlate with clinical and cognitive deficits in MS (Geurts and Barkhof, 2008).

In physiological conditions modulations in neuron population firing probability occur preferentially during a certain phase of the oscillatory activity (Schnitzler and Gross, 2005). Demyelination and axonal damage could lead to altered firing probability and therefore to altered oscillatory cortical activity in MS. Neurophysiological techniques, such as EEG and MEG, can be used to detect such changes in activity, as has been demonstrated for neurological diseases such as Alzheimer's disease (de Haan et al., 2008; Jeong, 2004; Stam et al., 2006), Parkinson's disease (Bosboom et al., 2006; Ponsen et al., 2013; Stoffers et al., 2007), low-grade glioma (Bosma et al., 2008), traumatic brain injury (Kumar et al., 2009), and stroke (van Putten and Tavy, 2004). Up to 70% of patients with MS suffer from cognitive impairment (Rao et al., 1991); attention, information processing speed and memory being the most commonly affected domains (Chiaravalloti and DeLuca, 2008). There is increasing evidence that changes in oscillatory brain activity may be related to cognitive dysfunction in neurological disease (Schnitzler and Gross, 2005; Stam and van Straaten, 2012; Uhlhaas and Singer, 2006). We therefore hypothesize that cognitive impairment in MS patients might be partially explained by pathological changes in oscillatory brain activity.

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To date, literature on EEG or MEG in MS is scarce. Visual inspection of EEG recordings from MS patients revealed more focal EEG abnormalities (slow activity) in patients with relapses compared to patients with a progressive course (Feng, 1981). A 5-year follow-up study did not show a significant correlation between visual EEG abnormalities and neurological disability (Quattrini et al., 1981). Yet, another group used computerized spectral analysis to demonstrate a positive relation between patients' disability and increased theta power over the temporal regions and increased beta power over the frontal regions, where visual interpretation of the EEG failed to demonstrate any correlations (Colon et al., 1981). Power spectral density analysis of EEG data, obtained during an auditory oddball task, revealed increased power in beta and gamma bands (especially over midfrontal areas) in MS patients compared to healthy controls (Vazquez-Marrufo et al., 2008). Similarly, for a visuo-spatial task, more beta and gamma power was found over occipital and right-frontal regions in relapsing remitting MS patients compared to a group of healthy controls, but no differences were found in the high frequency bands during resting-state, nor were there any significant correlations between quantitative EEG (QEEG) scores and Expanded Disability Status Scale (EDSS) (Vazquez-Marrufo et al., 2008).

Compared to EEG, MEG provides a reference free method and the magnetic fields are much less disturbed by the skull. MS research using EEG and MEG has recently focussed on altered functional connectivity, which referrers to statistical interdependencies between physiological time series (Cover et al., 2006; Leocani et al., 2000; Schoonheim et al., 2013; Tecchio et al., 2008), and changes in functional network topology (Hardmeier et al., 2012; Schoonheim et al., 2013). A more basic characterization, including for example global and local spectral analysis of the rhythmic MEG activity in MS patients has not been performed to date. Yet, knowledge of changes in local spectral power seems fundamental in comprehending the outcome of connectivity research. Additionally, the aforementioned studies were performed at the sensor level, i.e. results were estimated based on the extracranial recordings directly, making interpretation of these results in terms of the specific anatomical brain regions that are involved more difficult. In addition, investigation of abnormal MEG activity at the source-level facilitates comparison with other neuroimaging techniques, notably structural and functional MRI.

The aim of the present MEG study was therefore to explore differences in resting-state oscillatory brain activity in MS patients compared to healthy controls, and to relate these differences to cognitive performance, physical disability and structural deficits measured with MRI. A recently developed technique, projecting sensor-based data onto an atlas-based source-space using beamforming, was applied (Hillebrand et al., 2012) in order to provide a detailed anatomical mapping of cortical rhythms for 78 regions of interest (ROIs).

2. Methods

2.1. General study design

In this cross-sectional study MS patients and healthy controls underwent MEG, MRI, neurological examination and neuropsychological assessment on the same day. Outcome measures were global relative power, relative power per ROI (regional relative power), peak frequency, anterior–posterior gradients, diffuse slow-wave activity and the presence of asymmetry. These outcome measures were associated with cognition and MRI measures.

2.2. Subject characteristics

MS patients and healthy volunteers were recruited from an ongoing large clinical study at the Multiple Sclerosis Center of the VU University Medical Center, as described in a previous MEG study in the same subjects (Schoonheim et al., 2013). Our project involved 34 MS patients (17 women, mean age 41.4 ± 8.0 years, disease duration 8.1 ± 1.6 years) and 28 healthy controls (14 women, mean age 39.8 ± 10.5 years), matched for age, gender and educational level (using a Dutch classification system ranging from 1 (only primary education) to 7 (university degree)). Twenty four participants were excluded from further analysis due to unavailability of an anatomical MRI (n = 2), failed MEG/MRI co-registration (n = 10) and too many artifacts in the raw MEG data (n = 12). Consequently, 21 MS patients (mean age 41.9 ± 7.7, disease duration 6.8 ± 0.9 years) and 17 controls (mean age 39.8 ± 9.8) remained in the present study, who were still gender-, age- and education-matched. Patients were diagnosed with MS according to the revised McDonald Criteria (Polman et al., 2005). None of the healthy controls suffered from a neurological or psychiatric disease, nor did they use any medication or drugs. Eight patients were treated with interferon β since diagnosis, one of them switched to glatiramer acetate and two to natalizumab, which they received during this study. No other medication was used. Patients were assessed according to a clinical protocol, involving history taking, neurological examination, blood tests, neuropsychological tests, MRI of the brain and MEG. Physical disability was measured using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The study protocol was approved by the Local Research Ethics Committee, whose ethics review criteria conformed to the Helsinki declaration. All subjects had given written informed consent prior to participation.

2.3. MRI

An MRI scan was obtained from all subjects, using a 3 T-MRI system (GE Signa HDXT V15m). 2D dual-echo T2-weighted sequence (TR 9680 ms, TE 22/112 ms) and T1-weighted sequence (TR 475 ms, TE 9 ms) were obtained with 48 slices of 3 mm and 3D-T1 heavily T1-weighted sequence (FSPGR, TR 7.8 ms, TE 3.0 ms, TI 450 ms) with 1 mm slices covering the entire brain. All scans were inspected by an experienced rater (MMS). T1-hypointense and T2-hyperintense lesions in MS patients were marked and their volumes were measured using a local-threshold technique. Total normal gray matter volume (NGMV), total normal white matter volume (NWMV), and normal whole brain volumes (NBV), corrected for head size, were estimated using FSPGR images and SIENAX (Smith et al., 2002) version 2.5 (part of FSL 4.1, FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl). Thalamic volumes were outlined and volumes measured using FIRST (part of FSL), as described before for this cohort (Schoonheim et al., 2012). Left and right volumes were summed to give the total volume.

2.4. Neuropsychological evaluation

Cognitive function in all subjects was assessed according to the protocol used and described before (Schoonheim et al., 2012). A Brief Repeatable Battery of Neuropsychological Tests (BRB-N), the selective reminder test (SRT), the 10/36 spatial recall test (SPART), the symbol digit modalities test (SDMT), the word list generation test (WLG), the concept shifting test (CST), the Stroop color-word test and the memory comparison test (MCT) were administered. Individual patients' test scores were converted to z-scores, using the means and standard deviations of the entire group of participants. The z-scores for all tests were averaged for each subject, creating overall cognition z-score. Subsequently, individual scores on the tests were summarized into seven cognitive domains, namely (1) executive functioning (CST, WLG), (2) information processing speed (SDMT), (3) psychomotor speed (CST, SDMT), (4) attention (Stroop), (5) verbal memory (SRT), (6) working memory (MCT), and (7) visuospatial memory (SPART). Construction of these domains with comparable cognitive tests has been reported previously and was based on a principal component analysis using varimax rotation with Kaiser normalization performed on the z-scores for a large group of healthy controls (Klein et al., 2003), and these domains are commonly used in neurocognitive practice and research.