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Fluctuations of spontaneous EEG topographies predict disease state in relapsing-remitting multiple sclerosis

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ABSTRACT

Spontaneous fluctuations of neuronal activity in large-scale distributed networks are a hallmark of the resting brain. In relapsing-remitting multiple sclerosis (RRMS) several fMRI studies have suggested altered resting-state connectivity patterns. Topographical EEG analysis reveals much faster temporal fluctuations in the tens of milliseconds time range (termed "microstates"), which showed altered properties in a number of neuropsychiatric conditions.

We investigated whether these microstates were altered in patients with RRMS, and if the microstates' temporal properties reflected a link to the patients' clinical features.

We acquired 256-channel EEG in 53 patients (mean age 37.6 years, 45 females, mean disease duration 9.99 years, Expanded Disability Status Scale ≤4, mean 2.2) and 49 healthy controls (mean age 36.4 years, 33 females). We analyzed segments of a total of 5 min of EEG during resting wakefulness and determined for both groups the four predominant microstates using established clustering methods.

We found significant differences in the temporal dynamics of two of the four microstates between healthy controls and patients with RRMS in terms of increased appearance and prolonged duration. Using stepwise multiple linear regression models with 8-fold cross-validation, we found evidence that these electrophysiological measures predicted a patient's total disease duration, annual relapse rate, disability score, as well as depression score, and cognitive fatigue measure.

In RRMS patients, microstate analysis captured altered fluctuations of EEG topographies in the sub-second range. This measure of high temporal resolution provided potentially powerful markers of disease activity and neuropsychiatric co-morbidities in RRMS.

1. Introduction

Multiple sclerosis (MS) is characterized by recurrent inflammatory events and progressive neurodegeneration leading to disseminated demyelination and axonal loss in the central nervous system (Compston and Coles, 2008). The search for additional disease markers is needed (Filippi and Agosta, 2010) because conventional structural magnetic resonance imaging (MRI) of the brain and spinal cord (Rovira et al., 2015) does not capture the "hidden" axonal damage known to occur early in the normal-appearing brain tissue (Fu et al., 1998) and because there ispoor correlation between lesion load and clinical impairment (Barkhof, 2002).

MS has received much less attention from the EEG and MEG field than from the MRI community. Very few studies have looked at electrophysiological markers of the clinical course (Fuhr et al., 2001; Schlaeger et al., 2014), and only recently has interest grown in the functional connectivity and resting-state network analysis by EEG, with the aim to characterize altered neuronal conduction known to occur in MS pathology (Lenne et al., 2013; Leocani et al., 2000; Van Schependom et al., 2014). A few MEG studies investigated functional connectivity at rest in patients with MS and found altered connectivity patterns in specific frequency bands

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(Cover et al., 2006; Hardmeier et al., 2012; Schoonheim et al., 2013b; Tewarie et al., 2013; Van der Meer et al., 2013).

Alternative to frequency-band specific analyses with quantitative EEG or functional connectivity measures, brain activity can be described through scalp potential fields. During rest the broad-band EEG displays topographical fluctuations, among which meta-stable periods of some tens of milliseconds can be detected when a topographical clustering approach is used. These quasi-stable states have been termed "microstates" (Lehmann et al., 1987), and most studies have consistently obtained four prototypical topographies along which the fluctuations are described (Koenig et al., 2002; for reviews see Khanna et al., 2015; Lehmann et al., 2009). Both the spatial and temporal orders of these topographical fluctuations are not random, but follow a complex temporal structure, including long-range dependencies (Gschwind et al., 2015; Van De Ville et al., 2010). Simultaneous EEG/fMRI recordings in healthy subjects showed that the different microstates could be associated with the blood-oxygen-level dependent (BOLD) pattern of established resting-state networks (Britz et al., 2010; Yuan et al., 2012). This supported the idea that EEG microstates represent elementary short-lasting periods of coordinated synchronized communication within large-scale brain networks. Consequently, it was assumed that the EEG microstates could be the electrophysiological correlates of the periods of stable spatial patterns proposed in the global workspace theory (Baars, 2002, 2005; Changeux and Michel, 2004; Dehaene and Changeux, 2011).

Several studies over the last 20 years have shown that the temporal dynamics of EEG microstates are influenced by different states of consciousness such as hypnosis (Katayama et al., 2007), meditation (Kopal et al., 2014), and sleep (Brodbeck et al., 2012), and that they are altered in diseases such as schizophrenia (Kindler et al., 2011; Lehmann et al., 2014; Strelets et al., 2003), risk for schizophrenia (Andreou et al., 2014; Tomescu et al., 2014; Tomescu et al., 2015), and dementia (Dierks et al., 1997; Nishida et al., 2013; Strik et al., 1997) in a disease-specific way.

In the present study, we compared high-density EEG topographies (microstates) during rest between patients with RRMS and healthy subjects. Given that RRMS is characterized by relapsing episodes of distributed inflammation, leading to demyelination and axonal loss, we expected that a focal alteration of microstate topographies would not be observed, but instead a temporal alteration of the microstate switch, either as an increased speed due to compensatory or adaptive hyperactivation (decrease of microstate durations) or as decreased speed in the context of the slowdown of the neuronal transmission (increase of microstate durations). We hypothesized that such altered temporal dynamics could be related to a specific dysfunction of clinical or neuropsychological parameters (Schoonheim et al., 2013a; Schoonheim et al., 2015b). We asked whether such a temporal alteration would be found in all microstates classes as a general effect of the disease, or whether it would be specfic to certain microstate classes only, and therefore specific to certain brain networks related to these states. If the latter was the case, EEG microstate changes might serve as a possible surrogate marker of MS pathology.

2. Methods

2.1. Subjects

The study was approved by the local ethics committee, and all participants gave written informed consent for their participation in accordance with the Declaration of Helsinki. From a cohort of 86 patients with MS, in which 256-channel high-density EEG was recorded at the Outpatient Clinic of Neurology, University Hospital Basel, a total of 53 patients with confirmed relapsing-remitting multiple sclerosis (RRMS) according to McDonald's diagnostic criteria (Polman et al., 2011) were selected. The following criteria were used: (1) an Expanded Disability Status Scale (EDSS) ≤4 (Kurtzke, 1983); (2) right-handedness; (3) neither clinical relapse nor corticosteroid therapy for at least 6 weeks prior to inclusion in the study; and (4) no other neurological diagnoses or major psychiatric illnesess according to the DSM-IV-TR criteria. Matched to this patient sample, we also selected 49 right-handed healthy control subjects with no history of neurological or psychiatric condition. The demographic details are summarized in Table 1. There were more males in the control group, but the difference was not significant.

2.2. Neuropsychological assessment

Patients with RRMS and healthy controls who participated in the study underwent neurological examination and neuropsychological evaluation, including several established tests known to best describe the cognitive dysfunction in the context of MS (Papadopoulou et al., 2013): Laterality Index of Handedness (LIH) was assessed by the Edinburgh Handedness Inventory (Oldfield, 1971); right-handedness was defined by a LIH > 30. Visuoperceptual processing and psychomotor speed and working memory were tested with the Symbol Digit Modalities Test (SDMT; Benedict et al., 2008), giving the number of items processed in 90 s. Fatigue was evaluated using the Fatigue Scale for Motor and Cognitive Functions (FSMC), which was composed of both a cognitive sub-score (cog) and a motor sub-score (mot) (Penner et al., 2009); each sub-score summed the patient's rating on a 10-item scale. Depression was scored with the German version (Allgemeine Depressions Skala-L [ADS-L]) of the Center for Epidemiologic Studies Depression Scale (CES-D) (Hautzinger and Bailer, 1991), which resulted in a score from the patient's rating on a 20-item scale.

2.3. EEG data acquisition and preprocessing

During data acquisition, the participants sat calmly in a chair with their eyes closed, without falling asleep, and scalp EEG was recorded over 12 min with a high-density, 256-channel EEG system (Netstation 200, using a HydroCel Geodesic Sensor Net, Electrical Geodesics, Inc., Eugene, OR). The electrode net was placed relative to the preauricular points and Fz, Cz, and Oz as landmarks. Electrode impedances were kept below 40 kΩ in order to ensure good quality of data acquisition (Ferree et al., 2001). Recording band-pass was 0.1 to 100 Hz; the sampling frequency 1 kHz; and the vertex was used as the recording reference. A subset of electrodes was monitored online during recording in order to check for vigilance fluctuations and ensure that the participant did not fall asleep. Offline, the EEG was band-pass filtered between 1 and 40 Hz; electrodes on the cheeks and neck were excluded, resulting in 204 electrodes that were kept for further analysis. Artifact-free EEG epochs were then selected from each 12-min recording. Epoch length varied depending on the occurrence of visually identified artifacts, which included eye blinks, muscle activity and DC shifts, or any other intermittent high-amplitude deflections on any electrode. The total of artifact-free segments covered at least 5 min of resting EEG. Independent

Table 1
Demographics (mean and standard deviation).

	Patients		Controls	
	N = 53		N = 49	
Females/males	45/8		33/16	
Age [y]	37.69	±7.10	36.35	±8.20
Education [y]	14.64	±2.69	15.27	±2.22
Disease duration [y]	9.99	±6.09		
Annualized relapse rate (2y-ARR)	0.58	±0.68		
Expanded Disability Status Scale (EDSS)	2.12	±0.97		
Kurtzke Functional System Score – visual (FSS-vis)	0.32	±0.83		
Kurtzke Functional System Score – mental (FSS-ment)	0.91	±0.84		

For detailed patient specification, see Supplementary Table 1.