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Original article

Altered network recruitment in multiple sclerosis patients during resting state

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ABSTRACT

Background: Electroencephalography (EEG) allows a versatile recording of neuronal activity in neurological disorders. Signal analytical techniques like time-frequency analysis (TFA) can uncover latent information in the EEG of patients. Classically, EEG and TFA analysis relies on predefined frequency bands. Cluster-based permutation statistics provides an unbiased statistical comparison of high dimensional neurophysiological data, stabilizing the measured effect size and increasing the probability of uncovering the main effect present.
Methods: Resting state surface EEG recordings from 51 Multiple Sclerosis (MS) and 51 control patients were analyzed using TFA and compared by cluster-based permutation statistics. We further correlated results with disease characteristics, retinal nerve fiber layer (RNFL) thickness assessed by optical coherence tomography, evoked potentials (EPs), and neuropsychological data.
Results: We detected increased power in the low and high beta frequency bands in MS compared to control patients in a subset of recording sites. Spectral power in the high beta band of resting state EEG recorded at O1 negatively correlated with the RNFL thickness. Furthermore, differences in low and high beta power were dependent on the EP score of MS patients.
Conclusion: Our results suggest a more desynchronized EEG activity in MS patients compared to controls, correlating with clinical markers of disease severity. The findings indicate differential brain network recruitment that may be the result of compensatory mechanisms and the basis for clinical impairment in MS.

1. Introduction

Multiple Sclerosis (MS) is a frequent chronic inflammatory and neurodegenerative, demyelinating disease of the central nervous system (CNS) representing a major cause of disability, especially among young adults (Husseini et al., 2024). Based on the established classification, MS can be divided into relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary progressive MS (PPMS). The majority of MS patients initially present with a relapsing-remitting disease course characterized by clearly defined attacks of worsened neurologic symptoms followed by partial or complete recovery periods. After a longstanding disease duration, a considerable number of RRMS patients develop SPMS, classically characterized by substantial neurodegeneration (Lublin and Reingold, 1996). Only a minority of MS patients present with a primary progressive disease course from disease onset.

However, the traditional classification of MS has been challenged in the last years by considering MS as a continuum (Portaccio et al., 2024). Previous studies indicate that neurodegeneration is already present during early disease stages in parallel to overt neuroinflammation (Woo et al., 2024). Thus, a deepened understanding of the molecular and neuronal network mechanisms underlying MS will refine our understanding of disease phenotypes and might facilitate novel treatment concepts.

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Pathophysiologically, MS was initially conceived as a CNS white matter disease. However, increasing evidence supported the concept that MS pathology affects both white and gray matter of the CNS (Andica et al., 2019; Lie et al., 2022) leading to a diverse clinical disease manifestation including visual, motor and sensory symptoms, gait disability, signs of cerebellar or brainstem deficits, bowel or bladder dysfunction, and cognitive impairment. Cognitive dysfunction in MS is complex and multifactorial, with both white and gray matter damage being implicated in its pathogenesis (Chiaravalloti and DeLuca, 2008; DeLuca et al., 2015).

Surface electroencephalography (EEG) presents a non-invasive, cost-effective, and widely available tool to assess largescale and widespread neuronal activity with high temporal resolution in neurological and non-neurological disorders (Sanei and Chambers, 2009; Torabi et al., 2017; Hernandez et al., 2023). In MS, EEG may be useful for early detection and monitoring of cognitive deficits, when structural changes are not yet detectable by magnetic resonance imaging (MRI), or to support the diagnosis of MS (Angelakis et al., 2004; Carrubba et al., 2012; Torabi et al., 2017; Jamoussi et al., 2023). However, appropriate signal-processing algorithms have to be used to uncover latent information within EEG signals that might guide diagnosis and strategic interventions with respect to disease states (Beniczky and Schomer, 2020). Typical EEG recordings are classified based on their frequency bands as delta (0.5 - 4 Hz), theta (4 - 7 Hz), alpha (8 - 12 Hz), low beta (11 - 17 Hz), high beta (25 - 30 Hz) and gamma (36 - 90 Hz) activity. Spectral analysis of resting state (awake, eyes closed) EEG rhythms indicated that MS patients show abnormalities in EEG power density with an increase at low frequencies and a decrease at higher frequencies (Leocani and Comi, 2000). An increased theta/beta band ratio, particularly in frontal brain regions, might be indicative of deterioration in information processing speed and attention performance in MS patients (Keune et al., 2017; Keune et al., 2019).

Here we implemented time frequency analysis and non-parametric cluster-based permutation statistics to identify key network signatures in resting state EEG of MS patients and controls and to correlate network signatures to disease duration and clinical markers. The goal was to determine if EEG characteristics could serve as biomarkers in individuals with different MS states.

2. Methods

2.1. Identification of MS patients and controls

We retrospectively searched the clinical database of the Department of Neurology at the Heinrich Heine University (HHU) Düsseldorf, Germany, to identify patients diagnosed with MS (RRMS, SPMS, and PPMS) who have received an EEG recording between 2016 and 2021 as part of the clinical routine workup at that time. MS patients were diagnosed according to the current revision of the McDonald criteria at the time of EEG recording (Thompson et al., 2018). Patients without any signs of a neurological disorder affecting the central nervous system (CNS) were used as controls.

2.2. EEG recording

In each experimental subject, resting state EEG was recorded for a duration of 30 minutes using a standard 10-20 electrode system. Patients were seated in an armed chair and asked to relax with their eyes closed. EEG signals were filtered with a 0.53 Hz high-pass and 70 Hz low-pass filter and digitalized with a constant sample rate of 200 Hz by the Nihon Kohden (Shinjuku, Japan) acquisition system.

2.3. Assessment of demographics, disease characteristics, and clinical parameters

For all MS patients, basic demographics (age, sex) and clinical disease characteristics (type of MS, time since first symptoms, Expanded Disability Status Scale (EDSS), relapse at time of EEG recording, current and prior disease-modifying therapies (DMTs), comorbidities, treatment with anti-seizure medication (ASM), sedatives (SED), and antipsychotics (Apsych) were assessed. Furthermore, evoked potentials (EPs) and optical coherence tomography (OCT) scans were retrospectively analyzed (if available). Methodological details on EP recordings and OCT measurements are provided in supplementary methods.

Analysis and interpretation of VEPs, SSEPs, and MEPs were performed as described previously (Meuth et al., 2011). Cut-off values are summarized in Table 1. An ordinal EP score was calculated for MEPs, SEPs, and VEPs, respectively (Table 1).

Cognitive function was assessed using the Montreal cognitive assessment (MoCA) (Nasreddine et al., 2005). MoCA was performed by a trained neuropsychologist.

2.4. Data analysis and statistics

2.4.1. Data preprocessing

Preprocessing of the resting state EEG was performed offline using Spike2 analysis software.

Following direct current (DC) removal, EEG traces were subdivided into three seconds lasting bins and epochs containing movement artefacts were excluded from further analysis. Selected epochs were transferred to Matlab (The MathWorks, Natick, MA, USA) and subjected to time frequency analysis (TFA) using hanning tapering to assess spectral power (Mitra and Pesaran, 1999). TFA was performed between 1 - 30 Hz with an analysis window of 1 s shifting along the segments in steps of 50 ms, which yields a frequency resolution of 1 Hz.

2.4.2. Statistical analysis and data visualization

Statistical comparison between EEG power of time-frequency spectra derived from the EEG of MS patients and controls was performed by means of cluster-based permutation statistics providing a reliable statistical tool for the analysis of neurophysiological data requiring comparison along multiple time and frequency bins, with efficient control of type I errors (Maris and Oostenveld, 2007). In short, the following steps are taken:

1) First, the datasets of group 1 (MS patients) and group 2 (controls) are compared by Students' t-test. All data points (time-frequency points) reaching significant difference are grouped to a cluster based on

Table 1
Pathological values and interpretation of MEP, SEP, and VEP measurements.

MEP	SEP	VEP
CMCT latency depending on age	N20 latency (N.medianus) or P40 latency (N.tibialis) depending on body size	P100 latency > 120 ms
Latency side difference ≥ 1.5 ms	Latency side difference ≥ 1.2 ms (UE) or ≥ 2.3 ms (LE)	Latency side difference > 8 ms
Cortical amplitude < 15% of peripheral amplitude (UE) and < 10% (LE)	Amplitude ≤ 1.5 µV (UE) or ≤ 0.7 µV (LE)	N75-P100 amplitude < 5 mV
Amplitude side difference > 50%	Amplitude side difference > 50%	Amplitude side difference > 50%

EP score:
0 - no pathological value on both sides
1 - pathological value on one side, decrease in amplitude or abnormal latency
2 - pathological value on one side, abnormal amplitude and latency or pathological value on both sides, latency or amplitude
3 - pathological value on both sides, one side with abnormal latency and amplitude plus one side with abnormal amplitude or latency
4 - pathological values on both sides

CMCT - Central motor conduction time; EP - evoked potential; LE - lower extremity; MEP - motor evoked potentials; SEP - somatosensory evoked potentials; UE - upper extremity; VEP - visual evoked potentials.

temporal adjacency. For each cluster, the sum of the T-values (test-statistic of the previous t-test) is calculated.
2) Next, the original time-frequency datasets are randomly distributed to either group 1 or 2. By this, the difference between controls and patients' group is lost.
3) For each random distribution (in our case 500) step 1 is performed.
4) Lastly, the summed t-values of a cluster (calculated in step 1) for the real dataset and the random distributions are displayed in a histogram. In case the summed t-value computed from the real dataset is positioned below the 2.5-th or above the 97.5-th quantile of the histogram ($p < 0.05$ two-sided), the real dataset deviates (with a certainty of 95%) from randomized datasets, which do not have a difference between controls and patients. The real cluster is thus considered as representing a significant difference between controls and patients.

Time-frequency analysis and cluster-based permutation statistics were performed with the aid of FieldTrip, an open-source Matlab-based toolbox for advanced analysis of e.g. electrophysiological data (Oostenveld et al., 2011).

Following cluster-based permutation statistics the average spectral power was calculated for each identified significant cluster that indicates a significant difference in the spectral power between the EEG of MS patients and controls within a certain frequency range and at a certain recording location. The averaged power of a cluster was then correlated with the age of the subjects, the disease duration of the patient, the EDSS at time of EEG recording, the MoCa score as well as the thickness of the RNFL of the right and left eye. Statistical significance of the correlations was assessed by means of multiple regression analysis using SPSS (IBM Statistics, version 28).

Lastly, spectral power of the significant clusters was compared between MS patients classified based on the EP scores derived from the SEPs, MEPs, and VEPs, respectively, using ANOVA, with EEG power as dependent variable and severity class of the EP (EP score) as between subject factor (SPSS, IBM Statistics, version 28).

Figures were created using Inkscape v. 1.4 (Inkscape, http://www.inkscape.org).

3. Results

3.1. Clinical cohort characteristics

In total, 51 MS patients and 51 controls were included in the study. Basic demographics and disease characteristics are summarized in Table 2. 4/51 MS patients had a history of seizures (6 years, 3 years, 1 year, and 2 days prior to EEG recording) but no seizure activity was recorded during the resting state EEG measurements. None of the control patients experienced seizures before.

Table 2
Basic demographics and disease characteristics.

	MS cohort	Control cohort
Number of patients	51	51
Age (median with range) [y]	49 (23-73)	45 (18-84)
Sex (% female)	65	46
Type of MS (%)	RRMS: 34 SPMS: 13 PPMS: 4	N/A
Disease duration (median with range) [y]	14 (0-43) [*1]	N/A
Relapse at time of recording (%)	14	N/A
ASM/SED/Apsych (%)	29[*2]	18[*3]

ASM - anti-seizure medication; Apsych - antipsychotics; MS - multiple sclerosis; N/A - not applicable; SED - sedative; Y - years. [*1] 11 missing values
[*2] 24 missing values
[*3] 2 missing values

3.2. Preserved alpha power in the resting state EEG of MS patients

First, we compared resting state EEG recordings between MS patients and controls. Fig. 1A depicts exemplary recordings of an MS patient and a control subject, respectively. No visible differences in EEG waveform and morphology were observed between the groups.

For both MS patients and control subjects time frequency analysis revealed pronounced alpha activity characteristic for an EEG during relaxed wakefulness with eyes closed (Halgren et al., 2019) and no significant differences in alpha power were detected between MS patients and controls in any of the recording sites by cluster-based permutation statistics ($p > 0.05$) (Fig. 1B).

3.3. MS patients show altered spectral power of resting state EEG

Despite a preserved dominance of alpha power in the resting state EEG of MS patients, cluster-based permutation statistics revealed a significant alteration in the resting state EEG of MS patients compared to controls at higher frequencies. More specifically, MS patients showed more pronounced power in the low beta frequency range (11 - 17 Hz) at parietal (P3, P4, Pz) ($p = 0.008$, $p = 0.016$, and $p = 0.035$), temporal (T6, T4) ($p = 0.016$, $p = 0.01$), and occipital (O1, O2) ($p = 0.014$, $p = 0.012$) recording sites. Furthermore, a higher power in the high beta frequency range (25-30 Hz) at occipital (O1, O2) ($p = 0.04$, $p = 0.012$), parietal (P3) ($p = 0.04$), central (C3, C4) ($p = 0.031$, $p = 0.04$), and frontal (FP1) ($p = 0.035$) recording sites was observed in MS compared to control patients. These findings demonstrate a more desynchronized resting state EEG, likely caused by hampered communication between brain regions due to reduced myelination in MS patients (Fig. 2A).

To assess the effect of age on spectral power, average spectral power in the low beta (11 - 17 Hz) and high beta power of the resting state EEG were correlated with the age of the participants. Interestingly, while no significant correlation between spectral power and age was revealed in control subjects (all $p > 0.05$), a small but significant positive correlation between high beta power (25-30 Hz) and age was detected at central recording sites (C3, C4) of MS patients. These findings constitute a more desynchronized EEG (i.e. increasing power values in the high beta frequency range) with increasing age. Similarly, significant correlations between low beta power (11 - 17 Hz) and age were revealed at parietal recording sites in MS patients but not in controls (Table 3).

3.4. Relating clinical scores with resting state spectral power alterations

As mentioned above there was a significant positive correlation between beta power and age in the resting state EEG of patients. This increasing desynchronization over time, however, was not reflected in either the disease duration, the EDSS score or the MoCa score as indicated by non-significant beta-power X EDSS score, beta-power X disease duration and beta-power X MoCa score correlation (**Supplementary Table 1**).

On the other hand, the altered spectral power in the resting state EEG of MS patients was reflected in EP and OCT pathologies. More specifically, a marginally significant ($p = 0.05$) negative correlation ($r^2 = -0.29$) between spectral power in the high beta band (25 - 30 Hz) of resting state EEG recorded at the right occipital cortex (O1) and the thickness of the RNFL of the left eye was found. These findings demonstrate an increased desynchronization of the EEG of vision associated brain regions with increasing loss of the RNFL (Fig. 3A).

In addition to that, significant differences in averaged spectral beta power of resting state EEG were found between patients with different EP scores (Fig. 3B-E). Regarding the MEP of the UE, there was a significant increase in low and high beta power in EEG recordings taken at site P3 in the score group 1 compared to the score groups 0 and 2 ($p < 0.02$; Fig. 3B-C). A similar increase in high beta power in EEG recordings taken at site FP1 was seen in MEP score group 1 ($p = 0.012$; Fig. 3D). Regarding SSEPs, low beta power was increased in score group 3 in

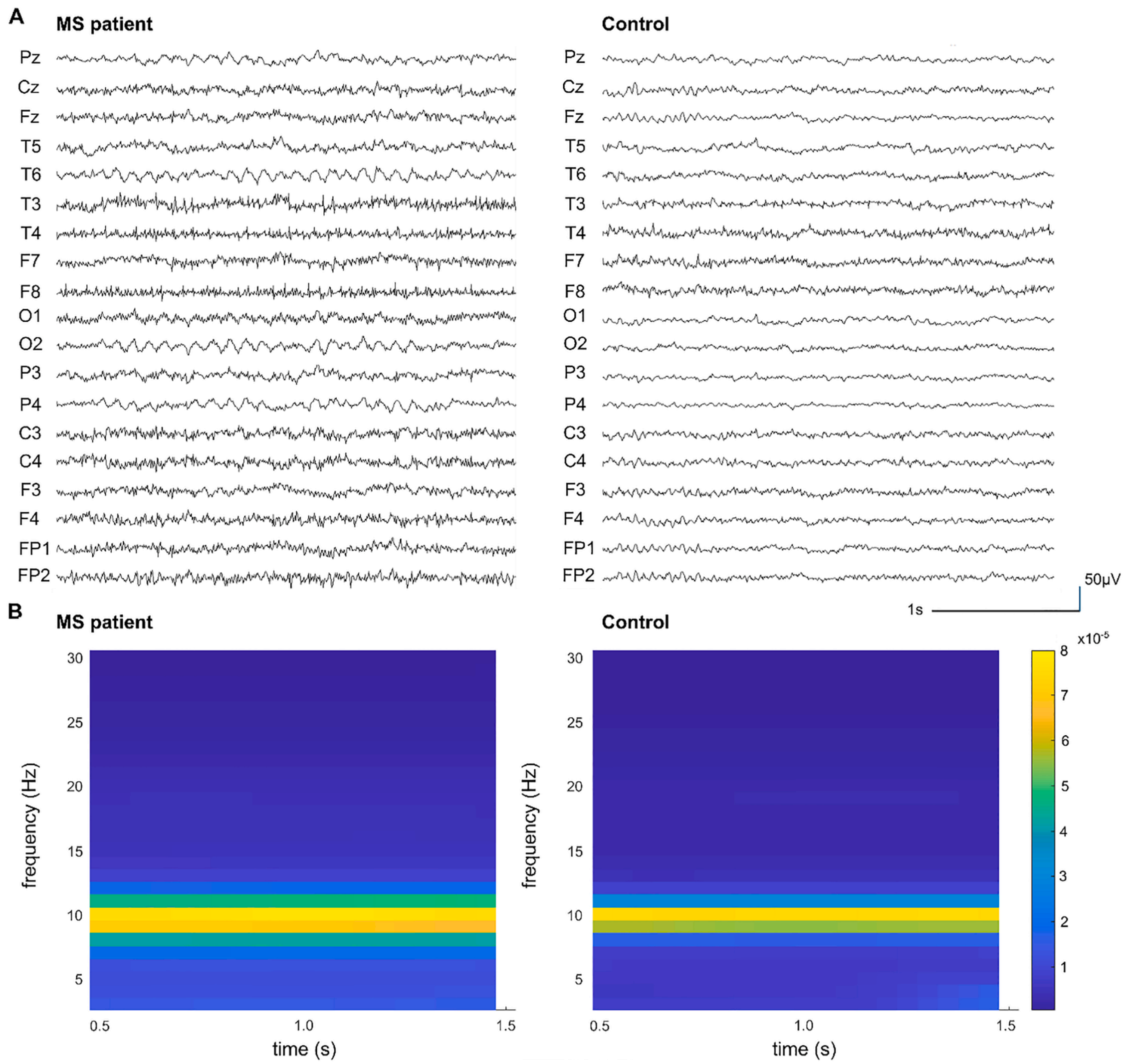

Fig. 1. No significant differences in alpha power between MS patients and controls. **A** Exemplary resting state EEG recording of a patient with MS (left) and a control subject (right). Patients were recorded in awake, relaxed condition with eyes closed for a duration of 30 minutes. **B** Average time-frequency power spectrum of the occipital EEG (O2) for patients with MS (left) and control subjects (right). Note the prominent presence of alpha activity (8 - 12 Hz) in both MS patients and controls typical for the resting state condition with eyes closed. No significant differences in occipital alpha power were revealed between MS patients and controls by non-parametric cluster-based permutation statistics. *EEG - electroencephalography; MS - multiple sclerosis.*

comparison to score groups 0 and 1 ($p = 0.04$; Fig. 3E).

4. Discussion

In the present study, we performed time frequency analysis of resting state EEG obtained from 51 MS patients and 51 controls. Differences in spectral power identified by cluster-based permutation statistics were correlated to clinical scores to assess if EEG power might function as a latent biomarker for disease severity. Spectral power in the high beta band (25 - 30 Hz) of resting state EEG recorded at the right occipital cortex (O1) negatively correlated with the thickness of the RNFL of the left eye. Furthermore, differences in low and high beta power were observed depending on the EP score group of MS patients.

Spontaneous resting EEG activity can serve as an objective measure to discriminate physiological from pathophysiological neuronal network function. Due to its high temporal resolution and at least for cortical recordings good spatial resolution, distinct network signatures of network adaptation and maladaptation can be assessed. Hereby global alpha power and the frontal theta/beta ratio were identified as candidate biomarkers (Seraji et al., 2021). In the present study, we detected a distinct network signature in patients with multiple sclerosis, characterized by alterations in the spectral power of resting state EEG recordings. We implemented cluster-based permutation statistics, a reliable statistical method for the analysis of neurophysiological data requiring comparison along multiple time and frequency bins, with efficient control of type I errors, i.e. false positives (Maris and Oostenveld, 2007). Moreover, since this test does not rely on averaging along predefined frequency bands, bearing the risk of occluding existing effects, this test can be regarded as unbiased in the detection of differences.

The most striking finding of the current study was a significant higher power in the low (11 - 17 Hz) and high (25 - 30 Hz) beta frequency range of MS patients mainly in central, parietal and occipital regions, indicating stronger desynchronization, while the alpha power in resting eyes closed conditions was preserved. A healthy neuronal network comprising of an optimized network structure, a balanced excitation / inhibition ratio and distinct numbers of hypo-, normo- and hyperactive neurons is the basis for normal brain function (Ellwardt et al., 2022) and characteristic EEG waves are their physical expression. Cortical beta activity is based on spiking interactions within local microcircuits composed of interconnected excitatory and inhibitory neurons (Jensen et al., 2005) via synchronization of excitatory synaptic

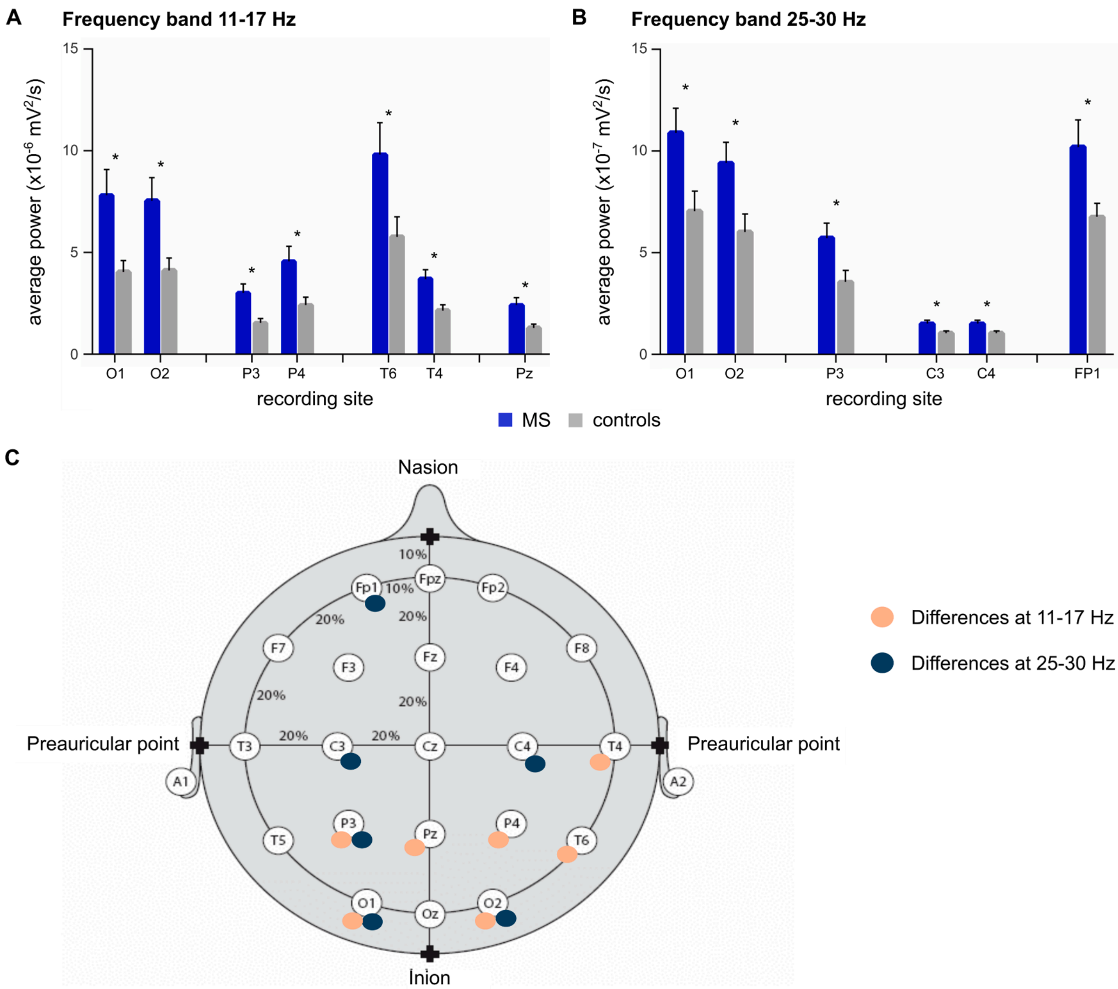

Fig. 2. Differences in beta frequencies between MS and control patients in a subset of recording sites. Barplots depicting the average spectral power in the low beta (11 - 17 Hz) (**A**) and high beta (25 - 30) frequency range (**B**) during resting EEG seen for patients with multiple sclerosis (blue) and control subjects (gray). While no significant differences were revealed for spectral power in the prominent alpha frequency range, significant higher spectral power was revealed for MS patients compared to controls in the low beta (left) and high beta (right) frequency range. Effects were seen across multiple recording sites (**C**) indicating a significantly more desynchronized EEG for MS patients compared to controls. *EEG - electroencephalography; MS - multiple sclerosis.*

bursts and modulation by subcortical or thalamic inputs (Sherman et al., 2016). Within this model, inhibition controls the firing rate produced by excitatory pyramidal neurons and transfer of activity via their connections, thereby affecting excitability level both locally and within distributed networks (Ulanov and Shtyrov, 2022). In MS models, periods of hyperexcitability represent damaging events that alter neuronal and network functions and are associated with behavioral changes (Cerina et al., 2017; Cerina et al., 2018; Ellwardt et al., 2022). Maladaptation on the level of ion channel expression and excitation / inhibition balance occur in thalamus and cortex (Chaudhary et al., 2022; Oniani et al., 2022; Kapell et al., 2023; Labbaf et al., 2023; Fazio et al., 2024; Stroh et al., 2024). Some of these plastic changes are associated with increased beta power of cortical activity. Since changes in beta oscillatory processes might be associated with behavioral changes in motor and cognitive function, the increased beta activity seen in the present study may be regarded as the result of response mechanisms that might be maladaptive.

Along those lines, a previous EEG study found increased beta power over frontal-central regions in MS patients (Colon et al., 1981). In this study, the amount of beta activity was associated with a higher degree of disability (Colon et al., 1981). Furthermore, increased beta and gamma band activity was detected over occipital and frontal areas during a sensory task with RRMS patients being more affected compared to a subgroup of patients with a benign disease course (defined as at least 8 years of disease evolution and an EDSS score ≤ 3.5) as well as compared to controls (Vazquez-Marrufo et al., 2008). The association between an increased beta activity and disease severity is not only limited to MS but has been described in other neurological conditions, e.g. neurodegenerative disorders (Morelli and Summers, 2023). While in our cohort no correlation between beta power and the EDSS score was revealed, altered spectral power in the resting state EEG of MS patients was reflected in more specific clinical markers for MS severity. Here, a negative linear correlation between spectral beta power in the occipital EEG of the right hemisphere and the thickness of the left retinal nerve fiber layer was detected. This indicates that a more desynchronized EEG is associated with a thinner retinal nerve fiber layer. In addition, altered spectral power in the resting state EEG of the parietal cortex showed a higher desynchronization with increasing severity scores of somatosensory evoked potentials. Lastly, a nonlinear relation (inverted bell shape) was revealed for beta power of the resting state EEG and severity score assessed with motor evoked potentials.

Visual dysfunction is among the most common and early symptoms of MS and RNFL thickness is a structural biomarker for axonal loss in the disease (Fisher et al., 2006). Visual tests addressing specific aspects of vision like spatial resolution revealed that MS preferentially affects visual sensitivity at lower spatial frequencies, thereby indicating that the

Table 3
Correlation of spectral power in the low and high beta frequency range and age of MS patients and controls.

Recording site	MS - r^2	MS - p-value	Control - r^2	Control - p-value
Low beta frequency range				
O1	0.090	0.520	0.120	0.790
O2	0.110	0.540	0.080	0.910
P3	0.120	0.040*	0.300	0.300
P4	-0.140	0.048*	0.170	0.980
T6	0.016	0.310	0.090	0.600
T4	-0.038	0.480	0.200	0.820
Pz	-0.07	0.170	0.150	0.290
High beta frequency range				
O1	0.024	0.400	0.060	0.680
O2	0.008	0.670	0.090	0.940
P3	-0.002	0.730	0.180	0.830
C3	0.140	0.039*	0.190	0.750
C4	0.150	0.038*	0.195	0.770
FP1	0.059	0.870	0.290	0.670

As differences in spectral power might be related to variances in age, the individual spectral power values in high and low beta frequency range were correlated with the age of each subject using linear regression. Displayed are the correlation coefficient r^2 as well as p-values revealed by multiple regression analysis, assessing the predictive value of power values at a certain recording site cleaned out for the effects of spectral power at other recording sites. Of note, while spectral power had no predictive value for age at any recording site in control subjects, a slight but significant predictive value was revealed in MS patients for low beta power of the parietal EEG at recording sites P3 and P4 and high beta power of the central EEG at recording sites C3 and C4.

magnocellular visual pathway is affected, which is most sensitive at low contrast and low spatial frequencies (Regan et al., 1977). In line with the increased desynchronization in occipital cortex found in the present study, it has been observed before that synchrony of the magnocellular visual pathway is reduced in MS patients (Seraji et al. 2021). The latter was associated with changed network properties, namely a reduction in the small-worldness of the respective neuronal network. It is accepted that beta and gamma bands are generated in frontal areas (Gómez et al., 2006). Therefore, the increment of spectral power in higher frequency bands in MS in more occipital areas may indicate maladaptive mechanisms in response to the progression of the disease.

In relation to other frequency bands, previous studies revealed an increased frontal theta/beta ratio in MS patients (Keune et al., 2017). In healthy young adults, the frontal theta/beta ratio is negatively correlated with executive function, while the respective frequency band alone is not (Perone et al., 2018). Smaller theta/beta ratios are indicative of better cognitive and executive control as well as increased vigilance (Putman et al., 2014; Angelidis et al., 2016; Angelidis et al., 2018; van Son et al., 2018).

The map of increased average beta activity (especially the low beta band) in the present study resembles activity during the EEG microstate B that is associated with the visual network (Tarailis et al., 2024). Microstates are transient (lasting some milliseconds up to seconds), reoccurring EEG activity patterns with fixed topography, but varying strength and polarity, that probably represent the neural correlates of consciousness (Michel et al., 2024). The microstate B, showed a significant increase in the beta band in fatigued MS patients compared to healthy subjects (Baldini et al., 2024). Alpha is the dominant frequency in the human EEG recordings of awake adults (Klimesch, 1999). Alpha power is changed with aging and in subjects with a variety of different neurological disorders. Previous studies revealed increased global alpha power in MS patients (Keune et al., 2017) or topographically widespread lower amplitudes of cortical sources of alpha rhythms in two sub-groups of MS patients (RRMS and SPMS) compared to the healthy control group (Babiloni et al., 2016). In the present patient cohort, the prominent alpha rhythm reflects a state of relaxation and wakefulness that is blocked during visual input. Likewise, the brain areas associated to the microstate B map that are located in the occipital lobe and involved in MS fatigue usually show both a spontaneous and dominant oscillation in the alpha band (Gobbi et al., 2014; Baldini et al., 2024). The increased contribution of the microstate B network to beta activity might point to possible alterations of sensory functions and contribution to the perception of fatigue. Unfortunately, fatigue was not assessed in our MS cohort. However, based on previous data it is conceivable that the increased beta activity is associated with fatigue on the symptom level.

Although there are some contradictory findings, several EEG studies indicate that resting state beta power tends to increase with age (Kang et al., 2024). Indeed, other studies reported that with the eyes closed beta absolute activity was either lower in older adults (Breslau et al., 1989; Vysata et al., 2012) or unchanged between age groups (Volf and Gluhih, 2011; Jabès et al., 2021). In the current study, we could not detect a significant correlation between spectral power and age in the control group, while there was a small but significant positive correlation in the MS cohort indicating that differences in beta power were not attributed to the normal physiological process of aging itself in our cohort.

Our study is limited by the small sample size, differences in sex between cohorts, and pre-treatment with different immunotherapies as well as co-medications. Even though we are aware that the disease course of MS patients can affect resting state EEG rhythms, no subgroup analyses could be performed as part of the current study. Previous studies reported an effect of immunotherapies and benzodiazepines on EEG activity (Colon et al., 1981; van Schependom et al., 2019). Thus, we cannot rule out a relevant confounding of our results by treatment. Furthermore, the presence of neuropathic pain of our patient group may have influenced the increase of beta power in the present study. Differences in spectral power of MS patients with and without central neuropathic pain were detected (Krupina et al., 2019). Only in the group with pain, the absolute and relative power spectral density (PSD) in the beta1 and beta2 bands increased and exceeded that in patients without pain. Selection bias has been reduced by offering EEG as an optional clinical routine workup to all MS patients at the Department of Neurology at HHU Düsseldorf between 2016 and 2021. Nevertheless, we cannot completely rule out that MS patients presenting with symptoms suggestive of a seizure, or with unusual clinical and/or radiological features, were more likely to undergo EEG analysis.

However, our study provides an unbiased statistical analysis of EEG data by performing cluster-based permutation statistics to identify alterations in EEG activity between MS patients and controls which correlate with clinical parameters of disease severity in the MS cohort.

5. Conclusion

The EEG characteristics of MS patients in states of relaxed wakefulness point to more desynchronized activity compared to controls and reveal activity in the visual network while eyes are closed. The findings indicate a distinctive network state as the basis for cognitive, sensory and motor dysfunction.

Ethical standards

The study was performed according to the Declaration of Helsinki and was approved by the local Ethics Committee of the Board of Physicians of the Region Nordrhein and of the Medical Faculty at HHU Düsseldorf, Germany (reference number: 5794R). Written informed consent was obtained from patients for the retrospective analysis of data collected during clinical routine workup.

Data sharing

Data underlying this study are registered with the ABCD-J data catalogue at https://data.abcd-j.de/dataset/1015ed7c-0a3d-4dfc-9c4f-11fe71673a41/a17732752d8df605f69bda66c244f112 857ba23c. Further information, resources, anonymized clinical and EEG data can

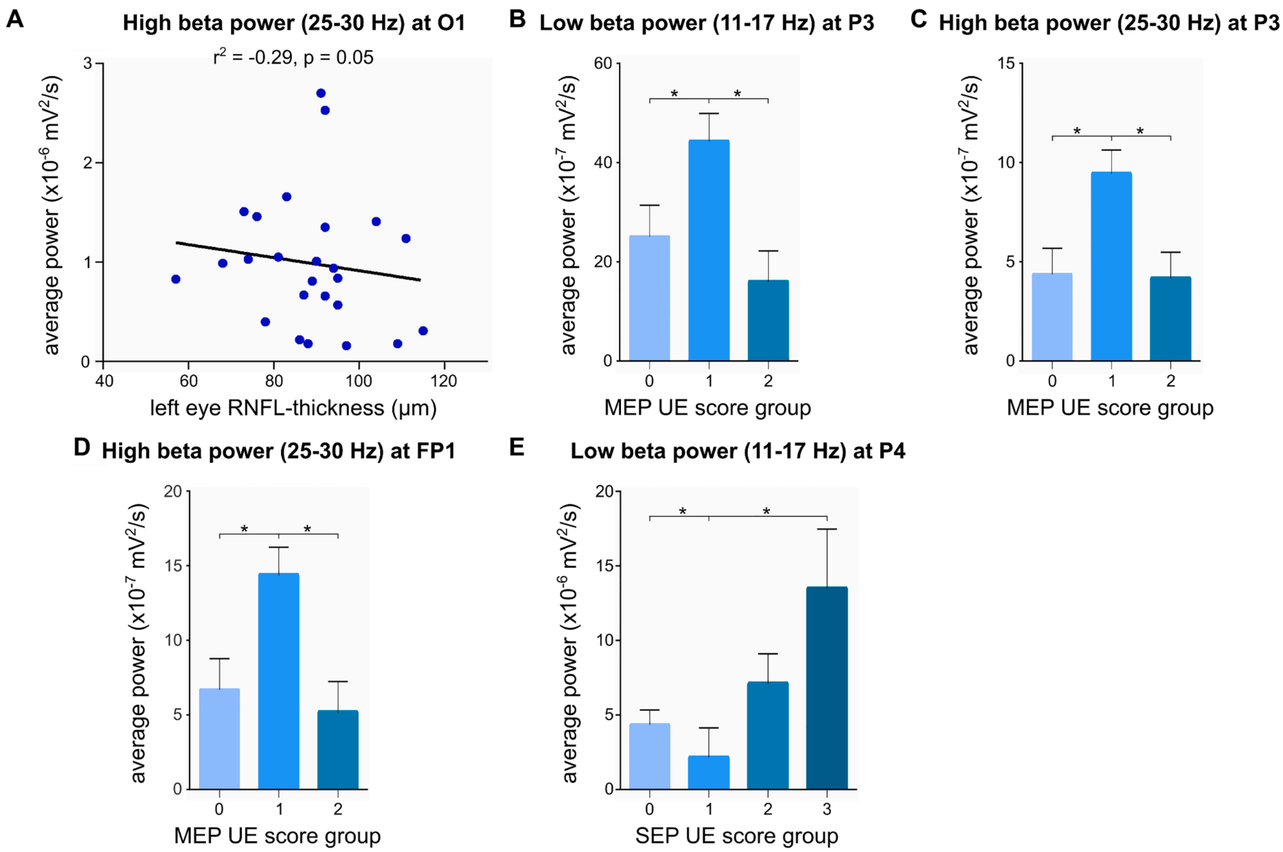

Fig. 3. Pathologies in EPs and OCT are associated with increased beta power in EEG recordings of MS patients. In a subset of MS patients MEPs for upper ($n = 22$) and lower ($n = 12$) extremities, VEPs ($n = 29$), SEPs for upper ($n = 28$) and lower ($n = 21$) extremities as well as the thickness of the RNFL of both eyes ($n = 35$) were measured. **A** Correlation between spectral beta power assessed in EEG recordings taken at recording site O1 and the thickness of RNFL of the left eye. Statistical significance of the correlations was assessed by multiple regression analysis. **B-E** Barplots depicting the significant differences in spectral power between EP scores, which were calculated based on MEP, SSEP, and VEP data, respectively (Table 1), and spectral beta power assessed in EEG recordings taken at recording sites P3 (B, C), FP1 (D), and P4 (E). Statistical significance was assessed using ANOVA, with EEG power as dependent variable and EP score as between subject factor. *EEG - electroencephalography; EP - evoked potentials; MEPs - motor evoked potentials; MS - multiple sclerosis; OCT - Optical coherence tomography; RNFL - retinal nerve fiber layer; SEPs - somatosensory evoked potentials; VEPs - visual evoked potentials.*

be requested via the catalogue item and will be fulfilled by the Lead Contact, Saskia Räuber (SaskiaJanina.Raeuber@med.uni-duesseldorf.de).

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CRediT authorship contribution statement

Annika Lüttjohann: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Saskia Räuber:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Melanie Korsen:** Resources. **Alice G. Willison:** Writing – review & editing. **Saskia Elben:** Investigation, Data curation. **Christina B. Schroeter:** Writing – review & editing. **Tobias Ruck:** Writing – review & editing, Resources. **Philipp Albrecht:** Writing – review & editing, Resources. **Marc Pawlitzki:** Writing – review & editing, Resources. **Albrecht Stroh:** Writing – review & editing, Resources. **Nico Melzer:** Writing – review & editing, Resources. **Thomas Budde:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Conceptualization. **Sven G. Meuth:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2026.107111.

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