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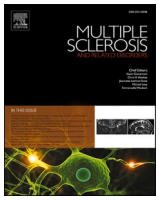

Fatigability-related oscillatory brain activity changes in people with MS

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ABSTRACT

Background: Fatigue, a multidimensional and challenging symptom associated with various underlying conditions, can manifest as a subjective feeling and a performance fatigability. The latter is often defined as an objectively measurable performance decline with time on task. Both syndromes are highly prevalent in people with multiple sclerosis (pwMS) and are often resistant to medical therapy. In the absence of valid and reliable objective parameters, the current cognitive fatigue diagnosis remains purely subjective. Assessing brain wave activity changes has repeatedly been a viable strategy for monitoring cognitive fatigue in healthy subjects. In this study, we aimed to investigate oscillatory brain activity changes and their associations with subjective fatigue in pwMS.

Methods: We enrolled 21 pwMS and 21 healthy controls (HC) in this study. Subjects performed a sustained attention task divided into six blocks over the course of 30 minutes, and underwent resting state EEGs before and after the task. During the task, subjects were repeatedly asked to rate their subjective levels of mental fitness, mental exhaustion, and mind wandering. Using Linear Mixed Models, we explored fatigability-related changes by focusing on the time course of changes in reaction time variability, subjective ratings of fatigability, as well as frontomedial theta, and occipital alpha power. We further investigated initial and fatigability-induced differences between pwMS and HC at rest. Finally, Pearson correlations were used to examine the relationship between subjective fatigue and objective fatigability parameters.

Results: Our results revealed a systematically stronger fatigability development in pwMS that was objectively measurable. PwMS reported lower mental fitness levels and demonstrated greater variability in reaction times with time on task. Occipital alpha power significantly increased during the task. Especially for upper alpha power, this increase was significantly more prominent in pwMS compared to HC. However, the time-on-task-induced changes in our study were not associated with the subjective fatigue ratings.

Conclusions: The results of this study expand the understanding of the neural mechanisms underlining cognitive fatigability and may complement the fatigue diagnosis and therapy monitoring with quantitative objective methods.

1. Introduction

Fatigue affects a large proportion of people with multiple sclerosis (pwMS) and often restricts their life already at the earliest stages of the disease (van der Vuurst de Vries et al., 2018). It dramatically worsens the quality of life in pwMS and is the leading cause of early retirement (Kobelt et al., 2017, Krause et al., 2013). Yet, to date, the pathophysiological mechanisms underlying MS-related fatigue are still unclear, and disease-specific therapy is lacking.

Fatigue is a multidimensional symptom with physical, cognitive, and psychosocial components (Fisk et al., 1994). From a clinical point of view, as is also reflected in the fatigue definition of the MS council, fatigue is a subjective symptom "that is perceived by the individual" (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Therefore, the current fatigue diagnosis is mainly based on subjective questionnaires that measure fatigue dimensions either individually or collectively. Those self-reports, however, are of retrospective nature and, therefore, mood-sensitive and subject to psychological biases. Additionally, many items coincide with items regarding symptoms of depression, making differentiation difficult (Bol et al., 2009). Thus, for a

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better pathophysiological understanding and treatment evaluation of MS-related fatigue, it is of utmost importance to expand the fatigue diagnosis with the objective assessment of its impact on patients' daily performance.

However, so far, available studies report little to no association between the perceived feeling of fatigue and an objectively measurable performance decline (Enoka et al., 2021; Linnhoff et al., 2019). Therefore, the current understanding of the fatigue concept includes both components as distinct symptoms. Fatigue, the subjective feeling of exhaustion, is referred to as the trait component. And fatigability, the inability to sustain physical or mental performance over an extended period of time, is the state component (Kluger et al., 2013; Linnhoff et al., 2019). Both can either occur simultaneously or distinct from one another in pwMS (Enoka et al., 2021, Hanken et al., 2014).

Recently, progress has been made in objectively measuring physical fatigability using walking endurance or maximal voluntary contraction (MVC) force as objective parameters (Enoka et al., 2021, Kim et al., 2018). In contrast, a variety of objective parameters have been examined to measure cognitive fatigue, with inconsistent results. Thus, despite subjective reports of high levels of cognitive fatigue, pwMS are often able to maintain their behavioral performance when measured with mean reaction times and accuracy (Linnhoff et al., 2019). As a result, finer-grained behavioral analyses have been proposed, such as the analysis of reaction time variability (Bodling et al., 2012; Bruce et al., 2010). Other neuropsychological assessments that have been proposed, like the Paced Auditory Serial Addition Test (PASAT), are susceptible to learning strategies and are aversive for the participants (Agyemang et al., 2021).

Electrophysiological parameters have the advantage that they are not subject to psychological biases or subjective manipulation. Additionally, they give further insights into the neuronal alterations underlying fatigue and fatigability. In healthy subjects, cognitive fatigability has repeatedly been associated with increased frontomedial theta (fm-theta) as well as occipital alpha power (Boksem et al., 2005; Craig et al., 2012; Linnhoff et al., 2021; Tran et al., 2020; Wascher et al., 2014). Thus, an increase in alpha power was observed during resting state EEGs (Barry et al., 2007) or along with increasing error rates and reaction times during exhausting tasks (Gharagozlou et al., 2015; Wascher et al., 2014). According to the oscillatory model of sustained attention by Clayton et al. (Clayton et al., 2015), fatigability results in a systematic shift from fast to low-frequency waves. The authors integrate findings on oscillatory changes with time on task and current theories of sustained attention. They postulate that when a person fatigues, the increase in frontomedial theta power may reflect compensatory mechanisms to improve theta-driven cognitive control processes, whereas alpha power increases over task-relevant cortical areas (e.g., occipital areas in a visual attention task) may reflect suppression of information processing resulting in attentional deficits.

Finally, a large number of imaging studies demonstrated relations between MS-related fatigue and structural and functional abnormalities in the cortico–striato–thalamo–cortical network, the fatigue network (Ayache and Chalah, 2017). In particular, frontal activity changes have often been associated with increased subjective trait fatigue (Ayache and Chalah, 2017, Barbi et al., 2022). Frontally modulated compensatory mechanisms, such as increased fm-theta activity, might therefore be disturbed in pwMS, resulting in a stronger increase of occipital alpha power. Thus, the present study aimed to investigate oscillatory brain wave activity changes with time on task in pwMS and healthy controls (HC). We hypothesized that pwMS, compared to HC, will experience greater cognitive fatigability with time on task. This will lead to a more significant increase in subjective ratings as well as objectively measurable differences in reaction time variability and oscillatory brain wave activity.

2. Material and Methods

2.1. Participants

We enrolled 21 pwMS and 21 HC (see Table 1 for demographic and clinical characteristics). Inclusion criteria for HC included no history of neurological or psychiatric disorders, no color blindness, and no current depression (Beck Depression Inventory II - Fast Screen, BDI-FS $\leq$ 4) or sleep disorder (Epworth Sleepiness Scale, ESS $\leq$ 10). Inclusion criteria for pwMS were a minimum of three months since the last relapse or use of corticosteroids, no color blindness, no current neurological or psychiatric comorbidities, and no current treatment with fatigue or antidepressant medication. According to the cut-off criteria by Strober and Arnett (2015), three included pwMS had clinically meaningful depression ratings ($>$ 4 points) but did not have a diagnosed depression or took antidepressant medication. All pwMS were diagnosed with clinically definite MS according to the McDonald criteria and were recruited from the outpatient pool of the University Hospital of Magdeburg. Nineteen subjects had a relapsing-remitting course of MS, one a primary progressive, and one a secondary progressive form. Disease-modifying therapy (DMT) consisted of Glatirameracetat (n = 5), Natalizumab (n = 3), Siponimod (n = 1), Fingolimod (n = 5), Dimethylfumarat (n = 1), Interferon-Beta (n = 1), Ocrelizumab (n = 2), and Cladribine (n = 1). Two subjects received no DMT.

Subjective trait fatigue severity was assessed using the Wuerzburg Fatigue Inventory (WEIMuS). Clinically meaningful trait fatigue was reported by ten pwMS based on the cut-off criteria by Flachenecker et al. (Flachenecker et al., 2008) (WEIMuS total score $>$ 32 points). In both groups, neurological or psychiatric disorders/ comorbidities were assessed using a questionnaire, inferred from current medication, and/or screened by a physician during clinical exams (in pwMS). The local ethic committee of the University of Magdeburg approved the study. All subjects provided written consent according to the Declaration of Helsinki and received a monetary reward (Euro 30 in total).

2.2. Procedure

All subjects signed informed consent and completed several questionnaires for handedness (Edinburgh Handedness Inventory), current mood (BDI-FS), and daytime sleepiness (ESS). PwMS additionally completed the Wuerzburg Fatigue Inventory (WEIMuS) to assess their subjective trait fatigue. All subjects performed Ishihara's Test for color blindness and the Symbol Digit Modalities Test (SDMT) to evaluate cognitive performance (Benedict et al., 2017). After electroencephalogram (EEG) mounting, the subjects received instruction for the following task and performed one training block consisting of 20 trials. The study then started with the presentation of electrical visual analog scales (VAS) from 0 to 100. To systematically investigate subjective state

Table 1
Baseline group characteristics, mean (± SD).

	pwMS	HC	
gender [f/m]	15 / 6	14 / 7	
handedness [right/left]	20/1	20/1	
age [years]	42.29 (± 12.81)	40.48 (± 13.21)	$p = .597$
BDI-FS [points]	2.43 (± 2.80)	1.29 (± 1.10)	$p = .161$
ESS [points]	10.86 (± 3.49)	5.71 (± 2.67)	$p < .001$
SDMT [points]	59.91 (± 10.07)	63.22 (± 8.68)	$p = .262$
$WEIMuS_{total}$ [points]	35.10 (± 15.50)	-	
$WEIMuS_{cognitive}$ [points]	17.76 (± 7.75)	-	
disease duration [years]	11.90 (± 9.29)	-	
EDSS [points]	2.67 (± 1.50)	-	

BDI-FS, Becks Depression Inventory – Fast Screen; *EDSS,* Expanded Disability Status Scale; *ESS,* Epworth Sleepiness Scale; *HC,* healthy controls; MS, Multiple Sclerosis; *SDMT*, Symbol Digit Modalities Test, *WEIMuS,* Wuerzburg Fatigue Inventory for Multiple Sclerosis

ratings, we used three different VAS scales. One was positively phrased, asking the subjects "how mentally fit" (VAS_{fit}) they felt "right now at this moment", one rather negatively phrased, asking "how mentally exhausted" (VAS_{ex}) they felt "right now at this moment", and the third asked about "how much their mind has wandered" (VAS_{mind}) during the last block. Before starting the task, only VAS_{fit} and VAS_{ex} were presented, as no mind wandering could have occurred then. Thereafter, an 8-minute resting-state EEG was recorded consisting of eight alternating one-minute blocks of eyes-open and eyes-closed (see Fig. 1 for an illustration of the study design).

The fatigability-inducing task (a continuous performance task, CPT) was adapted from Wascher et al. (Wascher et al., 2014). Subjects performed six blocks (B1-B6) á 110 trials (duration approximately 5 minutes per block). Every trial consisted of two sequentially presented frames. The first frame presented two gray bars left and right to a fixation cross. It was presented for 200 ms followed by a 50 ms blank interval and then the second frame for 200 ms. In the second frame, one of the two bars changed its color to red or blue. The subjects were asked to indicate which color change occurred (the right Ctrl key for red and the left Ctrl key for blue). A 90-second break separated every block. For every second block, the three VAS scales were presented. Directly after the CPT task, a second resting-state EEG was recorded.

2.3. EEG signal recording and preprocessing

EEG was recorded at Fp1, Fp2, F3, Fz, F4, FCz, C3, Cz, C4, P3, Pz, P4, POz, O1, Oz, and O2 using Ag/AgCl-electrodes mounted in an elastic cap (EasyCap GmbH, Germany). The ground electrode was attached to the AFz position, and all channels were referenced to the left and right mastoid. Additionally, an electrooculogram (EOG) was recorded. The data was recorded by Brain DC amplifier (Brain Products, Germany) sampled at 1000 Hz. Impedances were kept below 5 kΩ. EEG preprocessing and data analysis were carried out in BrainVision Analyzer 2.1 (Brain Products, Germany).

The EEG data were resampled to 512 Hz, band-pass filtered from 0.1 to 40 Hz, and then corrected for eye-movement artifacts using the Gratton and Cole method (Gratton et al., 1983). The data were then further analyzed separately for the pre and post resting state EEG segments and the six task blocks. Subsequently, 2 s long segments with an overlap of 200 ms were extracted from the continuous EEG and submitted to a fast Fourier transformation using a Hanning window with 10% of the total segment length. After averaging, spectral power was extracted for the theta (4.5 to 6 Hz), lower alpha (8 to 9.5 Hz), and upper alpha band (10 to 12.5 Hz) by averaging power values across respective 1-Hz bins. We conducted two regions of interest, the mid-frontal region (Fz, FCz, and Cz) to assess fm-theta power and the occipital region (POz and Oz) to assess occipital alpha power.

2.4. Statistical analyses

R Statistical Software (version 4.2.0, R Core Team, 2022) and JASP software (version 0.16.3, JASP Team, 2022) were used for statistical analyses and production of all plots.

To investigate the effects of time on task, we analyzed subjective (VAS scores), behavioral (reaction time variability, RT variability), and electrophysiological (lower, upper alpha, and fm-theta power) fatigability values. The data was analyzed using (General) Linear Mixed Models [(G)LMMs]. The subjective and behavioral data were normally distributed, whereas the band power values were log-distributed. Thus, LMMs using the *lmer* function and GLMMs using the *glmer* function, with gaussian log family, both from the *afex* (Singmann et al., 2022) package, were performed. The statistical significance of main effects and interactions was determined with the *anova()* function using F-Tests for LMMs and with the *Anova()* function from the *car* (Fox and Weisberg, 2019) package using Wald Chisquare Tests for GLMMs. P-values for the β-estimates were obtained using Sattersthwaite's approximation method. We excluded invalid and error trials as well as physiologically unreasonable reaction times below 200 ms from the RT data analysis. Furthermore, for all data analyses, outliers below or above 1.5 times the interquartile range were identified and adjusted to this limit to reduce the impact of outliers without having to remove them. Subjective data, RT variability, and band power data were considered as dependent variables. Time, group, and group x time were considered as fixed factors. Data from HC in block B1 were used as baseline. Individuals and their variation of the dependent variable over time were used as random effects. ESS scores were added as a covariate to account for group differences.

For the analysis of fatigability-induced changes during the resting-state EEGs, we analyzed spectral changes from the eyes-open condition of the resting state EEG data and performed 2 × 2 repeated measures of analysis of variance (ANOVAs) with the within-subject factor *time* (pre, post) and the between-subject factor *group* (pwMS, HC). The power data were log-transformed, as fm-theta and alpha power tended to be skewed.

3. Results

3.1. Fatigability-related changes with time on task

The results for the VAS_{fit} ratings showed a significant effect of *time* [$F(1,40) = 74.993$, $p < .001$, $\eta^2_p = .65$], no main effect of *group* [$F(1,40) = 0.393$, $p = .534$] but a significant interaction between *time* and *group* [$F(1,40) = 5.767$, $p = .021$, $\eta^2_p = .13$]. The initial VAS_{fit} ratings for the HC group were 81 points [$\beta_{intercept} = 80.971$, 95% CI (74.83, 87.12), $t = 16.317$, $p < .001$] and 74 points [$\beta_{intercept} + \beta_{group}$] for pwMS. With each new query, the ratings decreased by 7.50 points [$\beta_{time} = -7.505$, 95 % CI (-10.82, -4.19), $t = -4.425$, $p < .001$], while they more strongly decreased by 13.27 points [$\beta_{time} + \beta_{time*group}$; $\beta_{time*group} = -5.760$, 95 % CI (-10.45, -1.07), $t = -2.401$, $p = .021$] in pwMS (see Fig. 2A). The model explained approximately 64 % of the variance (fixed and random effects, $R^2 = 0.641$). The β-coefficients representing the fixed effects are listed in Table 2.

The models to predict VAS_{ex} as well as VAS_{mind} ratings showed a significant main effect of *time* [VAS_{ex}: $F(1,40) = 50.080$, $p < .001$, $\eta^2_p = .56$; VAS_{mind}: $F(1,40) = 15.070$, $p < .001$, $\eta^2_p = .27$] but no significant *time* x *group* interaction [VAS_{ex}: $F(1,40) = 0.038$, $p = .846$; VAS_{mind}: $F(1,40) = 0.123$, $p = .728$]. Furthermore, there was a significant main effect *group* in the VAS_{ex} ratings [$F(1,40) = 6.241$, $p = .017$, $\eta^2_p = .14$]

Fig. 1. Experimental design. After assessing demographic and clinical data via self-report questionnaires, an 8-minute resting state EEG with alternating eyes-open and eyes-closed segments was performed. A 30-minute continuous performance task (CPT) followed that consisted of six blocks (B1-B6) of 5 minutes each. The first resting state EEG and B1 of the CPT task were used as baseline measures. Before the first and after each second block, subjects were asked about their current perceived fatigue status on visual analog scales (VAS). Subsequently, a second resting state EEG was performed.

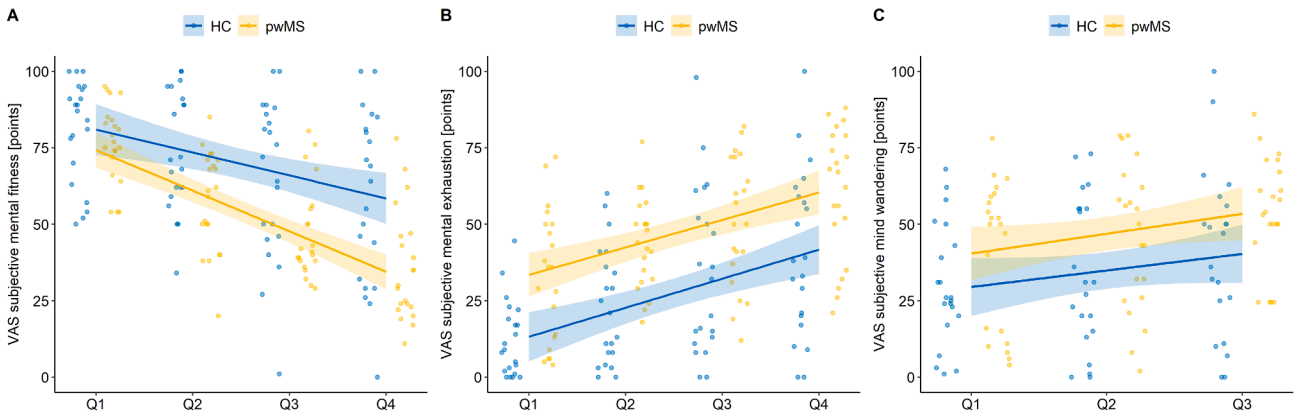

Fig. 2. Results of the linear mixed model to predict subjective state ratings: Regression plots representing perceived (A) mental fitness (VAS_{fit}), (B) mental exhaustion (VAS_{ex}), and (C) mind wandering (VAS_{mind}) against the number of queries (Q1-Q4) separate for the HC and pwMS groups.

Table 2
β-coefficients of (G)LMMs.

	β	SE β	t-value	p-value
VAS mental fitness [points]				
intercept	84.426	5.174	16.317	< .001
time	-7.505	1.696	-4.425	< .001
group	-3.626	5.788	-0.627	.535
time * group	-5.760	2.398	-2.401	.021
VAS mental exhaustion [points]				
intercept	7.662	5.443	1.408	.167
time	9.502	1.848	5.143	< .001
group	15.227	6.095	2.498	.017
time * group	-0.512	2.613	-0.196	.846
VAS mind wandering [points]				
intercept	26.234	7.743	3.388	.002
time	5.405	2.164	2.497	.017
group	8.005	8.747	0.915	.365
time * group	1.071	3.061	0.350	.728
RT variability [ms]				
intercept	66.146	9.351	7.074	< .001
time	1.026	1.383	0.742	.462
group	-14.976	10.405	-1.439	.158
time * group	5.147	1.955	2.632	.012
fm-theta power [log]				
intercept	1.226	0.100	12.300	< .001
time	0.014	0.009	1.487	.137
group	-0.069	0.112	-0.614	.539
time * group	-0.002	0.013	-0.155	.876
lower alpha power [log]				
intercept	0.568	0.226	2.514	.001
time	0.066	0.016	4.072	< .001
group	0.202	0.247	0.817	.414
time * group	-0.008	0.022	-0.352	.717
upper alpha power [log]				
intercept	0.867	0.188	4.600	< .001
time	0.026	0.013	1.949	.051
group	0.150	0.209	0.717	.474
time * group	0.035	0.018	1.973	.049

fm, frontomedial; log, log-transformed; RT, reaction time; SE, standard error; VAS, visual analog scale

(see Fig. 2B, 2C).

Analysis of RT variability showed a significant main effect of *time* [$F(1,40) = 13.554$, $p < .001$, $\eta^2_p = .25$], no significant main effect *group* [$F(1,40) = 2.072$, $p = .158$] but a significant interaction between *time* and *group* [$F(1,40) = 6.929$, $p = .012$, $\eta^2_p = .15$]. The initial RT variability for the HC group was 66 ms [$\beta_{intercept} = 66.146$, 95% CI (48.05, 84.24), $t = 7.074$, $p < .001$] and 51 ms [$\beta_{intercept} + \beta_{group}$] for the pwMS. While, in the HC group, RT variability remained stable with time on task [$\beta_{time} = 1.026$, 95 % CI (-1.68, 3.73), $t = 0.742$, $p = .462$], in pwMS, it significantly increased by 6.17 points [$\beta_{time} + \beta_{time*group}$; $\beta_{time*group} = 5.147$, 95 % CI (1.32, 8.97), $t = 2.632$, $p = .012$] per block (see Fig. 3). The

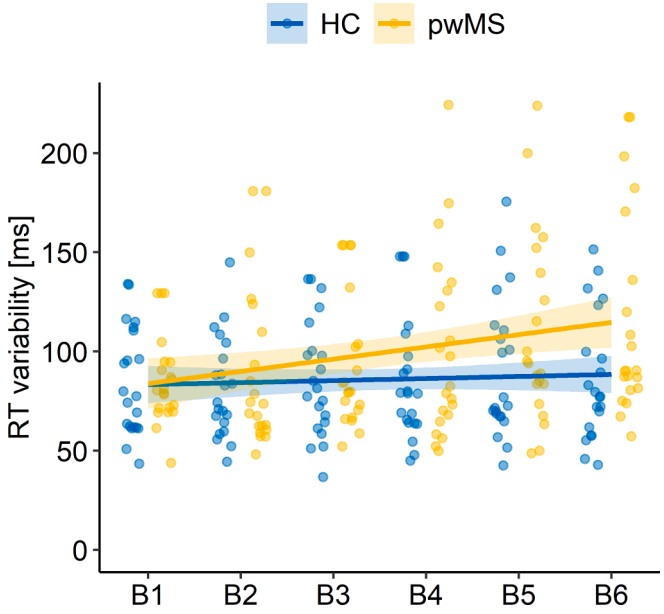

Fig. 3. Results of the linear mixed model to predict reaction time (RT) variability ratings: Regression plots representing RT variability against time on task (block B1-B6) separate for the HC and pwMS groups.

model explained approximately 66 % of the variance (fixed and random effects, $R^2 = 0.660$).

The GLMM to analyze fm-theta power showed a marginally significant main effect of *time* [$\chi^2(1) = 3.652$, $p = .056$] but no effect of *group* [$\chi^2(1) = 0.425$, $p = .515$] and no significant interaction of *time* and *group* [$\chi^2(1) = 0.024$, $p = .876$]. Thus, there was a trend of a fm-theta power increase with time on task, but this was unaffected by group. Fixed and random effects explained approximately 34 % of the variance ($R^2 = 0.349$).

Analyzing occipital lower alpha power showed a significant main effect of *time* [$\chi^2(1) = 32.116$, $p < .001$] but no significant effect of *group* [$\chi^2(1) = 0.620$, $p = .431$] and no interaction of *time* and *group* [$\chi^2(1) = 0.131$, $p = .717$]. Thus, similar to fm-theta power, lower alpha power increased with time on task, but this was unaffected by group. The model explained approximately 49 % of the variance (fixed and random effects, $R^2 = 0.493$).

The GLMM to analyze upper alpha power showed a significant main effect of *time* [$\chi^2(1) = 27.359$, $p < .001$], no significant main effect of *group* [$\chi^2(1) = 1.029$, $p = .310$] but a significant interaction of *time* and *group* [$\chi^2(1) = 3.891$, $p = .048$]. The model estimated that upper alpha

power increased with time on task by 0.52 μV^2 (SD = 0.71 μV^2) in HC [β_{time} (log-transformed) = 0.026, 95 % CI (-0.01, 0.05), t = 1.949, p = .051] and more strongly increased by 1.62 μV^2 (SD = 2.12 μV^2) in pwMS [$\beta_{time*group}$ (log-transformed) = 0.035, 95 % CI (0.01, 0.07), t = 1.973, p = .049]. Fixed and random effects explained approximately 45 % of the variance (R^2 = 0.455).

The linear regression plots of the non-transformed data of fm-theta and (low and upper) alpha power are shown in Fig. 4, and the β-coefficients representing the fixed effects are listed in Table 2. However, keep in mind that the data was analyzed using GLMMs with log link function. Hence, the predicted β-coefficients are log-transformed and not applicable to the Fig.

Finally, we investigated the general interrelationship between fatigue self-reports (WEIMuS cognitive scores and delta scores of subjective ratings on mental fitness) in pwMS and those objective parameters that indicated a different time on task dynamic of pwMS and HC (delta scores of RT variability and upper alpha power (log-transformed). However, the data showed no significant relationship between the changes in both objective parameters and subjective trait fatigue (all *ps* > .102).

3.2. Fatigability-related changes during resting-state EEGs

The pre vs. post analyses of the resting EEG data confirmed the task-related results. Thus, the upper alpha power showed no effect of *group* [F(1,40) = 0.315, p = .578] but a significant main effect of *time* [F(1,40) = 19.772, p < .001, η_p^2 = .33] with the power increase being more prominent in pwMS. However, the interaction was not significant [F(1,40) = 2.138, p = .151]. Furthermore, for the fm-theta power analyses, the ANOVA revealed no main effect of *time* [F(1,40) = 2.472, p = .124] and *group* [F(1,40) = 1.185, p = .283] and no significant interaction [F(1,40) = 0.080, p = .778]. Similarly, for lower alpha power, we found a significant main effect of *time* [F(1,40) = 14.497, p < .001, η_p^2 = .27] but no *group* effect [F(1,40) = 0.262, p = .612] and no interaction [F(1,40) = 0.139, p = .711]. The log-transformed power values as a function of time separate for both groups are shown in Fig. 5.

4. Discussion

This study systematically investigated fatigability-related spectral power changes in pwMS and HC. As hypothesized, pwMS experienced a greater fatigability with time on task compared to HC. They felt significantly less mentally fit, and, in the objective parameters, they showed greater RT variability and increased occipital upper alpha power. Comparable results were shown in resting state EEG data. The changes in the objective parameters, however, were not associated with the changes in subjective state ratings as well as with the trait fatigue scores.

4.1. Oscillatory changes

Our results revealed an increase in occipital alpha power in pwMS. Especially for upper alpha power, this increase was significantly more prominent in pwMS compared to HC. This, together with the subjective and behavioral data, supports the assumption of a more severe fatigability in pwMS. Thus, while our results revealed no initial differences in band power values in pwMS and HC, pwMS showed a systematically more severe and faster fatigability that was objectively measurable.

An increase in occipital alpha power during sustained attention tasks is generally in line with the previous literature (Boksem et al., 2005; Clayton et al., 2015; Craig et al., 2012; Gharagozlou et al., 2015). Alpha oscillations have consistently been associated with the suppression of distracting information by inhibiting sensory modalities irrelevant to the

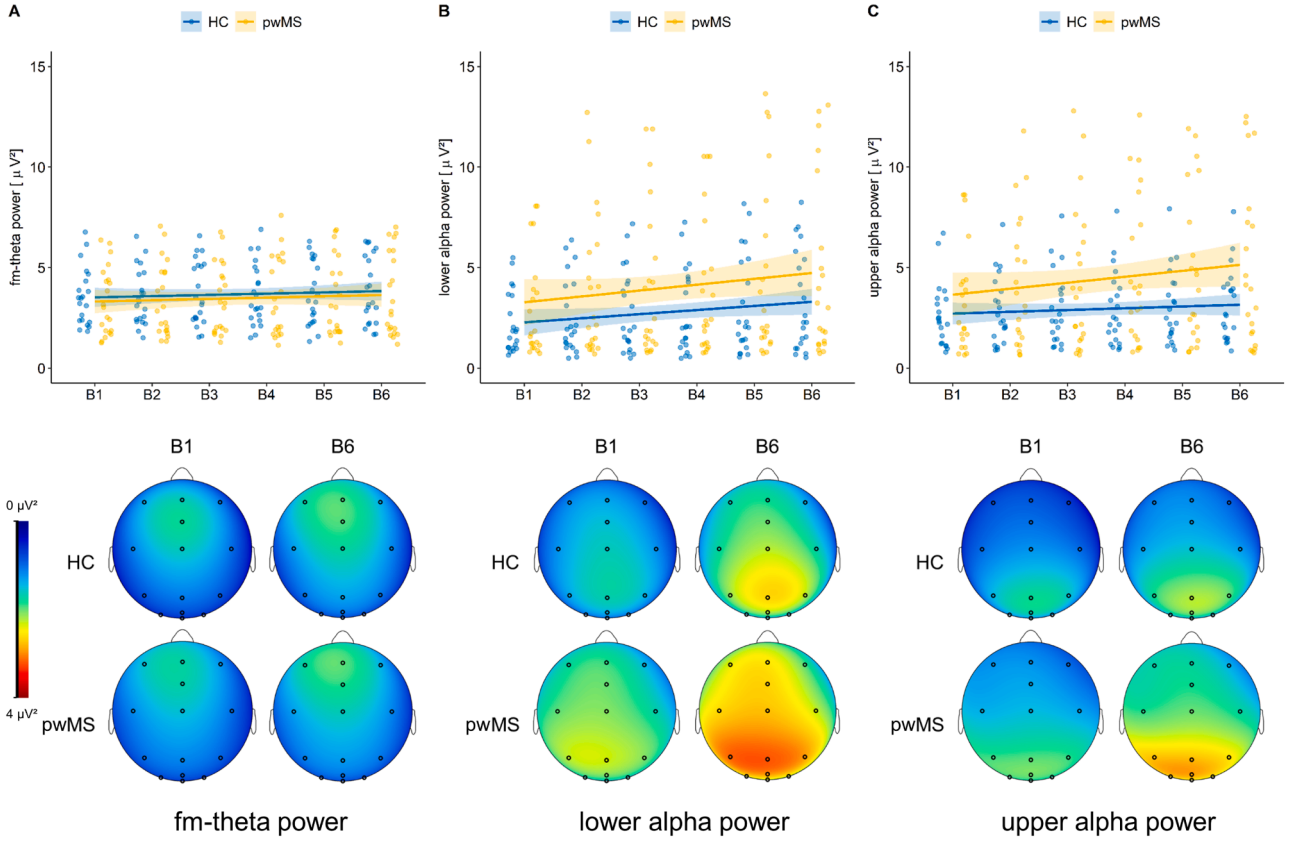

Fig. 4. Regression plots representing fm-theta power (A, top), occipital lower alpha power (B, top), and occipital upper alpha power (C, top) against time on task (block B1-B6) separate for the HC and pwMS groups. The bottom row represents fm-theta (A, bottom), occipital lower alpha (B, bottom), and occipital upper alpha (C, bottom) topography plots in B1 and B6 for the HC and pwMS groups.

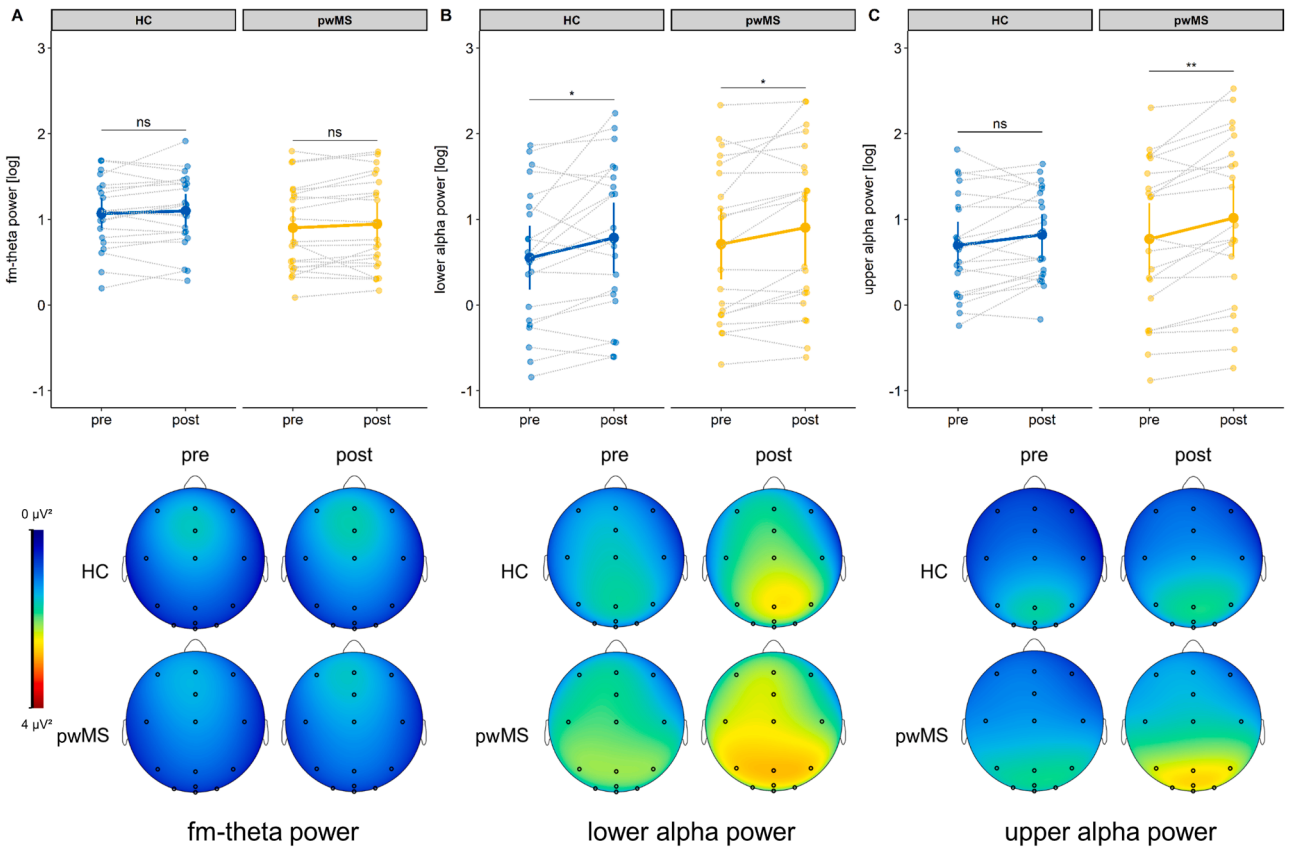

Fig. 5. Regression plots representing fm-theta power (A, top), occipital lower alpha power (B, top), and occipital upper alpha power (C, top) against resting state EEG session (pre, post) separate for the HC and pwMS groups. The bottom row represents fm-theta (A, bottom), occipital lower alpha (B, bottom), and occipital upper alpha (C, bottom) topography plots in pre and post session for the HC and pwMS groups.

task. Therefore, alpha power may play a pivotal role in fatigability development, impairing the attentional focus when increasing over task-relevant areas, such as the occipital cortex in a visual attention task (Clayton et al., 2015). In contrast, other studies report a controversial alpha power decrease with time on task (Ishii et al., 2013, Klimesch, 1999, Li et al., 2020). However, there are significant differences between the assessment methods, tasks, and also the duration of the tasks, so comparing the results is difficult. Additionally, all of the studies examined young, healthy subjects and no clinical subgroups. Nevertheless, more research is needed to use alpha power as a diagnostical marker for fatigability in pwMS.

On the contrary, we did not find an fm-theta power increase as reported in the previous literature (Boksem et al., 2005; Clayton et al., 2015; Craig et al., 2012; Wascher et al., 2014). For HC, this may result from a lower level of fatigability. Thus, HC in our study remained mentally fit and were able to uphold their behavioral performance. In addition, Wascher et al. reported that fm-theta power increased steadily over the course of four hours on the task (Wascher et al., 2014). Similarly, other studies have examined theta increases in healthy subjects over more extended periods of time than 30 minutes (Linnhoff et al., 2021, Tran et al., 2020). However, as the task was already very exhausting for pwMS, we decided not to extend it further. Contrary, in pwMS, who were demonstrably fatigued during our task, the lack of fm-theta power increase could be related to the malfunctioning cortico-striato-thalamo-cortical network that has been proposed in previous studies (Ayache and Chalah, 2017). In this way, results from several neuroimaging studies demonstrated relations between subjective trait fatigue and structural or functional abnormalities in different cortical regions, including the frontal cortex (Pardini et al., 2010, Roelcke et al., 1997, Sepulcre et al., 2009). According to Clayton's model of sustained attention (Clayton et al., 2015), this underactivity of the frontal cortex in fatigued pwMS might lead to the lack of compensatory fm-theta power mechanisms and, thus, to disturbed top-down control processes.

Our findings give new insights into fatigability-related oscillatory activity changes that may help to extend the therapeutic options for pwMS. As such, transcranial electrical stimulation (tES) may provide the unique opportunity to manipulate this maladaptive neural activity. In our recent study, we already demonstrated that transcranial direct current stimulation (tDCS) counteracted fatigability development in healthy subjects and reduced the increase of occipital alpha power (Linnhoff et al., 2021). Future studies might use transcranial alternating current stimulation (tACS) to stimulate targeted frequencies selectively and investigate the causal role of oscillational activity in a fatiguing brain. By using tACS in the gamma range while performing a vigilance task, Loeffler et al. aimed to decrease inhibitory alpha power in task-relevant cortical areas (Loeffler et al., 2018). Gamma tACS counteracted the increase in reaction times with time on task. However, the effects on occipital alpha power remain to be determined due to missing EEG recordings.

4.2. *Subjective assessment of fatigability*

In this study, we systematically investigated subjective state fatigue ratings with time on task via three different VAS scales. PwMS felt significantly less fit with time on task. On the contrary, ratings on mental exhaustion and mind wandering increased similarly in both groups, while pwMS reported higher exhaustion ratings at baseline.

Our results demonstrate how differently fatigue can be perceived and how important it is for future studies to pay attention to how scales are phrased. In general, self-reports are subject to psychological errors and strongly depend on individual trait complexes (Ackerman and Kanfer,

2009). PwMS are frequently asked about their current level of exhaustion during clinical exams, which increases their individual awareness of the syndrome. Consequently, especially for mental exhaustion, the higher baseline ratings may result from priming. Furthermore, our results confirm the complex relationship between subjective fatigue ratings and objectively measurable fatigability parameters. In this study, we did not find associations between changes in subjective ratings and the changes in the objective parameters. Thus, as demonstrated in previous studies, our results support the assumption that trait and state fatigue, as well as fatigability parameters, might be independent dimensions of an overall MS-related fatigue that may either jointly appear or occur independently of one another (Enoka et al., 2021, Hanken et al., 2014). In future studies, it might be helpful to use questionnaires that primarily assess fatigability, such as the Pittsburgh Fatigability Scale (PFS) (Glynn et al., 2015, Renner et al., 2021). It measures perceived mental fatigability in the daily life and might be a more suitable subjective marker for a correlation with the cognitive decline with time on task. In general, our findings demonstrate the importance of incorporating subjective and objective fatigue in clinical fatigue diagnosis and research. Future studies need to investigate fatigue as a holistic syndrome with fatigability being a part of it and need to pay attention to a unified fatigue taxonomy.

4.3. Limitations

A primary limitation of this study is the small sample size, which restricts the generalizability of the study results. Replication with larger sample sizes will strengthen these findings. The small sample size also prevented us from examining the impact of MS disease phenotypes. Thus, pwMS with relapsing-remitting MS form are overrepresented in our study, indicating that the effects may be specific for this subtype. However, excluding both pwMS with primary- and secondary-progressive MS forms did not change the results. Future studies should consider this and possibly investigate subtypical effects in more detail. Notwithstanding, it should be noted that the distribution of MS forms in our sample mirrors the general distribution among pwMS. Additionally, the power of the study was insufficient to distinguish between pwMS with and without cognitive impairment. Thus, we cannot fully exclude that cognitive impairment in some pwMS constituted a bias in the study outcome. It is important to note, however, that at baseline, we ensured that both groups did not differ in cognitive processing speed nor in the outcome parameters of our study, making a bias rather unlikely. Finally, the differently phrased VAS scales were always presented in the same order. Thus, we presented VAS scales with different polarizations in order to enhance task engagement by requiring subjects to read the VAS questions carefully. However, it might have resulted in order effects or increased self-awareness. As part of a clinical exam, pwMS are often asked about their current level of exhaustion, which increases their awareness of the syndrome. Consequently, VAS ratings might have been biased in pwMS when they were asked "how exhausted they felt." Future studies should consider this and pay attention to uniform VAS scales.

5. Conclusion

In summary, our results demonstrated a stronger fatigability development in pwMS compared to HC. PwMS reported a more prominent decrease in mental fitness ratings. Importantly, this systematic increase in fatigability was objectively measurable. Compared to HC, pwMS showed a stronger increase in RT variability as well as an enhanced increase in occipital upper alpha power. To our knowledge, this is the first study providing evidence for specific fatigability-related brain wave activity changes in pwMS. Our results provide new insights and might help to improve the understanding of fatigability-related pathomechanisms in pwMS as well as healthy subjects.

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Ethical standards

The local ethics committee of the University Hospital Magdeburg approved the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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