Frontal brain activity and cognitive processing speed in multiple sclerosis: An exploration of EEG neurofeedback training

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ABSTRACT

Background: Cognitive deficits including impaired information processing speed as assessed by the Symbol Digit Modalities Test (SDMT) are common in multiple sclerosis (MS). Oscillatory markers of processing speed may be extracted from magnetoencephalographic (MEG) and electroencephalographic (EEG) resting-state recordings. In this context, an increased proportion of frontal slow-wave (theta, 4–8 Hz) to fast-wave (beta, 13–30 Hz) EEG activity was indicative of impaired SDMT performance. Such an increased theta/beta ratio may reflect oscillatory slowing associated with deficits in attention control. Therapeutic approaches that consider atypical oscillatory activity in MS remain sparse.

Objectives: In a cross-sectional design, we examined the relation between SDMT performance, the EEG theta/beta ratio and its components. We also explored longitudinally, whether EEG neurofeedback could be used to induce a putatively adaptive alteration in these EEG parameters, toward a pattern indicative of improved processing speed.

Methods: $N = 58$ MS patients (RRMS/SPMS/PPMS N: 18/35/3, 2 cases excluded) participated in a neuropsychological examination and a resting-state EEG recording. Subsequently, $N = 10$ patients received neurofeedback training for two weeks in a hospitalized setting. The purpose was to reduce the frontal theta/beta ratio through operant conditioning.

Results: In the cross-sectional examination, patients with slow SDMT speed displayed an increased theta/beta ratio, relative to those with normal speed. This involved increased frontal theta power, whereas beta power was equal across groups. The theta/beta ratio remained stable during neurofeedback across sessions of the two-week training period. In an exploratory secondary analysis, within sessions a reduction in the theta/beta ratio during active training blocks relative pre/post session resting-states was observed, driven by reduced theta power.

Conclusions: These findings provide support for utilizing frontal EEG theta activity as an inverse marker of processing speed in MS. Across sessions, there was no support for successful operant conditioning of the theta/beta ratio during the two-week training period. The observed state-specific shift within sessions, involving a transient reduction in theta activity, nevertheless may provide a rationale for a further investigation of neurofeedback as a treatment approach in MS.

1. Introduction

Due to a pathologic autoimmune response that leads to demyelinization and axonal loss, multiple sclerosis (MS) patients may display various neurological symptoms, including sensory and motor deficits, as well as autonomic dysfunction (Compston and Coles, 2008; Burschka et al., 2012; Keune et al., 2015a, 2017b). About two thirds of patients also show clinically relevant cognitive deficits (Amato et al., 2006; Langdon, 2011; Hansen et al., 2015). These have been attributed to a disconnection syndrome of the brain, arising from the interplay of focal lesion burden and the disruption of critical white matter connecting fiber tracts (Filippi and Rocca, 2011; Calabrese et al., 2013; Rocca et al., 2014, 2015). While the resulting disruption of neural network efficiency may initially be compensated, cognitive deficits become chronic when compensatory mechanisms are exhausted (Schoonheim et al., 2015b). In turn, deficits may manifest in various cognitive domains,

including attention, executive function and memory (Langdon, 2010). To effectively diagnose and monitor cognitive deficits in routine clinical practice, various tests have been established (Langdon et al., 2012; Hansen et al., 2015), including the Symbol Digit Modalities Test (SDMT; Smith, 1982; Benedict et al., 2017), which addresses information processing speed and attention. SDMT performance partly relies on the integrity of structural connectivity in prefrontal regions and deep gray nuclei (Llufriu et al., 2017).

In a pioneering study, Van der Meer et al. (2013) reported a magenetoencephalographic (MEG) power decrease in resting-state alpha-2 oscillatory activity (10–13 Hz) and an increase in alpha-1 activity (8–10 Hz), yielding a decreased alpha peak frequency in MS patients relative to a healthy comparison group. Power in the lower alpha band was also negatively correlated with SDMT performance. These findings were further specified by showing that oscillatory slowing in MS occurs widespread in deep gray matter areas, is particularly pronounced in the thalamus and also manifests in increased theta activity (Schoonhoven et al., 2018). The thalamus serves as an integrative hub involved in the maintenance of cortical functional networks (Hwang et al., 2017). In this context, thalamic oscillatory slowing has been interpreted as a correlate of the impaired integration of cognitive processes, including attention and executive functions (Schoonheim et al., 2015a; Schoonhoven et al., 2018).

Results compatible with those of MEG studies were also obtained with more available EEG methods (Van der Meer et al., 2013; Keune et al., 2017a; Schoonhoven et al., 2018). In this context, the power ratio of frontal EEG slow-wave (theta, 4–8 Hz) to fast-wave (beta, 13–30 Hz) activity, which reflects a surface measure of oscillatory slowing, was negatively correlated with SDMT performance. These results are in accord with the notion that a relative increase in anterior oscillatory EEG slow-wave activity represents a putative correlate of reduced attention control, as previously suggested by others (Putman et al., 2010, 2014; Angelidis et al., 2018). Currently, it remains to be addressed if either of the two components underlying the frontal EEG theta/beta ratio, i.e. theta or beta power, shows a particularly robust association with SDMT processing speed in MS.

The finding that patients with slow SDMT speed may display an increased EEG theta/beta ratio might also be relevant for the development of new treatment approaches. Due to the lack of validated standard procedures for cognitive rehabilitation in MS, there has been a call for interventions developed based on and guided by findings from neuroimaging studies (Rosti-Otajärvi and Hämäläinen, 2014; Sokolov et al., 2018). With regard to atypical oscillatory brain activity, a procedure that could be explored is EEG neurofeedback, i.e. the application of the learning principle of operant conditioning to enhance or reduce power in specific bands of the EEG spectrum (Egner et al., 2004; Gruzelier and Egner, 2005). Neurofeedback has been applied in other disorders, e.g. attention-deficit/hyperactivity disorder (ADHD) and was shown to yield clinically meaningful effects (Arns

et al., 2009; Rubia, 2018), albeit its efficacy and specificity remain a matter of ongoing debate (Sonuga-Barke et al., 2013b; Sonuga-Barke et al., 2013a; Holtmann et al., 2014; Cortese et al., 2016; Pigott et al., 2017; Schönenberg et al., 2017a,b; Thibault et al., 2018). Also for theta/beta neurofeedback training, which might be a candidate to target atypical oscillatory slowing in MS, mixed results concerning a frequency-specific training effect have been reported for healthy groups and ADHD patients (Doppelmayr and Weber, 2011; Rogala et al., 2016; Janssen et al., 2017). Nevertheless, based on reports of atypical oscillatory slowing and the theta/beta ratio as a putative correlate of processing speed in MS, it appears warranted to explore the application of neurofeedback in this group of patients, in line with previous suggestions (Choobforoushzadeh et al., 2015; Buyukturkoglu et al., 2017; Sokolov et al., 2018).

In the current study, we firstly intended to specify in a cross-sectional examination, which frontal brain oscillatory marker, i.e. the theta/beta ratio, frontal theta or frontal beta power shows a robust association with patients' cognitive status based on SDMT performance. Secondly, with the intention to provide further exploratory data on neurofeedback in MS, we administered neurofeedback training in a hospitalized setting over the course of two weeks with the goal to reduce the frontal theta/beta ratio. A successful reduction may be regarded as a putatively adaptive alteration prone to improve attention.

2. Material and methods

2.1. Participants

The current study was approved by the ethics committee of the University of Bamberg, Germany. Participants were recruited in the MS-Center of the Klinikum Bayreuth GmbH, Department of Neurology, Bayreuth, Germany. Patients stayed in the clinic for a period of at least two weeks. Stays occurred for various reasons including periodic examinations of clinical status and disease progression and updating medical treatment. Inclusion criteria involved a verified MS diagnosis based on revised McDonald criteria (Polman et al., 2011), subjective reports of cognitive deficits during activities of everyday life, as reported by patients during routine medical visitations, as well as an age range of 18–75 years. Patients who reported subjective cognitive difficulties took part in an established neuropsychological screening procedure during the routine clinical process (Hansen et al., 2015, 2016). In this context, they were offered to participate in the study. Patients who gave informed consent subsequently also took part in a resting-state EEG assessment and were given the option to participate in neurofeedback training for two weeks following the initial diagnostics.

Clinical and demographic characteristics of patients included in the cross-sectional analysis on the relation between SDMT speed, the theta/beta ratio and its underlying components are presented in Table 1. As outlined in Section 2.2.1., the sample was divided into patients with

Table 1
Clinical and demographic information of patients with slow vs. normal SDMT speed.

	SDMT speed		Statistic	*p*-Value
	Slow (*N* = 25)	Normal (*N* = 31)		
N (male/female)	11/14	9/22	$\chi^2 = 1.35$	0.24
Age (M, SD)	48.68, 10.85	52.97, 9.23	$t = 1.60$	0.12
MS type (N: RRMS, SPMS, PPMS)	8, 17, 0	10, 18, 3	$\chi^2 = 2.64$	0.27
Treatment (N: current cortico-steroids: yes/no)	24/1	26/5	$\chi^2 = 2.13$	0.15
Disability level (EDSS: median, range)	4.0, 1.5–8.5	4.5, 1.5–7.0	$U = 338.5$	0.41
Time since MS-Diagnosis (years: M, SD)	13.40, 10.00	12.79, 7.89	$t = 0.25$	0.80
Current relapse (N: yes/no)	3/22	2/29	$\chi^2 = 0.52$	0.47
Overall fatigue (M, SD)	33.84, 13.43	32.61, 14.27	$t = 0.33$	0.74
Cognitive fatigue (M, SD)	16.68, 7.30	15.32, 8.74	$t = 0.02$	0.99
Somatic fatigue (M, SD)	17.16, 6.65	17.19, 7.04	$t = 0.62$	0.54

EDSS: expanded disability status scale; M = mean; PPMS = primary progressive MS; RRMS = relapsing remitting MS, SD = standard deviation; SPMS = secondary progressive MS. Note: Fatigue was assessed by the Würzburger Fatigue Inventory (WEIMUS, see text for references).

Table 2
Demographic and clinical characteristics of patients who received neurofeedback.

	Statistic
N (male/female)	3/7
Age (M, SD)	46.70, 12.20
MS type (N: RRMS, SPMS, PPMS)	6, 3, 1
Treatment (N: current cortico-steroids: yes/no)	9/1
Disability level (EDSS: median, range)	4.0, 2.5–7.0
Time since MS-Diagnosis (years: M, SD)	9.45, 6.05
Current relapse (N: yes/no)	0/10

EDSS: expanded disability status scale; M = mean; PPMS = primary progressive MS; RRMS = relapsing remitting MS, SD = standard deviation; SPMS = secondary progressive MS.

slow vs. normal SDMT speed. For this cross-sectional analysis, data of $N = 58$ patients was available. As two datasets were rejected from the analysis due to outliers in the EEG parameters, the final sample included $N = 56$ patients. As shown in Table 1, groups were comparable with regards to basic demographic and clinical parameters, including the distribution of MS subtypes, disease duration, current disability level as examined by the Expanded Disability Status Scale (EDSS, Kurtzke, 1983), current disease activity, number of patients under cortico-steroid treatment, as well as self-reported fatigue (Flachenecker et al., 2008). For the longitudinal analysis addressing the question whether it may be possible to modulate theta/beta activity in MS patients by neurofeedback training, data from $N = 10$ patients who showed low cognitive performance in the diagnostic assessment were available and included (Table 2). A prerequisite for a learning effect during neurofeedback may be seen in the occurrence of a linear trend in theta/beta ratio values across training blocks and sessions. To the best of our knowledge, the current exploratory study is the first in which theta/beta activity is analyzed across a neurofeedback intervention in MS (Choobforoushzadeh et al., 2015). A comparison group was not included since in context of this exploratory study, such a group is not essential for the preliminary examination of the occurrence of a linear trend as a prerequisite for a potential learning effect.

2.2. Procedure

2.2.1. Neuropsychological examination
All patients were examined in the clinic by trained and highly experienced neuropsychologists. The examination followed standard procedures of the center, involving a neuropsychological examination that included a short version of the Brief Repeatable Battery (BRB; Rao, 1990). In addition, patients completed a standardized self-report measure addressing symptoms of fatigue, i.e. the Würzburger Fatigue Inventory (Flachenecker et al., 2008). As previous studies provide a strong rationale for focusing on the relation between oscillatory brain activity and SDMT performance (Van der Meer et al., 2013; Keune et al., 2017a) and to reduce the risk of Type-I error inflation, the SDMT was chosen specifically as the parameter of cognitive processing speed. It requires patients to verbally match numbers with symbols as quickly as possible throughout a random sequence of symbols (Smith, 1982; Benedict et al., 2012). It yields a single parameter of processing speed that represents the total number of items solved in 90 s.

### 2.2.2. Resting-state EEG recording and data analysis
The resting-state EEG recording and data analysis followed standard procedures (Allen et al., 2004; Keune et al., 2011, 2012, 2013, 2017a). The recording was obtained with a 32-channel system (NeXus-32, MindMedia, Herten, The Netherlands) for the following channels: Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, O2, and mastoid electrodes M1, M2 at a frequency of 256 Hz with an average reference. Data were recorded for 8 min in one-minute eyes-

open (O) and eyes-closed (C) trials in the following order: C-O-C-O pause O-C-O-C. For data analyses, the software BrainVision Analyzer (Brainproducts GmbH, Germany) was used. A semi-automatic rejection procedure was used to exclude portions of data contaminated with artifacts from the analysis with a rejection criterion of ± 75 μV. Each of the 8 one-minute trials was divided into epochs with a length of 2 s with an overlap of 1 s. A Fast Fourier Transformation (FFT) was applied using a Hamming window, tapering the distal 10% of each epoch and power values were extracted in μV^2 in bins of 1 Hz. Average spectra were computed for eyes-open and eyes-closed trials separately. Afterwards spectra were averaged across eyes-open and eyes-closed trials. Spectral power was computed for the theta (4–7 Hz) and beta band (13–30 Hz) by averaging power values across the respective frequency bins. Based on this, also the theta/beta ratio was generated. The analysis focused on spectral activity obtained for midline electrodes in three regions, i.e. frontal (Fz), central (Cz) and parietal (Pz). Boxplots were used to screen data for outliers. Two cases were excluded as they involved individual values exceeding respective mean values of spectral power by 3 standard deviations (SD). The final dataset for the cross-sectional analysis addressing the relation between theta/beta activity, its underlying components and SDMT performance hence included data of $N = 56$ participants.

2.2.3. Neurofeeback training and data analysis
Patients received neurofeedback training over the course of two weeks during their stay in the hospital in five sessions, by means of common hard- and software (NeXus-32, biotrace, MindMedia, Herten, The Netherlands). Each session consisted of the following elements: a resting-state EEG recording of 2 min (C−O) followed by four blocks of neurofeedback (4 min/block) and another resting-state recording of 2 min (C−O). EEG was obtained with a frontal electrode (Fz) using a mastoid reference (M1, M2) and was continuously recorded during the training blocks. During training, patients were shown a training screen on which a vertical bar continuously displayed their current frontal theta/beta ratio. In addition, animated videos of moving objects were displayed. The videos kept playing if the current theta/beta ratio fell below a displayed threshold for at least 1 s. Patients were instructed to try to keep their theta/beta ratio below this threshold and to avoid movements to minimize motor artifacts. During the first training block, the threshold was set individually and was continually adjusted manually by the therapist who was present throughout the entire training. This approach was chosen based on the rationale that an appropriate reward level should be provided to maintain patients' motivation during training (Doppelmayr and Weber, 2011). Manual threshold adjustment based on that rationale was also implemented in training blocks 2–4. The therapist used the general guideline to decrease the threshold by at least 0.2 units of the theta/beta ratio when the theta/beta ratio had been below threshold at least 50% of the time. Such a threshold decrease is indicative of an increase in task difficulty. The threshold level was increased when the theta/beta ratio had only been below threshold 33% of the time. Respective percentages were derived from a point counter that was also shown on the training screen. A point was obtained when the current theta/beta ratio was below threshold for at least 1 s. As indicated, threshold setting and manual threshold adjustment occurred based on the therapist's evaluation as to how patients' motivation during training would best be maintained (Doppelmayr and Weber, 2011). This was prioritized over a rigid application of the guidelines above. To sensitize patients for the importance of minimizing movements, an additional horizontal bar indicated activity attributable to motor artifacts.

EEG data obtained during pre/post training resting-states were analyzed following the procedure outlined in Section 2.2.2 focusing on the respective eyes-open (O) recording. The same procedure was also applied to data obtained during the training blocks, so that for each of the five training sessions the frontal theta/beta ratio, as well as measures of frontal theta and beta power were available for pre/post
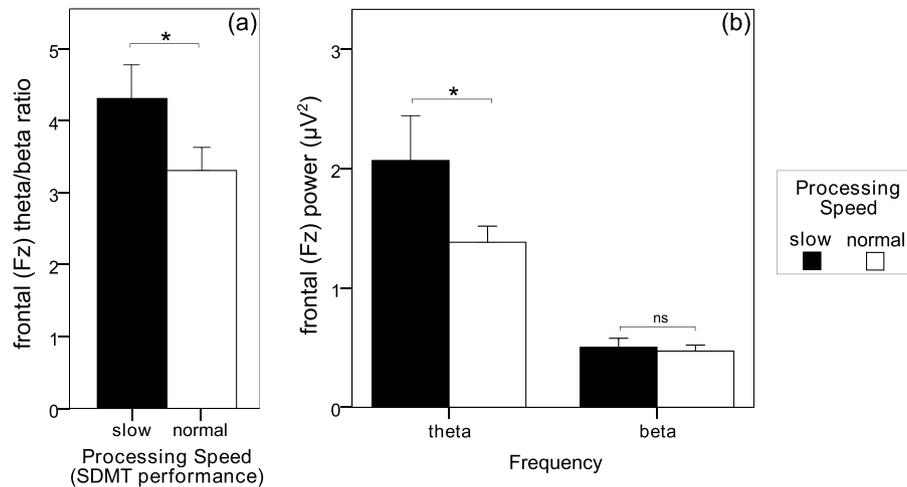
Fig. 1. Frontal (Fz) theta/beta ratio (a) and frontal theta and beta EEG spectral power (b) for patients with slow vs. normal performance on the SDMT. Error bars represent standard errors. *$p < .05$.

training resting-states and the four training blocks.

2.2.4. Statistical analysis

2.2.4.1. Cross-sectional analysis. For the cross-sectional analysis, a repeated measures analysis of variance (ANOVA) was implemented to examine whether the theta/beta ratio obtained for frontal (Fz), central (Cz) and parietal (Pz) regions varied as a function of SDMT speed. Datasets ($N = 56$) were divided into two groups, i.e. a group with slow processing speed and a group with normal speed. Groups were generated by transforming SDMT raw scores into percentage ranks (PR) relative to normative data (Scherer et al., 2004). Subsequently, a cutoff was set so that patients whose SDMT performance fell into the lowest quartile relative to the population, i.e. involving a PR < 25, were qualified as displaying slow SDMT speed. Patients whose percentage rank fell into the upper three quartiles were qualified as displaying normal SDMT speed. This cutoff criterion resulted in $N = 25$ patients with slow and $N = 31$ patients with normal SDMT speed (Table 1). The repeated measures ANOVA involved the within-subjects factor REGION (frontal, central, parietal) and the between-subjects factor SDMT-SPEED. A main effect of SDMT-SPEED indicates that patients with slow vs. normal processing speed differ in their theta/beta ratio. A REGION by SDMT-SPEED interaction indicates that group differences in the theta/beta ratio were region-specific across frontal, central and parietal regions. In order to examine which component of the theta/beta ratio, i.e. theta or beta band power, contributed to group differences in the theta/beta ratio, specifically for the frontal region a repeated measures ANOVA with the factors SDMT-SPEED and FREQUENCY (theta vs. beta power) was implemented. This model tested whether differences in frontal oscillatory band power between patients with slow vs. normal SDMT speed varied as a function of the examined frequency. Pairwise comparisons were used to respectively examine potential region- and frequency-specific differences in detail.

2.2.4.2. Longitudinal analysis. For the longitudinal analyses in which the potential occurrence of a decrease in the theta/beta ratio was tested, a repeated-measures ANOVA was used as well. The first part of this analysis tested for a gradual decrease in the theta/beta ratio across the four training blocks and five training sessions. The model included the within-subjects factor TRAINING ($1 - 20$) and a learning effect was assumed to manifest in a linear trend (Zoefel et al., 2011).

To explore a potential state-specific decrease in the theta/beta ratio within sessions relative to pre/post session resting-states, in a secondary analysis, the factors STATE with six levels (pre-training resting-state, training blocks 1–4, and post-training resting-state) and SESSION (1–5)

were included in a separate model. A main effect of STATE indicates that the respective EEG parameter varied within sessions, which suggests an alteration during training, relative to rest. Details of this main effect were examined by means of pairwise comparisons (resting-states vs. training blocks). To provide detailed information on the involved frequency bands, the indicated models were repeated separately for theta and beta activity.

Recently, it has been suggested that the issue of metric robustness ought to gain attention in studies involving neurophysiologic parameters (Hofstadt-van Oy et al., 2015; Keune et al., 2015b; Kappenman and Keil, 2017). Consequently, we also examined the reliability of each derived EEG parameter across the six within-session measures (pre-training resting-state, training blocks 1–4, post-training resting-state) and the five training sessions by means of intra-class correlations (ICC).

3. Results

3.1. Cross-sectional results

The theta/beta ratio differed between patients with slow vs. normal processing speed, as reflected by a significant main effect of SDMT-SPEED, $F(1,54) = 3.12$, $p = .04$, partial $\eta^2 = 0.11$. A pairwise comparison showed that patients with slow processing speed (M = 4.22, SE = 0.48) had a significantly higher theta/beta ratio than those with normal speed (M = 3.07, SE = 0.43, $M_{I-J} = 1.14$, $p = .04$).

The interaction REGION by SDMT-SPEED was not significant, F (2,108) = 0.17, $p = .84$, partial $\eta^2 = 0.006$. Due to our a priori hypothesis that patients would show differences in theta/beta activity particularly in anterior regions, exploratory region-specific comparisons were implemented. The theta/beta ratio was significantly increased in patients with slow processing speed in the frontal region (Fig. 1a) and the central region, while a similar increase in the parietal region did not reach significance (Table 3). The main effect of SDMT-SPEED on frontal and central theta/beta activity remained significant when current treatment with cortico-steroids, $F(53) = 3.19$, $p = .04$, partial $\eta^2 = 0.12$, disease activity, $F(1,53) = 3.59$, $p = .03$, partial $\eta^2 = 0.12$ and self-reported fatigue, $F(1,53) = 3.55$, $p = .03$, partial $\eta^2 = 0.12$, were considered as covariates.

The SDMT-SPEED by FREQUENCY interaction focusing on frontal derivations was significant indicating frequency-specific differences between patients with slow vs. normal processing speed, F (1,54) = 4.32, $p = .02$, partial $\eta^2 = 0.15$. Specifically frontal theta activity was increased in patients with slow SDMT speed (M = 2.07, SE = 0.38), relative to those with normal speed (M = 1.38, SE = 0.14; t

Table 3
Theta/beta ratio across regions for patients with slow and normal SDMT speed.

	SDMT speed				t-Statistic	p-Value
	Slow (N = 25)		Normal (N = 31)			
	M	SE	M	SE		
Frontal (Fz)	4.31	0.47	3.31	0.32	1.82	0.04
Central (Cz)	4.15	0.61	3.03	0.26	1.81	0.04
Parietal (Pz)	4.18	0.84	2.88	0.47	1.42	0.08

M = mean; SDMT: Symbol Digit Modalities Test (see text for references); SE = standard error.

(54) = 1.86, p = .03). There was no significant difference in beta power (M = 0.50, SE = 0.07 vs. M = 0.47, SE = 0.05; t(54) = 0.37, p = .72; Fig. 1b). The SDMT-SPEED by FREQUENCY interaction also remained significant when current treatment with cortico-steroids, F (1,53) = 3.81, p = .03, partial η^2 = 0.13, disease activity, F (1,53) = 4.12, p = .02, partial η^2 = 0.14 and fatigue, F(1,53) = 4.15, p = .02, partial η^2 = 0.15 were entered as covariates.

3.2. Longitudinal results

The theta/beta ratio remained relatively stable across training blocks and sessions. There was no significant main effect of TRAINING, F(19,171) = 0.72, p = .80, partial η^2 = 0.07, and no significant linear trend, F(1,9) = 0.11, p = .75.

In the secondary analysis, a state-specific shift in the theta/beta ratio was observed within sessions, as reflected by a significant main effect of STATE, F(5,45) = 5.02, p = .001, partial η^2 = 0.36, with a significant quadratic trend F(1,9) = 7.06, p = .03, partial η^2 = 0.44. As displayed in Fig. 2a and reported in detail in Table 4, within sessions, patients' frontal theta/beta ratio was significantly reduced during training blocks 1–4, relative to the pre- and post-session resting-states. This state-effect did not vary across sessions, as the STATE by SESSION interaction was not significant, F(20,180) = 0.73, p = .79, partial η^2 = 0.08.

For frontal theta power, a similar main effect of STATE F (5,45) = 10.43, p < .001, partial η^2 = 0.54, emerged, involving a quadratic trend F(1,9) = 16.27, p = .003. Theta power was significantly reduced during training, relative to the pre- and post-session

Table 4
Frontal theta/beta ratio values during training.

Pre-session resting-state		Training blocks 1–4					
M	SE		M	SE	M_{I-J}	SE	p-value
7.502	1.219	Block 1	5.861	0.914	1.641	0.711	0.046
		Block 2	5.075	0.692	2.427	0.883	0.023
		Block 3	5.071	0.658	2.430	0.826	0.016
		Block 4	5.457	0.748	2.045	0.794	0.030

Post-session resting-state		Training blocks 1–4					
M	SE		M	SE	M_{I-J}	SE	p-value
7.626	1.427	Block 1	5.861	0.914	1.765	0.813	0.058
		Block 2	5.075	0.692	2.551	1.081	0.043
		Block 3	5.071	0.658	2.555	1.063	0.040
		Block 4	5.457	0.748	2.169	1.009	0.060

Comparison of theta/beta ratios obtained for the pre-session resting-state assessment and during neurofeedback training blocks (top, a) and obtained for the post-session resting-state assessment and during trainings blocks (bottom, b). Values rounded to third digit after comma for display. M = mean; M_{I-J} = mean difference in beta power between respective resting-state and training block. SE = standard error.

resting-state assessments (Fig. 2b, Table 5). As was the case for the theta/beta ratio, the STATE by SESSION interaction was not significant for theta activity, F(20,180) = 0.86, p = .64, partial η^2 = 0.09. In case of frontal beta activity, the main effect of STATE, F(5,45) = 0.25, p = .94, partial η^2 = 0.03 (Fig. 2c) and the STATE by SESSION interaction were not significant, F(20,180) = 0.62, p = .90, partial η^2 = 0.06.

3.2.1. Reliability of longitudinal parameters

In the reliability analysis, ICC showed that the derived EEG measures involved excellent reliability across all implemented assessments (frontal theta/beta ratio ICC = 0.96, CI = 0.92–0.98; frontal theta ICC = 0.98, CI: 0.97–0.99; frontal beta ICC = 0.97, CI: 0.94–0.99, all p-values < .001).
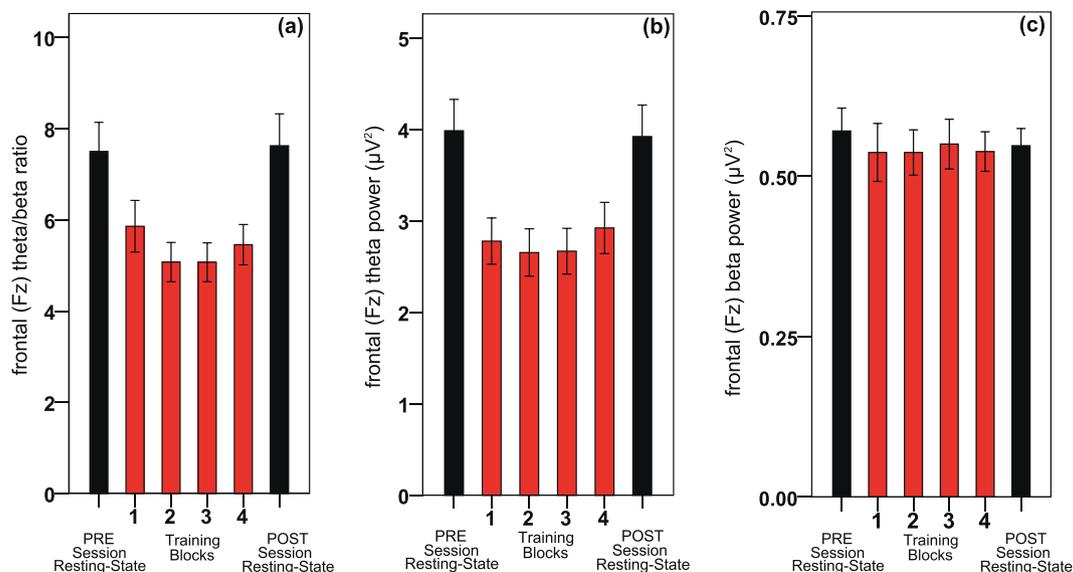
Fig. 2. Frontal (Fz) theta/beta ratio (a), theta power (b) and beta power (c) displayed for pre/post training resting-state assessments and the four training blocks, averaged across sessions. Error bars represent standard errors.

Table 5
Frontal theta power during training.

Pre-session resting-state			Training blocks 1–4				
M	SE		M	SE	M_{I-J}	SE	p-value
3.985	0.702	Block 1	2.778	0.488	1.207	0.299	0.003
		Block 2	2.653	0.528	1.332	0.304	0.002
		Block 3	2.668	0.486	1.317	0.312	0.002
		Block 4	2.922	0.558	1.063	0.303	0.007

Post-session resting-state			Training blocks 1–4				
M	SE		M	SE	M_{I-J}	SE	p-value
3.922	0.699	Block 1	2.778	0.488	1.143	0.245	0.010
		Block 2	2.653	0.528	1.268	0.355	0.009
		Block 3	2.668	0.486	1.254	0.381	0.010
		Block 4	2.922	0.558	0.999	0.383	0.015

Comparison of theta power obtained for the pre-session resting-state assessment and during neurofeedback training blocks (top, a) and obtained for the post-session resting-state assessment and during trainings blocks (bottom, b). Values rounded to third digit after comma for display. M = mean; M_{I-J} = mean difference in beta power between respective resting-state and training block. SE = standard error.

4. Discussion

The current work involved a cross-sectional examination of the relation between processing speed on the SDMT, the EEG theta/beta ratio and its underlying components. Additionally, it includes longitudinal exploratory data on whether EEG neurofeedback could be used to achieve a putatively adaptive alteration in the frontal theta/beta ratio and its components, toward a pattern indicative of improved processing speed.

4.1. Cross-sectional results: SDMT speed and oscillatory brain activity

In the cross-sectional analysis, results were generally supportive of the role of resting-state brain oscillatory activity as a marker of processing speed in MS (Van der Meer et al., 2013). In particular, slow processing speed on the SDMT was associated with an increased theta/beta ratio. The lack of a significant interaction across the examined regions indicates that the EEG theta/beta ratio represents a rather global marker of processing speed. Nevertheless, exploratory region-specific comparisons showed that there was a minor trend for the indicated association to be pronounced in frontal and central regions. The latter observation approximates the notion that a relative increase in anterior EEG oscillatory slow-wave activity represents a putative correlate of reduced attention control, as suggested by others and reported on before (Putman et al., 2010, 2014; Ogrim et al., 2012; Keune et al., 2017a; Angelidis et al., 2018).

The current results are also compatible with reports from MEG studies, where increased thalamic oscillatory slowing was observed in MS (Schoonhoven et al., 2018). The thalamus represents an integrative hub involved in the maintenance of cortical networks relevant for diverse cognitive processes, including attention and executive functions (Schoonheim et al., 2015a; Hwang et al., 2017; Schoonhoven et al., 2018). Based on the current findings, one may suggest that the EEG theta/beta ratio as a surface measure may tap the functional network involved in the mediation of SDMT performance. Future studies involving both, MEG and EEG methods may address this possibility in more detail. In this context, it is also recommended that potentially atypical EEG oscillatory activity in cognitively impaired MS patients is examined in relation to healthy controls, as has been done in previous work involving MEG (e.g. Van der Meer et al., 2013; Schoonhoven

et al., 2018).

MS patients are frequently affected by symptoms of fatigue which is known to negatively affect attention (Hansen and Lautenbacher, 2017). In the current study, the indicated association of an increased theta/beta ratio and slow processing speed on the SDMT remained significant when self-reported fatigue and further clinical variables were considered as covariates. This speaks to the robustness of this association and implies that the observed group difference in theta/beta activity was not confounded by fatigue.

The current work also provides new, original information on a frequency-specific association of frontal brain oscillatory EEG activity and SDMT processing speed in MS. Originally, we assumed that the frontal theta/beta ratio, implying an increase in frontal theta and a decrease in frontal beta power, would be increased in patients with slow processing speed. As specifically frontal theta power was responsible for the increased theta/beta ratio in patients with slow processing speed, one may suggest that reducing frontal theta activity might represent a study endpoint in clinical interventions seeking to improve processing speed in MS.

4.2. Longitudinal results: oscillatory activity during neurofeedback

In the longitudinal part of the current work, we intended to achieve a decrease in the frontal theta/beta ratio by means of neurofeedback training and further examined, which of the components underlying the theta/beta ratio was altered during training. Concerning this exploratory attempt, the results of the primary analysis were disconfirming. There was no support for successful operant conditioning of the theta/beta ratio across sessions, as no main effect or linear trend could be observed. A successful application of operant conditioning would imply that patients gradually learn to control spectral power (Egner et al., 2004; Gruzelier and Egner, 2005; Zoefel et al., 2011). The longitudinal part of the current work was exploratory in nature and there are several reasons due to which operant conditioning of the theta/beta ratio may have been unsuccessful, e.g. a brief intervention of five sessions, the training modalities themselves and the use of a small sample size. Currently, results from only a few studies related to neurofeedback in MS patients are available (Choobforoushzadeh et al., 2015; Buyukturkoglu et al., 2017; Jensen et al., 2018) and none of these addressed the question, whether and how the theta/beta ratio can be modulated in this group of patients. The extensive body of neurofeedback studies involving healthy individuals and other patient groups is heterogeneous concerning study designs, training duration and its modalities (Zoefel et al., 2011; Rogala et al., 2016; Sitaram et al., 2017). Nevertheless, it may be inferred for future studies involving MS patients, that the implementation of a validated and standardized treatment protocol in combination with a larger sample and longer treatment duration is required.

Despite the methodological limitations of the current exploratory application of neurofeedback in MS, it is noteworthy that in a secondary analysis, the frontal theta/beta ratio, i.e. an inverse marker of processing speed, was found to be reduced during the active training blocks, relative to pre/post session resting-state assessments (Fig. 2a). This shift emerged consistently throughout training sessions. Our results also revealed that specifically a shift in frontal theta power was driving this decrease in the theta/beta ratio (Fig. 2b). In contrast, beta power remained relatively stable (Fig. 2c). Others have reported compatible findings, e.g. in ADHD, where particularly elevated theta power was suggested as a potential marker of inattention and difficulties in executive functioning (Ogrim et al., 2012). It is important to note that in our cross-sectional analysis, increased theta power was shown to be indicative of slow SDMT speed, whereas beta power was not related to processing speed (Fig. 1b). The fact that a decrease in theta power was driving the decrease in the theta/beta ratio during training hence suggests that a neurophysiologic correlate of processing speed was manipulated. Due to the limitations of the current study design, the

origin of the observed shift in theta activity remains unclear and its occurrence cannot be attributed to neurofeedback specifically. Nevertheless, since theta power was shown to be negatively related to processing speed and was consistently reduced during training within sessions, results of this exploratory work suggest that a future examination of neurofeedback in MS may be feasible. It cannot be ruled out that such state-specific alterations might be of clinical relevance themselves. One may speculate that inducing such changes indicative of improved processing speed might support patients in the state-specific recruitment of cognitive resources, when situational demands require such recruitment. This notion also requires to be addressed in future studies examining the potential clinical relevance of the observed neurophysiologic alteration. In this context, an analysis of the latent state-trait structure of the theta/beta ratio and theta power in MS, that has previously been determined for other EEG markers in non-clinical populations (Hagemann et al., 2005), might provide useful information aiding the interpretation of state vs. trait-related alterations.

4.3. Reliability of the derived EEG measures

Metric robustness of parameters examined in studies with neurophysiologic measures is of critical importance (Hofstadt-van Oy et al., 2015; Kappenman and Keil, 2017). Our reliability analysis of each derived EEG parameter across the six within-session measures and the five training sessions by means of intra-class correlations (ICC) provided estimates of excellent reliability, which reflects a sound data analytic approach.

5. Conclusions

In sum, to the best of our knowledge, the current work is the first in which a cross-sectional examination of brain oscillatory correlates of SDMT performance is combined with the longitudinal application of neurofeedback training targeting the frontal theta/beta ratio. Frontal midline theta may represent an inverse marker of processing speed in MS. There was no support for successful operant conditioning of the theta/beta ratio across sessions. In a secondary analysis, a transient reduction in frontal theta power was observed during neurofeedback relative to rest, albeit its specificity and clinical relevance remain to be examined. Future work is required to address these issues in more detail. In particular, appropriate control conditions (e.g. sham feedback and specific training of frequency bands irrelevant for processing speed) are required to address the issue of specificity. MS is one of the most common chronic neurological disorders and there has been a call for the development of standardized treatments for cognitive rehabilitation (Browne et al., 2014; Sokolov et al., 2018). A further exploration of neurofeedback as a candidate for the expanding therapeutic repertoire complementing immune-modulating medication appears feasible (Burschka et al., 2014; Keune et al., 2015a; Gromisch et al., 2018).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

PMK designed and supervised the implementation of the study, analyzed the data and drafted the manuscript. SJ, TS, CK, SH and JK recruited the patients, administered the neuropsychological tests and EEG assessments and handled test scoring and data entry. EW designed and administered the neurofeedback treatment, recruited patients and administered the neuropsychological tests and EEG assessments. MS was involved in designing the study and supported drafting the manuscript. PO was involved in designing the study, supported drafting the manuscript and supervised the study implementation.

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