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Original Research Paper

Stimulus-related modulation in the 1/f spectral slope suggests an impaired inhibition during a working memory task in people with multiple sclerosis

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Abstract

Background: An imbalance of excitatory and inhibitory synaptic transmission in multiple sclerosis (MS) may lead to cognitive impairment, such as impaired working memory. The 1/f slope of electroencephalography/magnetoencephalography (EEG/MEG) power spectra is shown to be a non-invasive proxy of excitation/inhibition balance. A flatter slope is associated with higher excitation/lower inhibition.

Objectives: To assess the 1/f slope modulation induced by stimulus and its association with behavioral and cognitive measures.

Methods: We analyzed MEG recordings of 38 healthy controls (HCs) and 79 people with multiple sclerosis (pwMS) while performing an n-back task including target and distractor stimuli. Target trials require an answer, while distractor trials do not. We computed the 1/f spectral slope through the fitting oscillations and one over f (FOOOF) algorithm within the time windows 1 second before and after each stimulus presentation.

Results: We observed a flatter 1/f slope after distractor stimuli in pwMS compared to HCs. The 1/f slope was significantly steeper after stimulus for both HCs and pwMS and was significantly correlated with reaction times. This modulation in 1/f slope was significantly correlated with visuospatial memory assessed by the BVMT-R test.

Conclusion: Our results suggest possible inhibitory mechanism deficits in pwMS during a working memory task.

Keywords: Aperiodic, 1/f exponent, excitation/inhibition balance, magnetoencephalography, n-back task, working memory, multiple sclerosis

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Introduction

Multiple sclerosis (MS), a demyelinating neuroinflammatory and neurodegenerative disease, frequently imposes a significant cognitive burden on people with multiple sclerosis (pwMS).[1,2] Cognitive domains such as information processing speed[3] and working memory[4] are significantly affected. While the exact mechanisms underlying cognitive dysfunction in MS remain incompletely understood, evidence suggests a potential link between synaptic loss, particularly in inhibitory synapses, and cognitive impairment.[2]

Previous in vivo studies in MS[5,6] using magnetoencephalography/electroencephalography (MEG/EEG) have primarily focused on investigating the relationship between oscillatory biomarkers and cognitive performance during resting state and while performing a task. Nevertheless, it has also been shown that the non-oscillatory component of neuronal activity contains functionally relevant information. The slope, representing the steepness of the 1/f power-law component, has been associated with the excitation/inhibition ratio,[7] where a steeper slope indicates a higher level of inhibition.[7–9] The value of this novel

biomarker in MS is still poorly investigated, but our recent results support this interpretation in pwMS.[8]

Working memory is the capacity to actively and temporarily retain and manipulate a limited amount of information for a brief period of time.[10] Maintaining the appropriate balance between excitatory and inhibitory signals has been computationally shown to be essential for efficient information processing and working memory maintenance.[11] Excitatory signals stimulate neurons, while inhibitory signals suppress or dampen neural activity.

Working memory, crucial for various cognitive processes including learning and problem-solving,[12] relies on the ability to selectively pay attention and decode the relevant information and recall them while suppressing irrelevant stimuli and ignoring the distractors.[13–15] Memory processes deteriorate in pwMS, leading to impaired decoding and recalling of information.[16]

In this study, we aim to explore the role of the 1/f slope as a potential biomarker of excitation/inhibition balance in pwMS during a visual-verbal n-back task. We hypothesize that an impaired excitation/inhibition balance—as suggested in pwMS[2]—will lead to reduced inhibition during distractor trials. Since we have previously demonstrated the potential value of the 1/f slope as a proxy of excitation/inhibition balance in pwMS,[8] we expect a flatter 1/f slope in pwMS compared to healthy controls (HCs). We also hypothesize a correlation between a flatter 1/f slope and longer reaction times (RTs), similar to Kałamała et al.[17] where individuals with a flatter 1/f slope have a higher inverse efficiency score (i.e. adjusted RTs). Next, we investigate the 1/f slope modulation induced by the task. We hypothesize that the 1/f slope will be steeper post- versus pre-stimulus during the n-back task, similar to what has been observed in HCs,[18,19] and we will explore to what extent the level of 1/f slope modulation throughout a cognitive task relates to offline cognitive performance in MS.

Materials and methods

Participants

MEG data were acquired in 117 subjects during the n-back task: 38 HCs and 79 pwMS. Since we previously observed that benzodiazepines affect the 1/f spectral slope,[8] we divided the group of pwMS into two separate groups based on their treatment: 19 pwMS treated with benzodiazepines (pwMS(BZDp)) and 60 pwMS not treated with benzodiazepines (pwMS(BZDn)). All pwMS were recruited at the National MS Center Melsbroek and were required to meet the diagnostic criteria for MS according to McDonald's revised criteria[20] while having an Expanded Disability Status Scale (EDSS) score[21] less than or equal to 6 in order to participate in the MEG sessions independently. Exclusion criteria included experiencing a relapse or receiving corticosteroid treatment within the preceding 6 weeks, as well as having a pacemaker, dental wires, major psychiatric disorders, or epilepsy. Table 1 presents a detailed description of pwMS and HCs.

MEG data acquisition and pre-processing

The MEG acquisition and pre-processing[6] and parcellation[22] have been discussed as published before. Figure 1 demonstrates the n-back task paradigm and is described in detail.[6] The n-back task contains trials that require an answer and trials that do not. We call the former "target" trials and the latter "distractor" trials.

Power spectral analysis

As it is shown in Figure 2, we analyzed a time window spanning 1 second both before and after stimuli onset for each trial. Within this timeframe, we computed the power spectral density (PSD) using the default Welch function in SciPy with a window length of 250 samples (1 second) at each brain region for every subject. Then, we averaged the power spectra over trials within each subject for each time window pre- and post-stimulus. Furthermore, we applied the "fitting oscillations and one over f" (FOOOF) algorithm, as introduced by Donoghue et al.,[23] to estimate the 1/f exponent for the resulting power spectra. We set the lower border of the fitting frequency range to 3 Hz and the upper border to 45 Hz to avoid the notch-filtered peak around 50 Hz. Since the power spectrum followed an almost linear line in log-log space within the selected frequency range, we used the "fixed" mode for parameterization. The 1/f slope refers to the steepness of the 1/f aperiodic component (exponent "x" in $\frac{1}{f^x}$).

To estimate the periodic alpha power, we first separated the periodic component by correcting the power spectrum density for the aperiodic component and calculated the average alpha power in the 8–12 Hz band.

Neuropsychological assessment

Neuropsychological tests were performed on the same day as the MEG recording for all subjects. The

Table 1. Description of subjects.

	HCs	pwMS sub-groups		Group differences (*p*-values)		
	HCs	pwMS(BZDp)	pwMS(BZDn)	HCs vs pwMS(BZDn)	HCs vs pwMS(BZDp)	pwMS(BZDn) vs pwMS(BZDp)
N	38	19	60	–	–	–
Gender (M/F)	15/23	0/19	22/38	0.94	0.0040	0.0048
Age (yrs)	47 ± 11	47 ± 7	48 ± 10	0.89	0.99	0.91
Education (yrs)	15.2 ± 2	13 ± 2	14 ± 2	0.16	0.001	0.08
Disease duration (yrs)	–	13 ± 6	15 ± 8	–	–	0.34
EDSS median [IQR]	–	3.5 [3-4.25]	2.5 [2-3.5]	–	–	0.051
Cognitive assessment						
SDMT	53 ± 9	47 ± 7	49 ± 12	0.07	0.01	0.49
VGLT	66 ± 7	62 ± 10	63 ± 10	0.29	0.12	0.56
COWAT	17 ± 4	17 ± 4	15 ± 5	0.045	0.65	0.33
BVMT-R	28 ± 5	24 ± 6	26 ± 6	0.054	0.03	0.57

HCs: healthy controls; EDSS: Expanded Disability Status Scale; IQR: interquartile range; SDMT: Symbol Digit Modalities Test; COWAT: Controlled Oral Word Association Test; BVMT-R: Brief Visuospatial Memory Test revised.
We report the mean values and standard deviations for different clinical parameters. For EDSS, the median and interquartile range (IQR) are shown. The comparisons were performed using permutation testing with $N=5000$ for all parameters except gender for which a chi-square test was used. HCs: healthy controls, pwMS(BZDp) and pwMS(BZDn): pwMS with and without benzodiazepines. The "p" in the term for patients treated with benzodiazepines refers to the treatment status which is "positive." Conversely, "n" in the term for patients not treated with benzodiazepines refers to the treatment status which is "negative."

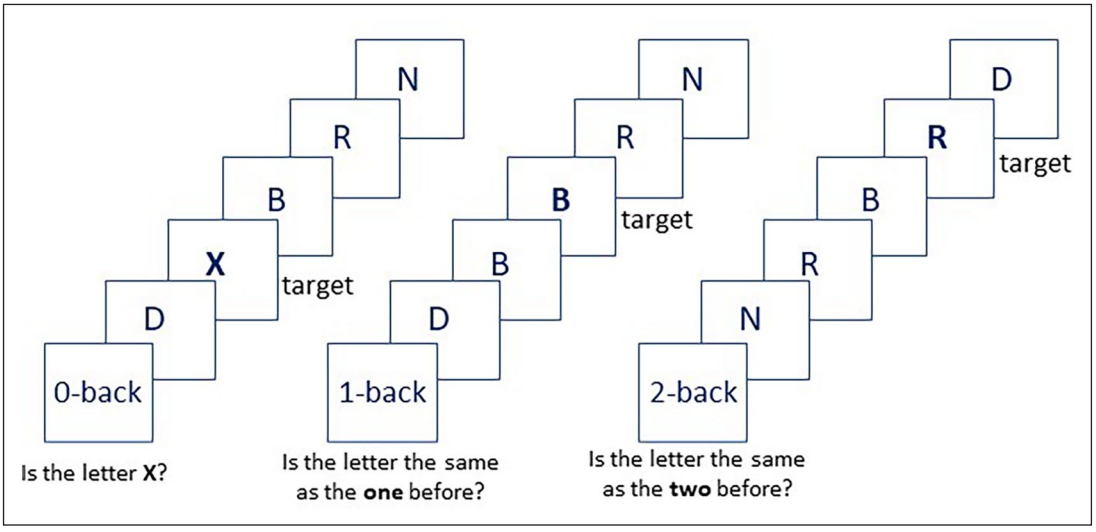

Figure 1. Illustration of the visual-verbal n-back paradigm. The 6 × 6.5 cm letter stimuli were projected onto a screen 72 cm from the front of the MEG helmet. Each stimulus was displayed on the screen for 1 second, with an inter-trial interval of 2.8 seconds. The instructions for the specific conditions were presented at the start of every block for 15 seconds.

neuropsychological tests described previously[6] included the Symbol Digit Modalities Test (SDMT) to capture information processing speed, the Dutch version of the California Verbal Learning Test (CVLT-II), Dutch version: VGLT to assess verbal memory, the Controlled Oral Word Association Test (COWAT) to assess verbal fluency, and the Brief Visuospatial Memory Test (Revised; BVMT-R) to assess spatial memory. Fatigue is assessed using the Fatigue Scale for Motor and Cognitive Function (FSMC), and depression is assessed using Beck's Depression Inventory (BDI).

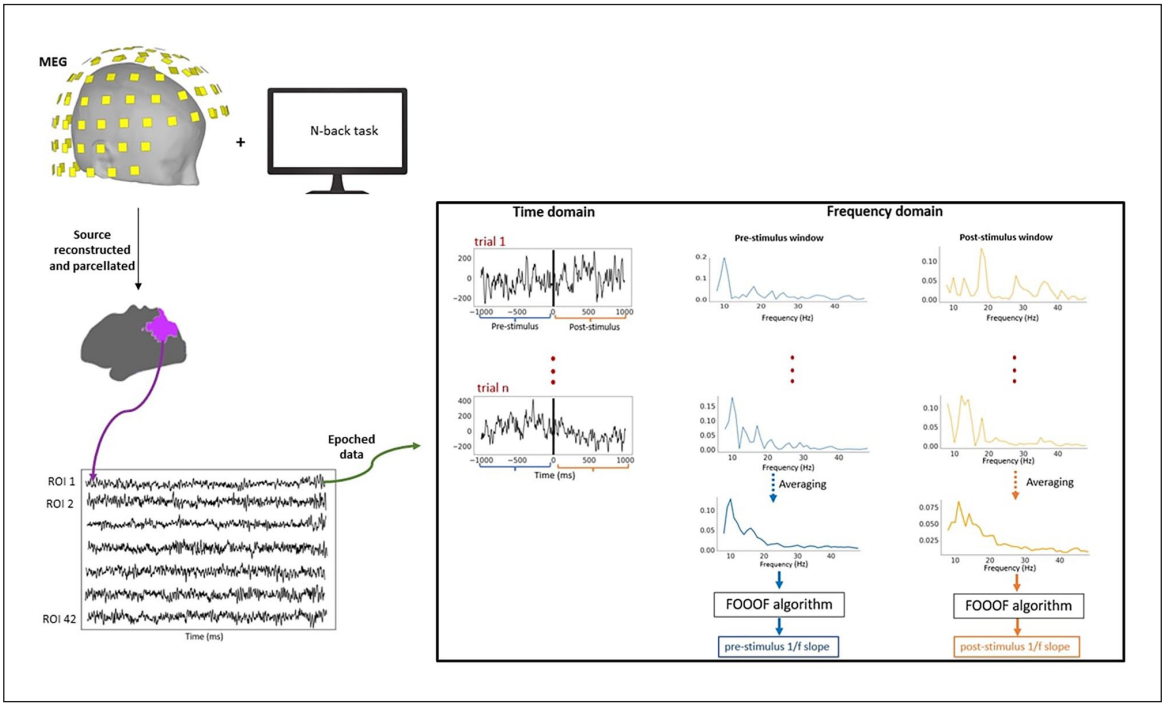

Figure 2. An illustration of the data analysis for a single subject, in a single condition, for a single trial, and at a single brain region. We determined the time window of 1 second before and after stimuli onset. Within this timeframe, we computed the PSD for each trial at each brain region for every subject. Then, for each time window before and after stimuli, we averaged the power spectra over trials within each brain region for each subject. Furthermore, we applied the "fitting oscillations and one over f" (FOOOF) algorithm to estimate the 1/f exponent for the resulting power spectra.

Statistics

All statistical analyses of neurophysiological markers used non-parametric tests. We used the two-way analysis of variance (ANOVA) model with two levels for between-group comparisons across all three groups and trials and the Wilcoxon rank-sum test for the post hoc analyses. We included the group in first level (HCs, MS(BZDn), MS(BZDp)), and the cognitive conditions in second level (0-back, 1-back, 2-back). The Wilcoxon signed-rank test was performed for the paired-wise comparisons. For the non-paired comparisons, we used either the Wilcoxon rank-sum test or the Mann–Whitney *U*-test depending on the presence of ties. When calculating tests for multiple cortical regions, the Benjamini–Yekutieli false discovery rate (FDR[24]) correction for multiple comparisons was applied to the *p*-values. We used the "cocor" package[25] to compare the dependent and independent correlations. For all *p*-values, a cutoff of 0.05 was used.

Ethics

The research was approved by the University Hospital Brussels's local ethics committees of the University Hospital Brussels (Commissie Medische Ethiek UZ Brussel, B.U.N. 143201423263, 2015/11) and the National MS Center Melsbroek (2015-02-12). All participants provided written informed consent.

Results

Behavioral data

Figure 3 shows an increasing median RT with increasing working memory load (0, 1, 2-back conditions) within each group of subjects. The median RT during the 0-back is significantly faster than the 2-back ($p < 0.0001$), and the same holds for the 1-back as compared to the 2-back ($p < 0.007$). These results align with working memory literature in which the direct positive association between RTs and working memory load is frequently reported. Furthermore, we observed a significantly longer RT in pwMS(BZDn) and pwMS(BZDp) compared to the HCs group. We also observed a significant difference in response accuracy between HCs and pwMS(BZDp) ($p < 0.0001$) in the 1-back condition and between HCs and pwMS(BZDn) ($p = 0.043$) in the 2-back condition, with better performance in HCs (Supplemental Figure S1).

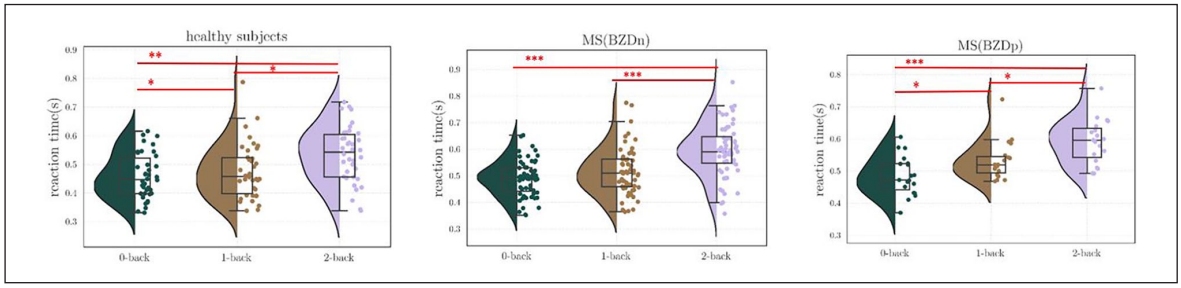

Figure 3. The distribution of the reaction times for three groups (HCs, pwMS(BZDn), pwMs(BZDp)) and three conditions (0-back, 1-back, 2-back). The Wilcoxon signed-rank test was used to compare the reaction times between different conditions within each study group.
*$p < 0.05$; **$p < 0.001$; ***$p < 0.0001$.

Table 2. Summary of the non-parametric ANOVA results on the rank transformed of 1/f slope after distractor stimuli.

	df	*F*	*p*
Group HCs, MS(BZDn), MS(BZDp)	2	3.23	**0.040**
Conditions 0-back, 1-back, 2-back	2	0.08	0.91
Group × conditions	4	1.66	0.15

Bold values denote statistical significance at the level p<0.05.

Comparing the 1/f slope between HCs and pwMS

As Table 2 shows the results of ANOVA on the rank transform of 1/f slope after distractor stimuli, there is a significant difference in the 1/f slope post-distractor trials between different groups ($p = 0.040$). Post hoc analyses show that after distractor stimuli, pwMS(BZDn) and pwMS(BZDp) demonstrated a significantly flatter slope (suggesting less inhibition) compared to HCs in all three conditions (Figure 4). The significantly flatter 1/f slope in the left inferior dorsal prefrontal cortex of pwMS emerged as a shared region in both 1-back and 2-back conditions. Figure 4 shows no significant difference in 1/f slope between pwMS(BZDn) and pwMS(BZDp) after distractor trials. Importantly, the 1/f slopes before and after target stimuli and before distractor stimuli were not significantly different between pwMS and HCs. The observed flatter slope in pwMS suggests less inhibition after distractor trials.

Correlation between 1/f slope pre- and post-stimulus and RT

Furthermore, we observed that a flatter slope is linked to a longer RT both before and after the onset of target and distractor stimuli across all subjects (see Figure 5 for target trials and Supplemental Figure S2 for distractor trials). Notably, this correlation was more pronounced in the 1-back and 2-back conditions than the 0-back condition, indicating a stronger relationship in the context of a higher cognitive load.

Stimulus-related modulation in the 1/f slope

We separately compared the 1/f slope pre- versus post-stimulus for target and distractor stimuli.

Significant 1/f modulation in target trials. In the case of target stimuli, we observed a statistically significant increase in the 1/f slope following stimulus onset across all three conditions (0-back, 1-back, and 2-back) for both HCs and pwMS(BZDn). However, this increase in the 1/f slope was not statistically significant for pwMS(BZDp), neither when considering the entire brain nor at the regional level. Figure 6(a) shows the averaged 1/f slope pre- and post-stimulus in the 0-back condition. Figure 6(b) presents the same analysis on a regional level. While the results for the 0-back condition of pwMS(BZDn) are displayed here, the results for the other working memory loads for pwMS(BZDn) and HCs are very similar (see Supplemental Figure S3).

Significant 1/f modulation in distractor trials. Similar to the analysis of the target stimuli, we observe a significantly steeper slope after the distractor stimuli, suggesting that the observed alteration in the 1/f slope cannot be solely attributed to button pressing. Figure 7 visually represents the averaged 1/f slope modulation over the entire brain and the cortical distribution of regions displaying statistically significant variations in 1/f slope between the pre-and post-stimulus onset. The results of all three groups of subjects for the three 0-back, 1-back, and 2-back conditions are shown. The reported *p*-values have been corrected for multiple comparisons. The most significant results are seen in the pwMS(BZDn) group. However, it

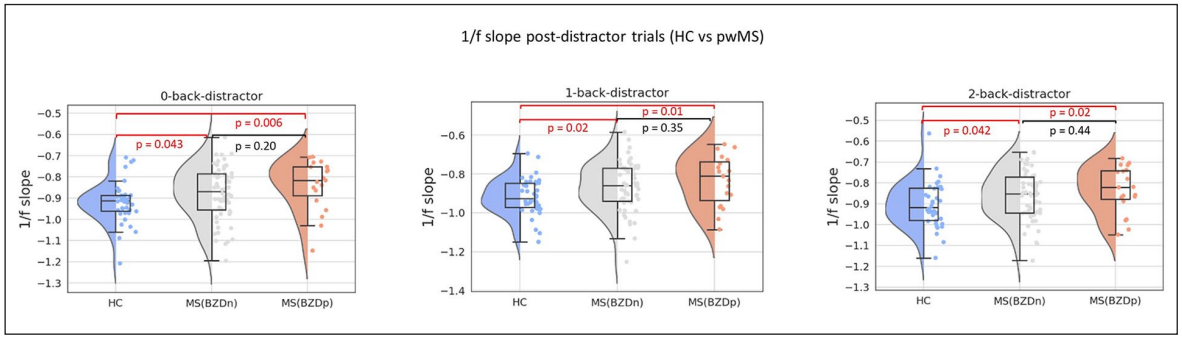

Figure 4. The distribution of post-distractor stimuli 1/f slope—averaged over the whole brain—for the HCs and pwMS groups in all three conditions (0-back, 1-back and 2-back). The Wilcoxon rank-sum test was used.

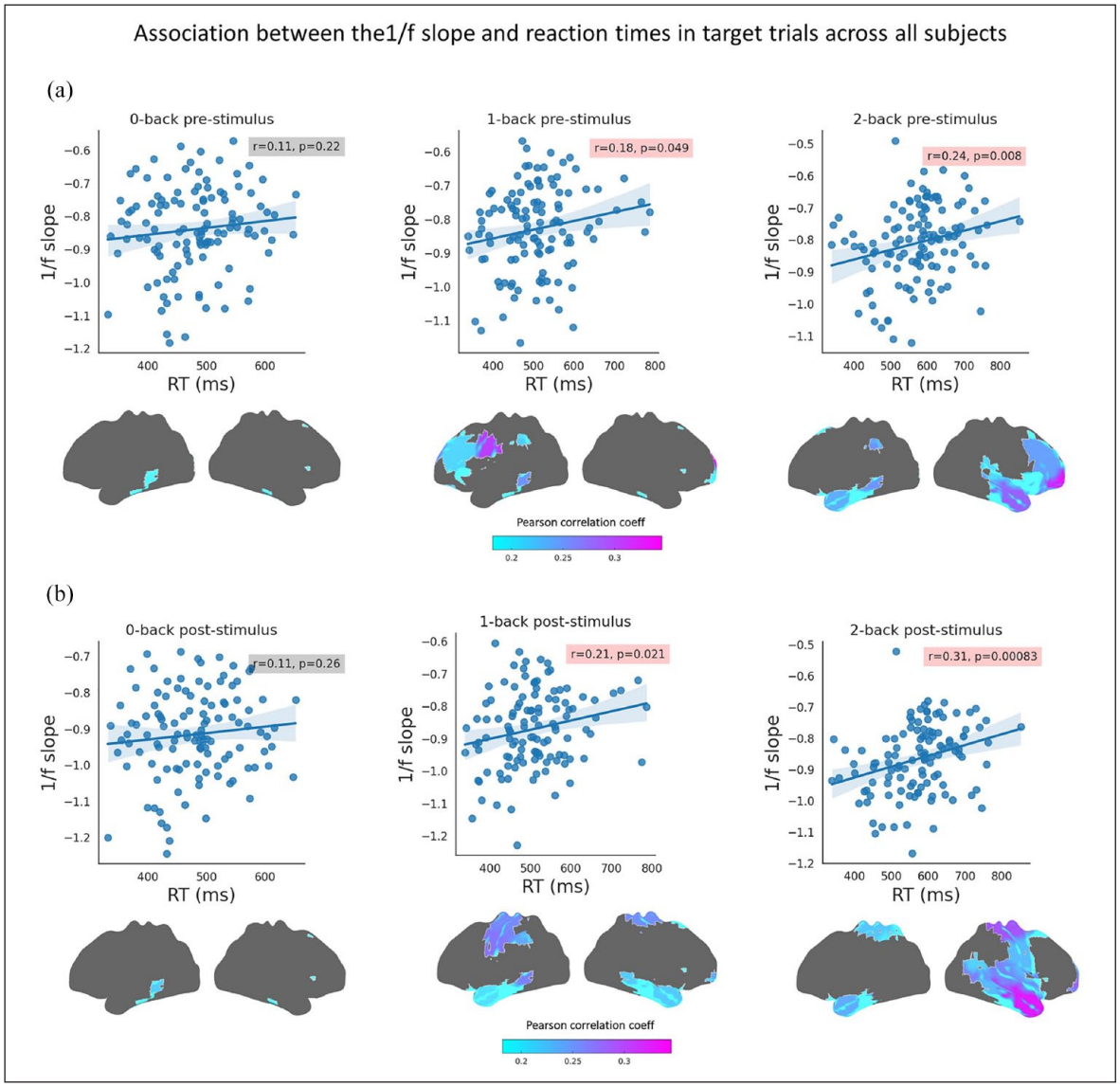

Figure 5. Correlation analysis between reaction time and 1/f slope of the time window (a) 1 second pre- and (b) 1 second post-target stimulus onset, both for averaged over the whole brain and at regional level over all subjects. The scatter plot shows the correlation for the averaged 1/f slope over the whole brain and reaction times and the cortical map shows the regions with significant correlation for the regional-level analysis. We included all subjects to increase the statistical power.

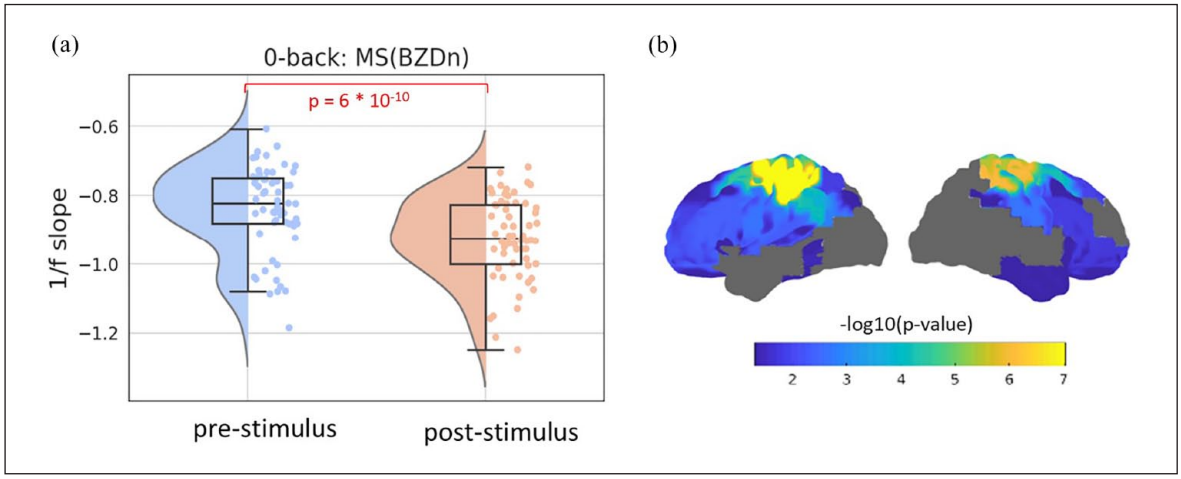

Figure 6. The pre- vs post-stimuli 1/f slope for pwMS(BZDn) group in target trials and 0-back condition (a) averaged over the whole brain and (b) in region level. Note that the $-\log10(p\text{-value}) > 1.3$ indicated the significant values and that *p*-values have been corrected for multiple comparisons across 42 regions. The Wilcoxon signed-rank test was used to compare the pre- and post-stimuli 1/f slope.

should be noted that this is also the largest group and the effect sizes are similar across all comparisons.

The relationship between the 1/f slope modulation and cognitive performance

To investigate the potential association between the 1/f slope modulation and cognitive performance, we conducted a Pearson correlation analysis between the 1/f slope modulation induced by stimuli and the offline cognitive performance measured through standardized neuropsychological tests. For the group of pwMS who had received benzodiazepines, no significant correlation was observed for BVMT-R, SDMT, VGLT, and COWAT for all three conditions, neither at the whole-brain level nor at the regional level (Supplemental Figure S4). It has to be noted that limited statistical power is available due to the relatively small sample size in this group ($n = 19$). Our results revealed a significant positive correlation between the 1/f slope modulation and BVMT-R scores for HCs. HCs with better visuospatial working memory performance tend to have a smaller increase in inhibition post-stimulus.

Conversely, a significant negative correlation was observed between these variables among pwMS who had not received benzodiazepines (pwMS(BZDn)) (see Figure 8 for target trials and Supplemental Figure S5 for distractor trials). These significant correlations were observed in brain regions within the parietal, temporal, and frontal lobes in HCs and parietal, temporal, and occipital lobes in pwMS(BZDn). Furthermore, we compared correlations between distinct groups, HCs, and pwMS (BZDn) in three conditions. Our analysis revealed a significant dissimilarity in the correlations between these two study cohorts, with a stronger positive correlation in HCs (p-value(0-back) = 0.0009, p-value (1-back) = 0.0015, p-value (2-back) = 0.0005). We did not observe an association between the 1/f slope modulation and the other cognitive scores: SDMT, VGLT, and COWAT.

Alpha power modulation by task

Following the stimulus onset, alpha power is decreased. While no correlation was found between alpha power pre- and post-stimulus and RTs, it was significantly correlated with BVMT-R scores. However, the task-induced modulation in alpha power (post-stimulus alpha power minus post-stimulus alpha power) was not correlated with cognitive scores. The details can be found in Supplemental Figures S6–S10.

Discussion

In this study, we investigated the modulation of 1/f slope as a non-periodic neurophysiological feature induced by a visual-verbal n-back task in pwMS and HCs. Our results showed a more pronounced decrease in 1/f slope in pwMS following the distractor stimuli compared to HCs and an association of 1/f slope task modulation with behavioral and visuospatial memory performance.

The flatter 1/f slope after distractor trials in pwMS suggests a less pronounced inhibition compared to

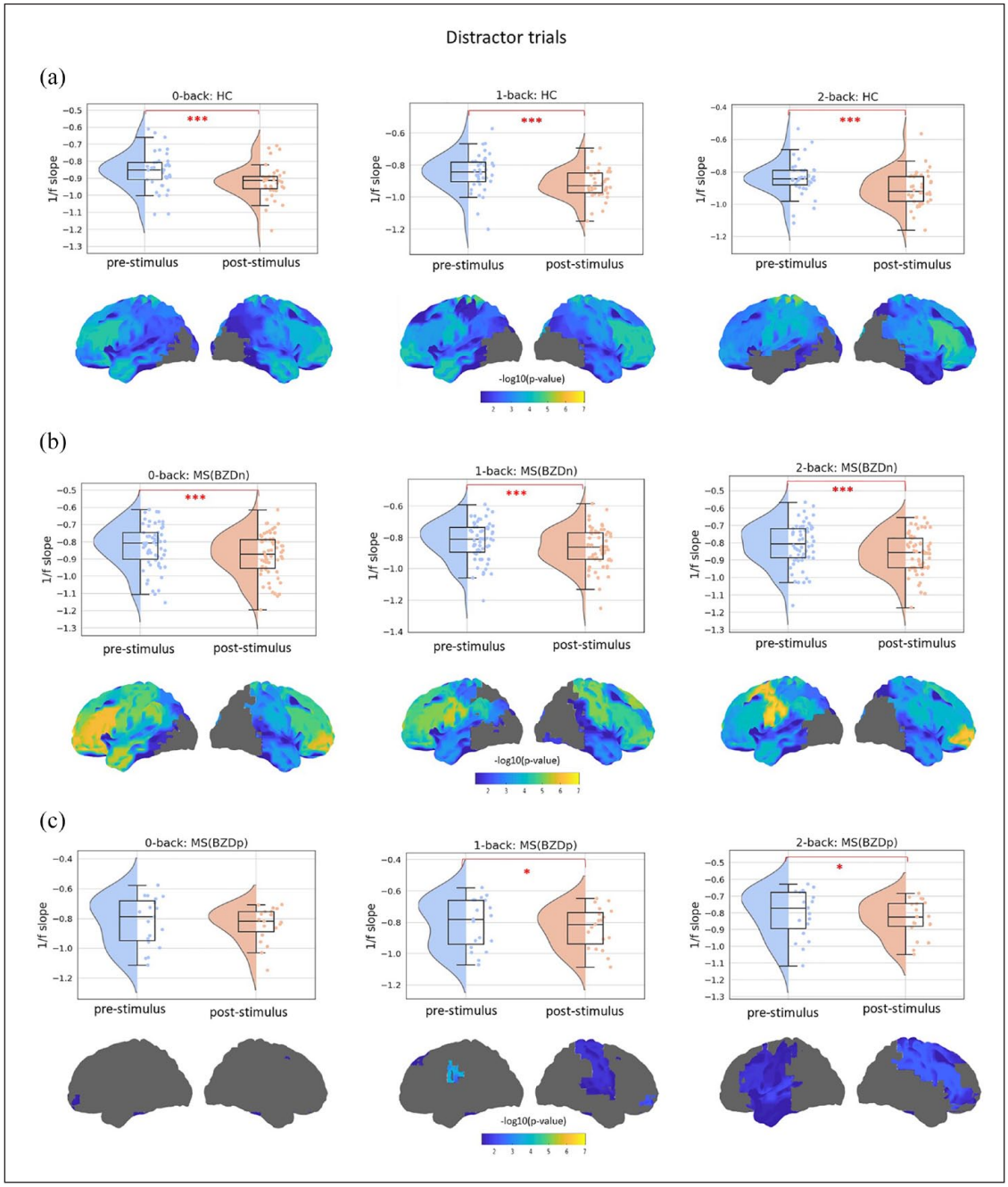

Figure 7. The pre- vs post-stimuli 1/f slope in distractor trials and three conditions (0-back, 1-back and 2-back), for both 1/f slope averaged over the whole brain and at regional level. Note that the $-\log10(p\text{-value}) > 1.3$ indicated the significant values and that p-values have been corrected for multiple comparisons across 42 regions. The Wilcoxon signed-rank test was used to compare the pre- and post-stimuli 1/f slope. (a) HCs, (b) pwMS(BZDn), and (c) pwMS(BZDp). $^{*}p < 0.05$; $^{**}p < 0.001$; $^{***}p < 0.0001$.

HCs, highlighting a potentially reduced cognitive control in MS. This finding also aligns with a previous study[2] that used a large post-mortem MS data set and a computational model to demonstrate that predominant inhibitory synaptic loss leads to network disinhibition and cognitive impairment in MS. The largest difference appeared in the left inferior dorsal prefrontal cortex, which has been shown to be more strongly activated in pwMS during an n-back task.[26]

The observed significant positive correlation between 1/f slope and RT corroborates the findings of a recent

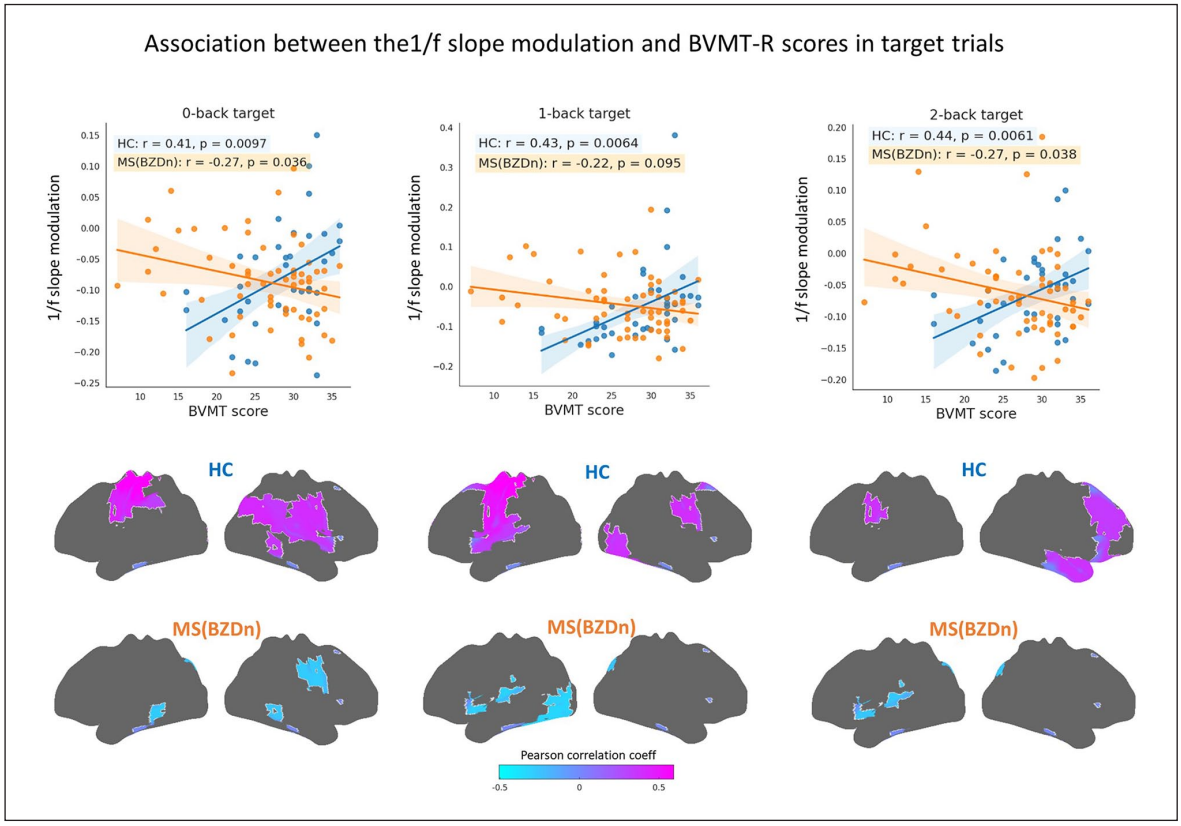

Figure 8. Correlation analysis between the 1/f slope modulation and BVMT-R scores both for averaged over the whole brain and at regional level for the HCs and pwMS(BZDn) groups in three conditions (0-back, 1-back and 2-back) in target trials. Only the regions with significant correlations are shown.

study,[17] which demonstrated that the 1/f slope is positively associated with RTs as a behavioral performance. Moreover, the stronger correlation in 1-back and 2-back conditions supports the involvement of more demanding WM processes, such as information updating and manipulation, which may contribute to the observed stronger relationship compared to the 0-back condition.

Our study also showed that the 1/f spectral slope increases following the onset of target stimuli. Similarly, Gyurkovics et al.[18] found a steeper 1/f slope after auditory oddball stimuli. This could suggest either a disruption of ongoing excitatory activity or an increase in inhibition level to facilitate further stimulus-specific processing. It is important to note that the increase in 1/f slope is most robust in the sensorimotor cortex following target stimuli. To rule out the potential influence of button presses on 1/f slope modulation in target trials, we also examined the 1/f slope modulation following distractor stimulus onset and observed that the 1/f slope modulation can thus not solely be attributed to the requirement to push a button.

Our study highlighted the potential clinical relevance of task-induced 1/f slope modulation by demonstrating significant positive and negative correlations with offline visuospatial memory as measured by BVMT-R[27] for HCs and pwMS(BZDn), respectively. A stronger modulation toward inhibition was correlated with better visuospatial memory in pwMS, whereas the opposite relationship holds for HCs. Observing these opposite correlations in the two cohorts is surprising, and future studies should aim to understand this relationship better before the 1/f modulation can be used as a clinical tool. Recent multimodality neuroimaging studies[28,29] have shown positive correlations between hippocampal GABA concentrations and receptor density with visuospatial and verbal memory in pwMS. Moreover, visuospatial memory emerges as the most important cognitive domain for distinguishing various cognitive profiles among pwMS.[30]

We also examined the modulation of alpha power in response to the task. We discovered a positive correlation between alpha oscillatory power and the 1/f slope, yet observed that the modulation in alpha power and

1/f slope following stimulus onset occurred in opposite directions. We observed a steeper 1/f slope, accompanied by the expected decrease in alpha oscillatory activity after the stimulus (known as alpha suppression[31]) (see Supplemental Materials). This observation indicates that oscillatory and non-oscillatory spectral components should be investigated together as they contain independent functional information.[19]

Our study has a possible limitation related to the constrained time frame before and after the stimulus onset. Due to the nature of our task paradigm, we had to restrict the analysis to a 1-second time window, which lowered the frequency resolution to 1 Hz. However, our data set exhibited high accuracy in fitting the 1/f aperiodic component (see Supplemental Figure S11). Furthermore, we arbitrarily determined the window size; other analyses enable the analysis of neurophysiological data in an intrinsically dynamic way.[32] Future research should also clarify whether the observed effects are specific to this working memory paradigm or generic across different cognitive paradigms.

Finally, it is important to note that the 1/f slope has been suggested as a proxy for the excitation/inhibition ratio. However, the 1/f slope is also determined by other factors,[33] and other alternative explanations have been proposed, for example, the 1/f scaling is hypothesized as the result of the rate fluctuations in the cortical up and down states transition in the brain[34] and also as a consequence arising from the damping of harmonic oscillators.[35] Future studies may explore the 1/f slope modulation across different task paradigms by integrating different neuroimaging techniques such as positron emission tomography (PET) and magnetic resonance (MR) spectroscopy to incorporate data on GABA receptor densities and neurotransmitter concentrations.

To conclude, this study is the first to investigate the stimulus-related modulation in the 1/f spectral slope of the brain activity during a visual-verbal working memory task in pwMS. Our findings shed light on the possible impaired inhibition in pwMS, suggesting a need for future research aimed at better understanding of impaired inhibitory mechanism in pwMS during working memory tasks.

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Data availability statement

Data are available upon reasonable request from the corresponding author.

Declaration of Conflicting Interests

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Supplemental material

Supplemental material for this article is available online.

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