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Cognitive fatigue-related sensory gating deficits in people with multiple sclerosis

Stefanie Linnhoff [a], Aiden Haghikia [a,b,c], Tino Zaehle [a,b,*]

[a] Department of Neurology, Otto-von-Guericke-University Magdeburg, Leipziger Street 44, Magdeburg 39120, Germany
[b] Center for Behavioral Brain Sciences (CBBS), Magdeburg 39106, Germany
[c] German Center for Neurodegenerative Diseases (DZNE), Magdeburg 39120, Germany

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ABSTRACT

Background: Cognitive fatigue is highly prevalent in people with multiple sclerosis (pwMS) and significantly limits their quality of life. Fatigue can be subdivided into a subjective feeling of constant (trait) or current (state) exhaustion, as well as an objective performance decline, also known as fatigability. However, the current fatigue diagnosis in pwMS is purely subjective, leaving fatigability mostly unattended. Sensorimotor and sensory gating deficits have recently been described as possible objective markers for fatigability in healthy subjects. Thus, this study aimed to investigate the potential of prepulse inhibition (PPI) ratios and the P50 sensory gating suppression as surrogate markers for cognitive fatigue in pwMS.
Methods: PPI and P50 sensory gating ratios were assessed before and after a 30-min fatigability-inducing AX-continuous performance task. Subjective trait fatigue was operationalized via self-report questionnaires, subjective state fatigue via visual analog scales (VAS), and fatigability via the change in both gating ratios. The data were analyzed using Linear Mixed Models and Pearson correlations.
Results: We included 18 pwMS and 20 healthy controls (HC) in the final analyses. The task-induced fatigability was more pronounced in pwMS. While the initial PPI and P50 ratios were similar in both groups, P50 sensory gating was significantly disrupted after fatigability induction in pwMS. PPI, on the other hand, decreased in both groups. Moreover, initial P50 sensory gating ratios were negatively associated with subjective trait fatigue in pwMS, indicating that higher trait fatigue is associated with disrupted sensory gating. Finally, fatigability-related changes in P50 sensory gating were associated with the changes in VAS ratings, but only in HC.
Conclusions: This study demonstrated that P50 sensory gating is a promising objective fatigue and fatigability parameter. Importantly, P50 sensory gating correlated with subjective trait and state fatigue ratings. Our results extend the subjective fatigue diagnosis and broaden the understanding of pathophysiological neuronal mechanisms in MS-related fatigue. This is the first study to present fatigue-related disruption of sensory gating in pwMS.

1. Introduction

Cognitive fatigue affects up to 80% of people with multiple sclerosis (pwMS) (Cook et al., 2013) and is associated with a decreased quality of life (Kobelt et al., 2017; Yamout et al., 2013). It is currently understood as a subjective syndrome with a trait characteristic. In contrast, the inability to maintain a certain performance level over a sustained period of cognitive effort is defined as fatigability (Holtzer et al., 2011; Kluger et al., 2013). In pwMS, Dettmers et al. (2021) recently reported that fatigability rather than fatigue predicts the employment status in pwMS. However, the current fatigue diagnostic purely focuses on subjective trait fatigue, leaving fatigability unattended (Linnhoff et al., 2019). Some objective parameters for assessing fatigability have been presented in the literature but with varying results. Additionally, very few studies find a relationship between subjective fatigue and fatigability (Linnhoff et al., 2019).

To date, there is no consensus on the neurological pathomechanisms responsible for the development of fatigue syndrome or its variability over time. Recently, several studies highlighted the important role of the thalamus in MS-related fatigue (Barbi et al., 2022; Capone et al., 2020). These studies report altered thalamus activity at resting in pwMS with trait fatigue but also during exhaustive tasks. The thalamus serves as a

* Corresponding author at: Department of Neurology, Otto-von-Guericke-University Magdeburg, Leipziger Street 44, Magdeburg 39120, Germany.
E-mail address: tino.zaehle@ovgu.de (T. Zaehle).

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pivotal hub in several cognitive processes. Therefore, even small changes in the thalamus activity might substantially impact the complex brain system, leading to objectively measurable differences in cognitive processes related to the thalamus. One of those processes that plays an important role in cognitive top-down control and is processed by the thalamus is sensory gating (Bak et al., 2014; Conte et al., 2020). By filtering out redundant or irrelevant information, it serves as an involuntary and preconscious mechanism to protect stimulus processing. Thus, it can be quantified via the percentage of prepulse inhibition (PPI) or the suppression of the P50 event-related potential. In both paradigms, processing a second stimulus is suppressed by a first stimulus, leading to a quantifiable reduction of reflex or amplitude to the second stimulus. Gating, in general, is a protective mechanism of the cortex to prevent the brain from overstimulation, allowing for coherent thought. Accordingly, it is likely to assume that deficits in gating may result in the misinterpretation of sensory information, subsequently leading to fatigue. Accordingly, disrupted sensory gating has already been reported in healthy subjects after cognitive (Linnhoff et al., 2021; Van der Linden et al., 2006) or physical exhaustion (Aleksandrov et al., 2016). Additionally, we recently showed that transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex counteracted fatigability development and reduced the gating deficits in healthy subjects (Linnhoff et al., 2021).

To date, no study has investigated sensorimotor and sensory gating deficits as a result of cognitive fatigue and fatigability in pwMS. Thus, the present study aims to develop a deeper understanding of the pathophysiological processes of MS-related fatigue and fatigability and to complement the purely subjective fatigue diagnostic in pwMS. We hypothesize that in pwMS with high subjective trait fatigue sensorimotor and sensory gating will be reduced and that task-induced fatigability will further disrupt gating.

2. Methods

2.1. Study sample

We included 18 pwMS and 20 healthy controls (HC) in the final analyses of this study (see Table 1 for group characteristics). Inclusion criteria for HC were no history of neurological or psychiatric disorders, no current depression (Beck Depression Inventory II - Fast Screen, BDI-FS $\leq$ 4), and no sleep disorder (Epworth Sleepiness Scale, ESS $\leq$ 10). PwMS had to be diagnosed with clinically definite MS according to the McDonald criteria (Thompson et al., 2018) and were included when there was a minimum of three months since the last relapse or use of corticosteroids, no current neurological or psychiatric comorbidities, as well as no treatment with fatigue or antidepressant medication. Disease-modifying therapy (DMT) consisted of Glatirameracetat ($n = 3$), Siponimod ($n = 1$), Fingolimod (n = 3), Dimethylfumarat (n = 1), Ocrelizumab (n = 3), and Cladribine (n = 1). Six participants received no DMT. All pwMS had a relapsing-remitting course of MS. Fatigue severity was assessed using the Wuerzburg Fatigue Inventory (WEIMuS). The local ethic committee of the University of Magdeburg approved the study. All participants provided written informed consent according to the Declaration of Helsinki.

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

	pwMS	HC	
Gender [f/m]	12 / 6	13 / 7	
Age [years]	44.61 (± 12.70)	47.90 (± 13.07)	$p = .437$
BDI-FS [points]	1.33 (± 1.24)	1.15 (± 1.23)	$p = .649$
ESS [points]	9.17 (± 4.00)	5.35 (± 3.01)	$p = .002$
SDMT [points]	57.11 (± 8.62)	61.05 (± 6.19)	$p = .112$
$WEIMuS_{total}$ [points]	29.56 (± 13.02)	–	
$WEIMuS_{cognitive}$ [points]	15.17 (± 7.05)	–	
Disease duration [years]	14.22 (± 10.87)	–	
EDSS [points]	3.28 (± 1.82)	–	

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

2.2. Procedure

In general, the study consisted of the two gating paradigms, the fatiguing task, and the subsequent re-presentation of both gating paradigms (see Fig. 1). Additionally, all participants performed the Symbol Digit Modalities Test (SDMT) to assess cognitive functioning.

The PPI paradigm consisted of three conditions: (i) the prepulse-alone condition (80 dB 20 ms white noise bursts, 20 trials), which served as a baseline condition, (ii) the startle-alone condition (105 dB 40 ms white noise bursts, 20 trials), and (iii) the prepulse-startle condition (20 trials) in that the startle stimuli were presented 120 ms after the presentation of the prepulse stimuli. White noise of 70 dB was presented one minute before the trials and persisted for the duration of the test as background noise. After the first minute, we presented five startle sounds as habituation stimuli, followed by 60 randomly presented trials, each belonging to one of the above conditions. Both stimuli' rise times were near-instantaneous, and the inter-trial interval ranged from 8 to 12 s.

The standard paired-click paradigm to evoke sensory gating consisted of 60 pairs of 80 dB white-noise clicks with a duration of 1 ms. The task began with one minute of 30 dB white noise that preceded as background noise. The click pairs were presented with a 500 ms inter-click interval and a random 8 to 11 s inter-trial interval.

The fatigability-inducing task (an AX- continuous performance task, AX-CPT) consisted of six blocks (B1-B6) á 53 trials (5 min). A red cue letter, two white distractor letters, and a red probe letter presented on a black background formed one sequence of letters. They were presented for a duration of 300 ms followed by a 1200 ms inter-stimulus interval. The blocks were separated by 90-s breaks. At the beginning, middle, and end of the task, two visual analog scales (VAS) from 0 to 100 were presented. One asked the participants "how mentally fit they felt right now at this moment" ($VAS_{fitness}$), and the other asked "how mentally exhausted they felt right now at this moment" ($VAS_{exhaustion}$).

2.3. EEG signal recording and preprocessing

EEG was recorded at Fz, Cz, and Pz electrodes using Ag/AgCl-electrodes. The ground electrode was attached to the AFz position. All channels were referenced to the left and right mastoid. An electrooculogram (EOG) of the left eye and an electromyography recording (EMG) of the right eye were recorded. EEG preprocessing was carried out in BrainVision Analyzer 2.1 (Brain Products, Germany) and was almost identical to the steps described in Linnhoff et al. (2021).

For the P50 analysis, the EEG data were epoched from −150 to 499 ms post stimulus and then offline band-pass filtered from 1 to 47 Hz. The data was then baseline corrected (−50 to 0 ms), manually inspected for eye-movement artifacts, and averaged. The P50 peak was evaluated at Channel Cz. Peaks were detected as a peak if (i) the P50 peak was the most positive peak occurring 30–80 ms after the stimulus, (ii) the peak was preceded by a negative (Na) and positive (Pa) deflection, and (iii) for the peak detection of the second stimulus (S2) if it occurred within ±10 ms around the latency of the prior detected peak of the first stimulus (S1). P50 amplitudes were defined as the difference between the P50 peak and the preceding negative trough, separately for S1 and S2. If there was no P50 peak in that range, the P50 amplitude of the second stimuli was scored as 0.01. The P50 suppression was calculated with: $(1 - (S2 / S1)) \cdot 100$. Accordingly, higher P50 suppression ratios indicate higher sensory gating, whereas ratios equal to or smaller than zero indicate a higher S2 peak compared to S1 and, thus, no sensory gating. To prevent outliers from distorting group means, we restricted ratios to -

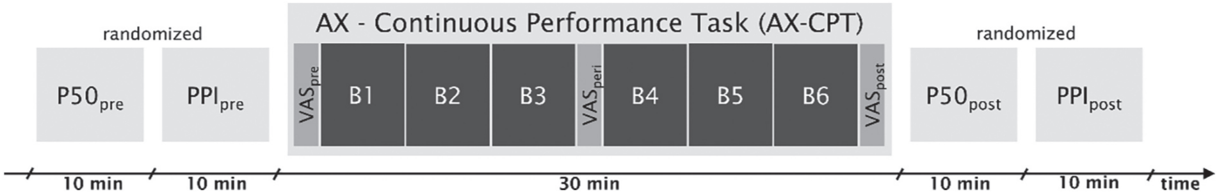

Fig. 1. Experimental design. After assessing demographic and clinical data via self-report questionnaires, participants performed the auditory P50 sensory gating and prepulse inhibition (PPI) paradigms in a randomized order (pre-session). A 30-min continuous performance AX-task (AX-CPT task) followed that consisted of six blocks (B1 - B6). Before the first, after the third and at the end, participants were asked about their current perceived fatigue status on visual analog scales (VAS_{pre}, VAS_{peri}, VAS_{post}). Subsequently, the auditory P50 and PPI paradigms were represented in a post-session.

200% (Thoma et al., 2020). Six participants (5 HC, 1 pwMS) had to be excluded from the P50 gating analysis for not showing sensory gating at the pre-session.

For the PPI analysis, the EMG data were band-pass filtered from 28 to 400 Hz with an additional notch filter of 50 Hz. For each participant, startle responses were segmented for each trial type (−100 to 200 ms after stimulus onset) and then baseline corrected (−100 to 0 ms). Subsequently, the EMG signal was rectified and smoothed with a moving average at a time constant of 11. A manual visual inspection followed, in which all trials featuring excessive noise or a spontaneous blink in the period immediately preceding the stimulus onset were excluded from further analysis. For each trial, the startle response was considered as the maximum blink amplitude in a response window from 20 to 120 ms after stimulus onset. As Van der Linden et al. (2006), we defined a valid startle response as a peak of at least 3 SD above baseline activity. Baseline activity was calculated as the average response to the prepulse in the prepulse-alone trials, except for those trials in which the startling activity caused by the prepulse exceeded 10 μV. The participants had to exhibit at least five startle responses. Five participants (2 HC, 3 pwMS) had to be excluded from the PPI analysis as they were classified as non-responders. PPI ratio was calculated with: (($M_{startle\text{-}alone}$ - $M_{prepulse\text{-}startle}$) / $M_{startle\text{-}alone}$) · 100. The average includes values of zero for non-responses. Thus, we report PPI magnitudes. Higher PPI ratios indicate higher sensorimotor gating.

2.4. Statistical analysis

Data analyses were carried out in R Statistical Software (version 4.2.0, R Core Team, 2022). We performed Linear Mixed Models (LMMs) using the *lmer* function from the *afex* package (Singmann et al., 2022). *P* values were obtained using Sattersthwaite's approximation method. Invalid and error trials were excluded from the reaction time data analysis. Furthermore, to reduce the impact of outliers, we winsorized outliers below or above 1.5 times the interquartile range to this limit. As dependent variables, we used the VAS scores, PPI and P50 sensory gating ratios. Time, group, and group x time were considered as fixed factors. Data from HC during pre-session or block B1 were used as baseline. Individuals and their variation of the dependent variable were used as random effects. Finally, Pearson correlational analyses were used to examine the relationship between the subjective trait and state fatigue scores and PPI as well as P50 sensory gating ratios.

3. Results

3.1. Manipulation check

The analysis of $VAS_{fitness}$ ratings revealed a significant main effect *time* [$F(1,36) = 18.724$, $p < .001$, $\eta_p^2 = 0.34$], a marginally significant main effect *group* [$F(1,36) = 3.815$, $p = .059$, $\eta_p^2 = 0.10$] as well as a significant interaction between *time* and *group* [$F(1,36) = 4.279$, $p = .046$, $\eta_p^2 = 0.11$]. The HC group rated their initial mental fitness with 75.51 points [$\beta_{intercept}$, 95% CI (67.05, 83.97)] and the pwMS group with 63.24 points [$\beta_{intercept} + \beta_{group}$, 95% CI (42.48, 83.99)]. With each new query, $VAS_{fitness}$ ratings decreased by 3.53 points [β_{time}, 95% CI (−7.74, 0.68)] in HC, whereas they decreased by 10.00 points [$\beta_{time} + \beta_{time*group}$, 95% CI (−20.33, 0.33)] in pwMS (see Fig. 2A).

$VAS_{exhaustion}$ ratings showed a significant main effect *time* [$F(1,36) = 8.608$, $p = .006$, $\eta_p^2 = 0.19$], a significant main effect *group* [$F(1,36) = 6.860$, $p = .013$, $\eta_p^2 = 0.16$] but no significant interaction between *time* and *group* [$F(1,36) = 0.894$, $p = .351$]. Thus, the HC group rated their initial mental exhaustion with 24.08 points [$\beta_{intercept}$, 95% CI (14.37, 33.80)] and the pwMS group with 42.97 points [$\beta_{intercept} + \beta_{group}$, 95% CI (19.14, 66.80)]. With each new query, $VAS_{exhaustion}$ ratings increased by 7.10 points [β_{time}, 95% CI (2.17, 12.03)] in HC and by 3.64 points in pwMS [$\beta_{time} + \beta_{time*group}$, 95% CI (−8.45, 15.73)] in pwMS (see Fig. 2B). Due to the lack of interaction in $VAS_{exhaustion}$ ratings, we conducted the following correlational analyses only with the $VAS_{fitness}$ ratings.

3.2. Prepulse inhibition

PPI ratios significantly decreased after fatigability induction [main effect *time*: $F(1,31) = 7.134$, $p = .012$, $\eta_p^2 = 0.19$]. However, we found no main effect *group* [$F(1,31) = 0.230$, $p = .635$] and no significant interaction between *time* and *group* [$F(1,31) = 0.215$, $p = .646$]. After fatigability induction, PPI ratios in HC decreased by 5.56% [β_{time}, 95% CI (−12.20, 1.09)] and similarly decreased by 7.90% [$\beta_{time} + \beta_{time*group}$, 95% CI (−24.39, 8.60)] in pwMS (see Fig. 3A). Correlational analyses on the relationship between initial PPI ratios and $WEIMuS_{cognitive}$ scores (subjective trait fatigue scores), as well as between the change in PPI ratios and $VAS_{fitness}$ ratings (subjective state fatigue scores) with time on task revealed no significant associations (all *ps* > .119). Two participants, one from each group, could be considered as outliers according to their PPI decline after fatigability-induction. However, excluding both participants from the analyses did not change the results.

3.3. P50 sensory gating

The LMM to analyze time on task effects on P50 sensory gating ratios revealed a significant main effect *time* [$F(1,30) = 6.470$, $p = .016$, $\eta_p^2 = 0.18$] but no significant main effect *group* [$F(1,30) = 1.481$, $p = .233$]. Importantly, we found a significant interaction between *time* and *group* [$F(1,30) = 7.134$, $p = .012$, $\eta_p^2 = 0.19$]. Post-hoc tests revealed a significant decrease of P50 gating ratios in pwMS [$t(16) = 3.264$, $p = .005$, Cohen's $d = 0.792$] but not in HC [$t(14) = -0.236$, $p = .817$]. Thus, in HC, P50 ratios slightly increased by 3.63% [β_{time}, 95% CI (−37.73, 44.99)] after fatigability induction, whereas they substantially decreased by 78.35% [$\beta_{time} + \beta_{time*group}$, 95% CI (−176.45, 19.75)] in pwMS (see Fig. 3B). Importantly, this decrease was driven by an increase in the S2 amplitude [$t(16) = -3.620$, $p = .002$, Cohen's $d = -0.878$] and not a decrease of S1 amplitude [$t(16) = 1.351$, $p = .195$].

Furthermore, we explored the relationship between initial P50 sensory gating ratios and $WEIMuS_{cognitive}$ scores (subjective trait fatigue scores). The analysis revealed a negative relationship that was, however, not significant [$r(15) = -0.382$, $p = .130$]. The scatter plot visually revealed one outlier (see Fig. 4A). After removing this outlier, the Pearson's correlation reached significance [$r(14) = -0.705$, $p = .002$]

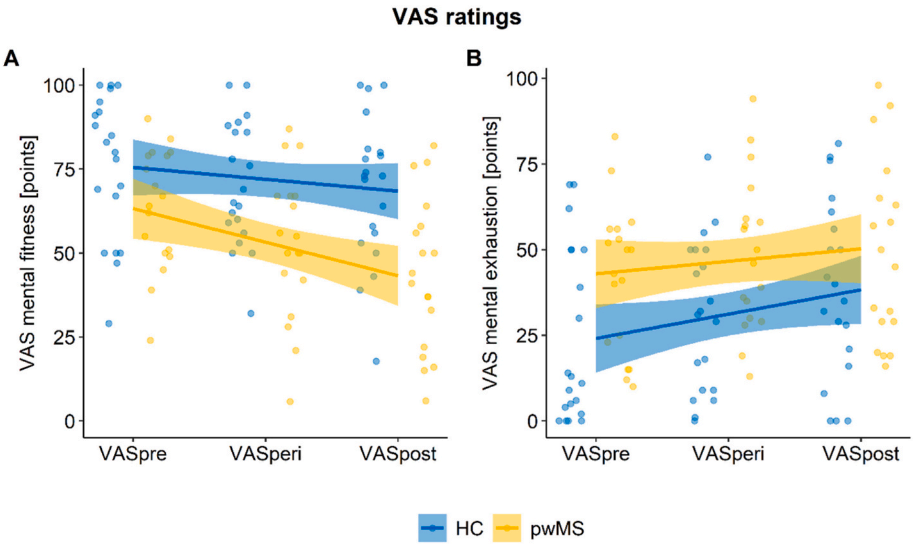

Fig. 2. Regression plots for the visual analogue scale (VAS) ratings of mental fitness (A) and mental exhaustion (B) against the VAS queries (VAS_{pre}, VAS_{peri}, VAS_{post}) separate for the HC and pwMS groups.

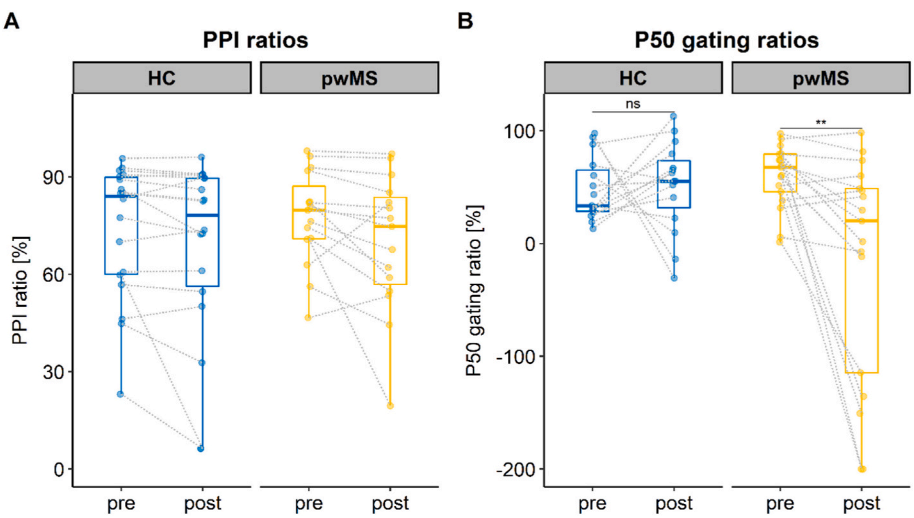

Fig. 3. PPI (A) and P50 gating ratios (B) as a function of session (pre, post) separate for the HC and pwMS groups.

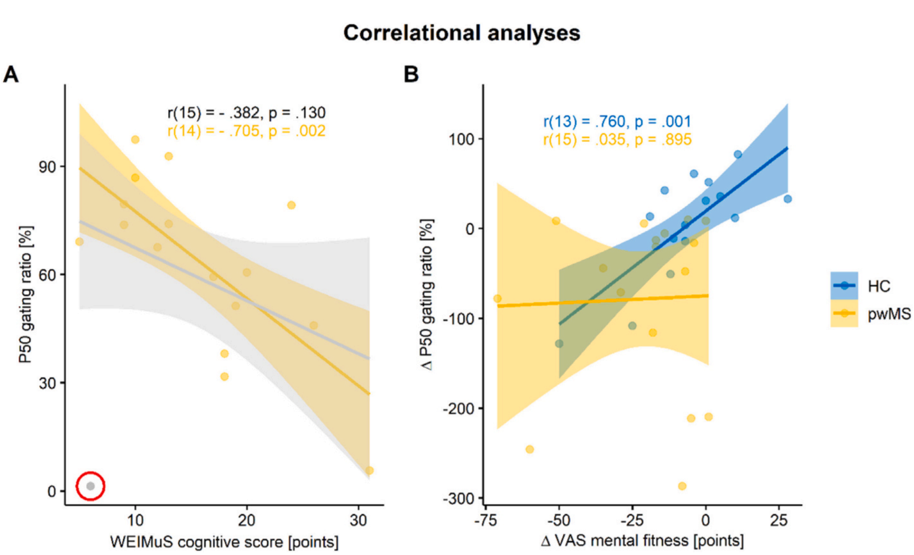

Fig. 4. Pearson's correlation analyses to analyze the associations between P50 sensory gating and subjective mental fatigue ratings. A: Association between the P50 gating ratios and WEIMuS cognitive scores at pre-session before (grey) and after (yellow) outlier removal (red circle). B: Association between the change in P50 sensory gating ratios and the change in subjective mental fitness ratings with time on task separate for the HC (blue) and pwMS group (yellow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(see Fig. 4A) suggesting that pwMS with higher trait fatigue tend to have smaller gating ratios at pre-session. Finally, we analyzed the relationship between the changes in P50 sensory gating ratios with time on task and the changes in $VAS_{fitness}$ ratings (subjective state fatigue scores). The analysis revealed a significant positive relationship [$r(30) = 0.375$, $p = .034$], suggesting that participants with a stronger decrease in $VAS_{fitness}$ ratings tend to have a stronger decrease in P50 sensory gating ratios. Interestingly, this relationship was strongly driven by the HC group [$r(13) = 0.760$, $p = .001$] rather than by pwMS [$r(15) = 0.035$, $p = .895$] (see Fig. 4B).

4. Discussion

This study explored fatigue- and fatigability-related changes in PPI and P50 sensory gating ratios in pwMS and HC. The initial gating ratios did not differ between both groups. However, we found a significant relationship between the initial P50 sensory gating ratios and subjective trait fatigue scores in pwMS. Accordingly, pwMS with higher trait fatigue showed reduced sensory gating at pre-session. To our knowledge, this is the first study reporting sensory gating deficits in fatigued pwMS. Our findings support the use of sensory gating as an objective marker for fatigue to extend the current subjective diagnosis. However, it is important to note that not all participants in our study showed sensory gating. Thus, we had to exclude some HC and pwMS from the analysis for not shown sensory gating at the pre session, challenging the universal use of P50 sensory gating as a diagnostic marker. Still, there has already been significant evidence that sensory gating functions as a reliable surrogate marker for various attention-related diseases, including schizophrenia (Shen et al., 2020; Xia et al., 2020) and attention-deficit hyperactivity disorder (Holstein et al., 2013; Micoulaud-Franchi et al., 2019). Consequently, P50 gating deficits might not be unique to a single disorder but may represent a general characteristic of attention-related disorders (Holstein et al., 2013). However, further studies are needed to replicate our findings and clarify the role of sensory gating in assessing trait fatigue in pwMS.

Furthermore, as hypothesized, P50 sensory gating strongly decreased after fatigability induction in pwMS and not in HC. Importantly, this effect was not a result of habituation but rather of disrupted sensory gating. In some participants, sensory gating even got completely suppressed. Our data are in line with previous studies that also reported gating deficits after fatigability induction in HC (Aleksandrov et al., 2016; Linnhoff et al., 2021). In this regard, P50 sensory gating may serve as a suitable marker for both, trait fatigue and fatigability. Additionally, we found a positive correlation between the change in P50 suppression and the change in subjective VAS ratings. Interestingly, however, this relationship was primarily found in HC. At the same time, the HC group was unaffected by fatigability. Thus, the exact nature of the relationship between objective fatigability and subjective state fatigue remains a still open question. Both might jointly appear or rather exist as two distinct constructs (Hanken et al., 2014; Kluger et al., 2013).

As hypothesized, the PPI ratios decreased with time on task, as has already been reported in previous studies (Linnhoff et al., 2021; Van der Linden et al., 2006). However, the PPI decline was similar in both groups. Furthermore, we found no relationship between the trait fatigue scores and the initial PPI ratios. Thus, PPI ratios changed differently from P50 gating ratios after fatigability-induction and were not associated with subjective fatigue. These intraindividual differences in P50 sensory gating and PPI have also been reported in previous studies that found no or only a weak association between both gating parameters (Braff et al., 2007; Holstein et al., 2013; Light and Braff, 2001; Oranje et al., 2006; Schwarzkopf et al., 1993). Thus, similar to our results, Holstein et al. (2013) reported significant P50 sensory gating deficits in people with schizophrenia, while they found no deficits in PPI. The authors argue that P50 suppression and PPI presumably represent different aspects of attention due to their different interstimulus intervals. Consequently, P50 suppression with a longer ISI of 500 ms may have a conceptually more direct relationship with attention than PPI with a shorter ISI of 120 ms. Additionally, although both parameters are considered to be preattentive, to reflect an inhibitory process, and to not require conscious effort (Braff et al., 2007), they are based on different responses. Thus, P50 sensory gating requires a cortical response, whereas PPI requires a motor response. Possibly, this may have contributed to the differing sensitivity of the two parameters to fatigability-induced changes. This should be further investigated in future studies.

The present results highlight the important role of the thalamus in the cortico-striato-thalamo-cortical fatigue network (Ayache and Chalah, 2017; Chaudhuri and Behan, 2000). Different hypotheses have been proposed about the role played by the thalamus in fatigue development. Hence, in some studies, thalamus activity increased with fatigue, while in others, it decreased (Barbi et al., 2022; Capone et al., 2020). Capone et al. (2020) attempted to combine the results of the existing literature and postulate that thalamic activity initially increases in a compensatory manner to counteract MS-related structural damage. When plasticity is no longer possible, functional connectivity drops, and fatigue becomes chronic. This initial increased thalamus activity has also been reported in healthy subjects after inducing mental fatigue (Batouli et al., 2020). Taken together, our findings contribute to a better understanding of the pathomechanisms involved in fatigue and fatigability. Consequently, changes in thalamus activity may result in permanent or temporary dysfunction of thalamus-dependent cognitive control mechanisms, such as sensorimotor and sensory gating. It should be noted that the results of our study are correlative, making it impossible to draw conclusions about causality.

4.1. Limitations

This study has a few limitations. First, the differently phrased VAS scales were always presented in the same order. Thus, we presented two VAS scales with different polarization, one positively and one rather negatively phrased. This increased task engagement as the participants had to read the questions carefully. However, it might have resulted in order effects or increased self-awareness. Thus, as part of a clinical examination, pwMS are often asked about their current level of exhaustion, which increases their awareness of the syndrome. Consequently, when asked "how exhausted they felt", VAS ratings might have been biased in pwMS. Future studies should consider this and pay attention to uniform and multidimensional VAS scales. Another limitation is the relatively large number of exclusions in the P50 and PPI gating paradigms, leading to different sample sizes. However, we used this procedure as it is consistent with the common evaluation criteria of PPI and P50 gating ratios, keeping the data comparable. Lastly, due to the lack of structural and functional MRI data, possible correlations with thalamic activity remain purely hypothetical. Future studies should additionally collect thalamic activity and size and investigate associations with trait fatigue and fatigability in pwMS.

4.2. Conclusions

This is the first study to report fatigue- and fatigability-related sensory gating deficits in pwMS. Especially P50 sensory gating seems to be a suitable marker to complement the subjective fatigue diagnostic. Gating paradigms are independent of learning effects or psychological biases. They are safe to administer and can easily be implemented in the current fatigue diagnostic and therapy monitoring. Additionally, this study gives new insight into the pathomechanisms of fatigue and fatigability in pwMS and highlights the important role of the thalamus in the fatigue circuit.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Stefanie Linnhoff: Conceptualization, Methodology, Software, Formal analysis, Visualization, Writing – original draft. **Aiden Haghikia:** Resources, Writing – review & editing. **Tino Zaehle:** Conceptualization, Validation, Resources, Supervision, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

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