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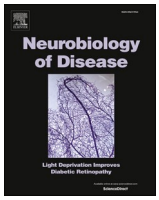

The neural correlates of walking fatigability in people with multiple sclerosis: An fNIRS study

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ABSTRACT

Walking fatigability (WF) is a common and disabling feature of people with multiple sclerosis (pwMS), yet its neural underpinnings are poorly understood. Here, we investigated real-time cortical activity during the 6-min walk test (6MWT) and its relationship with changes in gait speed and quality. PwMS with and without WF (n = 42), and healthy controls (HC, n = 25), completed a 6MWT. Using functional near-infrared spectroscopy, cortical activity was measured in the prefrontal, premotor and motor cortices. Concomitantly, inertial measurement units measured gait speed and quality on a minute-by-minute basis. PwMS with WF (Expanded Disability Status Scale-EDSS = 6 [2.62]) showed marked declines in speed and gait quality, accompanied by altered patterns of cortical activation throughout the 6MWT. While HC and pwMS without WF (EDSS = 3[1.75]) dynamically modulated activity across frontal (p < .004), premotor (p < .043) and motor (p < .032) regions to respond to the task demands, pwMS with WF exhibited sustained reliance on frontal cortical regions and limited engagement of the broader walking network. Across all groups and cortical regions, an overall cortical activity pattern was observed. Specifically, cortical activity peaked during the first minute, stabilised during minutes 2–4, and increased during minutes 5–6. In both HC and pwMS, correlation analyses (rho:324–597) indicate that greater increases in cortical activity were associated with better gait speed/quality. Nevertheless, while these associations suggest that HC can recruit a broader walking control network, pwMS demonstrated an executive-driven pattern of brain-gait control. These findings suggest that walking fatigability can be partly driven by impaired ability to flexibly recruit cortical resources during prolonged walking.

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease affecting the white and grey matter of the central nervous system (CNS). This pathophysiological process can cause many symptoms and alter the recruitment of neural resources to perform motor tasks (Peterson and Fling, 2018). It is well documented that people with MS (pwMS) have walking impairments compared to their peers (Comber et al., 2017), which can be exacerbated during long walks, known as walking fatigability (WF). Classically, fatigability is defined as a decrease in performance over time (Behrens et al., 2023; Kluger et al., 2013), and for walking/gait, it is investigated mostly during prolonged walking protocols, such as the 6-min walking test (6MWT) (Abasiyanik et al., 2022; Shema-Shiratzky et al., 2019; Van Geel et al., 2020a). In pwMS, these decrements can be seen either in distance walked (i.e., distance walking fatigability-DWF) (Leone et al., 2016;

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Santinelli et al., 2025; Van Geel et al., 2020b) or in gait quality as a decrease in foot-strike and toe-off angle, an increase in gait variability, and deterioration in balance (Abasiyanik et al., 2022; Arpan et al., 2020; Plotnik et al., 2020; Santinelli et al., 2024a). However, the underlying central mechanisms remain poorly explored.

The walking fatigability is caused by several factors. A previous study suggested that, to complete the 6MWT, pwMS adopt a strategy of slowing down during the task (Dalgas et al., 2014) or when there is increased concern (or fear) about falling (Abasiyanik et al., 2025). Another possible explanation is the exacerbation of MS-related symptoms. Van Geel et al. (2021a) observed that pwMS presenting with DWF at the end of the 6MWT presented higher perception of spasticity, loss of proprioception, dizziness and muscle weakness. For the latter, two studies found that the maximal muscle strength and muscle fatigability index of knee and ankle muscles are correlated with DWF (Ramari et al., 2018; Van Geel et al., 2021b). This might suggest that the ability to maintain contracting and sustain lower-limb muscle strength is important for WF. This reduced ability to sustain muscle contractions and fire motor neurons during a dynamic task such as walking might indicate that WF, among many factors, is caused by a lower neural reserve (i.e., an incapacity to cope with pathological brain processes) (Stern, 2009).

Motor fatigability is mediated by two main mechanisms: central and peripheral fatigue. While peripheral fatigue comprises failure of functional muscle properties to maintain muscle contraction, central fatigue refers to the failure of the CNS to keep up with firing neurons (Gandevia, 2001). In pwMS, there is evidence that central fatigue plays a larger role in the decrease in performance over time than peripheral mechanisms (Gaemelke et al., 2021; Leodori et al., 2023; Mamoei et al., 2020; Steens et al., 2012; Wolkorte et al., 2016; Zijdewind et al., 2016). More specifically, although the decrement in performance is either similar (Steens et al., 2012; White et al., 2009; Wolkorte et al., 2016) or higher (Gaemelke et al., 2021) during sustained or concentric maximal voluntary activation between pwMS and their healthy peers, there is a clear undercapacity of pwMS to recruit neural resources to maintain performance. In fact, it has been postulated by several studies (Abasiyanik et al., 2022; Abasiyanik et al., 2025; Arpan et al., 2020; Leone et al., 2016; Plotnik et al., 2020; Santinelli et al., 2024a) that walking fatigability might be driven by a lack of central capacity to maintain motor programming, planning, and attention during prolonged walking (i.e., 6MWT). However, these were just speculations, and direct measures of activation in the cortical regions responsible for walking control are needed. To the best of our knowledge, only Broscheid et al. (2022b) investigated the impact of a 6MWT on the cortical activity in a dual-task short-walking paradigm in pwMS. No differences between pre vs post 6MWT on cortical activation were observed, as well as no signal of fatigability in the walking domain. However, evaluating cortical activation only before and after the task may overlook the dynamic neural adaptations that occur while WF develops. Therefore, investigating cortical activity during the 6MWT is essential to understanding WF and its neural correlates.

Walking is a dynamic process that involves cortical, subcortical and peripheral components, which can be summarised in two distinct pathways. The walking automaticity pathway has little involvement of cortical regions and is primarily mediated by the basal ganglia, primary motor cortex (M1) and the central pattern generator at the spinal cord. In contrast, the executive walking control relies on processes such as planning and executive control, involving pre-motor regions such as the pre-frontal cortex (PFC), supplementary motor area (SMA) and pre-motor cortex (PMC) (Herold et al., 2017; la Fougere et al., 2010; Zwergal et al., 2012). Executive control is particularly relevant when a disruption in the CNS is present (i.e., MS), when effort increases or when changing walking speed from comfortable (Clark, 2015). Nevertheless, studies in pwMS and other neurological conditions have focused on discrete, short walking protocols either alone or in combination with a cognitive task (Bishnoi et al., 2021), leaving it unknown how cortical gait control is under prolonged walking protocols. Specifically in pwMS, an increased reliance on executive control has been shown under comfortable walking (Saleh et al., 2018; Santinelli et al., 2021; Santinelli et al., 2024c) or when performing a more demanding task, such as a dual-task (Baldasso et al., 2024; Hernandez et al., 2016; Holtzer et al., 2024). Nevertheless, results are inconsistent where pwMS are able to recruit additional neural resources in response to more demanding walking tasks (Hernandez et al., 2024; Kupchenko et al., 2023; Santinelli et al., 2024c), probably driven by more/less complex tasks applied among the studies. Because faster walking places greater demands on executive control (Alcock et al., 2023), examining walking performance under such conditions is highly relevant for our study, which uses the 6MWT, a test that naturally encourages participants to walk at a brisk pace. The neural reserve (Stern, 2009) and the limited capacity of recruitment of neural resources (Reuter-Lorenz and Cappell, 2008) provide theoretical explanations of the findings mentioned above. Both theories postulate that an ageing or pathological (neurodegenerated) brain can compensate for possible CNS dysfunctions by overactivating certain areas to maintain behavioural performance; while at higher-level task demands, the CNS is unable to overactivate, resulting in performance decline. When overactivation is linked to motor behaviour, it can be interpreted as dysfunctional or compensation (Fettrow et al., 2021), depending on whether the overactivation caused worsened or better performance, respectively. Despite these insights, understanding how cortical activation evolves during the 6MWT may help clarify the neural mechanisms underlying walking fatigability and the strategies pwMS use to sustain motor performance.

This study aimed to investigate the central mechanisms underlying WF in pwMS by means of cortical brain activation and its relationship with gait speed and quality fatigability metrics during a 6MWT. We hypothesised that pwMS presenting with DWF might not be able to overactivate cortical brain regions sufficiently to respond to the task demands and overcome CNS damage. As a result, walking performance will be deteriorated at the end of the 6MWT. Conversely, pwMS without DWF and healthy controls (HC) will be able to overactivate cortical brain regions and maintain normal walking performance (i.e., not showing abnormal WF), indicating neural compensation (Fettrow et al., 2021). We also hypothesised that, while HC rely on specific regions for particular gait adjustments (e.g., SMA/PMC for speed or distance walked), pwMS would rely on cognitive regions such as the PFC to compensate for CNS damage, resulting in a dedifferentiated pattern of gait control.

2. Materials and methods

2.1. Participants

Participants were recruited from the Belgian MS rehabilitation centres Melsbroek (National MS Center) and Overpelt (Noorderhart RMSC), and in the REVAL research Center at the University of Hasselt. HC were recruited via information flyers, the REVAL website, and the social media of REVAL, the Flemish MS society, and pwMS' relatives. Participants were eligible for this study if presented with i) age between 18 and 65 years old (also for HC), ii) Confirmed MS diagnosis according to the 2017 McDonald criteria, iii) EDSS from 1 to 6.5, iv) minimal walking impairment evidenced by a minimal report of two on the items 7, 10, 11 or 12 of the Multiple Sclerosis Walking Scale-12 (MSWS-12), v) At least 1 month relapse free preceding the study visit and vi) ability to walk for 6 min without taking a rest. If participants had any cognitive decline that could hinder understanding of the study instructions, or a known pregnancy or musculoskeletal disorders unrelated to MS, they were not included.

2.2. Experimental procedure

This study is the main component of a larger study, "Walking Fatigability and Brain Activity in People With Multiple Sclerosis"

(NCT06672484), which aims to investigate the underlying central mechanisms of WF in pwMS. Participants were informed about the study objectives and procedures and provided written informed consent. The study was approved by the leading University of Hasselt (B1152024000007) and local ethical committees of the MS Belgian centres. Following their consent, participants had their head measurements taken for the functional near-infrared spectroscopy (fNIRS) or received instructions to do so. Several questionnaires were given, and participants were instructed to complete these prior to the in-person visit. During the in-person visit, participants performed the Symbol Digit Modality test (SDMT) and the timed 25-ft walking test (T25FW). Subsequently, they were prepared with the positioning of the inertial measurement units and the fNIRS for gait analysis and cortical activity measurement, respectively. Before performing the 6MWT, participants completed additional short walking bouts as well as a foot-tap test, which will be reported elsewhere. The entire protocol lasted approximately 1 h and 30 min.

2.3. Clinical assessment/screening

Level of disability, in the MS group, was defined by EDSS scores. In order to characterize our cohort, the participants responded to the following questionnaires: Falls Efficacy Scale International (FES—I) (Yardley et al., 2005) for fear of falling, MSWS-12 (Hobart et al., 2003) and 10 questions encompassing gait items for walking perceived ability (Strzok et al., 2018), Pittsburgh Fatigability Scale (PFS) for perceived fatigability (Glynn et al., 2015), Modified Fatigue Impact Scale (MFIS) (Kos et al., 2005) and the Fatigue Scale for Motor and Cognitive Functions (FSMC) (Penner et al., 2009) for trait fatigue and its impact, the Brief Pain Inventory (BPI, short form) (Cleeland and Ryan, 1994) for the assessment of perceived pain, Multiple Sclerosis Spasticity Scale 88 (MSWS-88, section 5 and 6) (Hobart et al., 2006) to verify the subjective impact of spasticity in the walking and movement ability and Brief Self-Control Scale (BSCS) (Tangney et al., 2004) for self-control evaluation.

2.4. 6-min walking test (6MWT) and equipment procedure

Preceding the beginning of the 6MWT, participants were instructed to remain standing still for 30 s. To prevent mind wandering and to standardise the fNIRS baseline across participants, a simple mental task, counting down from 50 (i.e., 50, 49, 48…), was performed (Herold et al., 2017). At the end of this period, a standard countdown and a beep sound signalled the participant to begin the 6MWT. The Psychophy (V2023 2.3) (Peirce, 2007) software was used for the provision of the start and end commands of the 6MWT.

For the 6MWT, participants were instructed to walk as fast and safely as possible to cover the maximum distance within six minutes along a 25-m walkway with turns at both ends (Goldman et al., 2008). The research staff informed participants of the elapsed time at each minute, and no verbal encouragement was provided during the test. The distance walked in each minute was noted for subsequent DWF calculation (see the formula below). Participants also rated their perception of effort, before and immediately after the 6MWT, using the Borg scale (1−10).

Participants were equipped with eight wearable sensors (128 Hz, Opal V2, Clario, USA) placed at the top of each foot, each tibia, each thigh, on the lumbar (L4) and sternum. Data acquisition and gait data analysis were performed using Moveo Explorer® software (APDM, Portland, USA). Participants wore a portable fNIRS cap with a backpack containing the fNIRS device (NIRSport 2, wavelength 730–850 nm, 5.1 Hz, NIRx, Germany) to measure cortical brain hemodynamics (oxyhemoglobin-HbO and deoxyhemoglobin-HHb). The Aurora software (NIRx, Berlin, NIRx, Germany) was used for fNIRS data acquisition. The fNIRS cap, which was composed of long- and short-separation channels (48 long and 8 short channels, Supplementary material Fig. S1), was placed bilaterally, over the primary motor cortex (M1, Brodmann area 4), PMC (Brodmann area 6), supplementary motor area (SMA, Brodmann area 6) and prefrontal cortex (Brodmann area 9, and 46-dorsolateral prefrontal cortex (DLPFC) and Brodmann 10, frontopolar cortex- FPC). The channel corresponding to each cortical region was defined by using the fNIRS optodes location decider (fOLD) (Zimeo Morais et al., 2018) using the 10–10 international system electrode placement. An additional black shower cap was placed over the fNIRS cap to minimise the interference of environmental noise. Participants were asked at multiple time points during the assessment if the fNIRS cap was causing pain using a visual analogue scale (Nagels-Coune et al., 2020), which was used for data quality check.

2.5. Data analysis

The meters walked in every minute of the 6MWT were used to calculate the distance walked index (DWI- see formula below) (Leone et al., 2016; Van Geel et al., 2020b). Gait quality characteristics were derived from Moveo Explorer® data exported on a cycle-by-cycle basis. The following gait quality characteristics were obtained: gait speed, cadence, step duration and its variability (assessed via the coefficient of variation), double support, stride length, and foot strike and toe-off angle (Santinelli et al., 2024b). Afterwards, the data were segmented at 1-min intervals to compute the fatigability index for each gait quality characteristic. In this context, the variable of interest (e.g., distance walked or stride length) replaced the “variable” term in the formula below. Lower limbs were classified as least and most affected based on step duration comparison, with the leg exhibiting the shortest step duration designated as the least affected.

$$\textit{Fatigability index} = \left(\frac{\textit{variable at minute } n - \textit{variable at minute } 1}{\textit{variable at minute } 1}\right) * 100$$

2.6. Functional near-infrared spectroscopy (fNIRS)

fNIRS data were processed using custom MATLAB code complemented by functions from Homer3 (Huppert et al., 2009). Raw data were first converted to optical density (hmrR_Intensity2OD). Movement-related artefacts were mitigated through wavelet correction (hmrR_MotionCorrectWavelet) (Brigadoi et al., 2014). The HbO and HHb were obtained by converting optical density to hemoglobin concentration with the differential path length factor applied (hmrR_OD2Conc) according to Duncan et al. (1996) (Duncan et al., 1996). A visual inspection was conducted to identify and exclude channels with poor quality. Specifically, the channel was maintained for further analysis if showing systemic noise such as heartbeat, Mayer waves, and respiration, as well as an anti-correlation pattern between HbO and HHb. To further attenuate systemic artefacts, including heartbeat, respiration, high noise artefacts and Mayer-waves (i.e., blood pressure), data were filtered with a 5th-order low-pass Butterworth filter at 0.09 Hz (Pinti et al., 2018). To account for extracerebral systemic noise affecting long channels (originating from the skin and systemic circulation), signals were regressed by the nearest valid short channel using a 1st order polynomial regression. For each region of interest, the corresponding channels were averaged separately for the left and right hemispheres. The first 10 s of the baseline were excluded from the analysis. Relative HbO and HHb concentrations were obtained by subtracting the average of the remaining 20-s baseline from the 6MWT. These relative concentrations were then segmented on a 1-min basis. Fig. 1 illustrates the time points at which the relative HbO and HHb were obtained. To assess cortical activity changes related to the 6MWT, the delta of HbO and HHb between minutes 6 and 1 was calculated. In addition, the classification of the least and most affected lower limbs based on the step duration was also used to interpret the brain activity. Thereby, the contralateral to the most affected limb and the ipsilateral hemisphere to the least affected lower limb were analysed to assess cortical activation.

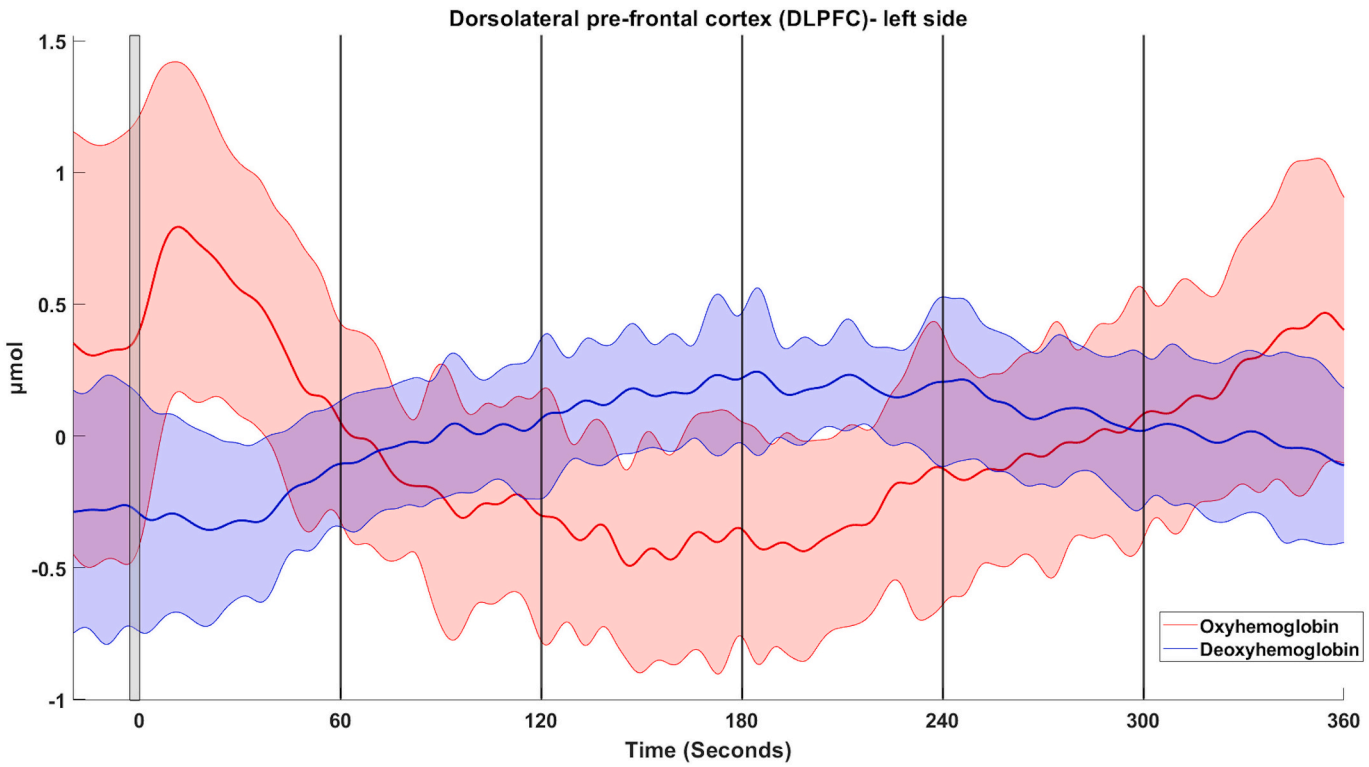

Fig. 1. Mean (lines) ± standard deviation (shadow area around the lines) of oxyhemoglobin (HbO, in red) and deoxyhemoglobin (HHb, in blue) over the 6-min walking test. The healthy control group is represented, specifically for the left side of the dorsolateral prefrontal cortex (DLPFC). The grey shadowed area corresponds to the countdown and auditory cue at the start of the 6MWT, which was excluded from the final analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.7. Statistical analysis

The RStudio software (2025.05.1) was used for the statistical analysis, and the alpha level was set at 0.05 with Bonferroni corrections for multiple comparisons where appropriate. Normality of variables was assessed using Shapiro-Wilk test, q-q plots and histograms. Anthropometrics, clinical, and cortical activity, as well as fatigability indices, were compared across three groups: HC, pwMS with (pwMS-DWF) and without (pwMS-NDWF) DWF. Grouping of pwMS was based on the cut-off of −10% in the DWI (Van Geel et al., 2020b). Anthropometric and clinical characteristics were compared using one-way ANOVA or Kruskal-Wallis test, depending on data distribution. Sex and MS phenotype were compared through the chi-square test. The Borg scale was analysed across groups and time by a two-way ANOVA. Correlation analysis was restricted to the HC and pwMS groups, as splitting the groups would reduce power, and our objective is to understand the overall impact of changes in cortical activity on gait speed and quality changes.

For cortical activity (HbO and HHb), a two-way ANOVA with group and time factors, with repeated measures for time, with age entering as a covariate, was performed to investigate the dynamics of cortical activity through the 6MWT (i.e., whether groups differed from each other and whether there was a change over the 6MWT). Effect sizes were reported as partial eta-squared, interpreted as small (0.01), medium (0.06), or large (≥ 0.14).

Gait characteristics and fatigability indices were summarised as means ± standard error per group (DWF-pwMS x NDWF-pwMS x HC), analysed on a minute-by-minute basis throughout the 6MWT. Next, DWI and gait fatigability indices were compared between groups using either one-way ANOVA or Kruskal-Wallis tests, depending on data distribution.

To explore the association between cortical activity (delta HbO and HHb) and gait changes (fatigability indices) over the 6MWT in pwMS and HC, correlation analysis was performed. Pearson or Spearman rank correlations, with 95% confidence intervals, were calculated between fatigability indices and the delta of HbO and HHb, for each region of interest. Correlation strength was interpreted as negligible (0–0.1), weak (0.1–0.39), moderate (0.4–0.69), strong (0.7–0.89), and very strong (0.9–1.0) (Schober et al., 2018).

3. Results

In total, 76 participants were enrolled in the study. One pwMS did not complete the 6MWT due to increased spasticity of the knee flexors, four participants had problems with the fNIRS device: one fNIRS bundle was broken during data acquisition, and three participants were found to have very poor data quality of fNIRS data. Therefore, data from 25 HC and 42 pwMS (18 DWF and 24 NDWF) are reported (Table 1).

Overall, pwMS-DWF were older, demonstrated higher disability levels as indicated by the EDSS-score, longer disease duration and reported increased spasticity (MSSS-88 sections 5 and 6) along with a higher impact of MS on their walking ability (MSWS-12), relative to pwMS-NDWF. MS subtypes were similar between MS groups. Moreover, pwMS-DWF walked less (6MWT), presented worse cognitive performance (SDMT), and higher trait fatigue (impact) (MFIS-total and FSMC) compared to both HC and pwMS-NDWF. Compared to HC, both MS groups were more physically, cognitively, and psychosocially trait-fatigued (MFIS), had greater perceived fatigability (PFS), higher fear of falling (FES—I), and increased pain severity and interference (BPI), and were slower on the T25FW. Furthermore, pwMS-NDWF also walked a shorter distance in the 6MWT than HC.

3.1. Gait characteristics, fatigability indexes and Borg scale

Mean and standard error on a minute-by-minute basis, as well as fatigability indexes for walking distance and gait quality, are reported in Fig. 2.

Table 1
Mean ± standard deviation or median [interquartile range] for anthropometric and clinical characteristics.

Variables	HC (n = 25)	DWF (n = 18)	NDWF (n = 24)	Statistics	p-value
EDSS	/	6 [2.62]$^{\#}$	3 [1.75]	**7.28**	**0.007**
MS phenotype (RR/SP/PP/NR)	/	7/6/3/2	14/5/2/3	2.01	0.571
Diagnosis (years)	/	16.83 ± 9.48	10.92 ± 7.86	**4.88**	**0.033**
Age (years)	52.4 ± 7.7	56.2 ± 7.2$^{\#}$	47.9 ± 12	**4.05**	**0.022**
Gender (F/M)	17/8	14/4	14/10	1.78	0.411
Weight (kg)	72.2 ± 14.9	73.9 ± 17.6	76.6 ± 15.0	0.46	0.632
Height (cm)	170.2 ± 9.5	168.5 ± 8.9	172.6 ± 9.2	1.07	0.349
T25FW (s)	3.4 [0.6]	7.05 [4.20]*	4.4 [1.7]*	**39.34**	**<0.001**
6MWT (m)	640.0 [85.0]	292 [172]*$^{\#}$	557.0 [192.2]*	**39.00**	**<0.001**
MSWS-12 (%)	/	76.7 [22.9] $^{\#}$	48.3 [49.2]	**2.36**	**0.018**
SDMT (0−110)	57.8 ± 7.6	43.8 ± 12.9*$^{\#}$	58.0 ± 12.7	**8.10**	**<0.001**
MFIS-total (pts, 0–84)	14.6 ± 12.3	52.5 ± 11.9*$^{\#}$	37.9 ± 14.6*	**45.28**	**<0.001**
MFIS-Physical (pts, 0–36)	6.0 [9.0]	25.0 [8.5]*	17.0 [7.5]*	**33.36**	**<0.001**
MFIS-Cognitive (pts, 0–40)	7.0 [8.0]	24.0 [12.5]*	18.0 [13.5]*	**25.56**	**<0.001**
MFIS-Psychosocial (pts, 0–8)	0.0 [2.0]	5.0 [2.0]*	4.0 [3.0]*	**26.45**	**<0.001**
PFS-Physical (pts, 0–50)	11.0 [7.0]	34.0 [12.0]*	24.0 [12.5]*	**22.20**	**<0.001**
PFS-Cognitive (pts, 0–50)	5.0 [5.0]	30.0 [24.0]*	14.0 [15.0]*	**24.46**	**<0.001**
FSMC (pts, 20–100)	32.1 ± 10.8	79.2 ± 12.6*$^{\#}$	63.5 ± 13.9*	**57.03**	**<0.001**
FES-I (pts, 14–64)	16.0 [2.0]	38.0 [10.0]*	27.0 [17.5]*	**39.48**	**<0.001**
BSCS (pts, 13–65)	49.5 [11.5]	43.0 [7.0]	42.5 [6.7]	**5.02**	**0.020**
BPI severity (pts, 0–10)	0.75 [1.4]	3.1 [3.6]*	2.2 [2.1]*	**12.71**	**0.001**
BPI interference (pts, 0–10)	0 [0.25]	2.6 [4.0]*	1.71 [2.79]*	**16.71**	**<0.001**
BPI walking (pts, 0–10)	0 [0]	0.0 [5.0]*	1.0 [3]*	**16.69**	**<0.001**
MSSS-88 section 5 (pts, 0–40)	/	28.0 [9.0]$^{\#}$	13.0 [13.5]	**11.48**	**<0.001**
MSSS-88 section 6 (pts, 0–40)	/	29.0 [11.0]$^{\#}$	11.0 [11.5]	**14.87**	**<0.001**

Note. Healthy controls (HC), people with multiple sclerosis with walking fatigability (DWF) or non-walking fatigability (NDWF).Expanded Disability Status Scale (EDSS), female (F), male (M), relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP), non-reported (NP), timed-25 ft walking test (T25FW), Symbol Digit Modalities Test (SDMT), Modified Fatigue Impact Scale physical (MFIS), Pittsburgh Fatigability Scale (PFS), Fatigue Scale for Motor and Cognitive Functions (FSMC), Brief Pain Inventory (BPI), Multiple Sclerosis Walking Scale-12 (MSWS-12), Multiple Sclerosis Spasticity Scale 88 (MSWS-88) section 5 and 6 which refer to the impact of spasticity in the walking ability and Brief Self-Control Scale (BSCS). *indicates differences from HC; # indicates differences from the non-distance walking fatigability (NDWF) group.

Significant differences were observed for the DWI ($\chi^2(2) = 39.33$, $p < .001$), cadence ($F_{2,64} = 26.17$, $p <. 001$), gait speed ($F_{2,64} = 32.55$, $p < .001$), double support ($\chi^2(2) = 14.25$, $p < .001$), stride length ($F_{2,64} = 22.94$, $p < .001$), toe-off angle (most-affected, $F_{2,63} = 6.97$, $p = .001$), step duration (most-affected: $\chi^2(2) = 22.06$, $p < .001$, and least-affected: $F_{2,64} = 14.44$, $p < .001$). Post-hoc analyses demonstrated that the DWF group systematically worsened across all parameters listed above compared to the HC and NDWF groups ($p < .001$; see Fig. 2).

The Borg scale data are presented in the supplementary material (Fig. S2). While no interaction between group and time was found [$F_{2,63} = 1.36$, $p = .261$, $\eta^2 = 0.042$], main effects for group [$F_{2,63} = 20.38$, $p < .001$, $\eta^2 = 0.393$] and time [$F_{1,63} = 155.22$, $p < .001$, $\eta^2 = 0.711$] were observed. Specifically, pwMS-DWF reported higher Borg scores than both HC and pwMS-NDWF ($p < .001$). Additionally, perceived fatigability increased from the beginning to the end of the 6MWT ($p < .001$).

3.2. Cortical activity

Statistics for the cortical activity across groups and time, as well as for the corresponding delta values, are summarised in Table 2. Considering the significant differences between the MS groups for age and disability level, we perform an additional analysis controlling for these factors only for the MS groups (see Table S1 in supplementary material).

The minute-by-minute mean and standard error, along with the delta values, are presented in Fig. 3. Group x time interactions were observed in the following regions: contralateral FPC (HbO and HHb), contralateral and ipsilateral DLPFC (HHb), ipsilateral (PMC-HHb) and contralateral PMC (HbO and HHb) and contralateral SMA (HbO) (see Table 2).

No group effects were detected for any of the chromophores (HbO or HHb) across the regions and their respective hemisphere. For the delta values, only a group difference was observed in the contralateral FPC-HbO. The main effects of time and their post-hoc comparisons are presented in the supplementary material.

3.3. Frontopolar cortex

The post-hoc comparisons indicated that for pwMS-NDWF, a decrease was observed from minute 1 to 2 (HHb- $p < .026$), followed by an increase from minute 3 vs 5 (HHb-$p < .024$). For HC, a constant decline in cortical activity was shown in the contralateral cortex from 1st vs 2nd-5th (HHb- $p < .003$) and 2nd vs 3rd (HHb- $p < .043$) minutes. However, an increase in cortical activity was observed in minute 6 compared to minutes 3, 4 and 5 (HbO-$p < .009$). No main effects of group or time were observed.

For the delta of cortical activity, a significant effect was found in the contralateral FPC (HbO), where HC showed higher delta values than both pwMS-DWF and pwMS-NDWF ($p < .003$ and $p < .007$, respectively).

3.4. Dorsolateral prefrontal cortex

No changes were detected in pwMS-DWF for both contralateral and ipsilateral hemispheres. For pwMS-NDWF, a constant decline in cortical activity in the ipsilateral cortex was observed from minute 1 vs 2–3 (HHb-$p < .008$). Specifically for HC, a decline was seen from minute 1 vs 2–5 (HHb- $p < .005$), minute 2 vs 3–4 ($p < .016$). Regarding the contralateral cortex for HC, lower cortical activity was evident in minutes 2–6 relative to minute 1 for (HHb-$p < .034$). Higher cortical activity was observed in minute 1 vs 2–3 (HHb- $p < .001$) in pwMS-NDWF.

3.5. Pre-motor cortex

For the ipsilateral PMC in the HC group, a decrease in cortical activity was observed in minutes 2–6 vs 1 (HHb- $p < .002$) and minutes 3–5 vs 2 (HHb- $p < .019$). For the contralateral PMC in HC, a decline in cortical activity was detected from minutes 2–4 (HbO/HHb-$p < .005$) and minutes 5–6 (HHb- $p < .001$) vs minute 1, and from minutes 2 vs minutes 3–5 (HHb-$p < .017$), with an increase at minute 6 compared to minutes 3–5 (HbO-$p < .012$). Additionally, in pwMS-NDWF, cortical activity decreased in minutes 2 and 3 compared to minute 1 (HHb-$p < .015$). Lastly, pwMS-DWF decrease PMC activity in minutes 3 and 4 compared to minute 1 vs HC (HbO- $p < .025$).

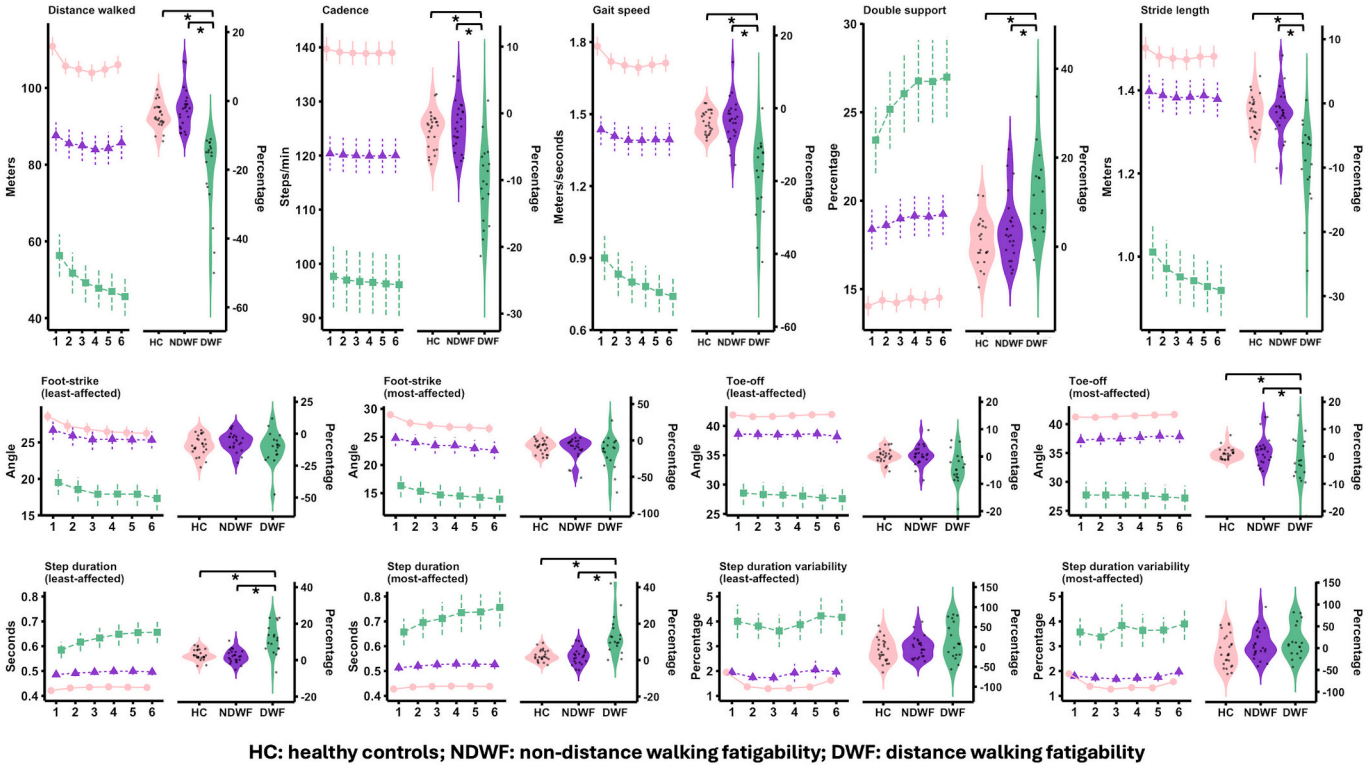

Fig. 2. Mean and standard error of gait characteristics minute-by-minute. Groups are healthy controls-HC, people with multiple with-WF and without-NDWF walking fatigability. The fatigability indexes are shown in violin plots, with each dot representing a participant in the corresponding group. *indicates significant differences between groups.

Table 2
Statistical analysis of the cortical activity data controlled by age.

ROI	Hemisphere	Delta			Group			Time			Group x time		
		F	p	EF	F	p	EF	F	p	EF	F	p	EF
Oxyhemoglobin													
FPC	Ipsilateral	0.147	0.864	0.005	0.058	0.943	0.002	1.633	0.151	0.027	0.911	0.524	0.029
	Contralateral	**7.947**	**<0.001**	**0.212**	0.170	0.844	0.006	**3.850**	**0.002**	**0.060**	**2.572**	**0.005**	**0.079**
M1	Ipsilateral	1.815	0.172	0.060	2.577	0.085	0.084	0.889	0.489	0.016	1.627	0.098	0.055
	Contralateral	0.343	0.711	0.011	1.861	0.165	0.059	0.342	0.887	0.006	1.542	0.124	0.050
DLPFC	Ipsilateral	1.266	0.289	0.039	0.987	0.378	0.030	**3.118**	**0.009**	**0.047**	1.301	0.229	0.040
	Contralateral	0.444	0.643	0.014	0.136	0.873	0.004	**6.463**	**<0.001**	**0.093**	1.421	0.170	0.043
PMC	Ipsilateral	0.855	0.430	0.026	1.719	0.187	0.052	**2.386**	**0.038**	**0.036**	1.196	0.293	0.037
	Contralateral	0.137	0.872	0.004	1.403	0.253	0.043	**3.229**	**0.007**	**0.049**	**2.176**	**0.019**	**0.065**
SMA	Ipsilateral	1.786	0.178	0.067	1.008	0.372	0.038	0.676	0.642	0.013	0.299	0.981	0.012
	Contralateral	0.713	0.495	0.027	0.723	0.490	0.027	1.556	0.173	0.029	**1.890**	**0.047**	**0.068**
Deoxyhemoglobin													
FPC	Ipsilateral	0.726	0.488	0.024	1.914	0.156	0.060	0.952	0.448	0.016	1.461	0.153	0.046
	Contralateral	2.379	0.102	0.073	3.015	0.057	0.091	**3.429**	**0.005**	**0.054**	**2.617**	**0.005**	**0.080**
M1	Ipsilateral	2.274	0.112	0.075	1.445	0.244	0.049	1.721	0.130	0.030	1.828	0.056	0.061
	Contralateral	0.134	0.875	0.004	0.292	0.748	0.010	2.195	0.055	0.036	0.557	0.848	0.019
DLPFC	Ipsilateral	0.734	0.484	0.023	2.485	0.091	0.073	2.019	0.076	0.031	**2.471**	**0.007**	**0.073**
	Contralateral	1.836	0.168	0.055	2.054	0.137	0.061	**4.489**	**<0.001**	**0.067**	**1.972**	**0.036**	**0.059**
PMC	Ipsilateral	2.577	0.084	0.076	2.660	0.078	0.078	**3.154**	**0.009**	0.048	**2.301**	**0.013**	**0.068**
	Contralateral	1.658	0.199	0.005	1.283	0.284	0.039	**6.797**	**<0.001**	**0.097**	**2.115**	**0.023**	**0.063**
SMA	Ipsilateral	1.257	0.293	0.048	0.740	0.482	0.028	0.291	0.917	0.006	0.213	0.995	0.008
	Contralateral	0.028	0.972	0.001	0.145	0.865	0.006	**3.720**	**0.003**	**0.067**	0.378	0.955	0.014

Note. F-values, *p*-values and effect sizes (EF) are reported. Dorsolateral prefrontal cortex (DLPFC), supplementary motor area (SMA), pre-motor cortex (PMC), primary motor cortex (M1) and frontopolar cortex (FPC). In bold, significant effects are presented.

3.6. Supplementary motor area

Although the statistical analysis showed a significant effect, the results were not sustained in the post-hoc analysis.

3.7. Associations between fatigability indexes and changes in cortical activity

Fig. 4 displays a brain heatmap illustrating the significant correlation between fatigability indices and changes in cortical activity (delta). The full correlation analysis is available in the supplementary material

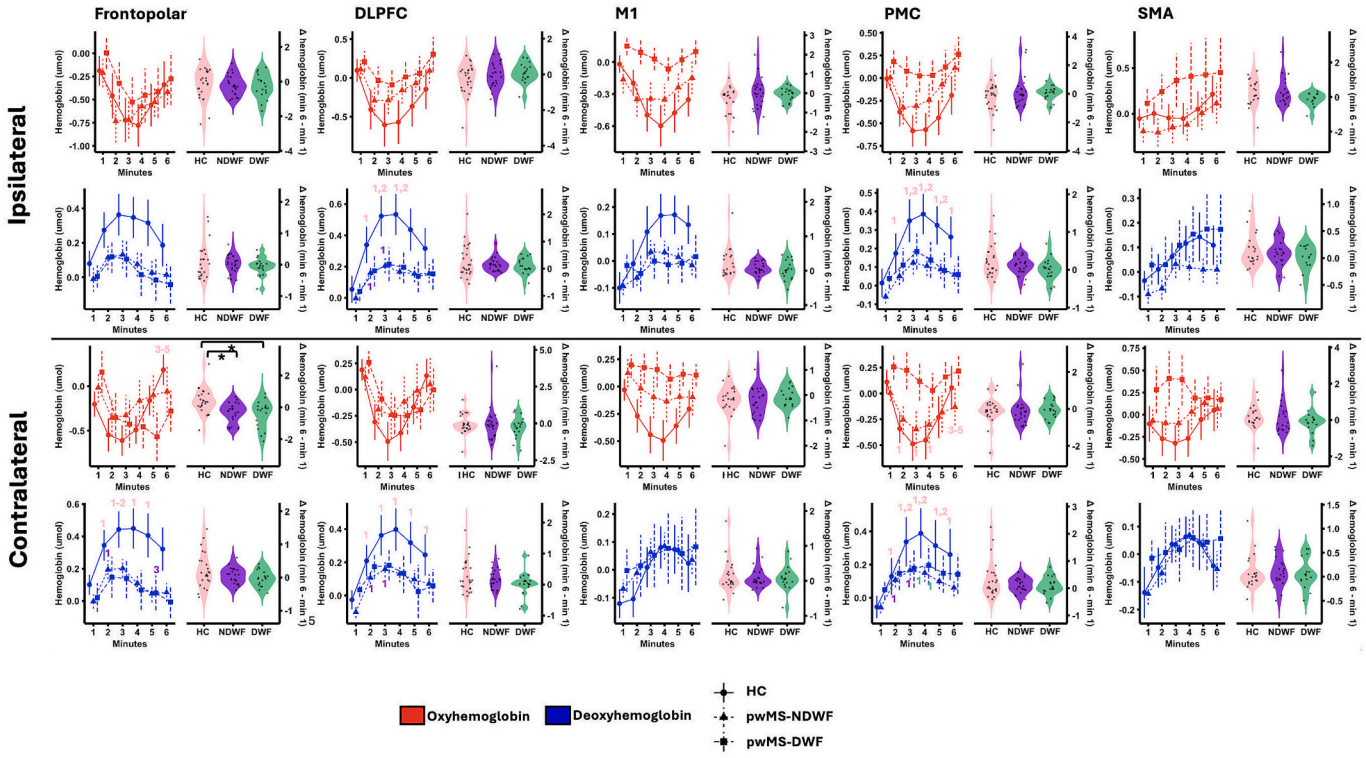

Fig. 3. Mean and standard error of cortical activity. Data is presented minute-by-minute and separated by group (healthy controls-HC, people with multiple with-DWF and without-NDWF walking fatigability) and delta values. [1] represents significant differences from minute 1; [2] represents significant differences from minute 2; [3] represents significant differences from minute 3; [4] represents significant differences from minute 4; [5] represents significant differences from minute 5; * represents significant difference between groups.

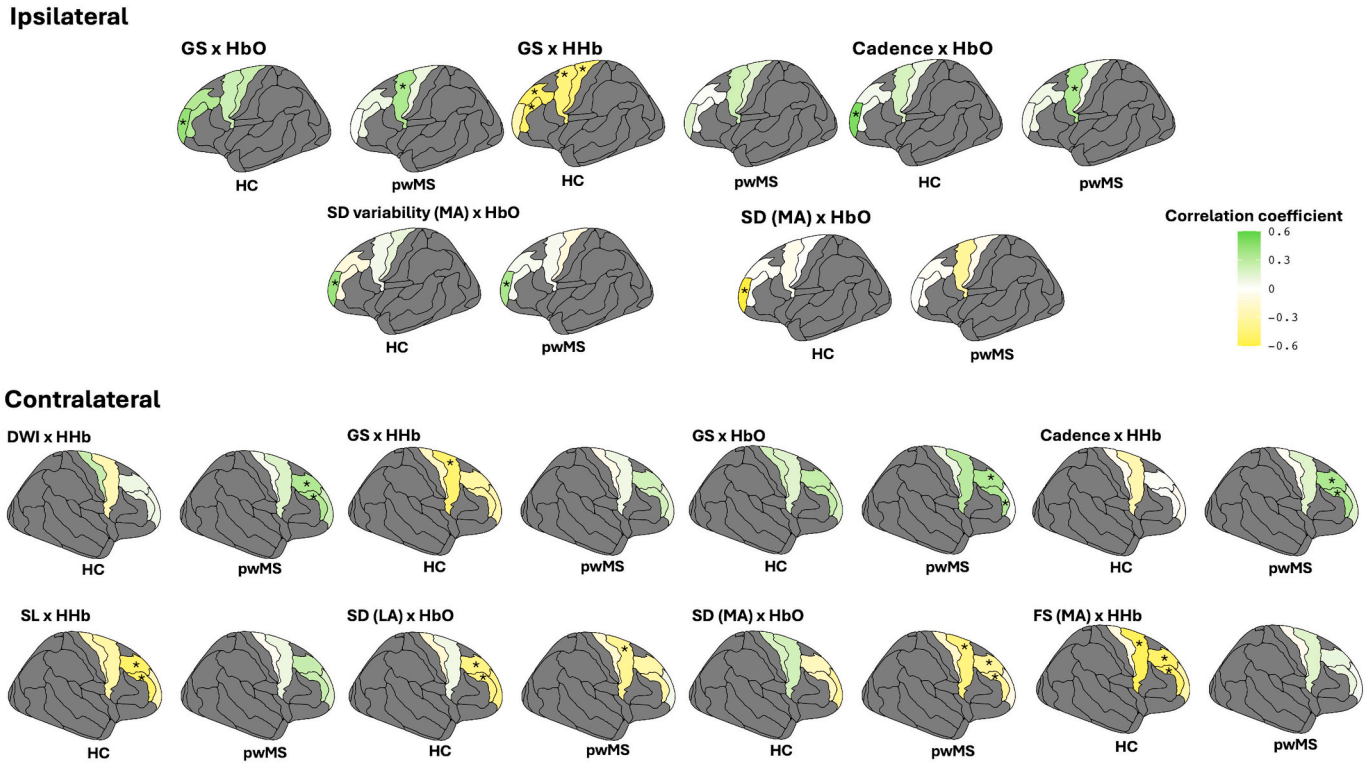

Fig. 4. Correlation coefficient map. The colored coefficients plotted in the brain based on the ipsilateral and contralateral sides, separated per group (healthy controls-HC and people with multiple sclerosis-MS). MA: most-affected; LA: least-affected; HHb: deoxyhemoglobin; HbO: oxyhemoglobin; DWI: distance walking index; GS: gait speed; SD: step duration; SL: Stride length; FS: foot-strike* indicates significant correlation in the cortical region.

(Table S1).

For the DWI, only the delta HHb of the contralateral DLPFC showed a significant, albeit weak, positive correlation in the MS group (rho = 0.332 [0.032–0.578], $p = .032$). No significant correlation was observed for HC (rho = 0.082 [−0.324–0.461], $p = .032$).

Regarding the gait speed fatigability index, the pwMS presented a significant weak positive correlation with the delta HbO in the contralateral DLPFC (rho = 0.329 [0.028–0.575], $p = .034$) and the ipsilateral SMA (rho = 0.340 [0.002–0.608], $p = .049$). In contrast, HC exhibited significant moderate positive correlations (HbO) for the FPC cortex ($r =$ 0.429 [0.032–0.710], $p = .036$) and moderate negative (HHb) for the ipsilateral DLPFC (rho = −0.506 [−0.751- -0.139], $p = .011$), ipsilateral PMC (rho = −0.437 [−0.710- -0.050], $p = .030$), contralateral SMA (rho = −0.474 [−0.757- -0.039], $p = .036$) and contralateral M1 (rho = −0.464 [−0.757- -0.039], $p = .036$).

For the cadence fatigability index, the pwMS presented a moderate positive correlation with the HbO in both SMA hemispheres (ipsilateral: $r = 0.340$ [0.002–0.608], $p = .049$; contralateral: $r = 0.451$ [0.143–0.678], $p < .006$), HHb in the contralateral DLPFC (rho = 0.347 [0.049–0.589], $p = .024$), whereas the HC showed a moderate positive correlation with the HbO in the ipsilateral FPC ($r = 0.500$ [0.121–0.752], $p = .013$). Only the HC demonstrated a significant moderate negative correlation between the HHb in the contralateral DLPFC and stride length (rho = −0.493 [−0.743- -0.122], $p = .013$).

Concerning step duration on the least-affected side, pwMS showed a weak negative correlation with the HbO in the contralateral SMA (rho = −0.360 [−0.616- -0.036], $p = .031$). In contrast, HC displayed a moderate negative correlation but with the HbO in the contralateral DLPFC (rho = −0.411 [−0.693- -0.019], $p = .042$). Similar correlations were observed for the step duration on the most-affected side, which correlated negatively with the HbO in the contralateral SMA (rho = −0.430 [−0.664- -0.118]-moderate, $p = .009$) and the contralateral DLPFC (rho = −0.339 [−0.583- -0.039]-weak, $p = .028$) in pwMS. Additionally, in HC step duration on the most-affected side correlated negatively with the HbO in the ipsilateral FPC ($r = −0.597$ [−0.806- -0.254]-moderate, $p = .002$). Furthermore, both groups presented significant correlations between step duration variability of the most-affected side and HbO in the contralateral FPC (pwMS: $r = 0.351$ [0.045–0.598]-weak, $p = .026$; HC: $r = 0.410$ [−0.007–0.698]-moderate, $p = .046$).

Finally, only HC showed significant moderate negative correlations between the foot-strike angle (most-affected side) and the HHb of the contralateral DLPFC, SMA and PMC (rho = −0.496 [−0.745- -0.126], $p = .012$; rho = −0.537 [−0.791- -0.123], $p = .016$; rho = −0.514 [−0.756- -0.150], $p = .009$).

4. Discussion

The objective of this study was to enhance the understanding of the cortical activity mechanisms of WF in pwMS and HC. This is the first study to investigate real-time cortical activity using fNIRS concomitantly with measurement of gait speed and quality changes during a 6MWT. Minute-by-minute analyses suggest that the temporal dynamics of cortical activity were modulated similarly across MS and HC groups in the M1 and SMA. However, cortical activity modulated according to 6MWT effort demands in specific cortical regions: the FPC, and both the DLPFC and PMC in the HC and pwMS-NDWF groups. However, with less flexibility in the pwMS-NDWF in modulating cortical activity in these regions. Correlation analyses showed that increased cortical activity (i.e., delta between minute 6 and minute 1) was linked to increased gait speed and related spatial-temporal parameters in both pwMS and HC. In addition, the delta of the cortical activity was positively associated with changes in the foot-strike angle only in HC. However, the increased FPC activity associated with greater step duration variability in both pwMS and HC might suggest a deleterious consequence of excessive cortical recruitment.

The group-by-time comparison showed that the dynamics of cortical activity during the 6MWT differed between pwMS and HC in certain cortical regions. In HC, and to a lesser extent in pwMS-NDWF, cortical activity in the FPC, DLPFC, PMC, and SMA normally decreases during minutes 2–4 compared to minute 1 and then increases again in minutes 5–6 compared to the preceding minutes, aligning with the walking speed pattern (see below). For pwMS-DWF, this pattern of temporal dynamics of cortical activity might be restricted to some cortical regions (i.e., SMA and DLPFC). The remaining cortical regions tend to maintain constant cortical activity throughout the entire 6MWT. Overall, in terms of the cortical activity dynamics, regardless of cortical regions, it aligns with the findings of Broscheid et al. (2022a) who investigated gait dynamics behaviourally through the limit-cycle attractors (i.e., a metric that indicates the steady-state of a gait pattern). The authors demonstrated that from the second minute, gait becomes more stable and variability diminishes, indicating a transition toward a steady-state walking pattern. The first minute of the 6MWT is normally the fastest minute, and therefore may require higher cortical output. After this initial effort, from minutes 2–4, spinal circuits, including the central pattern generator, could be more involved in maintaining rhythm and pace, resulting in reduced cortical involvement and a more automatic form of gait control. Aligning with a characteristic “U-shape” trajectory (i.e., an increase in gait speed in minute 6 compared to minutes 2–5) (Leone et al., 2016; Santinelli et al., 2025; Santinelli et al., 2024a), a higher involvement of cortical resources is needed (Alcock et al., 2023). Thus, it might reflect heightened executive control and the engagement of higher-order networks that support indirect gait regulation toward the end of the 6MWT.

Contrary to our hypothesis that walking fatigability would be partially explained by the limited capacity of neural resources recruitment (Reuter-Lorenz and Cappell, 2008; Steens et al., 2012; White et al., 2009; Zijdewind et al., 2016), pwMS-DWF did not exhibit a pronounced decline in cortical activity as the task became more physically demanding. In fact, pwMS with distance-walking fatigability exhibited constant cortical activity throughout the 6MWT, whereas HCs and, to a lesser extent, pwMS-NDWF modulated cortical activity in response to task demands. A similar pattern has been observed in people with Parkinson's disease, where those presenting with sustained overactivation in the prefrontal cortex during a two-minute walking, also showed worse walking performance and gait quality (Silva-Batista et al., 2024). This sustained cortical activation likely reflects a reliance on executive control (Clark, 2015; Yogev-Seligmann et al., 2008) or an endeavour to augment neural drive to motoneurons (Rocca et al., 2004). This could align with the concept of loss of gait automaticity in pwMS (Hernandez et al., 2016), where executive control of walking is needed in order to mitigate possible disruptions in the “automatic” walking network. This finding is also consistent with previous studies on normal and dual-task walking, where pwMS presented the so-called loss of gait automaticity (Hernandez et al., 2016), given the higher cortical activity already present in normal walking and with less ability to increase when the dual-task is presented (Kupchenko et al., 2023; Santinelli et al., 2024c). According to prior work (Abasiyanik et al., 2022; Abasiyanik et al., 2025; Arpan et al., 2020; Plotnik et al., 2020; Santinelli et al., 2025; Santinelli et al., 2024a; Shema-Shiratzky et al., 2019), gait characteristics for both pwMS groups and fatigability indices for the pwMS-DWF were worse than those of HC. This sustained cortical activation, concomitant with poor performance, aligns with the theory of dysfunctional (Fettrow et al., 2021) or maladaptive (Peterson and Fling, 2018) neuronal activity. In other words, the amount of cortical activity is not sufficient to overcome neural deficits and preserve walking performance.

When looking at the coupling of cortical activity with gait behaviour, by means of correlation analysis, HC exhibited a broader neural network (i.e., FPC, DLPFC, M1, SMA and PMC) association with modulation in gait speed and related parameters. Conversely, associations in pwMS were observed only in a subset of this network, primarily the DLPFC and SMA. These regions were associated with changes in gait speed and

related spatial-temporal parameters such as step duration, cadence and stride length. The involvement of the DLPFC, FPC, SMA, PMC and M1 in modulating gait speed has been previously described in normal and more complex walking tasks (Alcock et al., 2023; Belli et al., 2021; Hamacher et al., 2015; Harada et al., 2009). As task demands increase, additional regional involvement might mitigate declines in motor performance and prevent walking fatigability. This could be interpreted as a compensatory mechanism or reflect greater neuronal efficiency (i.e., higher cortical activity and engagement of diverse cortical regions may support better motor performance) (Chatterjee et al., 2019; Fettrow et al., 2021). In pwMS, however, the lack of a correlation between changes in gait speed-related parameters and changes in the activity of the PMC, M1, and FPC suggests a reduced capacity for gait speed modulation when the task becomes overly demanding. Specifically, insufficient M1 activity leads to a reduction in central drive (Gandevia, 2001), whereas FPC activity provides executive and attentional control of walking (Mirelman et al., 2014; Yogev-Seligmann et al., 2008). Concomitantly, probable disruption of the PMC would impair gait adaptation (Suzuki et al., 2004). Thus, the lack of association between these cortical regions and changes in gait speed and quality might contribute to WF in pwMS. Consequently, our results suggest that pwMS might have a restricted association pattern of cortical activity, with gait speed changes primarily associated with DLPFC and SMA activity, suggesting a simplified, cognitively driven gait control and reduced downstream motor scaling. Hence, the modest strength of these associations indicates that cortical activity likely represents only one of several factors contributing to walking fatigability.

Beyond gait speed, gait quality measures reveal how cortical resources are functionally coupled to locomotor control. Such gait quality and cortical activation associations have been poorly explored by previous studies. According to our knowledge, only Zhou et al. (2026) have investigated this association in children with cerebral palsy. In our cohort, changes in cortical activation of the PMC, SMA, and DLPFC were positively correlated with a smaller decline in foot-strike angle, albeit this effect was observed only in HC. This pattern can reflect a flexible up-regulation of cortical resources to maintain gait quality during prolonged walking in neurologically intact individuals. The increased engagement of PMC, SMA, and DLPFC may represent the functional recruitment of sensorimotor and executive networks that support online adjustment of locomotor output as effort demands accumulate. Both PMC and SMA are involved in motor planning, sequencing, and sustained control of walking (Miyai et al., 2001), while DLPFC contributes to executive monitoring and attentional control of gait, facilitating error detection and correction under increased demands (Bigliassi and Filho, 2022; Yogev-Seligmann et al., 2008). Together, these associations could suggest that preserved capacity to engage multiple cortical regions facilitates effective brain-behaviour coupling, stabilising gait quality (e.g., foot-strike angle), during prolonged walking. In contrast, this reserve-dependent mechanism may be attenuated or disrupted in pwMS, contributing to their reduced gait quality maintenance.

Gait variability, by means of the step duration variability fatigability index, was positively correlated with changes (i.e., the delta) in FPC activity in both pwMS and HC. This co-increase could suggest that greater executive control of walking accompanies higher gait variability, confirming our previous statements. While enhanced executive engagement may help maintain performance under effort conditions, it can also introduce “noise” within the system (i.e., more variability) (Clark, 2015). However, this could, to some extent, be a maladaptive behaviour. Literature suggests that an increase in gait variability is linked to higher chances of falling in both pwMS and HC (Hausdorff et al., 2001; Hernandez et al., 2026) and higher cortical activity (Mirelman et al., 2017; Nobrega-Sousa et al., 2020; Santinelli et al., 2024c). Consequently, the two groups might be facing a trade-off: improving gait speed and quality toward the end of the 6MWT is accompanied by rising gait variability, which might increase fall risk and reflect a compensatory overload (Hulzinga et al., 2025).

5. Limitations

Some methodological constraints must be acknowledged. First, given our sample size, we could not have multiple groups with different manifestations of gait quality fatigability (Santinelli et al., 2024a). Therefore, generalising our findings to all manifestations of gait quality fatigability is not possible. Moreover, our study was the first to investigate cortical activity during a 6MWT using fNIRS or any mobile brain imaging. Consequently, no formal a priori power analysis was performed because no data were available to estimate effect sizes, which might have affected some of our analyses. We expect that our study will guide power analysis for future studies. Second, multiple repetitions of a task are generally required in fNIRS research to obtain robust and stable cortical activity dynamics (Menant et al., 2020; Yucel et al., 2021). In the present study, administering two or more 6MWTs in a single day was impractical for the patient population, given fatigability accumulation. Thus, a single 6MWT was employed as the most feasible protocol. We also recognise that fNIRS is limited to the cortical level, so it is unknown how subcortical locomotor networks are engaged and how they may contribute to WF in pwMS. Third, the pwMS-DWF exhibited a higher disability level and were older than the pwMS-NDWF. Prior research has not investigated whether disability severity in pwMS systematically alters cortical activation during walking. Nevertheless, the difference in disability levels between the two MS groups may account for the variations in cortical dynamics. In fact, we performed an additional analysis comparing the MS groups while controlling for disability level (see supplementary material), in which only a time effect was observed for the DLPFC. This effect indicates that age and disability level for the MS groups seem to moderate some of our findings. This is likely due to the higher prevalence and magnitude of walking fatigability in pwMS with higher disability (Santinelli et al., 2025; Santinelli et al., 2024a). Differences in cortical activity between disability levels were previously demonstrated in other motor tasks (Peterson and Fling, 2018; Reddy et al., 2002). In addition, ageing is known to impact cortical activity and gait (Nobrega-Sousa et al., 2020). However, our analysis was controlled for age, which mitigates potential confounding. Future studies should aim to recruit a larger number of participants to enable stratification by age distribution and, if possible, disability level. Fourth, we did not record medication intake by our participants. Some types of medication could impact the fNIRS response (e.g., antidepressants) (Takamiya et al., 2017). We recommend that future studies record specific medication intake as a potential confounding factor in cortical responses. Lastly, we ask for caution when interpreting the correlation findings. The cross-sectional design of the study does not allow for inference of causation but only for association. Moreover, the correlations were generally weak to moderate in magnitude and should therefore be interpreted with caution.

6. Conclusion

A decrease in gait speed and quality during a prolonged walking protocol such as the 6MWT is associated, to some extent, with the capability to recruit neural resources at the end of the test. While HC engage a broader walking network, pwMS appears to be limited, relying predominantly on the DLPFC and SMA, which is considered a more executive walking control. Taken together, walking fatigability in pwMS appears to be driven by complementary mechanisms: i) limited flexibility of neural resources recruitment at the end of the 6MWT, and ii) reduced engagement of the cortical walking control network. The temporal dynamics of the cortical activity across the 6MWT further reveal that minutes 1, 5 and 6 require a greater cortical activity contribution (i.e., executive gait control), whereas minutes 2–4 show a steadier, more automatic gait pattern. This shift toward executive control is markedly attenuated in pwMS who exhibit distance walking fatigability.

Studies in Human

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place.

This study was approved by the Medical Ethical Committee of the University of Hasselt.

(Approval No. B1152024000007)

Clinical Trials

The results of this clinical trial and any associated work have been posted in a registry.

This clinical trial was registered with number NCT06672484 (Walking Fatigability and Brain Activity in People With Multiple Sclerosis).

CRediT authorship contribution statement

Felipe Balistieri Santinelli: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Cintia Ramari:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Kim-Charline Broscheid:** Writing – review & editing, Visualization, Formal analysis. **Rodrigo Vitorio:** Writing – review & editing, Visualization, Formal analysis. **Daphne Kos:** Writing – review & editing, Resources, Investigation. **Bart Van Wijmeersch:** Writing – review & editing, Resources, Investigation. **Miguel D'Haeseleer:** Writing – review & editing, Resources, Investigation. **Pieter Meyns:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Peter Feys:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Conceptualization.

Informed consent and patient details

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nbd.2026.107579.

Data availability

Data will be made available on request.

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