


## Theoretical Notes

## Impaired temporal processing in multiple sclerosis



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## ABSTRACT

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that damages grey and white matter and reduces neural transmission efficiency. Volumetric MRI studies indicate early neurodegeneration in subcortical structures, including the basal ganglia (BG), with microstructural damages and altered tissue anisotropy reported across all MS subtypes, affecting BG functional connectivity while also being linked to fatigue. Given the BG's central role in temporal processing, we hypothesized that people with MS (pwMS) would show impaired perceptual and motor timing. Twenty-two pwMS (14 females) with relapsing–remitting MS completed the Battery for the Assessment of Auditory Sensorimotor and Timing Abilities (BAASTA) on a tablet, performing perceptual tasks and finger-tapping motor tasks. Compared to normative data, pwMS exhibited increased motor variability during unpaced tapping and reduced synchronization consistency to rhythmic auditory cues. Perceptual deficits included poorer detection of metronome alignment with musical beats and reduced sensitivity to deviations from a regular beat. These perceptual impairments correlated with higher patient-reported Expanded Disability Status Scale (prEDSS) scores and perceived fatigue levels, as evaluated with the Multidimensional Fatigue Inventory (MFI). These findings suggest timing measures as a potential candidate for behavioral biomarkers of disease progression and fatigue in MS.

## 1. Introduction

Rhythm is part of our daily life and across all cultures, humans synchronize and move with musical rhythms (Kotz et al., 2018). One of its most notable features is the temporal structure, particularly the *beat*, which refers to the level of periodicity at which humans tend to move along. The ability to structure movement to sound is acquired early in life (Phillips-Silver and Trainor, 2005; Sowiński and Dalla, 2013). Furthermore, the ability to synchronize is scaffolded by neuronal networks that include cortical and subcortical structures. They involve two main, distinct networks. The first is the basal ganglia–thalamocortical network (BGTC) which is engaged in attention-dependent evaluation of temporal intervals and self-generation of movements. This network is involved in action initiation and explicit timing (i.e., overt estimation of

stimulus duration). Second is the cerebellar–thalamocortical (CTC) network, which is involved in the preattentive encoding of event-based temporal structure and matching of movements to exogenous cues (Dalla Bella et al., 2015; Schwartz and Kotz, 2013). In the healthy brain, the BGTC and CTC networks afford the extraction of temporal features of a predictable auditory sequence (e.g., the musical beat), the development of temporal expectations via entrainment, and the coupling of action to salient events such as the beat in the temporal structure. These processes can be further clarified by the differentiation between implicit timing, which refers to the automatic, unconscious processing of temporal information to anticipate events, and explicit timing, which involves the conscious estimation of and attention to time intervals or durations (Béget et al., 2017). Further, motor timing concerns the timing of actions, whereas sensory timing is related to

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perceiving temporal features of stimuli (Allman and Meck, 2012). Neuroanatomically, implicit timing primarily engages the cerebellum, supporting automatic temporal predictions and sensorimotor integration, whereas explicit timing recruits the basal ganglia (BG) for conscious temporal judgments (for a more thorough review on the neural basis of timing, see (Paton and Buonomano, 2018). Altogether, this is referred to as *timing abilities*.

Since the BG are involved in temporal processing (Allman and Meck, 2012), focal lesions in the BG have a disruptive effect on sensorimotor synchronization with auditory stimuli and on perceptual timing abilities. This is particularly notable in Parkinson's disease, in which it is a hallmark of the pathology (Benoit et al., 2014; Grahn and Brett, 2009; Magalhães et al., 2018), but also BG stroke (Antonioni et al., 2025; Aparicio et al., 2005; Coslett et al., 2010), and potentially, multiple sclerosis (MS), which was the focus of the current study.

MS is a chronic inflammatory autoimmune pathology of the central nervous system. MS eventually results in neuronal damage both in grey and white matter, ultimately decreasing the efficiency of neural transmission. MS symptoms are varied and can affect sensory, motor, and/or cognitive domains (Horakova et al., 2012). Volumetric MRI studies show that among cerebral regions, deep grey nuclei such as the BG are susceptible to neurodegeneration early in the course of the disease (Bergsland et al., 2012). Increased tissue anisotropy of the BG has been reported in relapsing-remitting (RRMS, i.e., with "clearly defined disease relapses with full recovery or with sequelae") and secondary-progressive (SPMS, i.e., relapsing-remitting MS which is "followed by progression with or without occasional relapses, minor remissions, and plateaus," Lublin and Reingold, 1996) MS patients (Hasan et al., 2011). This damage has also been noted in rarer forms of MS such as primary progressive (PPMS, i.e., "progression from onset with occasional plateaus and temporary minor improvements," (Lublin and Reingold, 1996) MS (Ceccarelli et al., 2010) and clinically isolated syndrome (CIS) (Deppe et al., 2016).

Interestingly, the BG are also well identified as a key structure involved in fatigue (Chaudhuri and Behan, 2000). Being one of the most common symptoms experienced by people with MS (pwMS), fatigue is characterized by an overwhelming sense of physical and mental exhaustion (Induruwa et al., 2012). Furthermore, it is known to negatively impact cognitive processing speed, attention, and executive functions (Pessiglione et al., 2025), all of which are critical for temporal perception and timing tasks. Recent findings have also associated deep grey matter lesions and atrophy with sensorimotor impairment in pwMS (Morozumi et al., 2024). These results were linked to disability severity as evaluated with the Expanded Disability Status Scale (EDSS), the standard for assessing disability in pwMS. Distinct alterations of the BG functional connectivity in pwMS were associated with fatigue (Finke et al., 2015; Román et al., 2022) while the EDSS scores were identified as a predictor of fatigue severity (Ezzeldin et al., 2023). Finally, BG atrophy and its associated symptoms have been identified as a marker of MS progression (Trufanov et al., 2023).

Altogether, these known alterations in MS potentially link disability severity, fatigue, and timing impairments through BG dysfunction, making investigations of timing impairments in pwMS a potentially promising direction for study and clinical assessment. In this domain, finger tapping tests have been shown to assess motor performance in MS and to be good markers of disease progression (Gulde et al., 2021). However, these studies focused on the tapping rate as a biomarker, not on the quality of the motor performance and patients' timing and sensorimotor abilities. Thus, little is known about timing abilities in MS. Knowing that timing abilities are multidimensional (Fiveash et al., 2022), a thorough assessment of these abilities in MS is in order to uncover any signs of impairment in this condition. Gaining a better understanding of timing and rhythmic abilities in MS is very relevant to better understand the pathology progression and its effects on cognition, and potentially offer a biomarker for MS severity.

Thus, the current study aimed at characterizing timing abilities in

pwMS and evaluating the impact of disability severity on these abilities alongside the perceived fatigue felt before performing the timing tasks. To this end, we evaluated a broad range of perceptual and production timing abilities and examined individual differences in timing profiles using the Battery for the Assessment of Auditory Sensorimotor and Timing Abilities (BAASTA, (Dalla Bella et al., 2017)). Norms have been recently published for a version of BAASTA on a mobile device (Dalla Bella et al., 2024), which facilitates the detection of timing disorders in clinical populations. We predicted that pwMS would show a disruption in synchronization abilities and an impairment in perceptual timing tasks. These deficits are expected to increase with disability severity. Furthermore, we hypothesized that fatigue, previously associated with disease progression and BG dysfunction, would correlate with timing ability impairments.

## 2. Materials & Methods

### 2.1. Inclusion and exclusion criteria.

Adults with MS (CIS/RRMS/PPMS/SPMS) were recruited. The following exclusion criteria were applied: (a) the presence of other neurological or major psychiatric disorders; (b) MS relapse or systemic corticosteroid use within the previous 30 days; (c) change in symptomatic or disease-modifying medication within the previous 30 days; and (d) self-reported hearing/vision problems that could interfere with participating in the tasks on the tablet. Clinical/demographic data (disease duration, current medication, diagnostic confirmation, MS subtype, education, and musical education) and the presence/absence of exclusion criteria were obtained with a structured medical/demographic screening interview. Neurological disability was rated using the patient-reported Expanded Disability Status Scale (prEDSS) (Collins et al., 2016).

### 2.2. Population

Thirty non-musicians pwMS undergoing active treatment for RRMS volunteered to take part in the study. Data from 8 pwMS was removed due to standardized quality checks (see "Preliminary analysis" section), resulting in a final sample of 22 pwMS (14 females,  $M_{Age} = 42.18 \pm 9.77$ ). The participants received no rewards for participation. The median prEDSS score of the group was 2.5 with an interquartile range of 2 (see Table 1). The mean number of years since the patients' were given a diagnosis was 11.4 years ( $\pm 7.4$ ).

### 2.3. Measures

The BAASTA is a battery of tasks assessing timing abilities. It consists of four perceptual tasks and five production tasks (for a thorough description of the tasks, see (Dalla Bella et al., 2017)). In the current study, the following perceptual tasks were used: the Beat Alignment Test (BAT) which evaluates the detection of the alignment between the musical beat and a superimposed metronome sound, Duration Discrimination, which evaluates the ability to distinguish between tones of various duration, and Anisochrony Detection with tones, or "the ability to perceive a temporal irregularity [...] in an isochronous sequence of tones" (Dalla Bella et al., 2017). Regarding production tasks, we used Unpaced Tapping, which evaluates tapping rate and variability in the absence of auditory stimulation, and Paced Tapping with tones at various tempi (450, 600 and 750 ms interbeat interval), which evaluates synchronizing to a presented beat.

In the current study, the BAASTA was implemented as an application

**Table 1**  
Sample statistics.

| pwMS | Gender | Age | prEDSS | Years wMS | FMSC | MFI |
|------|--------|-----|--------|-----------|------|-----|
| 1    | F      | 36  | 2,5    | 8         | 66   | 51  |
| 2    | F      | 61  | 4      | 20        | 52   | 40  |
| 3    | M      | 39  | 2,5    | 1         | 24   | 20  |
| 4    | M      | 39  | 4,5    | 20        | 74   | 69  |
| 5    | F      | 35  | 3      | 3         | 42   | 39  |
| 6    | F      | 48  | 3      | 16        | 61   | 58  |
| 7    | M      | 38  | 1      | 3         | 31   | 23  |
| 8    | M      | 41  | 2,5    | 14        | 56   | 36  |
| 9    | M      | 47  | 3      | 12        | 49   | 64  |
| 10   | F      | 38  | 4      | 17        | 76   | 59  |
| 11   | F      | 40  | 2      | 11        | 22   | 36  |
| 12   | F      | 52  | 2,5    | 22        | 68   | 60  |
| 13   | F      | 25  | 2      | 7         | 74   | 68  |
| 14   | M      | 52  | 2,5    | 16        | 71   | 48  |
| 15   | M      | 32  | 4      | 3         | 68   | 63  |
| 16   | M      | 27  | 2      | 0         | 47   | 44  |
| 17   | F      | 61  | 2      | 23        | 30   | 40  |
| 18   | F      | 47  | 4      | 2         | 66   | 53  |
| 19   | F      | 40  | 5,5    | 16        | 82   | 62  |
| 20   | F      | 51  | 4,5    | 18        | 49   | 60  |
| 21   | F      | 48  | 4      | 6         | 82   | 72  |
| 22   | F      | 31  | 1,5    | 12        | 27   | 41  |

*Note.* pwMS = people with multiple sclerosis (MS) in the current study. prEDSS = The patient-reported Expanded Disability Status Scale. EDSS scores are given on a scale from 0 to 10. Years wMS = the number of years since a given pwMS' MS diagnosis. FMSC = The Fatigue Scale for Motor and Cognitive Functions. FMSC scores are given on a scale from 20 to 100. MFI = The Multidimensional Fatigue Inventory. MFI scores are given on a scale from 20 to 100.

on a tablet (Samsung Galaxy Tab E running Android 7.1).<sup>1</sup> Auditory stimuli were delivered to pwMS via a pair of headphones connected to the tablet. pwMS' responses in the perceptual tasks were communicated verbally to the experimenter who entered them on the tablet. Finger-tapping performance was collected by having participants tap within a green rectangle (10.0 × 8.8 cm) on the tablet touchscreen (see (Dalla Bella et al., 2024)).

The EDSS is the criterion standard for assessing the severity of disability in MS (Çinar and Yorgun, 2018; Meyer-Moock et al., 2014). It consists of assessing overall wellness, degree of mobility, sensation in the limbs, limb strength, balance and coordination, vision symptoms, face and neck symptoms, and bowel and bladder symptoms. The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability severity. In the current study, the neurologist worked alongside the patient to complete the prEDSS to provide a standardized way for patients to report their disability status (Collins et al., 2016).

The Multidimensional Fatigue Inventory (MFI, Smets et al., 1995) in a Polish version by Buss et al. (2014) was used to assess self-reported current fatigue. The Polish MFI consists of 20 items elaborated to reflect five dimensions of fatigue: general fatigue, physical fatigue, mental fatigue, reduced activities and reduced motivation. Full score is obtained by summing all subsections.

The Fatigue Scale for Motor and Cognitive Functions (FMSC, Penner et al., 2009) in a Polish translation created for the purposes of the current study was additionally used to assess self-reported fatigue in a longer perspective (i.e., the FMSC asks pwMS to describe their "everyday life" whereas the MFI asks about how the pwMS have been feeling "lately"). The FMSC consists of 20 items pertaining to motor fatigue and cognitive fatigue about problems in everyday life which are directly associated with an extreme form of tiredness. The Polish version of the FMSC is available upon request to the corresponding author and was translated into Polish through an independent back-translation

<sup>1</sup> The Android version of the BAASTA is available via the BeatHealth S.A. company (<https://www.beathealth.tech/>) via subscription, licensing agreements, or on a Pay-Per-Use (PPU) basis.

procedure carried out by two authors following a fixed set of guidelines (Van De Vijver and Hambleton, 1996). The original English-language FSMC was first translated into Polish by one of the authors. That Polish version was then retranslated back into English by another author who did not participate in the first translation. The English retranslation was compared to the English original with the assumption that a close similarity of these versions indicates that the Polish translation was accurate. Any ambiguities or differences were jointly resolved at this stage by the two authors.

#### 2.4. BAASTA timing interval selection

We used the BAASTA to probe the perceptual and sensorimotor mechanisms of rhythm and timing at ranges where human sensitivity is highest. On a perceptual level, Anisochrony Detection used an interonset interval of 600 ms to probe subsecond interval timing with high auditory precision. It implicates both BG and cerebellar involvement, but the cerebellum is more directly involved in precise timing and maintaining stable temporal predictions of event onsets, while the BG contribute more to the rhythmic and beat-based aspects of timing (Criscuolo et al., 2025). Duration Discrimination was centered in the subsecond range (~600–1000 ms) to minimize counting strategies and emphasize the automatic CTC network (Boven and Cerminara, 2023). This task is predominantly cerebellar-related, with the BG playing a more dominant role in rhythm and beat-based temporal processing such as that targeted by the BAT. Our version sampled musical tempi in the ~450–750 ms period (similar to paced tapping), engaging beat-based temporal prediction supported by the BGTC networks (Hoddinott and Grahn, 2024).

#### 2.5. Procedure

pwMS were tested individually for a duration of around one hour in a quiet environment at the Department of Neurology, Medical University of Warsaw, Poland, by trained neurologists. The prEDSS was administered by the medical team and provided for further analysis. The pwMS first filled out a demographic data form, the MFI, and the FMSC. Then, the participants completed tasks from the BAASTA.

The study was approved by the Commission for Research Ethics at the University of Economics and Human Sciences in Warsaw, Poland (application no. 3o.03.2021). Written consent was obtained from each pwMS, which explained the purpose of the experiment, the scope of the collected data, and the procedure. All collected data were treated anonymously.

#### 2.6. Preliminary analysis

Data were subjected to quality checks and preliminary analyses. Regarding the BAASTA, for perceptual data (i.e., BAT, Duration Discrimination, and Anisochrony Detection), across all tasks, 2 thresholds were removed for analysis following the quality check. For production data (i.e., Unpaced Tapping and Paced Tapping), all tasks were pre-processed following the same procedures adopted for computer-collected data (Dalla Bella et al., 2017). Following a manual review of tapping trials based on automatic diagnostic measures, a production task demonstrating a high coefficient of variation of the intertap interval (> 0.15) on a tapping trial was removed from analysis (representing 10 trials across all production tasks). These removed trials explain the different degrees of freedom of the various analysis reported in this study. A detailed description of the procedure is specified in International Patent No WO 2020/128088 A1 and further described in the normative data presentation (Dalla Bella et al., 2024).

#### 2.7. Analysis of BAASTA data

For Duration Discrimination and Anisochrony Detection with tones, we averaged the threshold obtained from the staircase procedure in two

trials (2 down/1 up; see Experiment 2 in (Dalla Bella et al., 2017)). The threshold was expressed as a percentage of the standard duration or interval. In the BAT, we calculated the sensitivity index ( $d'$ ) based on the proportions of hits (correct detections) for misaligned metronomes and of false alarms (when a misalignment was erroneously reported for aligned metronomes) for the entire set of 72 stimuli.

For the Unpaced Tapping task, we calculated the coefficient of variation of the intertap interval (CV ITI, i.e., the  $[SD \text{ of the ITI}] / \text{mean ITI}$ ) as a measure of motor variability. Moreover, we computed measures of phase synchronization in the Paced Tapping task using circular statistics (see (Dalla Bella et al., 2017)). Further analysis in Paced Tapping of the performance consistency used the logit-transformed vector length, as was done in previous studies (Dalla Bella et al., 2024). This was done as the CV ITI is not a measure of synchronization, but of tapping variability regardless of the stimulus.

Finally, pwMS' results were compared to the normative data using z-scores, or the corresponding number of standard deviations separating an individual pwMS's performance from the mean in the normative distribution. The normative data was obtained with this version of BAASTA from 116 healthy adults between the ages of 18 and 87 years in a test-retest protocol and were adjusted to the age group of the patient (Dalla Bella et al., 2024). The data were divided into four age groups: 18–21 years (no pwMS in the current study), 22–29 years (2 pwMS), 30–54 years (18 pwMS) and 55–87 years (2 pwMS). The age range of each group in the normative study was determined to ensure a comparable sample size in each group, based on the tested participants.

## 2.8. Statistical analysis

Evaluation of the data distribution was assessed by the Kolmogorov-Smirnov test. Based on these results, parametric or nonparametric statistical analysis was used accordingly. We used paired t-tests (parametric) or Wilcoxon matched-pairs signed rank test (nonparametric) to compare individual z-scores to zero because each z-score reflects how a single patient's performance deviates from a normalized dataset with a known mean of zero. We did not apply a correction for multiple comparisons because our analyses were hypothesis-driven and focused on a limited set of planned comparisons, rather than on broad exploratory testing. Applying a correction such as Bonferroni in this context could have increased the risk of Type II errors. However, as cognitive impairment could have an impact on pwMS' performance, we conducted correlations between timing outcomes and cognitive subscales of the MFI and FSMC. These sensitivity analyses aimed to exclude participants with possible confounding factors.

Further analysis was carried out using Pearson's (parametric) or

Spearman's correlation (nonparametric) to quantify the linear relationship between the variables. Based on the above findings that indicate a clear link between the impairment of the BG and the variable correlated (timing impairments z-score, fatigue rating evaluated by the MFI score and disability severity represented by the prEDSS score), one-tailed correlations were performed.

## 3. Results

### 3.1. Perceptual tasks

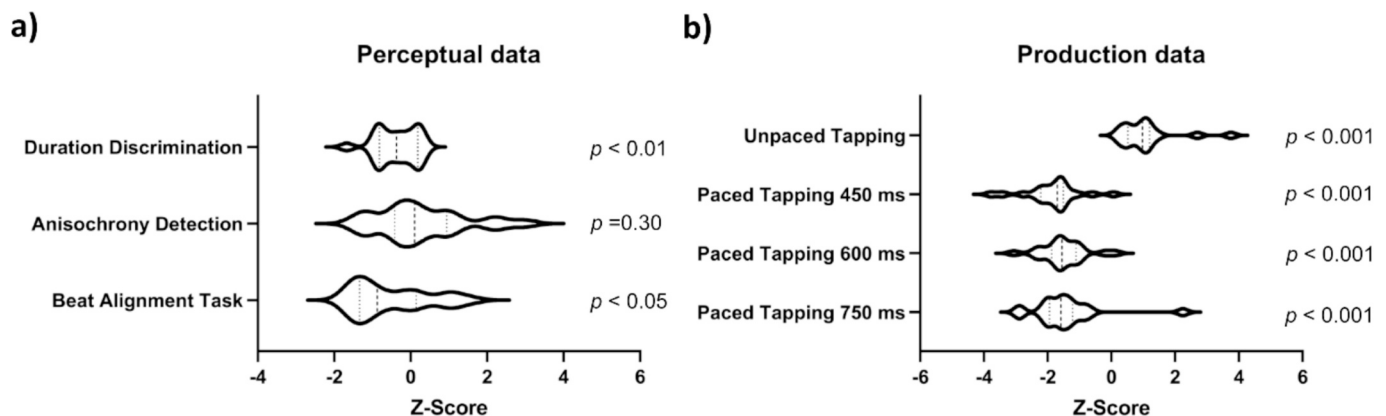
The results obtained from perceptual tasks are presented in Fig. 1a in the form of z-scores. Duration Discrimination and Anisochrony Detection thresholds were normally distributed, however, the BAT  $d'$  was not. The threshold evaluated for Duration Discrimination deviated statistically significantly from the norm,  $t(20) = 3.14, p < 0.01$ . Anisochrony Detection demonstrated more interindividual variability and was not statistically significant,  $t(20) = 1.07, p = 0.30$ . The BAT  $d'$  was statistically significantly different from the normative data,  $W = 139, p < 0.05$ . Therefore, we conclude that pwMS demonstrated some level of impaired perceptual timing when compared to healthy participants.

### 3.2. Production tasks

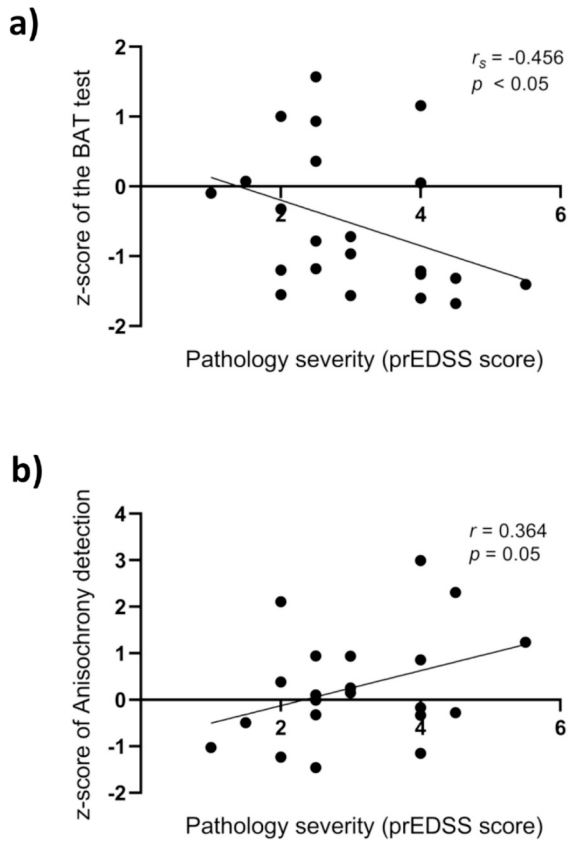
The results obtained from the production tasks are presented in Fig. 1b in the form of z-scores. The logit-transformed vector length of the Paced Tapping at 450 and 600 ms intervals were normally distributed, while the one for Paced Tapping at the 750 ms interval was not. The CV ITI of the Unpaced Tapping task also followed a non-normal distribution. In all four production tasks, pwMS deviated from the normative data (Paced tapping 450 ms:  $t(20) = 9.54, p < 0.0001$ , Paced Tapping 600 ms:  $t(21) = 10.07, p < 0.0001$ , Paced Tapping 750 ms:  $W = 156, p < 0.001$ , Unpaced Tapping:  $W = -153, p < 0.0001$ ). Therefore, pwMS demonstrated disrupted synchronization when compared to healthy participants.

### 3.3. Correlation of timing abilities with disability severity

The results obtained from the correlation between the z-scores of the BAASTA tasks and disability severity in MS evaluated with the prEDSS are presented in Fig. 2. We obtained statistically significant correlations on two perceptual tasks, namely, the BAT (see Fig. 2a):  $rs(20) = -0.46, p < 0.05$ , and the Anisochrony Detection (see Fig. 2b):  $r(19) = 0.36, p = 0.05$ . Duration Discrimination correlation showed a trend:  $r(19) = 0.29, p = 0.10$ . For the production tasks, none of the correlations were



**Fig. 1.** Performance by the current sample in the tasks of the BAASTA compared to the normative data set in the form of z-scores. a) Performance in the perceptual tasks: Duration Discrimination and Anisochrony Detection with tone thresholds were expressed as percentages of the standard duration or interval. BAT performance was expressed as the sensitivity index ( $d'$ ). b) Performance in production tasks: Unpaced Tapping motor variability used the coefficient of variation between intertap intervals and Paced Tapping performance consistency used the logit-transformed vector length.



**Fig. 2.** Perceptual performance in the Beat Alignment Test (BAT) (a) and Anisochrony Detection (b) correlated statistically significantly with disability severity evaluated with the patient-reported Expanded Disability Status Scale (prEDSS).

statistically significant. A trend was observed for Unpaced Tapping:  $r_s(15) = 0.32, p = 0.10$ . In Paced Tapping, results were not statistically significant: 450 ms:  $r(18) = -0.11, p = 0.31$ , 600 ms:  $r(20) = -0.14, p = 0.27$ , 750 ms:  $r_s(17) = -0.23, p = 0.17$ . Therefore, in pwMS, timing impairments were correlated with MS progression for perceptual timing, but not for synchronization tasks.

**3.4. Correlation of timing abilities with fatigue**

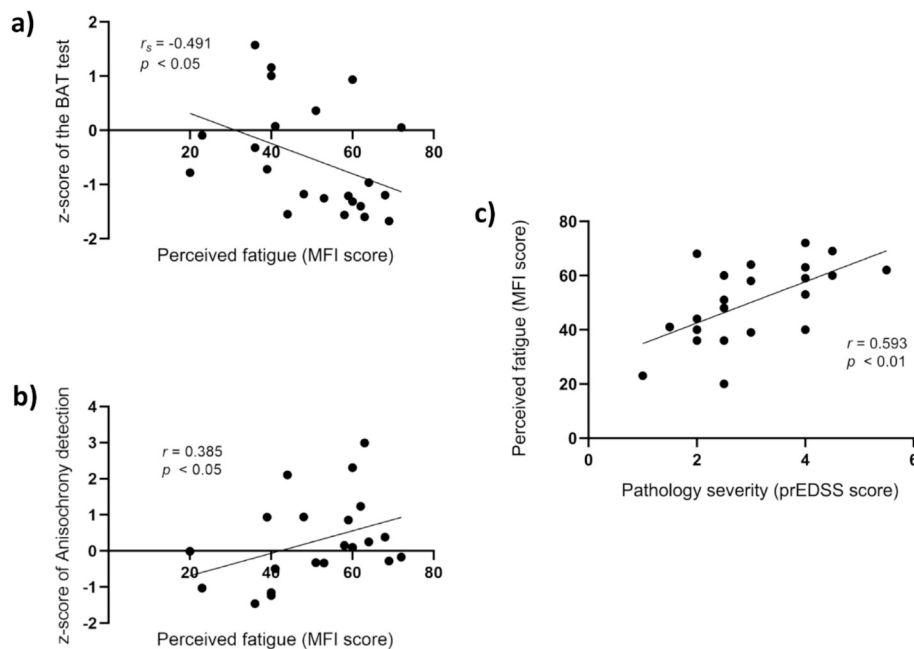
The results obtained from the correlation between the z-scores of the BAASTA tasks and the level of fatigue evaluated with the MFI are presented in Figs. 3a and 3b. We obtained statistically significant correlations for two perceptual tasks when compared the MFI, namely, the BAT (see Fig. 3a):  $r_s(20) = -0.49, p < 0.05$ , and Anisochrony Detection (see Fig. 3b):  $r(19) = 0.38, p < 0.05$ . The correlation with Duration Discrimination was not statistically significant:  $r(19) = -0.03, p = 0.45$ . When compared to the FSMC, the BAT showed a trend:  $r_s(20) = -0.34, p = 0.06$  while Anisochrony Detection ( $r(19) = 0.26, p = 0.12$ ) and Duration Discrimination ( $r(19) = 0.22, p = 0.16$ ) were not statistically significant. Therefore, MS timing impairments were observed concomitantly with fatigue, but the pattern of results was not fully consistent. Control analyses for attentional fatigue were carried out. Excluding participants with high cognitive fatigue (top quartile of the cognitive subscale of the FSMC) did not alter the direction or significance of any adjusted effects.

**3.5. Correlation of fatigue with disability severity**

The results obtained from the correlation between the level of fatigue evaluated with the MFI and disability severity in MS evaluated with the prEDSS are presented in Fig. 3c. We obtained statistically significant correlations between both the fatigue scores and the prEDSS, namely, for the MFI:  $r(20) = 0.59, p < 0.01$ , and the FSMC:  $r(20) = 0.62, p < 0.001$ . This aligns with previous studies (Ezzeldin et al., 2023).

**3.6. Associations with disease duration**

Disease duration showed no statistically significant correlations with



**Fig. 3.** Perceptual performances in the Beat Alignment Test (BAT) (a) and Anisochrony Detection (b), as well as disability severity evaluated with the patient-reported Expanded Disability Status Scale (prEDSS) (c) correlated statistically significantly with fatigue ratings evaluated with the Multidimensional Fatigue Inventory (MFI).

disability (prEDSS,  $r(20) = 0.25, p = 0.13$ ), fatigue measures (MFI,  $r(20) = 0.27, p = 0.12$ ; FSMC,  $r(20) = 0.18, p = 0.22$ ), or timing outcomes (Anisochrony Detection:  $r(19) = -0.24, p = 0.14$ ; Duration Discrimination:  $r(19) = -0.054, p = 0.40$ ; BAT:  $s(20) = 0.19, p = 0.20$ ). Adding disease duration as a covariate to the primary models left all main effects unchanged.

#### 4. Discussion

The main goal of this study was the assessment of perceptual and sensorimotor timing in pwMS. Data from the standardized BAASTA (Dalla Bella et al., 2017; Dalla Bella et al., 2024) revealed that pwMS presented impairments in both the production and perceptual domain when compared to a healthy, age-specific normative dataset. Moreover, we showed that timing ability impairments were negatively associated with disability severity for the perceptual domain, a result that was not observed in the motor tasks.

The main limitation of the current study is the lack of access to individualized brain scans, as pwMS are known to show substantial variability in brain damage locations. Notably, some pwMS demonstrate damage to the CTC tracts (Bonacchi et al., 2022). These cerebellar dysfunctions are linked to worse motor performance in MS (Boonstra et al., 2020). Considering the importance of the CTC in sensorimotor synchronization (Dalla Bella et al., 2015), further demonstrated in cerebellar stroke patients (Antonioni et al., 2025), it cannot be clearly stated that the impairments observed in Paced Tapping across all tempi arose from deep grey nuclei like the BG. Furthermore, little is known about the frequency and severity of hand dysfunction in MS. However, it is commonly impaired in pwMS (Newsome et al., 2019). Considering finger tapping tests are a good marker of MS progression (Gulde et al., 2021), it was expected that pwMS would present impairment in sensorimotor synchronization. Further investigation is needed to fully characterize these findings from a neurological perspective and to better disentangle the timing impairments from the tapping execution. However, the current study serves as a promising starting point.

This is why perceptual tasks offer an interesting source of data, as they remove the motor element of the assessment. pwMS in our study demonstrated impairments in their ability to discriminate two subsequent durations and to detect alignment between the musical beat and a superimposed metronome sound. For both the BAT and Anisochrony Detection these results are in line with the recent results from (Morozumi et al., 2024) in which grey matter lesions and atrophy correlated with the EDSS in motor disability as the pathology worsens, as both tasks are used to evaluate explicit timing and are known to recruit the BGTC network (Criscuolo et al., 2025; Hoddinott and Grahn, 2024). However, these findings need to be interpreted with caution, as we did not directly examine brain imaging data in our study. Motor variability in Unpaced Tapping, a task which revolves strongly on the BGTC network (Schwartz et al., 2011), showed a trend of worsening with the pwMS' degree of disability severity (assessed by prEDSS scores). This also hints at BG damage in pwMS but needs to be interpreted with caution and requires further study to examine the corresponding brain markers.

It was recently demonstrated that fatigue increases in pwMS as disability progresses (Ezzeldin et al., 2023). Using a cross-sectional design, we replicated these findings using two distinct fatigue questionnaires in our Polish sample. Since BG functional connectivity in pwMS is associated with fatigue (Finke et al., 2015; Román et al., 2022), we sought to evaluate whether the observed perceptual timing impairments correlated with fatigue to further link BG deregulation in MS and to offer a stronger interpretation of the timing impairment denoted. As cognitive fatigue leads to slowed reaction times that are not attributable to declines in motor preparation (Peters et al., 2022), it seems relevant in the context of the evaluation of perceptual timing abilities to focus on the cognitive domain as the perceptual tasks, by design, should circumvent motor fatigue. Using the MFI, we observed a significant link

between the BAT and Anisochrony Detection and perceived level of fatigue. However, this relationship was not replicated for the FSMC. Altogether, these standardized questionnaires offer a subjective evaluation of fatigue and are prone to variability. As fatigue is a subjective, unpleasant, and multifactorial construct, it raises questions as to the tool used to quantify it. The FSMC is more binary, as it tries to focus on motor and cognitive domains of everyday life, while the MFI is more versatile and considered an efficient tool to evaluate moderate-to-severe fatigue at a more circumscribed moment (Lim and Son, 2022). This distinction might explain why we observed a correlation between perceptual subtests of the BAASTA with the MFI, but not with the FSMC. Moreover, we used a Polish translation of the FSMC which we created for the purposes of the current study. Although we followed the prevailing standards of questionnaire back-translation, a fully psychometrically adapted version would allow for a more robust measurement. However, this was beyond the scope of our current study. Furthermore, it is important to emphasize that neuronal network alterations, including BG dysfunction, have been the center of interest to better understand fatigue in MS (for a review, see Bertoli and Tecchio, 2020). It is difficult to target an isolated structure as the major driver of fatigue, but we believe that presenting these results brings further insight to the impaired temporal processing in pwMS.

Additionally, although this study's findings need to be interpreted carefully considering our sample size, our reliance on self-report, and the cross-sectional character of our data, they do raise the need to further research links among BG dysfunction, timing impairments, and fatigue. Indeed, are patients not performing well because of the fatigue, or are timing impairments the neurological effect of the disease progression? As stimulation of the motor cortex and corticospinal tract is an effective approach to assess human muscle fatigue (Gruet et al., 2013), it would be relevant to include such an assessment to better dissociate the peripheral effects of fatigue on pwMS from the central ones. Moreover, longitudinal studies appear warranted in light of the current study. Other potential studies in MS could explore the cerebellar contribution to timing and cognition using a more detailed exploration of subdomains of the prEDSS. This would further help to disentangle the cerebellar contributions to timing and cognition and the systems-level coupling of the cerebellum with frontoparietal and BG networks (Caligiore et al., 2017; Schmahmann et al., 2019). We also note that we did not include supra-second intervals in the BAASTA (>1 s), which could represent a useful direction for future work as they heavily tax the fronto-striatal control (Repp and Su, 2013).

The BAASTA has been proposed as a screening tool for individualized rhythm-based intervention (Dalla Bella et al., 2017). Interestingly, a meta-analysis suggests that the application of rhythmic auditory cueing in conventional rehabilitation approaches to enhance gait performance in pwMS is meaningful and should be further studied (Ghai and Ghai, 2018). This type of approach to other brain disorders (i.e., Parkinson's disease) demonstrated the potential to improve walking patterns, but also that auditory cueing can improve timing impairments, as evaluated with the BAASTA (Benoit et al., 2014). It would be relevant to further dissociate individual biomarkers in MS, rhythmical or neurophysiological, in auditory rehabilitation protocols to better provide clinicians and patients with a clear overview of the potential such approach yields for pwMS. Also, as fatigue worsens with MS severity (Ezzeldin et al., 2023), it would be very useful to counteract the effect of fatigue on cognitive performance. The use of transcranial direct current stimulation (tDCS) as a new method in the treatment of fatigue symptoms in patients with MS is garnering increasing interest (Ashrafi et al., 2020; Ferrucci et al., 2014). Considering that this technology can be used safely in a home setting (Antonioni et al., 2024), combining this approach with other forms of trainings would be very interesting to research further.

In conclusion, to our knowledge, this study is the first to demonstrate that pwMS demonstrate impaired timing and sensorimotor abilities.

## CRedit authorship contribution statement

**Szymon Paubinski:** Writing – review & editing, Methodology, Investigation. **Nicholas E.V. Foster:** Writing – review & editing, Validation, Software, Data curation. **Simone Dalla Bella:** Writing – review & editing. **Aleksandra Podlecka-Piętowska:** Investigation. **Monika Nojszewska:** Investigation. **Joanna Rychter:** Investigation. **Joanna Flis:** Investigation. **Natalia Szejko:** Investigation, Writing – review & editing. **Beata Zakrzewska-Pniewska:** Resources. **Piotr Kałowski:** Writing – review & editing, Methodology. **Charles-Étienne Benoit:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization.

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## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CEB & SDB are on the board of the BeatHealth company dedicated to the design and commercialization of technological tools for assessing rhythm abilities such as BAASTA tablet and implementing rhythm-based interventions. Other authors have no competing interest to disclose.

## Data availability

Data will be made available on request.

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