Technology-Assisted Solutions to Enhance Auditory-Motor Synchronization During Walking in Progressive Multiple Sclerosis

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Title: Technology-assisted solutions to enhance Auditory-Motor synchronization during walking in Progressive Multiple Sclerosis.

Running title: Technology-Enhanced Gait Synchrony in PwPMS

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Abstract

Background. Studies show that beat-based cues from music and metronomes benefit gait in persons with progressive multiple sclerosis (PwPMS) during short walking. While useful for controlled assessment, prolonged walking better reflects real-world function. Adaptive beat-alignment algorithms using biofeedback may enhance synchronization and benefit gait dynamics but their effects in PwPMS remain unknown.

Aims. To investigate the effect of walking with and without an adaptive beat-alignment algorithm on synchronization consistency during eight minutes of walking compared to walking in silence, and its effects on gait. We also examined how clinical factors like dynamic balance and cognition affect synchronization consistency during walking with music and metronomes, with and without adaptive beat alignment.

Methods. Healthy controls (HCs) and PwPMS walked for eight minutes under five conditions: silence, music, and metronomes, with or without adaptive beat alignment, at their preferred pace. The algorithm adjusted phase and tempo in real time to restore baseline cadence. We measured synchronization, gait parameters, dynamics, and clinical outcomes.

Results. Twenty-one PwPMS and 18 HCs participated. Adaptive beat-alignment improved synchronization consistency and gait dynamics compared to fixed-tempo walking. Cognitive flexibility and working memory explained 10% of variance in the non-adaptive and 6% in the adaptive conditions, while dynamic balance (40%) impaired synchronization across both algorithms. Auditory cues resulted in slower walking and shorter strides compared to silence.

Conclusion. This study demonstrates the feasibility of adaptive beat-alignment strategies enhancing synchronization consistency and gait dynamics in PwPMS;

however, cognitive flexibility, working memory, and dynamic balance influenced synchronization performance.

Introduction

Walking impairments are prevalent in Multiple Sclerosis (MS) and even more so in progressive forms of MS (1). MS is increasingly conceptualized as a disease spectrum rather than a singular pathological entity, with progressive phenotypes distinguished by pervasive inflammation, pronounced neurodegeneration, and the breakdown of compensatory neural mechanisms (2). It has been proven that several aspects of gait, such as step length, balance and walking speed are affected in MS and even more so in PwPMS (3-6). Persons with MS frequently exhibit diminished motor function and physical performance, accompanied by elevated levels of fatigue during ambulation (7-9). To address these impairments in walking-related rehabilitation, task-oriented training strategies, such embedding walking in auditory-motor synchronization paradigms have been proposed (10-12). During auditory-motor synchronization, a motor rhythm, such as footsteps, aligns with auditory beats in music or metronomes, leading to the steps to synchronize with the beats over time, and reaching a state of synchronization. Previous studies in PwMS have shown that synchronization is feasible in relapsing remitting (10, 13) as well as progressive MS (12) during shorter bouts of three minutes of walking. However, in progressive MS, studies have also shown that motor and cognitive factors do effect synchronization consistency. To elaborate, studies using finger-tapping paradigms have shown that disability level influences synchronization consistency when tapping to metronomes, whereas cognitive functioning plays a greater role in synchronization consistency when tapping to music (14). Yet, during walking, dynamic balance appeared to influence synchronization consistency when participants synchronized to both music and metronomes (15).

Although short walking bouts of three minutes allow for controlled examination of auditory-motor synchronization, extending the duration to prolonged walking more accurately reflects real-world locomotor behavior and thus enhances ecological validity. For example, in daily life, walking is often sustained over longer periods, for commuting, leisure, or routine activities, rather than performed in isolated, brief episodes. Specific to prolonged auditory-motor synchronization studies in MS, one study investigated coupling to auditory stimuli for a duration of 12 minutes, demonstrating that patients synchronization consistency started declining at minute nine when walking to music and at minute six when walking to metronomes (16). Furthermore, the study showed that in the music condition, perceived cognitive fatigue was lower and motivation was higher compared to walking to metronomes.

To harness the full extent of their beneficial impact, technological advancements can be strategically implemented within auditory-motor synchronization paradigms, as a close-loop adaptive biofeedback system. Such systems utilize real-time algorithms to adjust the phase and tempo of auditory stimuli so that they align with the target motor tempo, particularly when a person's movements deviate from that tempo. In other neurological diseases, such as Parkinson’s disease, adaptive beat-alignment algorithms have been used to effectively increase synchronization consistency and promote healthier gait dynamics. In PwMS, gait dynamics have been shown to vary across auditory–motor synchronization paradigms, with music eliciting better gait dynamicscompared to metronome cues (17).

As previously outlined, synchronization consistency during gait is influenced by both cognitive and motor capacities. Persons with progressive forms of MS frequently exhibit a gradual decline in cognitive domains, including information processing speed, working memory, attention, and executive functioning (18). These cognitive impairments are associated with more extensive and chronic neurodegenerative processes, including cortical atrophy and diffuse white matter damage, which are more pronounced in the progressive course of the disease. Furthermore, progressive MS is frequently characterized by substantial motor deficits, notably in dynamic balance and ambulatory function (19), which manifest as alterations in spatiotemporal gait parameters, such as decreased gait speed and reduced step length (20). Therefore, walking at a comfortable pace is likely more suitable for PwPMS, as it accommodates their motor and balance impairments and reduces the risk of fatigue or instability.

Given the above, the current study aims to investigate the difference in synchronization consistency during an eight minute auditory-motor walking protocol at comfortable speed between healthy controls and PwPMS. We chose eight minutes of walking to extend the duration compared to our previous three-minute protocol, while still ensuring feasibility for participants with progressive MS. This longer duration also enhances ecological validity, as it was shown before longer durations of walking mirrors the walking behavior in daily life as compared to shorter durations (21).Additionally, we aim to examine whether an adaptive beat-alignment algorithm can improve synchronization consistency and gait dynamics in PwPMS. We also aim to compare the effects of walking to music versus metronomes under both algorithms (adaptive and non-adaptive) on spatiotemporal gait parameters, relative to walking in silence. Furthermore, we aim to investigate the differences between walking to music and metronomes in terms of synchronization consistency. Finally, we aim to explore how various clinical factors influence synchronization consistency in all conditions.

We hypothesize that the adaptive beat-alignment algorithm will enhance synchronization consistency and gait dynamics over time, with a more pronounced benefit observed in healthy controls compared to PwPMS. Furthermore, we hypothesize that the adaptive algorithm and non-adaptive algorithm would benefit spatiotemporal gait parameters as compared to walking in silence. Additionally, we hypothesize higher synchronization consistency when walking to metronomes compared to music. Last, we hypothesize that clinical factors such as cognitive impairment, self-reported fatigue and motor functioning might negatively impact synchronization consistency.

Methodology

2.1 Participants

This observational study was approved by the Medical Ethical Committees of Hasselt University, the National MS Centre Melsbroek, and the Noorderhart Rehabilitation and MS Centre on January 20, 2021 (B1152020000019), and is registered in clinicaltrials.gov website (registration number: NCT04856384). Participants were recruited using study flyers distributed via social media and in the MS centres and advertisements on MS-related social media platforms such as the University MS Centre (UMSC) and the MS Liga Vlaanderen. Once recruited, they were screened for inclusion criteria. Patients were included if they had been diagnosed with progressive MS (> 1 year before recruitment), having an Expanded Disability Status Scale (EDSS) score below 6.5. Participants were excluded if they had hearing problems, were pregnant, or had cognitive impairment that interfered with understanding the study instructions. The study was conducted at the Rehabilitation and MS centers in Pelt and Melsbroek and the Hasselt University campus in

Diepenbeek. Before the start of the experiment, participants signed an informed consent form.

Figure 1

2.2 Experimental procedure

The study consisted of a descriptive clinical evaluation session followed by the experimental walking session.

2.2.1 Session 1: descriptive clinical evaluation

The first session consisted of descriptive tests, encompassing the collection of general information about the participants, such as demographic information (e.g., education level, etc.), disease-related data (e.g., EDSS) and musical abilities, the latter scored using the Montreal Battery for Amusia (subscale rhythm) (22). Additionally, standardized tests and patient-reported outcomes were employed to assess motor and cognitive functions:

Motor functions. Assessments of walking capacity included 6MWT (23), Dynamic Gait Index (DGI) (24), Timed 25-Foot Walk (T25FW) (25), and Timed Up and Go (TUG) (26). With the Modified Ashworth Scale (MAS) (27) we assessed the muscle tone of the hamstrings, triceps surae and quadriceps, and with the Motricity Index (MI) (28) we evaluated the strength of the hip flexors, knee extensors and dorsi flexors muscles.

Cognitive functions. Participants completed the Buschke Selective Reminding Test (BSRT) (29) for verbal learning and memory, the 7/24 Spatial Recall Test (30) for visual learning and recall, and the Controlled Oral Word Association Test (COWAT) (31) for verbal fluency. The Paced Auditory Serial Addition Test (PASAT) (32) was administered to evaluate sustained attention, auditory information processing speed, and flexibility, and the Symbol Digit Modalities Test (SDMT) (33) to further assess information processing speed, independently of auditory networks. Finally, the Stroop Color Test (34) was used to examine executive functions and inhibitory control.

Self-reported questionnaires. Perceived walking ability was registered using the twelve-item Multiple Sclerosis Walking Scale (MSWS-12) (35). The Activities Specific Balance Confidence Scale (ABC) (36) recorded participants' confidence in avoiding falls when engaging in specific activities that require balance, and the Modified Fatigue Impact Scale (MFIS) (37) the impact of fatigue on motor, cognitive and psychosocial domains. The Hospital Anxiety and Depression Scale (HADS) (38) was employed to detect symptoms of depression or anxiety and the Barcelona Music Reward Questionnaire (BMRQ) (39) provided insights into participants' global sensitivity to music reward.

2.2.2 Experimental session

Participants were equipped with four APDM sensors (OPAL, USA) to measure spatiotemporal gait parameters. Two sensors were attached to the participants' feet and two attached to the wrists. Additionally, they were equipped with the D-jogger, an interactive music player, which was used to deliver the experimental conditions. The D-jogger consisted of headphones, two ankle sensors, and a laptop equipped with a dedicated software (40, 41). When participants reported using a cane in daily life, for standardization during the testing sessions, they were instructed to use a rollator during the experiments. This was done because the cane often makes rhythmic contact with the ground that can be misinterpreted as an additional step. This procedure was applied to minimize potential confounding effects of walking aid use on synchronization outcomes and was a standardization procedure also used in previous studies investigating auditory-motor synchronization in PwMS (10, 12, 13, 16).

First, preferred walking cadence (baseline) was established by asking , participants to walk in silent for three minutes at their comfortable walking cadence. All walking conditions were performed in a rectangular pathway (6x8 meters). Participants then performed five experimental walking conditions, these were walking: in silence, then twice to music and metronomes, once with and once without the adaptive beat-alignment algorithm. All conditions were randomized, and each had a duration of eight minutes. In addition, the target tempo for each condition was set to the participant's preferred baseline walking cadence.

For the non-adaptive algorithm, participants were instructed to walk in synchrony to the auditory stimuli that were fixed at their preferred walking cadence.

For the adaptive beat-alignment algorithms, participants were again asked to walk in synchrony to the auditory stimuli. However, in this case, the system dynamically adjusted the phase and tempo of the stimuli in real time to push the participants steps to their preferred walking cadence (i.e. target tempo), when a deviation from the target cadence were detected.

Table 1

2.2.4 Outcome measures

An overview of the key terminology can be found in Table 1.

2.2.4.1 Primary outcome measures

Synchronization consistency and accuracy of the steps to the auditory beat was assessed using the resultant vector length (RVL) and relative phase angle (rPA) respectively. The RVL indicates the consistency of timing differences between two periodic signals. The timing difference of individual steps relative to their nearest beats, thus the synchronization accuracy, was determined, also known as the rPA. By averaging the sine and cosine coordinates of each phase angle, RVL was calculated. RVL represents how well participants aligned their steps in time to the beats, indicated by a value ranging from zero to one. Higher values illustrate more consistent synchronization, whereas lower values indicate inconsistent synchronization (10).

2.2.4.2 Secondary outcome measures

Spatiotemporal gait parameters: The mean cadence (steps per minute), speed (meters per second), and stride length (meters) were recorded for each walking condition.

Alpha: Detrended fluctuation analysis was applied to compute alpha (42), replicating the methodological approach conducted in our previous work (17). Alpha is introduced as a metric to quantify the anti-persistence of the gait pattern in terms of gait dynamics (42). It is delineated by a numerical value within the range of 0 to 1. A value below 0.5 signifies higher variability in the inter-step-intervals over time. This would indicate a highly variable gait, missing a constant flexible structure of inter-step-intervals: described as anti-persistent. Inversely, values >0.5 indicate low variability in consecutive inter-step-intervals over time, thus a persistent gait pattern which is characteristic of healthy populations (43). In addition, in order to be certain that the results found in the gait dynamics (alpha) were not due to random processes observed within the experimental data, as is methodologically recommended to conduct (44, 45), surrogate time series were created by shuffling each original time series collected for each participant and experimental condition 50 times, resulting in the outcome of alphaShuffled.

2.3 Data-analysis

2.3.1. *Participants*

The descriptive data were tested for normality using the Shapiro-Wilk test. Subsequently, normally distributed data were subjected to analysis using a t-test to explore inter-group differences. For non-normally distributed data, analysis was performed using the Wilcoxon signed-rank test.

2.3.2. *Synchronization parameters*

Before the analyses, the eight-minute spatiotemporal gait data was collapsed in time-windows of two minutes, resulting in four timepoints. A mixed model analysis of variance (ANOVA) was applied for the synchronization outcome measures (RVL and rPA), with group (HC vs. PwPMS) as a between-subjects factor and algorithm (adaptive vs. non-adaptive) and stimuli (music vs. metronome) and Time (minutes 1-2; minutes 3-4; minutes 5-6; minutes 7-8) as within-subjects factors. The residuals of the models were checked for heterogeneity, and those not complying were exponentially transformed, as was the case with RVL.

2.3.3. *Spatiotemporal parameters*

All data from spatiotemporal gait parameters were normalized relative to the participant's mean gait parameter outcome when walking in silence. This percentage change compared to walking in silence was used to perform the analyses. Before the analyses, the eight-minute spatiotemporal gait data was combusted in time-windows of two minutes, resulting in four timepoints. A mixed model analysis of variance (ANOVA) was applied to the spatiotemporal gait parameters (cadence, stride length, and speed) with group (HC vs. PwPMS) as a between-subjects factor and algorithm (adaptive vs non-adaptive), stimuli (music vs metronome) and Time (minutes 1-2; minutes 3-4; minutes 5-6; minutes 7-8) as within-subjects factors.

2.3.4. *Gait dynamics*

Additionally, a mixed model analysis of variance (ANOVA) was applied to the gait dynamics data (alpha) and the surrogate shuffled data (alphaShuffled) with group (HC vs. PwPMS). Silence was added as an additional level of the stimulus factor (music, metronome, silence). The factor time was not included, as the measure was computed over the entire time series.

When interactions were present, a multiple comparisons Tukey's test was further performed as a post hoc test. Missing data accounted for <6% of all data collected due to technical sensor errors . All analyses were performed using SAS JMP Pro 17.0.0 with a significance level set to <0.05.

2.3.5. *Clinical factors*

Univariate regression analyses were performed to examine synchronization consistency across algorithms (adaptive, non-adaptive) and stimulus types (music, metronome). Additional univariate models were used to assess the influence of clinical factors, including TUG, COWAT, SDMT, PASAT and MFIS, on synchronization consistency.

3. Results

3.1 Participants

In total 18 HCs (mean age = 56.50, SD = 2.32) and 21 PwPMS (mean age = 52.42, SD = 2.13) completed the experiment (Figure 1). One PwPMS was removed from the study by visual inspection of the data due to the presence of technical sensor errors. Additionally, one HC was completely excluded from the study due to a technical error. No significant differences were found in age, gender, and education between HCs and PwPMS. Table 2 presents the clinical characteristics of the participants. Two participants reported using a cane in daily life, but were asked to use a rollator during the experimental sessions. In the cognitive domain, significant differences in performance were found in several tests, including the Buschke ($t = 5.19$, $p < 0.0001$), PASAT ($t = -5.46$, $p < 0.0001$), SDMT ($t = -5.52$, $p < 0.01$), Stroop Color Test I (seconds) ($t = 3.42$, $p < 0.01$), and Stroop Color Test III (seconds) ($t = 1.47$, $p = 0.0160$). Furthermore, participants did not differ or show impairments in terms of auditory rhythmic processing as assessed by the Montreal Battery of Evaluation of Amusia (MBEA). Baseline spatiotemporal parameters were significantly different for mean baseline cadence ($t = -3.11$, $p = 0.004$), mean stride length ($t = -2.71$, $p = 0.01$), and mean gait speed ($t = -3.30$, $p = 0.002$) between HCs and PwPMS when walking three minutes at comfortable speed.

Table 2

3.2 Synchronization outcomes

The results for the synchronization outcomes can be found in Figure 2.

3.2.1 Resultant Vector Length

A significant main effect of algorithm ($F(1,504)=15.52$, $p<0.0001$, $\eta2=0.004$)), stimuli ($F(1,504)=4.01$, $p=0.045$, $\eta2=0.003$), and group ($F(1,42)=10.07$, $p=0.002$, $\eta2=0.009$) was found. Results indicate an overall higher synchronization consistency for HCs (mean RVL=0.92) compared to PwPMS (mean RVL=0.71), and when walking to metronome (mean RVL=0.82) compared to music (mean RVL=0.79) conditions. As well as a significantly higher synchronization consistency when walking to the adaptive (mean RVL = 0.86) compared to non-adaptive algorithms (mean RVL = 0.75). No significant interaction effects were found.

Figure 2

3.2.2 Relative Phase Angle

Results show a significant main effect of time ($F(3, 504)=5.63$, $p<0.001$, $\eta2=0.016$), indicating that participants stepped further away from the beat for timepoint one compared to timepoint three (t=-3.10, p=0.011) and for timepoint one compared to timepoint four (t=-3.88, p<0.001). No significant interaction effects were found.

3.2.3 Alpha

Results show a significant main effect of stimuli ($F(1,203)=10.56$, $p<0.001$, $\eta2=0.15$) and algorithm ($F(1,203=16.91$, $p<0.001$, $\eta2=0.18$). Post-hoc analysis indicated a significantly higher alpha, indicating a more persistent gait dynamics when walking to the music (mean alpha = 0.66) compared to metronome (mean alpha = 0.53) conditions and when walking in silence (mean alpha = 0.84) as compared to metronome (mean alpha = 0.53). Moreover, more persistent gait dynamics were seen when walking to with the adaptive (mean alpha = 0.69) compared to non-adaptive algorithm (mean alpha = 0.49) and between walking in silence (mean alpha = 0.84) as compared to walking with the non-adaptive algorithm. The same analysis was performed on the alpha shuffled data resulting in no significant results, confirming that the results obtained for alpha were not due to random processes (see Figure 3).

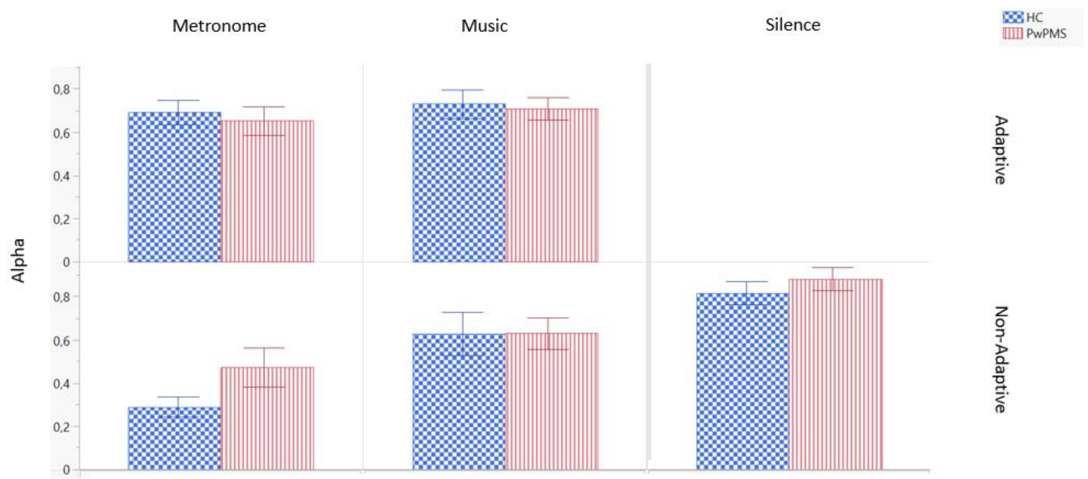

Figure 3

3.2.4 Spatiotemporal parameters

The results for the spatiotemporal parameters can be found in Figure 4.

Gait speed: Results show a significant main effect for algorithm ($F(1,395)=4.80$, $p=0.03$, $\eta 2=0.006$). No interaction effects were found. This result indicated a significant lower gait speed compared to walking in silence for the adaptive algorithm (mean=-4.59) compared to the non-adaptive algorithm (mean=-2.55).

Cadence: Results show a significant main effect of group ($F(1, 60)=4.53$, $p=0.037$, $\eta 2=0.022$). No interaction effects were found. Post-hoc analysis indicated an overall lower cadence compared to walking in silence for HCs (standardized mean cadence=-2.13) compared to PwPMS (standardized mean cadence=-0.36).

Stride length: Results show a significant main effect of algorithm ($F(3,394)=5.86$, $p=0.02$, $\eta 2=0.005$). No interaction effects were found. Post-hoc analysis indicated a significant lower stride length compared to walking in silence for the adaptive (mean=-3.36) compared to the non-adaptive algorithm (mean=-1.53).

Figure 4

3.2.5 Regression analysis of clinical factors on synchronization consistency

Univariate A regression analyses were performed to evaluate the effect of clinical factors (TUG, COWAT, PASAT, SDMT and MFIS) on synchronization consistency for each algorithm (adaptive and non-adaptive) or each stimuli (music and metronomes).

results show:

Non-adaptive algorithm

- Metronomes: TUG ($p<0.001$, RSquare = 0.44), COWAT ($p=0.01$, RSquare = 0.09).
- Music: a significant effect of TUG ($p<0.001$, RSquare = 0.33) and COWAT ($p=0.003$, RSquare = 0.11)

Adaptive algorithm

- Metronomes: A significant effect of TUG ($p<0.001$, RSquare = 0.37) and COWAT ($p=0.03$, RSquare = 0.06).
- Music: : a significant effect was seen for TUG ($p<0.001$, RSquare = 0.46) and COWAT ($p=0.04$, RSquare = 0.05).

4. Discussion

The study investigated prolonged auditory-motor coupling to music and metronomes with and without an adaptive beat-alignment algorithm, to observe its effects on synchronization consistency and gait in PwPMS compared to healthy controls. Results show an overall more consistent synchronization when walking to the adaptive beat-alignment algorithm compared to the non-adaptive algorithm, validating the effectiveness of the adaptive algorithm. Higher synchronization consistency for the adaptive beat-alignment algorithm is in line with previous research testing an adaptive algorithm, in people with Parkinson's disease, with similar objectives and study design: showing better synchronization consistency when walking with the adaptive beat-alignment strategy (46). Another study on interpersonal entrainment, which is the synchronization and coordination between individuals, showed that when walking in synchronization with a virtual robot, greater dynamic stability was obtained when its footsteps were synchronously presented in the form of sounds (47). This could imply that, when synchronization consistency is maintained, better gait dynamics can be adopted and sustained over time. Our present study confirmed these findings, as we found better gait dynamics, in terms of less random inter-step intervals, for an adaptive compared to non-adaptive algorithm (12, 17). This could indicate that an adaptive beat-alignment algorithm promotes better gait dynamics as compared to walking to a non-adaptive beat-alignment algorithm. Furthermore, consistent with other study findings, our work has shown that walking to music results in a more dynamic gait pattern compared to walking to metronomes (12). Walking to music in the adaptive beat-alignment condition resulted in similar gait dynamics as compared to walking in silence. This finding suggests that the use of an adaptive beat-alignment algorithm in combination with music may create a less restrictive auditory environment, allowing for greater movement freedom and more flexible gait patterns compared to walking to a fixed rhythmic cue. Future studies are needed to determine whether repeated gait training using music combined with adaptive beat-alignment can lead to improvements in balance and walking capacity beyond those achieved with music alone or walking without any auditory stimulation.

As hypothesized, results show an overall higher consistent synchronization for HCs compared to PwPMS in all conditions. Given that our sample of PwPMS did not exhibit deficits in rhythm perception, as indicated by performance on the rhythm subscale of the MBEA test, it is unlikely that the observed differences in synchronization consistency are attributable to impairments in rhythm processing. Moreover, our recent work has indicated preserved auditory perception in PwPMS, yet influenced by cognitive functioning (14). Rather, the findings suggest that reduced synchronization consistency may be primarily driven by motor and cognitive impairments in our sample. This is further supported when considering clinical factors, as our findings indicate that both deficits in dynamic balance and cognitive impairment appear to negatively influence synchronization consistency in all conditions when walking to both music and metronomes as seen in our previous research during finger tapping and walking (15). More specifically, dynamic balance seems to influence synchronization consistency in all conditions. Dynamic balance is often impaired in PwPMS due to widespread neurodegeneration affecting sensorimotor control pathways controlling the ability to maintain full stability while the body is in motion (48). Reduced control over the center of mass makes it difficult to synchronize motor actions with auditory cues, as effective auditory-motor integration relies on precise postural adjustments. The influence of dynamic balance on synchronization consistency may also be attributed to the nature of our experimental tasks, which involved a rectangular walking path necessitating 90° turns by participants. These directional changes may have affected synchronization consistency, as effective turning demands the generation of ground reaction forces to reorient the center of mass, an ability commonly assessed in dynamic balance evaluations (49). Our findings suggest that the auditory-motor coupling paradigm employed was conducted feasibly and safely even in individuals with balance impairments. In addition, the results also indicated that walking to music does not negatively affect gait dynamics either. However, as this study did not assess training effects or long-term outcomes, it remains to be determined whether repeated exposure through an interventional program could translate into measurable improvements in gait or balance. Cognitive impairment seemed to differentially relate to synchronization consistency when walking with and without adaptive beat-alignment algorithms. Working memory and cognitive flexibility capacities were related to synchronization in all conditions, yet this effect was larger for the non-adaptive music algorithm. This may suggest that the adaptive beat-alignment algorithm required less working memory and cognitive flexibility capacity, possibly lowering the cognitive load during walking. The impact of these cognitive functions can be explained by the fact that synchronizing motor output to auditory beats relies on temporal processing, the ability to perceive, estimate, and respond to time-based information (50). Literature has shown that this process is fundamentally supported by executive functions such as working memory and cognitive flexibility (51, 52). Working memory plays a critical role in maintaining and manipulating temporal representations, allowing individuals to track intervals, anticipate rhythmic patterns, and coordinate responses accordingly (53, 54). This is particularly evident in auditory-motor synchronization tasks, where accurate performance depends on the ability to retain and update timing information in real time. Cognitive flexibility further contributes to temporal processing by enabling individuals to adapt their internal timing models in response to changes in external rhythms or task demands. Although cognitive impairment, as measured by the SDMT (reflecting information processing speed), and self-perceived fatigue, assessed using the MFIS, were significant predictors in the multiple regression model, they accounted for only a small proportion of the variance. Moreover, their significance did not persist in the single regression models.

Synchronization consistency did not decrease over time across all conditions. One explanation for this could be that the eight minutes of walking at comfortable speed did not induce fatigue in our sample, while the decline shown in previous studies was because of instruction to walk as fast as possible (16). Furthermore, our results demonstrate an improvement in synchronization accuracy (phase angle) over time, suggesting that participants became more accurate in synchronizing as walking progressed. This pattern may be explained by a transient adjustment period at the onset of walking (55). Similar to treadmill walking, PwMS often require an initial phase to stabilize their gait, with the first minute typically showing greater variability before more consistent patterns emerge (56). Thus, the observed increase in synchronization accuracy likely reflects this early adaptation followed by steadier performance.

In terms of spatiotemporal gait parameters, results show that participants walked slower with auditory inputs as compared to walking in silence. One explanation could be attributed to the additional cognitive load imposed by the auditory stimulus compared to walking in silence. Additionally, walking to music, and more specifically for the adaptive-algorithm resulted in a lower gait speed. Music introduces a complex auditory environment that engages multiple cognitive processes, including attention, working memory, and emotional processing (57). This increased demand can divert attentional capacity away from motor control, particularly in individuals with already limited cognitive reserves (58). Furthermore, gait speed and stride length were significantly different between both algorithms. The adaptive beat-alignment algorithm may have introduced perceptible changes in the rhythm of the music or metronome, potentially disrupting participants' internal representation of the beat and creating uncertainty. This disruption could have reduced their confidence in step timing, leading to a more conservative, slower gait as a strategy to avoid missteps or loss of balance. Furthermore, the reduced gait speed and stride length associated with the adaptive beat-alignment algorithm, relative to the non-adaptive condition, may stem from the algorithm's design, specifically it dynamically adjusted the phase of the stimuli in real time to push the participants steps to their preferred walking cadence. In other words, when participants slowed down, the adaptive beat-alignment algorithm responded by altering the phase to regain synchrony; once synchronization was re-established, the algorithm gradually increased the tempo to return to the baseline pace. Additionally, lower stride lengths when walking to auditory beats may function as a compensatory gait strategy to maintain consistent synchronization, aligning with our previous findings that stride length decreased relative to baseline when walking to varying tempi in order to preserve entrainment (12).

Our findings suggest that an adaptive beat-alignment strategy is safe and feasible for PwPMS, even in the presence of balance or gait impairments. By adjusting tempo in real time, it promotes more stable and efficient gait dynamics patterns. The approach is effective with both music and metronome cues and can be applied during prolonged walking to support sustained mobility and engagement. Given that such rhythmic cueing inherently engages attention and temporal prediction processes, it is important to consider the potential cognitive demands associated with this strategy. In our previous work, we observed that cognitive attending during sustained auditory-motor coupling indeed came at a cost, reflected in reduced spatiotemporal gait parameters. To elaborate, the dynamic attending of the beat (59) and forming of temporal predictions constitutes to a form of cognitive load. However, this effect appears to depend on several factors, including the tempo threshold one is synchronizing to, as well as the participants' cognitive functioning (13). In the current context, walking to music can be considered a dual-task situation, involving concurrent cognitive (auditory processing and temporal prediction) and motor (gait control) demands. Furthermore, adaptive algorithms can be embedded in mobile or wearable devices (e.g., apps, smart shoes, or Bluetooth headphones), enabling home-based, self-guided gait training. This supports long-term use, increases therapy dosage, and extends care beyond clinical settings.

Some methodological factors should be considered. Different songs were selected to match various tempos, which might have affected synchronization consistency, familiarity with certain songs could have varied among participants. Additionally, the experiment took place on a 6 m x 8 m rectangular walking path, which may have posed a limitation due to the frequent turns required while walking. Nonetheless, all participants completed their walking trials on the same standardized track under identical conditions. Moreover, the relatively small sample size (n = 21) constitutes a limitation of the study. Nonetheless, we have provided a detailed description of participants' demographic and clinical characteristics, including age, sex, disease duration, and EDSS scores. Moreover, in the current study, participants had a mean 6MWT distance of 362.70 ± 108.26m and a T25FWT time of 8.43 ± 2.24s, both below the established cut-offs for unimpaired walking capacity (446m and 5.5s, respectively) (61), indicating the presence of walking impairments. The mean TUG time (11.45 ± 5.25s) and DGI score (20.17 ± 5.73) further suggest mild to moderate mobility and balance limitations (62, 63). These characteristics are consistent with the clinical profile observed in PwPMS (62, 64), which supports the representativeness of our sample. While this detailed characterization enhances interpretability, caution remains warranted when generalizing the findings, and confirmation in larger and more diverse cohorts. Last, anthropometric data, such as body length and body mass were not collected in the present study. Anthropometric characteristics such as body length and body mass may act as potential confounders in synchronization consistency. Height and leg length could influence stride length and cadence, which in turn may affect the ability to align steps with external rhythms (65, 66). Likewise, body mass may affect gait stability and postural control, introducing variability that could influence rhythmic synchronization (67, 68). Accounting for anthropometric characteristics in future work would enable a more precise understanding of how body dimensions influence gait synchronization.

5. Conclusion

The current study demonstrates the feasibility of using an adaptive beat-alignment algorithm to enhance synchronization consistency and improve gait dynamics in PwPMS. While synchronization consistency was influenced by clinical factors such as working memory, cognitive flexibility, and dynamic balance, achieving high consistency likely reflects effective engagement of the underlying auditory-motor mechanisms, including temporal prediction and motor planning. In this sense, synchronization should be considered a measurable state that indicates engagement of these mechanisms, rather than an outcome in itself. By engaging these mechanisms through consistent auditory-motor coupling, training effects may emerge that are tailored to specific clinical goals, such as improving gait quality (e.g., cadence, stride length), increasing overall ambulation, extending exercise duration, or promoting community-based walking.

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References

1. Motl RW, Goldman MD, Benedict RH. Walking impairment in patients with multiple sclerosis: exercise training as a treatment option. Neuropsychiatr Dis Treat. 2010;6:767-74.
2. Kuhlmann T, Moccia M, Coetzee T, Cohen JA, Correale J, Graves J, et al. Multiple sclerosis progression: time for a new mechanism-driven framework. Lancet Neurol. 2023;22(1):78-88.
3. Willis MA, Fox RJ. Progressive multiple sclerosis. CONTINUUM: Lifelong Learning in Neurology. 2016;22(3):785-98.
4. Feys P, Bibby BM, Baert I, Dalgas U. Walking capacity and ability are more impaired in progressive compared to relapsing type of multiple sclerosis. Eur J Phys Rehabil Med. 2015;51(2):207-10.
5. Zackowski KM, Freeman J, Brichetto G, Centonze D, Dalgas U, DeLuca J, et al. Prioritizing progressive MS rehabilitation research: A call from the International Progressive MS Alliance. Multiple Sclerosis Journal. 2021;27(7):989-1001.
6. Abasıyanık Z, Kahraman T, Veldkamp R, Ertekin Ö, Kalron A, Feys P. Changes in gait characteristics during and immediately after the 6-minute walk test in persons with multiple sclerosis: a systematic review. Physical Therapy. 2022;102(7):pzac036.
7. Dalgas U, Langeskov-Christensen M, Skjerbæk A, Jensen E, Baert I, Romberg A, et al. Is the impact of fatigue related to walking capacity and perceived ability in persons with multiple sclerosis? A multicenter study. Journal of the neurological sciences. 2018;387:179-86.
8. Kalron A. Association between perceived fatigue and gait parameters measured by an instrumented treadmill in people with multiple sclerosis: a cross-sectional study. Journal of neuroengineering and rehabilitation. 2015;12:1-9.
9. Burschka JM, Keune PM, Menge U, Oy UH-v, Oschmann P, Hoos O. An exploration of impaired walking dynamics and fatigue in multiple sclerosis. BMC neurology. 2012;12(1):1-8.
10. Moumdjian L, Moens B, Maes PJ, Van Nieuwenhoven J, Van Wijmeersch B, Leman M, et al. Walking to Music and Metronome at Various Tempi in Persons With Multiple Sclerosis: A Basis for Rehabilitation. Neurorehabil Neural Repair. 2019;33(6):464-75.
11. Moumdjian L, Sarkamo T, Leone C, Leman M, Feys P. Effectiveness of music-based interventions on motricity or cognitive functioning in neurological populations: a systematic review. Eur J Phys Rehabil Med. 2017;53(3):466-82.
12. Vanbilsen N, Moumdjian L, Kinnaert F, Degens B, Moens B, Goetschalckx M, et al. Step to the Beat: Auditory-motor coupling during walking to Higher and Lower Tempi with Music and Metronomes in Progressive Multiple Sclerosis: an observational study. Multiple Sclerosis and Related Disorders. 2024:106152.
13. Moumdjian L, Moens B, Vanzeir E, De Klerck B, Feys P, Leman M. A model of different cognitive processes during spontaneous and intentional coupling to music in multiple sclerosis. Annals of the New York Academy of Sciences. 2019;1445(1):27-38.
14. Vanbilsen N, Feys P, Rosso M, Van Wijmeersch B, Kos D, Leman M, et al. Preserved auditory-motor synchronization during finger-tapping to music and metronomes at various tempi in progressive multiple sclerosis. Frontiers in Neurology. 2025;16:1547573.

15. Vanbilsen N, Moumdjian L, Kinnaert F, Degens B, Moens B, Goetschalckx M, et al. Step to the beat: Auditory-motor coupling during walking to higher and lower tempi with music and metronomes in progressive multiple sclerosis: An observational study. Multiple Sclerosis and Related Disorders. 2024;92:106152.
16. Moumdjian L, Moens B, Maes P-J, Van Geel F, Ilsbroukx S, Borgers S, et al. Continuous 12 min walking to music, metronomes and in silence: Auditory-motor coupling and its effects on perceived fatigue, motivation and gait in persons with multiple sclerosis. Multiple Sclerosis and Related Disorders. 2019;35:92-9.
17. Moumdjian L, Maes PJ, Dalla Bella S, Decker LM, Moens B, Feys P, et al. Detrended fluctuation analysis of gait dynamics when entraining to music and metronomes at different tempi in persons with multiple sclerosis. Sci Rep. 2020;10(1):12934.
18. Ruet A, Deloire M, Charré-Morin J, Hamel D, Brochet B. Cognitive impairment differs between primary progressive and relapsing-remitting MS. Neurology. 2013;80(16):1501-8.
19. Fritz NE, Marasigan RER, Calabresi PA, Newsome SD, Zackowski KM. The impact of dynamic balance measures on walking performance in multiple sclerosis. Neurorehabilitation and neural repair. 2015;29(1):62-9.
20. Givon U, Zeilig G, Achiron A. Gait analysis in multiple sclerosis: characterization of temporal–spatial parameters using GAITRite functional ambulation system. Gait & posture. 2009;29(1):138-42.
21. Gijbels D, Alders G, Van Hoof E, Charlier C, Roelants M, Broekmans T, et al. Predicting habitual walking performance in multiple sclerosis: relevance of capacity and self-report measures. Multiple Sclerosis Journal. 2010;16(5):618-26.
22. Peretz I, Champod AS, Hyde K. Varieties of musical disorders: the Montreal Battery of Evaluation of Amusia. Annals of the New York Academy of Sciences. 2003;999(1):58-75.
23. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. Multiple Sclerosis Journal. 2008;14(3):383-90.
24. Shumway-Cook A, Baldwin M, Polissar NL, Gruber W. Predicting the probability for falls in community-dwelling older adults. Physical therapy. 1997;77(8):812-9.
25. Hauser SL, Dawson DM, Lehrich JR, Beal MF, Kevy SV, Propper RD, et al. Intensive immunosuppression in progressive multiple sclerosis: a randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. New England Journal of Medicine. 1983;308(4):173-80.
26. Podsiadlo D, Richardson S. The timed “Up & Go”: a test of basic functional mobility for frail elderly persons. Journal of the American geriatrics Society. 1991;39(2):142-8.
27. ASHWORTH B. Preliminary trial of carisoprodol in multiple sclerosis. The practitioner. 1964;192:540-2.
28. Demeurisse G, Demol O, Robaye E. Motor evaluation in vascular hemiplegia. European neurology. 1980;19(6):382-9.
29. Hannay HJ, Levin HS. Selective reminding test: an examination of the equivalence of four forms. Journal of Clinical and Experimental Neuropsychology. 1985;7(3):251-63.
30. Gontkovsky ST, Vickery CD, Beatty WW. Construct validity of the 7/24 spatial recall test. Applied neuropsychology. 2004;11(2):75-84.
31. Benton A, Hamsher dS, Sivan A. Controlled oral word association test. Archives of Clinical Neuropsychology. 1994.
32. Gordon A, Zillmer E. Integrating the MMPI and Neuropsychology: A Survey of NAN Membership. Archives of clinical neuropsychology. 1997;4(12):325-6.
33. Smith A. Symbol digit modalities test. The Clinical Neuropsychologist. 1973.
34. Stroop JR. Studies of interference in serial verbal reactions. Journal of experimental psychology. 1935;18(6):643.
35. Hobart J, Riazi A, Lamping D, Fitzpatrick R, Thompson A. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). Neurology. 2003;60(1):31-6.
36. Powell LE, Myers AM. The activities-specific balance confidence (ABC) scale. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 1995;50(1):M28-M34.

37. Multiple. Sclerosis Council for Clinical Practice Guidelines. Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis. Paralyzed Veterans of America Washington, DC; 1998.
38. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica scandinavica. 1983;67(6):361-70.
39. Mas-Herrero E, Marco-Pallares J, Lorenzo-Seva U, Zatorre RJ, Rodriguez-Fornells A. Barcelona Music Reward Questionnaire. Music Perception. 2013.
40. Moens B, Leman M. Alignment strategies for the entrainment of music and movement rhythms. Annals of the New York Academy of Sciences. 2015;1337(1):86-93.
41. Moens B, Muller C, van Noorden L, Franek M, Celie B, Boone J, et al. Encouraging spontaneous synchronisation with D-Jogger, an adaptive music player that aligns movement and music. PLoS One. 2014;9(12):e114234.
42. Hausdorff JM, Peng C-K, Ladin Z, Wei JY, Goldberger AL. Is walking a random walk? Evidence for long-range correlations in stride interval of human gait. Journal of applied physiology. 1995;78(1):349-58.
43. Hausdorff JM. Gait dynamics, fractals and falls: finding meaning in the stride-to-stride fluctuations of human walking. Human movement science. 2007;26(4):555-89.
44. Schreiber T, Schmitz A. Surrogate time series. Physica D: Nonlinear Phenomena. 2000;142(3-4):346-82.
45. Theiler J, Eubank S, Longtin A, Galdrikian B, Farmer JD. Testing for nonlinearity in time series: the method of surrogate data. Physica D: Nonlinear Phenomena. 1992;58(1-4):77-94.
46. Moens B, Van Noorden L, De Wilde W, Lesaffre M, Cambier D, Dotov D, et al., editors. Effects of adaptive-tempo music-based RAS for Parkinson’s disease patients. Proceedings of the ESCOM 2017 conference; 2017.
47. Miyake Y. Interpersonal synchronization of body motion and the Walk-Mate walking support robot. IEEE Transactions on Robotics. 2009;25(3):638-44.
48. Trapp BD, Vignos M, Dudman J, Chang A, Fisher E, Staugaitis SM, et al. Cortical neuronal densities and cerebral white matter demyelination in multiple sclerosis: a retrospective study. The Lancet Neurology. 2018;17(10):870-84.
49. Almajid R, Goel R, Tucker C, Keshner E. Balance confidence and turning behavior as a measure of fall risk. Gait & Posture. 2020;80:1-6.
50. Ivry RB, Spencer RM. The neural representation of time. Current opinion in neurobiology. 2004;14(2):225-32.
51. Peters J, Büchel C. Overlapping and distinct neural systems code for subjective value during intertemporal and risky decision making. Journal of Neuroscience. 2009;29(50):15727-34.
52. Allman MJ, Meck WH. Pathophysiological distortions in time perception and timed performance. Brain. 2012;135(3):656-77.
53. Lewis PA, Miall R. A right hemispheric prefrontal system for cognitive time measurement. Behavioural processes. 2006;71(2-3):226-34.
54. Coull JT, Cheng R-K, Meck WH. Neuroanatomical and neurochemical substrates of timing. Neuropsychopharmacology. 2011;36(1):3-25.
55. Vieten MM, Weich C. The kinematics of cyclic human movement. PLoS One. 2020;15(3):e0225157.
56. Broscheid K-C, Behrens M, Bilgin-Egner P, Peters A, Dettmers C, Jöbges M, et al. Instrumented assessment of motor performance fatigability during the 6-min walk test in mildly affected people with multiple sclerosis. Frontiers in neurology. 2022;13:802516.
57. Koelsch S. Brain correlates of music-evoked emotions. Nature reviews neuroscience. 2014;15(3):170-80.
58. Woollacott M, Shumway-Cook A. Attention and the control of posture and gait: a review of an emerging area of research. Gait & posture. 2002;16(1):1-14.
59. Jones MR. Time will tell: A theory of dynamic attending: Oxford University Press; 2018.

60. Ghai S, Ghai I, Schmitz G, Effenberg AO. Effect of rhythmic auditory cueing on parkinsonian gait: a systematic review and meta-analysis. Scientific reports. 2018;8(1):506.
61. Juhl C, Byskov K, Hvid LG, Dalgas U, Pommerich UM, Skjerbæk AG. Cut-points of the 6-min walk test, the six spot step test, and the timed-25-foot walk test discriminating impaired from non-impaired walking capacity in persons with Multiple sclerosis. Multiple Sclerosis Journal–Experimental, Translational and Clinical. 2025;11(1):20552173251324600.
62. Forsberg A, Andreasson M, Nilsagård YE. Validity of the dynamic gait index in people with multiple sclerosis. Physical therapy. 2013;93(10):1369-76.
63. Sebastião E, Sandroff BM, Learmonth YC, Motl RW. Validity of the timed up and go test as a measure of functional mobility in persons with multiple sclerosis. Archives of physical medicine and rehabilitation. 2016;97(7):1072-7.
64. Quinn G, Comber L, McGuigan C, Galvin R, Coote S. Discriminative ability and clinical utility of the Timed Up and Go (TUG) in identifying falls risk in people with multiple sclerosis: a prospective cohort study. Clinical rehabilitation. 2019;33(2):317-26.
65. Schubert AG, Kempf J, Heiderscheit BC. Influence of stride frequency and length on running mechanics: a systematic review. Sports health. 2014;6(3):210-7.
66. Taylor-Haas JA, Garcia MC, Rauh MJ, Peel S, Paterno MV, Bazett-Jones DM, et al. Cadence in youth long-distance runners is predicted by leg length and running speed. Gait & Posture. 2022;98:266-70.
67. Jeong H, Johnson AW, Feland JB, Petersen SR, Staten JM, Bruening DA. Added body mass alters plantar shear stresses, postural control, and gait kinetics: Implications for obesity. PLoS One. 2021;16(2):e0246605.
68. Ku PX, Osman NA, Yusof A, Abas WW. Biomechanical evaluation of the relationship between postural control and body mass index. Journal of biomechanics. 2012;45(9):1638-42.