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Title: "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"

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Key words: rehabilitation, progressive MS, music, metronomes, walking, auditory-motor coupling

Highlights:

1) Persons with progressive multiple sclerosis are able to synchronise steps to beats in music and metronomes.

2) Best synchronization found at preferred walking cadence and lower (-4%).

3) Synchronisation to metronomes showed more consistency, while music favoured gait dynamics in terms inter-step-interval variability.

4) Dynamic balance impairments impacted synchronisation consistency negatively.

Abstract

Background. Many persons with multiple sclerosis (MS) are confronted with fatigue and difficulties with walking and even more so in persons with progressive subtypes of MS. Task-oriented training, and more specifically in the form of auditory-motor coupling, where persons are asked to synchronise their steps to beats in music and metronomes, is promising. However, it is currently not known whether persons with progressive MS (PwPMS) can synchronise their steps to beats in music and metronomes and if they can adapt their gait to slower and higher tempi.

Methods. The study is a case control study where participants with progressive MS (PwPMS) and healthy controls (HCs) were asked to synchronise their steps during overground walking to beats in music and metronomes at five different tempi, ranging from slow (-8%, -4%), baseline (0%) and high (4%, 8%) while synchronisation, spatiotemporal parameters and gait dynamics were recorded. Mixed model analyses were performed on synchronisation outcome measures and spatiotemporal gait parameters. Additionally, a regression analysis was performed to identify clinical factors such as cognition and motor function influencing synchronisation consistency.

Results. In total, 18 PwPMS (mean age = 52.4, median EDSS = 4.24) and 16 healthy controls (HCs) (mean age = 56.5) were included in the study. Results show that both groups were able to synchronise their steps to beats in music and metronomes, but highest synchronisation consistency was reached for metronome conditions compared to music conditions and for HCs compared to persons with progressive MS. Highest synchronisation consistency for persons with progressive MS was found at -4% and 0%. Additionally, more variability in inter-step-intervals and thus a more anti-persistent gait pattern was found for metronome compared to music conditions. Last, lower performance on the Timed Up & Go Test negatively impacted synchronisation consistency.

Conclusion. PwPMS are able to synchronise steps to beats in music and metronomes. Overall, more consistent synchronisation is seen for metronome conditions. All participants are able to adapt their cadence to all tempi, yet, PwPMS struggle to adapt gait speed to high tempi. Noteworthy, participants walk with more random inter-step-interval fluctuations when walking to metronome compared to music conditions. Last, dynamic balance significantly impacted synchronisation consistency. These results show the potential of using auditory-motor coupling for walking related rehabilitation for PwPMS, however, tempo and auditory stimulation should be carefully considered.

Introduction

In Multiple sclerosis (MS), a chronic inflammatory and neurodegenerative disease affecting the central nervous system (1), walking-related symptoms are present (2). To date, MS has been described as a continuum where progressive subtypes are characterized by widespread inflammation and neurodegeneration together with failure of compensatory mechanisms (3). Progressive forms of MS are shown to lead to more severe walking-related symptoms compared to relapsing and remitting MS (4). Additionally, persons with progressive MS (PwPMS) report more fatigue and walking difficulties on patient-reported outcomes as compared to relapsing-remitting MS (5).

For the rehabilitation of walking capacity, previous studies have predominantly focused on exercise training, primarily targeting relapsing and remitting MS (6-8). Exercise training has been proven to be beneficial in MS showing longer distances walked (9) and higher gait speed (10), however, the effect of exercise training in progressive MS remains unclear and its effects are small in more disabled populations (11, 12).

Task-oriented training, such as walking, has been shown promising in persons with MS (PwMS) by providing intensive multisensory input (vision, vestibular, proprioceptive) (13) and can induce activity-dependent neuroplastic changes, leading towards a direct effect on improving the trained task (13). A specific form of walking-related task-oriented training is auditory-motor coupling. Auditory-motor coupling occurs when entraining a motor rhythm (footsteps) to an auditory rhythm (beats in music or metronomes). In other words, the motor rhythm entrains to the auditory rhythm, so that over time, the steps lock to the beats, establishing a state of synchronisation (14, 15). Studies showed higher consistent synchronisation for metronome compared to music conditions (16). Highest consistent synchronisation for music was seen between +2% and +8% and for metronomes up to 10% (16), suggesting that coupling walking to beats at an individualised pace has the potential to be used for functional gait training in PwMS. Additionally, in order to investigate the dynamic interaction during synchronisation, a study by Moumdjian, Maes (17) explored gait dynamics in the form of fluctuations of consecutive inter-step-intervals, indicating more random fluctuations in gait dynamics (here inter-step-intervals) when walking to metronome compared to music and more when walking to lower compared to high tempi, indicating that the precision between the coupling of steps to music and metronomes differs.

The abovementioned studies only investigated walking to faster tempi, and the majority of participants were diagnosed with relapsing-remitting MS. The novelty of this study is twofold as we introduce the use of slow tempi during walking with inclusion of PwPMS. Slow tempi may be more beneficial as they include longer inter-beat intervals (i.e. duration between one beat and the next) providing more time in order to process each sound. In addition, slower tempi impose challenges to the motor system due to the need for inhibitory control, more postural control and higher gait variability compared to walking at a comfortable tempo (18). Specific to PwPMS, the effect of negative tempi has not been examined, while it was demonstrated that active cognitive control was required to synchronise to tempi higher than 4% (19). In PwPMS reduced neural capacity due to progressed demyelination and loss of neural connectivity, could delay the processing of sounds. Our recent systematic review has indicated the slower processing of sounds in terms of longer latencies in neurological populations, such as MS, compared to healthy subjects (20). Specific for MS, research has indicated impairments in terms of central auditory processing (21). This is due to damage along the auditory pathways from auditory nerve to the cerebral cortex, altering its integrity, showing delayed auditory-evoked potentials in MS (22), which could be more pronounced in PwPMS. Moreover, in PwPMS more severe cognitive impairments are present (23), more specifically in terms of information processing speed, likely compromising the temporal processing and generation of an internal representation of temporal units of rhythmic structures (24). Last, due to progression of the disease, decline in sensorimotor function is seen resulting in a decrease in maximal capacity to activate the muscles and a reduction in number of functioning motor units objectified by reduced amplitude measured by electromyography of the plantar flexor muscle, reducing voluntary control (25). Investigating the difference between music and metronomes during an auditory-motor coupling task is of clinical relevance as studies show more reduced perceived fatigue when exercising to music compared to silence (26, 27).

Given the above, this study aims to investigate the use of slow tempi specific in persons with MS with higher disability, more specifically PwPMS. We first investigate the synchronisation of steps to beats in music and metronomes at high and low tempi compared to baseline cadence in PwPMS compared to HCs. Additionally, the impact of the coupling of the steps to the auditory conditions on spatiotemporal parameters of gait and gait dynamics will be investigated. We hypothesise that PwPMS will synchronise with lower consistency when walking to the auditory stimuli at high tempi compared to the lower tempi due to potential slower processing of the auditory stimuli at high tempi, and that this would be achieved by adapting their gait parameters accordingly to the tempi. We further hypothesise that synchronisation to metronomes will be more consistent compared to music due to the clear nature of the beats seen in metronomes, yet the lower variability in gait dynamics would be expected in the music condition due to the less noticeable errors when walking to music due to the continuous inter-beat-interval structure making the response to the errors potentially less immediate. Last, we hypothesised that factors such as motor impairment and impaired cognition may negatively impact synchronisation consistency in PwPMS.

Methodology

This observational case-control 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.

Inclusion criteria: a diagnosis of progressive MS (> 1 year), absence of exacerbation in the preceding month, an average comfortable walking speed of minimally 0.4 m/s (28) during three minutes of walking and being older than 18 years.
Exclusion criteria: pregnancy, amusia, hearing impairment, or cognitive impairment hindering the understanding of the study instructions. Before the start of the experiment, participants signed an informed consent form.

The experiment consisted of two separate sessions, each lasting a maximum of two hours including rest periods.

Session 1: Descriptive demographic and clinical information

During the first session, descriptive tests were conducted, encompassing the collection of general information about the participants, such as demographic information, disease-related data (e.g., EDSS, education level, etc.) and musical abilities using the Montreal Battery for Amusia (subscale rhythm) (29). Additionally, standardised tests and patient-reported outcomes were employed to assess motor and cognitive functions.

Motor functions. Assessments included the 6-Minute Walking Test (6MWT) (30), Dynamic Gait Index (DGI) (31), Timed 25-Foot Walk (T25FW) (32), and Timed Up and Go (TUG) (33). The Modified Ashworth Scale (MAS) (34) assessed muscle tone and the Motricity Index (MI) (35) evaluated muscle strength of the hip flexors, quadriceps and hamstrings.

Cognitive functions. Participants underwent assessments such as the Buschke Selective Reminding Test (BSRT) (36) for verbal learning and memory, the 7/24 Spatial Recall Test (37) for visual learning and recall, and the Controlled Oral Word Association Test (COWAT) (38) for verbal fluency. The Paced Auditory Serial Addition Test (PASAT) (39) evaluated sustained attention, auditory information processing speed, and flexibility, and the Symbol Digit Modalities Test (SDMT) (23) was used to assess information processing speed. The Stroop Color Test (40) focused on executive function and inhibitory control.

Self-reported questionnaires. Perceived walking ability was measured using the twelve-item Multiple Sclerosis Walking Scale (MSWS-12) (41). The Activities Specific Balance Confidence Scale (ABC) (42) was used to measure participants' confidence in avoiding falls during specific activities and the Modified Fatigue Impact Scale (MFIS) (43) to assess the impact of fatigue on motor, cognitive and psychosocial domains. The Hospital Anxiety and Depression Scale (HADS) (44) detects symptoms of depression or anxiety and the Barcelona Music Reward Questionnaire (BMRQ) (45) provided insight into global sensitivity to music reward.

Session 2: Experimental session

Participants were equipped with APDM sensors (OPAL, USA) to measure spatiotemporal gait parameters. Three sensors were used, with two attached to the participants' feet and one to their sternum. Additionally, they were equipped with the D-jogger. The D-jogger consisted of headphones, two ankle sensors, and a laptop equipped with specialized software (46). The D-Jogger delivered auditory stimuli at varying tempi through headphones, simultaneously assessing gait-music synchronisation and gait dynamics. A music database was utilized, encompassing songs with tempos ranging from 80 to 130 beats per minute. The songs were categorized into six genres: disco, pop, soft pop, pop rock, instrumental and variety. Participants were asked to select one of these genres to walk to, additionally, the system selected a song matched to each specific tempo within the chosen genre. Before the experiment the volume of the sound was adjusted for each participant for comfortable hearing was not changed across conditions. Participants were asked to walk for three minutes to 5 different tempi (-8%, -4%, 0%, 4%, 8%) in two conditions (music and metronomes) in a big rectangle (6x8 meters). They were not informed about the tempo of each trial.

Prior to conducting the experimental conditions, participants were asked to walk three minutes at comfortable tempo on the 'walking path' to quantify baseline cadence, stride length and gait speed. Participants then underwent familiarization of synchronisation to the song "Sanctum" by the artist "Shades of the Abyss", as it has a clear rhythmic structure, was administered. Participants were instructed to synchronise their steps with the beat of the music.

Participants were asked to walk to five tempi for three minutes each in two conditions (music and metronomes). The tempi were -8%, -4%, 0%, 4%, and 8% of their individual baseline cadence. The order of administration of the conditions and tempi within the conditions were randomized. Each tempo entailed walking for five seconds in silence, followed by three minutes with the auditory stimuli, with a sufficient five minutes rest period in between.

Primary outcome measures

The primary outcome measures are related to synchronisation consistency and accuracy. For a detailed overview please see Moumdjian, Buhmann (47).

Resultant Vector Length (RVL)

The RVL is a measure from 0-1 and measures the stability of the Relative Phase Angle (rPA) over time. A steep distribution of the rPAs over time results in a high RVL (maximum value of 1) and would indicate a high consistency of the relative phase angles over time. Conversely, a low RVL (minimum value of 0) suggests an unstable synchronisation with a broad and multimodal distribution of the rPA over time

Relative Phase Angle (rPA)

The rPA is a measure expressed in degrees and measures the timing of the footfall relative to the beat. This can be either negative, footfall before the beat, or positive, footfall after the beat.

Secondary outcome measures

Spatiotemporal gait parameters: the mean and coefficient of variation (CoV) of cadence (steps/min), gait speed (m/s) and stride length (m).

Alpha: Detrended fluctuation analysis was applied to compute alpha (48), 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 (48). It is delineated by a numerical value within the range of 0 to 1. A value below 0.5 signifies more variability in the inter-step-intervals over time. To elaborate, this is indicative of gait being highly variable without a constant flexible structure of inter-step-intervals, described as being anti-persistent. While values >0.5 indicates low variability in the consecutive inter-step-intervals over time, thus a persistent gait pattern which has been associated with healthy gait. 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 (49), 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.

Statistical analysis

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. A mixed model analysis of variance (ANOVA) was applied by backward model building to the primary (RVL and rPA) and the secondary (cadence, speed, stride length, alpha and alphaShuffled) outcome measures (cadence, speed and stride length are reported as percentage changes from the baseline, with group (HC vs PwPMS), condition (music vs metronomes) and experimental tempi (in total 5) as between-subjects factors. A multiple comparisons Tukey's test was performed as a post hoc test when interactions were present. The residuals of the models were checked for heterogeneity, and those not complying were exponentially transformed, which was RVL. Missing data accounted for <6% of all data collected. All analyses were performed using SAS JMP Pro 17.0.0 with a significance level set to <0.05.

Additionally, a linear regression analysis was performed on the effect of cognitive and motor impairments (TUG, EDSS, SDMT, COWAT, PASAT, 6MWT and T25FW) on synchronisation consistency (RVL) as dependent variable.

Results

Participants

In total, 21 PwPMS (mean age = 52.42, SD=2.13) and 18 age-matched healthy controls (HCs) (mean age = 56.50, SD = 2.32) were included in the study. Two participants in each group dropped out, and thus experimental data was analysed on 18 PwPMS and 16 HCs (Figure 1). No significant differences were found in age, gender, and education between HCs and PwPMS.

Table 1 shows the clinical characteristics of the participants. In the cognitive domain significant differences in the cognitive functions were observed in Buschke ($t = 5.19$, $p = <.0001$), PASAT ($t = -5.46$, $p = <.0001$), SDMT ($t = -5.52$, $p < 0.01$), Stroop Color Test I (seconds) ($t = 3.42$, $p < 0.01$), and Stroop Color Test III (seconds) ($t = 1.47$, $p = 0.0160$). When cognitive results are compared to normative data, an impaired score was found for PwPMS on the PASAT only (50) indicating impaired information processing speed and sustained divided attention. Overall, our sample of included participants showed on average impairments in terms of motor functions for the distance walked on the 6MWT (51) and the time needed on the T25FW (52), and showed low scores in terms of spasticity (overall mean = 1.36/5) (53), and muscle weakness (overall mean for each muscle on the motricity index = 26.22/33) where a score of 33 indicates normal strength and a score of 0 indicates no muscle resistance. PwPMS also showed high scores in terms of fatigue. Last, PwPMS overall experience reward when listening to music as measured by the BMRQ. Overall no indication of depression or anxiety was seen.

Baseline spatiotemporal parameters were significantly different for mean baseline cadence ($t = -3.11$, $p < 0.01$), mean stride length ($t = -2.71$, $p = 0.01$), and mean gait speed ($t = -3.30$, $p < 0.01$) between HCs and PwPMS when walking three minutes at comfortable speed. Furthermore, significant differences were observed in the coefficient of variation (CoV) for baseline cadence ($t = 3.06$, $p = 0.0053$), stride length ($t = 4.09$, $p < 0.001$), and gait speed ($t = 2.82$, $p < 0.01$) between HCs and PwPMS.

Insert Figure 1

Insert Table 1

Outcome Measures

A summary of the main effects and interactions observed as a result of the statistically mixed models on the primary and secondary outcome measures are summarised in Table 2.

Primary outcome measures

Resultant Vector Length

In Table 2, a comprehensive overview of both primary and secondary experimental data results is provided.

Significant interactions were found between group*condition*tempi ($F(4,280) = 2.92$, $p = 0.022$) (standard error of the mean (SEM) of RVL =2.72). Post-hoc analyses indicate a significantly higher RVL for HCs compared to PwPMS when walking to the metronome condition at all tempi except for -8% compared to tempi -4%, 0%, 4%, 8%, and the music condition, at tempi -8% compared to -4%, 0% and 4%. Within the PwPMS group, the combination of metronome with tempi -4% or 0% resulted in the best synchronisation consistency (Figure 2A).

Relative Phase Angle

In general, all participants anticipated the beat (see Figure 2B). Significant main effects were observed for tempi ($F(4,269) = 11.00$, $p < .0001$) (SEM=3.18). No significant interactions were found. The post hoc analysis revealed that participants have a significantly lower rPA when walking to the higher tempi compared to the lower and comfortable tempi.

Insert Figure 2

Insert Table 2

Clinical factors impacting RVL

The TUG was a significant factor to remain consistent synchronization over all tempi as revealed by our regression analysis. Results show a significant effect of TUG on RVL for all tempi: -8% ($p=0.025$, RSquare = 0.132), -4% ($p=0.014$, RSquare = 0.196), 0% ($p< 0.01$, RSquare = 0.218), 4% ($p=0.029$, RSquare = 0.155), 8% ($p=0.002$, RSquare = 0.071), indicating that as dynamic balance and walking impairment becomes more pronounced (higher TUG values), the less synchronisation consistency is achieved at all tempi.

Additionally, MFIS (total score), EDSS, 6MWT, DGI, T25FW, COWAT, SDMT PASAT were included as factors but did not show significant results.

Secondary Outcome Measures:

Data presented below are percentage changes of the parameter during the experimental condition compared to the individual baseline performance.

<u>*Speed*</u>

Results show a significant main effect was observed for condition ($F(1,277) = 9.82$, $p = 0.002$) indicative that persons walked at a significantly lower speed with metronomes compared to the music condition. An interaction effect of group*tempi was found ($F(4,277) = 3.72$, $p = 0.006$). Post hoc analysis revealed that HC showed significantly reduced gait speed at lower tempi and increased speed at higher tempi. However, PwPMS showed fewer adaptations in gait speed across different tempi, particularly at higher speeds (Figure 3C).

<u>*Cadence*</u>

Significant main effects were identified for tempi ($F(4,277) = 26.80$, $p < 0.001$). Post hoc comparisons showed that both PwPMS and HCs adjust their cadence by taking less steps to lower tempi and more steps per minute at higher tempi (Figure 3A).

Stride length

A significant main effect of tempi ($F(4,277) = 2.46$, $p = 0.046$) was found indicating that participants decreased their stride length when walking to 0% ($t = -2.95$, $p = 0.004$), as well as when walking at tempi -8% compared to tempi -4% ($t = -2.25$, $p = 0.025$), 4% ($t = -2.17$, $p = 0.031$) and 8% ($t = -2.01$, $p = 0.045$).

Alpha

Significant main effects of condition ($F(1, 269) = 16.91$, $p < 0.001$) and tempi ($F(4, 269) = 2.59$, $p = 0.037$) were observed. There is a significantly higher alpha for music (alpha = 0.53) compared to metronome (alpha = 0.37) conditions ($t = -4.11$, $p < 0.001$), indicating a higher persistent gait pattern for music compared to metronome conditions. Post hoc tests of tempi showed a significantly lower alpha for tempi -4% compared to 8% ($t = -2.33$, $p = 0.021$), tempi 0% compared to 8% ($t = -2.83$, $p = 0.005$) and tempi 4% compared to 8% ($t = -2.19$, $p = 0.029$) (Figure 4).

Results of the mixed model on the alpha when shuffled fifty times revealed no significant main or interaction effects, indicating that results observed on the outcome of alpha were due to the imposed experimental conditions. For completeness, supplemental Figure 1 illustrates the shuffled alpha across tempi, stimuli and group.

Insert Figure 3

Insert Figure 4

Variability in spatiotemporal gait parameters

In Table 3, the significant main effects on the variability of speed, cadence, and stride length are presented, along with additional results from post hoc analysis. No significant interactions were identified. Overall, higher variability in gait parameters was observed for PwPMS compared to HCs both for metronome and to music conditions as seen in Figure 3.

Insert Table 3

Discussion

This study aimed to investigate the effect of auditory-motor coupling to music and metronomes at various tempi and its effect on gait patterns and gait dynamics in PwPMS. Additionally, we explored the effect of motor and cognitive functions on synchronisation consistency.

In total 18 PwPMS and 16 HCs completed the experimental session. The results show PwPMS's overall ability to synchronise to different tempi to beats in metronomes and music. However, HCs showed an overall higher consistent synchronisation pattern compared to PwPMS, indicating higher synchronisation variability in PwPMS. These results are consistent with previous findings where the sample included mostly PwMS with the relapsing- and remitting subtype (16).

Best synchronisation consistency was found for -4% and 0% in PwPMS rather than the higher tempi. Poor synchronisation at high tempi could be due to a general delay in neural processing due to degeneration inducing a general slowness in the motor control of PwPMS and the slower processing of auditory sounds as seen in neurological populations (20). High tempi could also impose more cognitive demands surpassing the cognitive capacity in PwPMS with cognitive impairment (16). Although, cognition was not a significant factor in our regression analysis.

Our regression analysis did reveal that the TUG (dynamic balance control and walking ability) was a significant factor to maintain consistent synchronisation for all tempi for PwPMS. Therefore, not synchronising consistently to higher tempi, which requires a higher motor threshold, can be explained by the dynamic balance impairments seen in our sample PwPMS. Additionally, in our sample, the PwPMS overall show other impairments such as impaired distance walked on the 6MWT and T25F. Noteworthy, the regression analyses did reveal that the other tests were no significant factors. Specific to the experimental tasks, the set-up of our experimental design included a rectangular walking path, where walking included making 90° turns. This may have influenced synchronisation consistency as successful turning requires ground reaction forces that orient the center of mass in the new direction as measured during dynamic balance tests (54). This may also explain why the -4% and 0% were optimal tempi for participants to obtain a high synchronisation consistency. Noteworthy is that -8% produced an opposite effect which indicates that walking too slow also compromised synchronisation as a result of the added strain on the motor control. To elaborate, literature shows that during slow walking, more gait variability is seen, challenging the motor control of gait (18). Additionally, walking at slower speeds increases the cost of walking indicating higher energy expenditure (55).

In terms of gait, the results indicated that PwPMS were adapting their gait parameters according to the different tempi. Mainly, cadence was adapting to the different tempi, in terms of taking fewer or more steps in both groups, while stride length decreased in both groups when compared to the baseline for all tempi. This is most probably a strategy in order to align and synchronise. However, PwPMS in contrary to HCs were not able to change their gait speed, speciality to the higher tempi, as opposed to the HCs. This could potentially be explained by the clinical profile of the PwPMS as they show impaired scores on information processing speed due to decreased neural connectivity. At high tempi, less time is provided between each beat making it more difficult to process and to recruit timely sufficient muscle strength, which is shown by decreased amplitudes in the plantar flexion muscles with progression of the disease, in order to adapt to the tempo.

Overall, higher consistent synchronisation was seen for metronome compared to music conditions. Previously, it has been shown in both healthy individuals and persons with MS with relapsing and remitting forms that synchronizing to metronomes is easier compared to music (16, 56). This can be attributed to the stable and clear pulses of the metronome, making them easier to anticipate, compared to the more complex rhythms often found in music (57). While musical structure is more complex (56), causing an increased difficulty of extracting the temporal information from the music. This is reflected on our results, where PwPMS synchronise best with metronomes compared to music, and more so at 0 and -4% compared to HCs. This can be explained by the progressive pathophysiology due to decreased demyelination and loss of neural reserve seen in PwPMS, impairing both cognitive functioning and motor execution. Thus, explaining why the optimal synchronisation is achieved with metronomes (i.e. stimuli with clearest and easiest processing requirement) and -4% and 0% tempi (i.e. a threshold sufficient to cope with motor demands given the loss in neural connectively). Overall, all participants anticipated the beat which is a common indication of action prediction and anticipation mechanisms at play during auditory-motor coupling.

Yet, regardless of synchronisation consistency, the gait dynamics, in terms of fluctuations in inter-step-intervals, were altered between the music and metronomes. These results are consistent with previous studies, indicating that walking to music resulted in more non-random fluctuations in inter-step-intervals as compared to metronomes (17). This can also be an explanation of the interaction between the audio and the beat. Our results showed that gait dynamics in both groups elicited a more variable and thus anti-persistent gait pattern for metronomes compared to music conditions, indicating more structure in inter-step intervals for music compared to metronomes over time and is consistent with previous work (17, 57). This result can be attributed to the task-related context as metronomes impose faster corrections of gait resulting in non-structured intervals (17). In contrast, with music, we posit that errors in step-to-beat alignment were less noticeable due to the continuous inter-beat-interval structure so that a response to errors may be less immediate but more structured over time. Additionally, higher persistent gait patterns were observed for high tempi compared to comfortable and slow tempi up to -4% of their baseline cadence. However, a more persistent gait pattern, thus more consistent fluctuations in the inter-step-intervals, was seen for -8% of the baseline cadence. This could be due to lower precision of the coupling to the beats at high and very low tempi. Our results iterate previous evidence for the promising use of auditory-motor coupling for task-oriented training in persons with MS (16) now incorporating progressive MS. In addition, we provide evidence for clinical implications in terms of tuning and selection of the ingredients (tempi and stimuli) applied during the auditory-motor coupling strategies in terms of tempi and stimuli enabling personalized therapy. Additionally, the use of adaptations in tempo could be beneficial to train gait adaptability as it is an important feature in daily life where one has to adapt one's speed in order to slow down or speed up according to different life demands. Last, when used in a training intervention, auditory-motor coupling and even cued motor imagery have been found to improve walking in PwMS (58). Moreover, the use of music during rehabilitation has been shown to improve therapy adherence (59) and quality of life (60).

Some methodological considerations apply. The experiment was conducted on a 6m x 8m rectangular walking path which could be a limitation as it induced many turns while walking. However, all walking conditions were conducted in the same standardized track by all participants. Additionally, different songs were used for different tempi. This could have influenced the synchronisation consistency as some songs may have been familiar while others were not. Intensity of the auditory stimuli, which provides fundamental information for perceiving spatial information concerning gait (61), and has been shown to impact the perception of sounds was not adapted. However, volume was adjusted for each participant for comfortable hearing and was not changed across condition. In this study, an unequal distribution of gender is seen. One may argue that gender inequality may have impacted the study results, however, studies have indicated that the effect of gender music perception are negligible and show mixed results (62). Additionally, to our knowledge, no study so far has reported on the effects of gender on synchronisation consistency and accuracy during sensorimotor synchronisation tasks such as finger tapping or walking in adults. However, for verification, the factor of gender was included in the mixed-model analysis, and results showed no main or significant interaction effects. However, it was not our primary goal to evaluate gender differences on synchronisation abilities and the sample size of our study was too small to investigate this potential effect. We do recommend further studies to include an even distribution of males and females or to investigate the effect of gender on synchronisation consistency. Last, no baseline motor function in HCs is are reported in the article as it was not assessed in the experiment. All patient data was compared to normative values existing in literature.

Conclusion

Our results show new evidence that progressive persons with MS are able to synchronise steps to beats in music and metronomes, with best consistency achieved at 0 and -4% of their preferred walking cadence. Synchronization to metronomes resulted in more consistency compared to music, yet walking music favoured gait dynamics. Contrary to healthy controls, PwPMS were not able to increase their gait speed when walking to the higher tempi, yet they were able to adapt to the different tempi by adjust their cadence.

Overall, the results suggest the feasibility of using auditory-motor coupling for walking-related rehabilitation for PwPMS and can be used in rehabilitation practices as it may benefit for walking related training in PwPMS, however, tempo and auditory stimulation should be carefully considered in view of personalization based on impairments presented. High tempi can be used to potentially train gait speed while low tempi could potentially lead to better quality of movements. Additionally, walking to music elicits a more natural like walking pattern while metronomes elicit higher levels of synchronisation consistency.

Declaration of conflicting interests

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