



## Clinical trial

# 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

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## ABSTRACT

**Background:** In Persons with Multiple Sclerosis (PwMS), coupling walking to beats/pulses in short bursts is reported to be beneficial for cadence and perceived fatigue. However it is yet to be investigated if coupling and its effects can be sustained for longer durations, required for task-oriented training strategy in PwMS.

**Aims:** To investigate if PwMS compared to healthy controls (HC) sustain synchronization for 12 min when walking to music and metronome, and its effects on perceived physical and cognitive fatigue, motivation and gait compared to walking in silence.

**Methods:** Participants walked for 12 min in three conditions (music, metronome and silence). The tempo of the auditory conditions was individualized. Auditory-motor coupling and spatio-temporal gait parameters were measured during walking. The visual analogue scale was used for perceived fatigue, and the Likert scale for motivation.

**Results:** 27 PwMS and 28 HC participated. All participants synchronized to both stimuli, yet PwMS synchronized better to music. Overall, participants had lower cadence, speed and stride length when over time all conditions, with an exception of HC, with increasing cadence during the music condition. PwMS perceived less cognitive fatigue, no difference in perceived physical fatigue and a higher motivation walking to music compared to metronomes and silence.

**Conclusion:** 12 min of uninterrupted walking was possible in PwMS in all conditions, while better synchronization, low perception of cognitive fatigue and high motivation occurred with music compared to other conditions. Coupling walking to music could offer novel paradigms for motor task-oriented training in PwMS.

## 1. Introduction

Motor symptoms ranging from muscle weakness and spasticity, to dysfunctions of balance and co-ordination (Motl et al., 2010) are prevalent in persons with multiple sclerosis (Benedict et al., 2011), resulting in walking impairments (Motl et al., 2010). As fatigue and fatigability (Kluger et al., 2013) are prevalent in PwMS, these symptoms may also have an effect on walking. For example, walking-related fatigability has been reported in PwMS with marked disability, seen as a decrease in the walking distance progressively over time during the 6 min walking test (Leone et al., 2016). Task-oriented training is shown to induce activity-dependant neuroplastic changes, having a direct

effect towards improving the task trained (Baird et al., 2018). However, it is reported that mild and moderate subgroups of PwMS rarely walk more than six uninterrupted minutes at a moderate intensity in daily life (Neven et al., 2016), whereas walking for 10 min, in bouts of three times a day, five days a week is the required physical activity recommendations (U.S. Department of Health and Human Services, 2008; Marshall et al., 2009). The question thus remains if PwMS are able to maintain walking continuously for 10 min at tempi higher than their usual walking tempi. In this study, auditory-motor coupling to facilitate walking while reducing perceived fatigue in PwMS is proposed.

Within the context of walking to beats/pulses of the music or metronomes, the process of auditory-motor coupling entails that the steps

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of the walker and the beats/pulses perceived in the auditory-stimuli interact with each other, and with time they lock in a phase-related manner (Repp and Su, 2013; Leman, 2016). At this instance of phase-locking, the motor system and auditory system is in a state of synchronization (Repp and Su, 2013; Leman, 2016). The process underlying the auditory-motor coupling is termed entrainment. It engages reticulo-spinal tracts (Thaut, 2015) and central pattern generators. In PwMS, one study investigated the positive effects of walking to auditory stimuli training on gait and fatigue, yet within the context of motor imagery (Seebacher et al., 2017).

In a previous study, we investigated if PwMS were able to synchronize when walking 3 min to music and metronomes at different tempi, ranging from 0 to 10% in increments of 2%. Our results showed that intended coupling and synchronization was possible and that PwMS perceived less fatigue when walking with music, compared to metronomes (Moundjian et al., 2019a). In this study, we expand our investigation to prolonged walking. Thus, in PwMS and in healthy controls, we investigate if coupling when walking with music and with metronomes, for 12 min at an optimal tempo can be sustained, and its effect on perceived fatigue, motivation and gait in PwMS, when compared to walking for 12 min in silence. We hypothesise that the coupling will allow PwMS to walk for prolonged duration at a higher threshold than when walking at their preferred cadence in silence, while perceiving lower fatigue and higher motivation when walking to music compared to metronomes.

## 2. Methods

### 2.1. Setting and participants

This case-control study was approved by the Medical Ethical Committees of universities Hasselt and Gent (Belgium) and multiple sclerosis centres (National MS center Melsbroek and Rehabilitation and MS center Overpelt). The data presented in this paper is a part of a larger experimental study, registered in clinicaltrials.gov (NCT03281330). We aimed to include 60 participants; 30 PwMS and 30 age and gender matched HC from the MS centers and universities using study flyers. Recruited participants were screened for inclusion criteria, which were: a diagnosis of MS (>1 year), no exacerbation in the last month, an average comfortable walking speed between 0.4 and 1.2 meter per seconds (m/s) (Bohannon and Williams Andrews, 2011) and older than 18 years of age. Additionally, participants were excluded if they were pregnant, or had hearing impairment, or cognitive impairment hindering the understanding of instructions. Once included, the informed consents were signed.

### 2.2. Study design

The study was composed of a descriptive and an experimental session held on different testing days. Fig. 1 illustrates participant flow and experimental procedure.

#### 2.2.1. Descriptive session

**2.2.1.1. Descriptive tests.** These included general demographic, disease information and musical experience. The subscales of rhythm and scale of the Montreal Battery for Amusia was conducted to evaluate amusia. Additionally, the following tests were conducted:

**2.2.1.2. Motor functions.** Timed 25-Foot Walk (25FWT) for walking, the Six Minute Walk Test (6MWT), for walking capacity and endurance.

**2.2.1.3. Self-reported measures.** The MS Walking Scale (MSWS) for walking abilities and the Modified Fatigue Impact Scale (MFIS) for the impact of their fatigue on daily living.

#### 2.2.2. Experimental session

**2.2.2.1. Procedure.** Participants were asked to walk in their comfort tempo in a square of 4.5 by 6 m three times for 1 min, to determine the average preferred walking cadence of the day. This was followed by a familiarisation task, using the song ‘Sanctum’ by the artist ‘Shades of the Abyss’ to instruct participants to synchronize by stepping to the beat. This was repeated with metronomes as well. All participants walked 12 min to three conditions: Music, metronomes, and in silence, with a 15-min rest period between each condition. In the auditory conditions, an individualised optimal tempo was generated, obtained in a previous session (Moundjian et al., 2019a). On average, this optimal tempo was +2.8% and +3.4% of the preferred walking cadence for music and metronomes respectively for PwMS, and 4.6% and 4.9% respectively for HC. The order of conditions were digitally randomized

**2.2.2.2. The equipment.** Participants were equipped with D-Jogger (Moens et al., 2014), an adaptive music player, consisting of a software, headphones (Sennheiser, Germany) and two wireless inertial measurement units strapped at the ankles for measuring cadence and step times (iPod, Apple, USA). The software altered tempo of the beats in the music or the ticks in the metronome to match the individualized tempo. Participants were also equipped with three OPAL wearable sensors (Mobility lab, APDM, USA) two strapped on their ankles, and one strapped on the sternum, to measure the spatiotemporal gait parameters (Washabaugh et al., 2017).

**2.2.2.3. Primary outcome measures. Average relative phase angle (rPA) (expressed in degrees).** This is a measure of the timing of the footfall relative to the closest measured beat and can be expressed as either a positive (footfall after the beat) or a negative (footfall before the beat) angle in degrees.

**The resultant vector length (RVL) (expressed as a value from 0 to 1).** This is a measure of the coherence or stability of the rPA over time. A high RVL indicates more stable synchronization. For details see Moundjian et al., (2018).

**Perceived physical and cognitive fatigue and motivation.** After each experimental condition, participants were asked to rate how they perceived their physical and cognitive tiredness on a visual analogue scale of 0–10 (0 not tired at all and 10 exhaustion), and how motivating it was to walk to the stimuli, using a Likert scale of 1–5 (1 not motivating at all and 5 highly motivating).

**2.2.2.4. Secondary outcome measures. Spatiotemporal gait parameters.** The APDM sensors (OPAL, USA) sensors collected the cadence (steps/min), velocity (m/s), and stride length (m). Distance walked was derived from the velocity and time.

### 2.3. Statistical analysis

The descriptive data was checked for normality by the Shapiro–Wilk test. Normal distributed data was analysed by a *t*-test. Non-normal distributed data was analysed by Wilcoxon signed rank test. For the RVL and spatiotemporal gait measures, an average per three minutes was calculated, followed by calculating the percentage change of the averaged blocks relative to the average of the first three minutes, and used in the analysis. For the rPA measure, the blocks of 3 min averages were used in the analysis (and not the percentage change, in order to interpret the results of this measure). A mixed-model analysis of variance (ANOVA) was applied by backward model building on all outcome measures, with group (HC and PwMS) as between-subjects factor, and conditions (music, metronome, and silence) and timepoints (1–3, 4–6, 7–9, and 10–12) as within-subjects factors. Timepoints were not used when fitting the model for perceived fatigue and motivation outcomes, as this data was collected once per condition. A multiple comparisons Tukey's test was further performed as a post-hoc test on the significant main and interaction effects. All analyses were performed

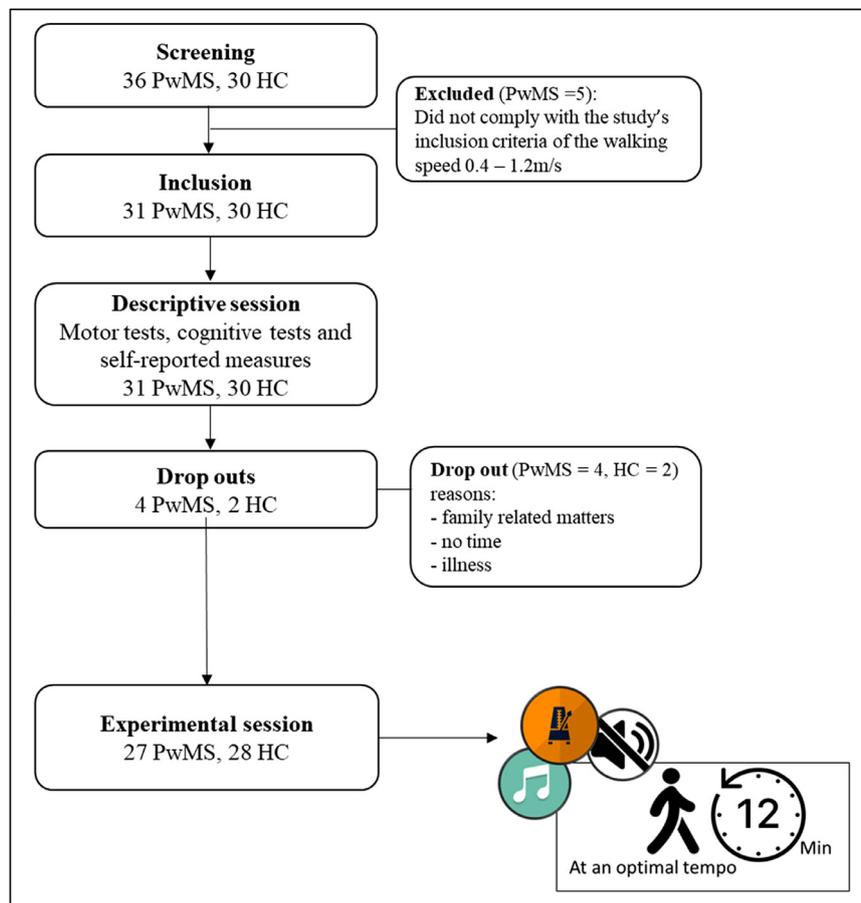


Fig. 1. Flow chart illustrating participant flow and experimental procedure.

using SAS JMP Pro 13.2.0 (copyright SAS Institute Inc., USA). No technical errors occurred with data collection on the primary outcomes measures, however, technical errors occurred when collecting data on the secondary outcome measures (with the OPAL sensors), resulting in missing data from minutes 5–12 of 7% of PwMS and 32% of HC. When missing data were present, the software ignored that data-point when it was used in the model. The *significance* level was set at  $p < 0.05$ .

### 3. Results

#### 3.1. Descriptive session

##### 3.1.1. Participants

Of 66 participants that were screened (36 PwMS and 30 HC), 61 fit the inclusion criteria (31 PwMS and 30 HC) of which 57 participants (27 PwMS and 28 HC) completed the experimental session. No differences in demographic, musical experience or amusia were detected between groups. Significant differences were found between PwMS and HC for the motor tests, with lower scores observed in the MS group. Nine PwMS used an assistive device, and three PwMS used an ankle-foot orthosis (AFO). The perceived impact of fatigue in the physical, cognitive and psychological domains in daily living was significantly higher in PwMS than in HC, and based on the MFIS (Flachenecker et al., 2002), 15 PwMS reported having abnormal fatigue ( $52.73 \pm 8.7$ ). Table 1 shows the descriptive characteristics of study participants.

#### 3.2. Experimental session

##### 3.2.1. Primary outcome measures

3.2.1.1. *Resultant vector length*. Significant main effects were found for conditions ( $F(1266) = 12.53, p = 0.0005$ ) and timepoints ( $F$

(2263) = 503,  $p = 0.0072$ ). The post-test showed that synchronization to music was higher than to metronomes ( $t = -3.54, p = 0.0005$ ), and that synchronization ability dropped in the last 3 min compared to minutes 3–6 ( $t = 3.13, p = 0.0056$ ).

3.2.1.2. *Relative phase angle*. A significant main effect was found for timepoints ( $F(3373) = 3.74, p = 0.01$ ), and a significant interaction effect for group\*condition ( $F(1374) = 12.02, p = 0.0006$ ). The post-hoc tests indicated that participants deviated from  $-30^\circ$  (the norm (Buhmann et al., 2018)) over time ( $t = -2.63, p = 0.0485$ ), and that PwMS stepped closer to  $-30^\circ$  when walking to music compared to when walking to metronomes ( $t = 3.11, p = 0.01$ ).

3.2.1.3. *Perceived physical fatigue*. Significant main effect was found for group ( $F(1,53) = 16.32, p = 0.0002$ ). The post-hoc test showed that PwMS perceived higher fatigue compared to HC ( $t = -4.04, p = 0.0002$ ).

3.2.1.4. *Perceived cognitive fatigue*. Significant main effects were found for group ( $F(1,53) = 6.49, p = 0.01$ ) and conditions ( $F(2106) = 8.77, p = 0.0003$ ). The post-hoc tests showed that PwMS perceived more cognitive fatigue compared to HC ( $t = -2.55, p = 0.01$ ), and that participants perceived walking to music less cognitively fatiguing compared to walking to metronomes ( $t = 4.14, p = 0.0002$ ).

3.2.1.5. *Motivation*. A significant main effect was found for conditions ( $F(2105) = 28.41, p < 0.0001$ ). The post-hoc test showed that all participants perceived walking to music to be more motivational than walking to both metronomes ( $t = -5.36, p < 0.0001$ ) and silence ( $t = 7.26, p < 0.0001$ ).

**Table 1**  
Descriptive characteristics of study participants.

Descriptive	PwMS (n = 31)	HC (n = 30)	t-test (Prob >  t )
<b>Demographic</b>			
Age (years)	53.45 ± 10.61	51.77 ± 11.40	ns <sup>a</sup>
Gender (M/F)	8/23	8/22	ns <sup>a</sup>
Height (cm)	170.81 ± 8.53	170.1 ± 7.95	ns
Weight (kg)	69.10 ± 13.73	71.15 ± 12.39	ns
Education (Years)	13.84 ± 1.92	14.17 ± 2.39	ns <sup>a</sup>
<b>MS specific</b>			
Type of MS (RR/PP/SP)	20/6/4	/	N/A
Years since diagnosis	17.19 ± 9.83	/	N/A
<b>Motor functions</b>			
T25FW (s)	7.81 ± 2.11	5.58 ± 0.80	<0.0001 <sup>a</sup>
6MWT (m) <sup>b</sup>	377.56 ± 105.43	559.46 ± 78.13	<0.0001
<b>Self-Reported Measures for walking and fatigue</b>			
MSWS-12 (100)	50.65 ± 34.37	/	N/A
MFIS Total (84)	35.77 ± 20.23	15.93 ± 15.70	0.0002 <sup>a</sup>
MFIS Physical (36)	18.37 ± 9.39	6.83 ± 7.12	<0.0001 <sup>a</sup>
MFIS Cognitive (40)	15.59 ± 10.16	8.18 ± 6.66	0.0049 <sup>a</sup>
MFIS Psychological (8)	3.17 ± 2.07	1.47 ± 1.59	0.001 <sup>a</sup>
<b>Music and Amusia</b>			
Music experience (Yes)	8	12	ns <sup>a</sup>
<b>Montreal Music Battery of Amusia</b>			
Scale	12.11 ± 1.74	12.66 ± 1.76	ns
Rhythm	13.15 ± 1.77	13.59 ± 1.45	ns

<sup>a</sup> Non-parametric Wilcoxon Signed Rank Test (Prob > |Z|), for the non-normal distributed data. Abbreviations: PwMS- persons with multiple sclerosis; HC- healthy controls; M- male; F- Female; RR- relapsing remitting; PP- primary progressive; SP- secondary progressive; T25FW- time 25 foot walk; 6MWT- 6 min 6 minute walk test; MSWS-12- multiple sclerosis walking scale-12; MFIS- modified fatigue impact scale.

<sup>b</sup> The 6MWT was conducted in a square room with dimensions 4.5 by 6 meters.

**3.2.2. Secondary outcome measures**

**3.2.2.1. Cadence.** Significant main effects were found for group (F(1,55) = 7.82, p = 0.0071) and conditions (F(2349) = 13.38, p < 0.0001). The post-hoc tests showed that HC's had higher cadence compared to PwMS (t = 2.80, p = 0.0071), and that participants had a

higher cadence when walking to metronomes and music as compared to walking in silence (t = 4.63, p < 0.0001 and t = 4.28, p < 0.0001 respectively).

**3.2.2.2. Speed.** A significant main effect was found for conditions (F(2347) = 8.74, p = 0.0002), and a significant interaction effect was found for group\*condition (F(2347) = 4.28, p = 0.01). The post-hoc tests showed that PwMS had lower speed less walking to metronomes compared to walking to music (t = 3.21, p = 0.0042) and in silence (t = 3.95, p = 0.0003).

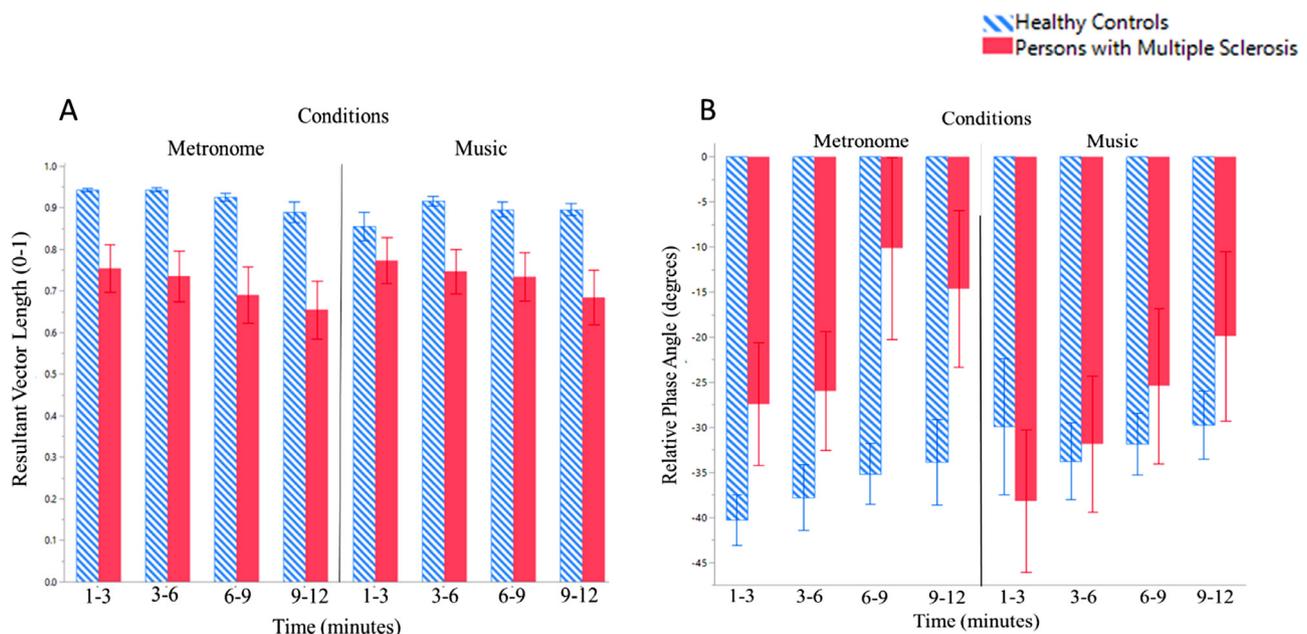
**3.2.2.3. Stride length.** A significant main effect was found for conditions (F(2348) = 7.09, p = 0.001) and a significant interaction effect was found for group\*conditions (F(2348) = 4.31, p = 0.01). The post-hoc test indicated that in PwMS took more smaller steps when walking to music compared to when walking to metronomes (t = 5, p < 0.0001).

Figs. 2–4 illustrates the results above graphically. Table 2 shows the averages, standard deviations and statistics of the distance walked in 12 min across conditions.

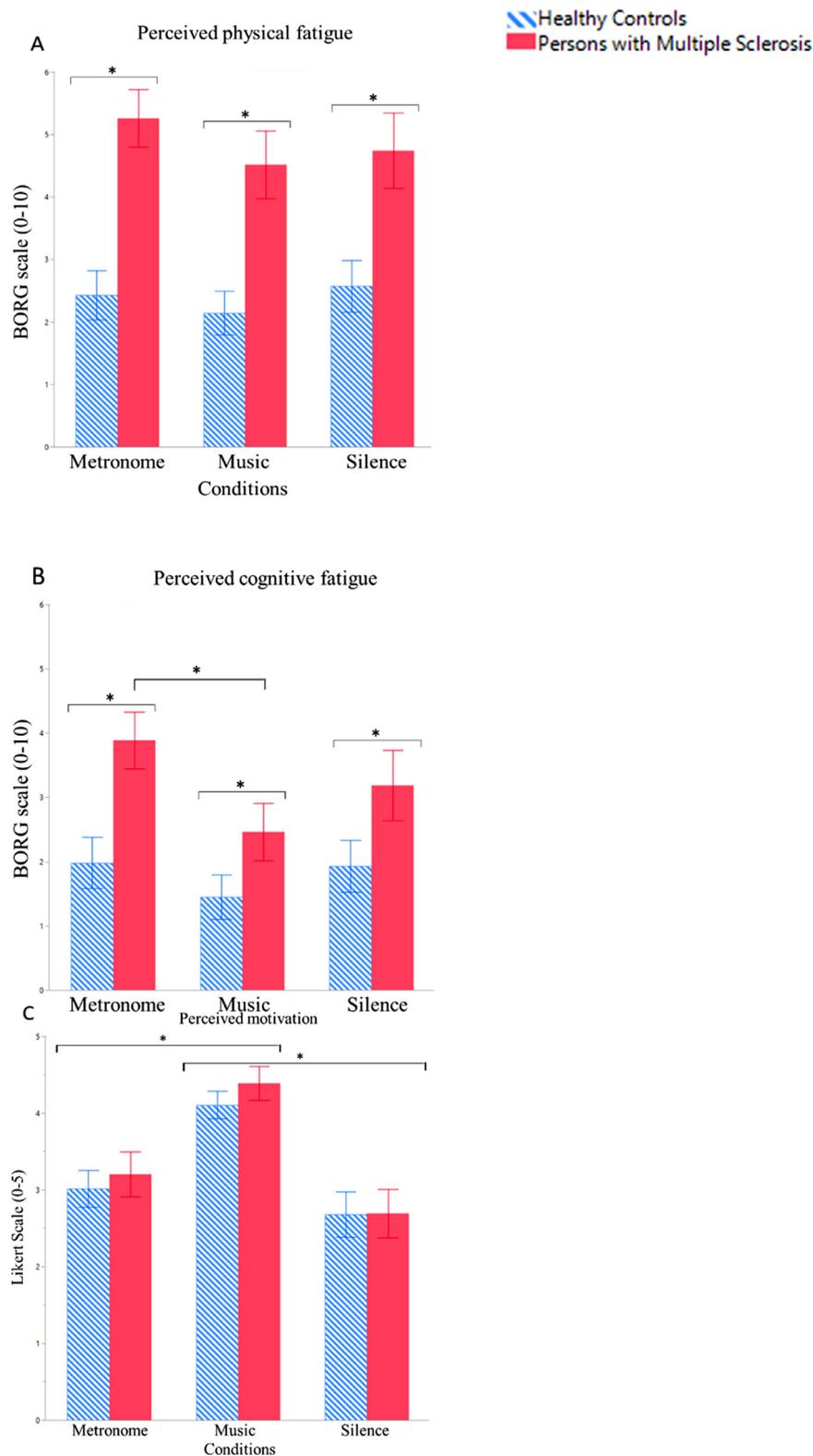
**4. Discussion**

In this study, we investigated if persons with multiple sclerosis (PwMS) compared to healthy controls (HC) were able to couple their steps to beats/pulses in music and metronomes for 12 min continuously at an optimal tempo and thereafter, if entraining had an effect on the perceived fatigue and gait compared to when walking in silence.

All participants synchronized to both stimuli, however PwMS synchronized better when walking to music, compared to metronomes. These results were contrary to results from our previous study, showing that PwMS synchronised better to metronomes compared to music when walking for a shorter 3 min duration at tempi 0–10% in increments of 2% (Moundjian et al., 2019a). Therefore, the choice of music as the auditory stimuli is proposed when coupling for longer periods in PwMS. Moreover, when walking to music, all participants anticipated the beats; which is an indication of auditory-motor coupling. However, the coupling decreased significantly in the last 3 min of walking to both stimuli. When auditory-motor coupling occurs, it means that participants entrain: They align their steps with the beat/pulse according to a



**Fig. 2.** A-Resultant vector length and B- relative phase angle, when walking to metronome and music for 12 min in Persons with Multiple Sclerosis and Healthy Controls. Data is shown per average of three minutes. Mean and standard errors are shown.

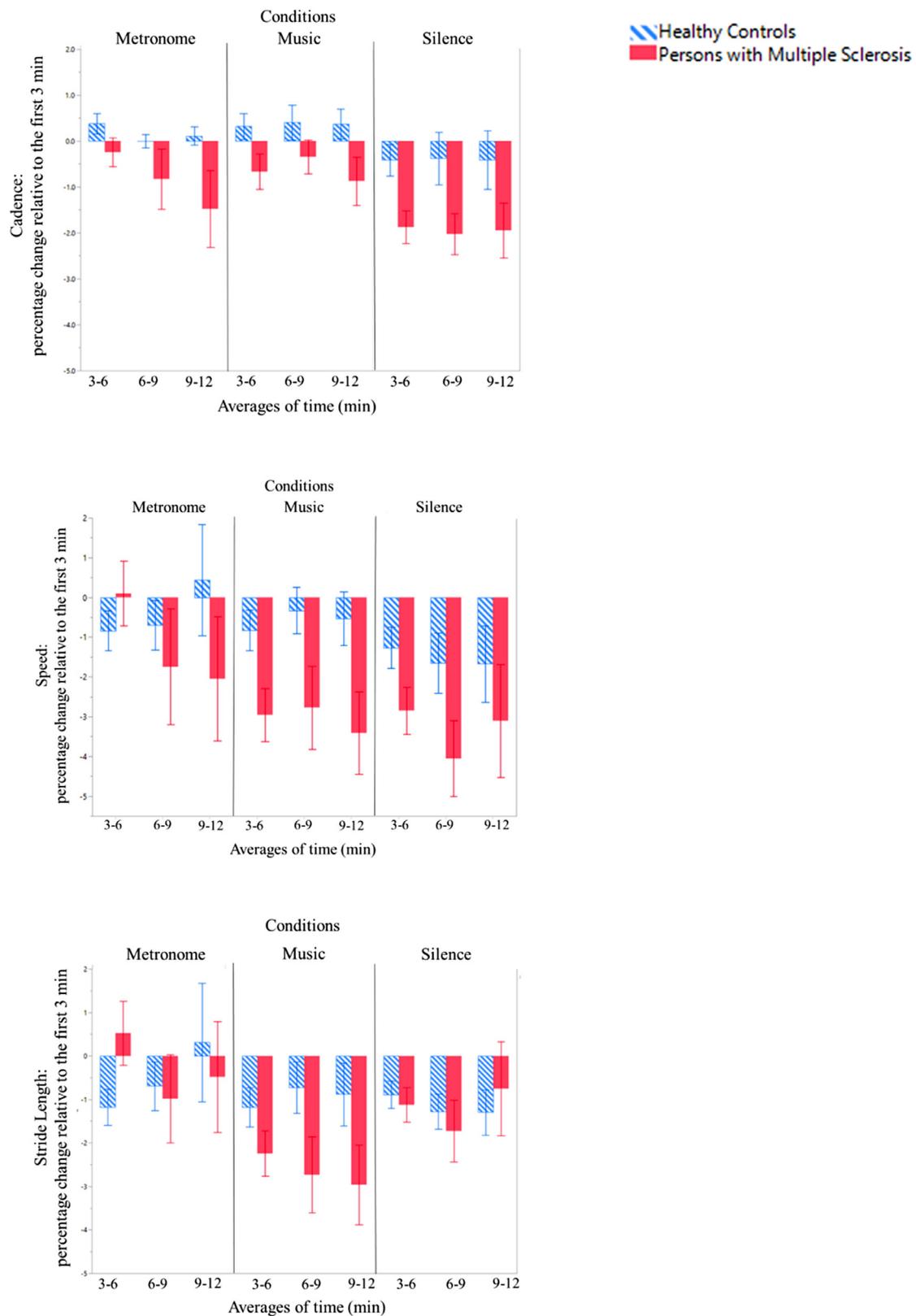


**Fig. 3.** A-Perceived physical fatigue B- perceived cognitive fatigue C- perceived motivation when walking to metronomes, music and in silence for 12 min in Persons with Multiple Sclerosis and Healthy Controls. Mean and standard errors are shown.

temporal prediction model that minimizes the timing errors between steps and beats/pulses. Given the fact that the optimal tempo was on average about 3% above the preferred walking cadence, it is likely that the entrainment required cognitive attending (Moundjian et al., 2019b). We suggest that this attending served as a cognitive load for our participants, as seen by the reduced spatio-temporal gait

parameters. However, this is by no means a negative attribute to the coupling.

To elaborate, PwMS reported less perceived cognitive fatigue when walking to music compared to both metronomes and in silence, and perceived similar physical fatigue levels across the conditions. As illustrated in Fig. 5, the study results suggest that sustained coupling to



**Fig. 4.** Cadence, speed and stride length when walking to the experimental conditions (metronome, music and silence) in Persons with Multiple Sclerosis and Healthy controls. The results are shown as percentage change per three minute averaged blocks relative to the average of the first three minutes Mean and standard errors are shown.

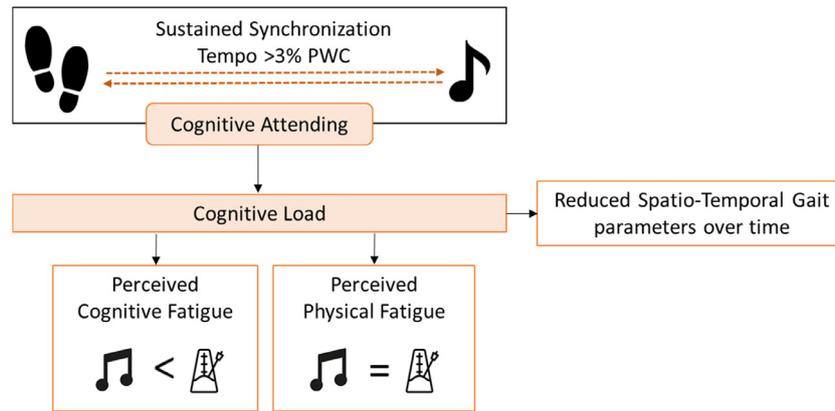
music required less unconscious attention compared to sustained coupling to metronomes, yet similar physical effort. Moreover, music consists of complex sound-arrangements (of timbre, pitch, rhythm, articulation, metre) compared to ambiguous and repetitive ticks found in

metronomes, which appeal to the biosocial nature of human corporeal expression (Leman, 2016; Buhmann et al., 2018; Leman et al., 2013) and therefore facilitates auditory-motor processing. Therefore, music, more than metronome stimuli, engages extensive cortical and

**Table 2**

Distance walked in 12 min with metronomes, music and in silence by Persons with Multiple Sclerosis (PwMS) and healthy controls (HC).

Conditions	PwMS	HC	Mixed Model ANOVA ( <i>p</i> value)		Timepoint	Interactions
			Group	Condition		
Silence	619.9 ± 192.9	885.5 ± 96.0				
Metronome	615.8 ± 230.0	942.2 ± 140.6	< 0.0001	< 0.0001	0.0179	Group*Stimuli 0.00009
Music	628.8 ± 207.3	917.2 ± 121.8				



**Fig. 5.** A graphical illustrative summary of cognitive attending during sustained coupling to music and metronomes on perceived fatigue when walking at an average tempo of 3% higher than the preferred walking cadence.

subcortical brain networks (Merchant et al., 2015), and thus has increased activation pattern as more complex rhythms are perceived (Chen et al., 2008).

The figure illustrates that the process underlying sustained synchronization called entrainment requires cognitive attending. Although cognitive attending resulted in a cognitive load seen by the reduced spatiotemporal gait parameters when walking to both stimuli, differences in perceived fatigue was observed. When walking to music, PwMS perceived significantly lower cognitive fatigue and no significant difference of perceived fatigue compared to walking to metronomes. The results are suggestive that sustaining coupling to music requires lower unconscious attention compared to sustaining coupling to metronomes.

Overall, HC walked more distance than PwMS across all conditions, a result that is in line with current literature (Goldman et al., 2008). One case-control study, asking their PwMS participants to walk for 12 min, found two trends on the distance walked, based on the level of MS impairment (Burschka et al., 2012). The first was a constant linear decrease of distance walked over time in PwMS with moderate impairment, and the second, a slight decrease in distance between the first four minutes, that was then kept constant over time in PwMS with mild impairment (Burschka et al., 2012). Our PwMS did not exhibit motor fatigability during walking at a comfortable speed (Leone et al., 2016). With the above in mind, we can say that our participants with both mild and moderate MS maintained a constant distance over time in all three conditions. Our results are in line with the results found in the study of Burschka et al. (2012) for the mild impaired PwMS, but contrary for the moderate impaired PwMS. However, their participants were instructed to walk as fast as possible, while in our study, participants walked at their optimal tempo in the auditory conditions and at their comfortable tempo during the silent condition.

Regarding the cadence, compared to the first three minutes, HC slightly increased their cadence and got more into phase-locking in the music and metronomes conditions compared to the silent condition, while PwMS slightly decreased their cadence towards the end of the 12 min, compared to the first three minutes. As PwMS walked at tempi higher than their comfortable walking cadence (+2.8% and +3.4% with music and metronomes respectively) the decrease of cadence could indicate that they returned to their usual walking cadence. To our

knowledge, only one study investigated the immediate effects of cues on gait in PwMS (Baram and Miller, 2007). Contrary to our results, they reported an increase of spatio-temporal gait parameters, yet the method of cue application was different: the participants received an auditory cue which corresponded to their steps in a closed loop, while our participants were asked to follow the beats/pulses. Thus, direct comparisons cannot be made. For future work however, we recommend finding methods to instruct patients to maintain their stride length and increase speed together with increasing cadence during the coupling. Lastly, it is worthwhile to mention that a study conducting an intervention of four weeks with an experimental condition of motor imagery using music and metronomes, reported improvements of the spatiotemporal parameters of gait compared to their corresponding control conditions (Seebacher et al., 2017). Although we cannot directly compare our results with their study, we can endorse that the underlying mechanisms of improved spatio-temporal parameters were due to the auditory-motor coupling, even within the context of imagery.

Some methodological limitations apply. Our walking track was 4.5 by 6 m square is considered as a limitation to our study as it induced many turns. However, we believe that these turns did not have a substantial impact on the results as all walking conditions were conducted in the same standardized track by all participants.

## 5. Conclusion

This study provides an insight of the components needed for motor task-oriented training strategies in the context of auditory-motor coupling. The use of music as an auditory stimulus is advised, as PwMS sustained synchronization for 12 min, with low cognitive fatigue and high motivation.

## Conflict of interest statement

Authors declare no conflict of interest.

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