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Maaseik, 05-06-2018 C.G.

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RESEARCH CONTEXT

With a prevalence of 108 patients per 100.000 persons in Europe, multiple sclerosis (MS) is one of the most common neurological disorders and leading cause of disability in young adults (Koch-Henriksen & Sorensen, 2010; WHO, 2013). Cognitive and motor impairments are frequently present in persons with MS (PwMS), which could be the cause of different gait problems (Conklyn et al., 2010; Givon, Zeilig, & Achiron, 2009; Kelleher, Spence, Solomonidis, & Apatsidis, 2010; Leone et al., 2016; Martin et al., 2006). Fatigue and gait disturbances are the most common symptoms in PwMS (Kelleher et al., 2010; MacAllister & Krupp, 2005). Around 70% of the PwMS report that gait disturbances are the most challenging aspects of the disease. This is not only because it affects mobility, it also has a negative impact on emotional health(Larocca, 2011).

Auditory cueing and rhythmical cueing has been positively used for gait rehab in patients with Parkinson Disease and stroke. In these populations, improvements were found on velocity, stride length and cadence (Arias & Cudeiro, 2010; In Mo Park, 2010; Lim et al., 2005; Thaut et al., 2007; Thaut et al., 1996). It is possible that musical rhythm has the same effect on gait for PwMS.

This project is a duo-master thesis and part of a broader interdisciplinary research project “The effects of motor entrainment to music and sounds on the gait movement quality and perceived fatigue in persons with MS”, which is the PhD project of Lousin Moumdjian. The PhD project is for 50% funded by the University of Ghent, music research center IPEM, and 50% by the BOF grant from University of Hasselt. IPEM is a music research center focused on embodied music cognition and expressive music interaction. An observational study was done under supervision of promotor prof. dr. Peter Feys and co-promotor Lousin Moumdjian at research centre REVAL, university of Hasselt, Diepenbeek. For this observational study, a central format was applied. Data collection was done by two master students and co-promoter Lousin Moumdjian, which took place at REVAL Diepenbeek, MS & Rehabilitation Clinic Overpelt and MS Centre Melsbroek. Analyses and writing of the thesis was done by the two students together and verified by promotor prof. dr. Peter Feys and co-promoter Lousin Moumdjian. The research question of this project is defined in consultation with the two master students and co-promoter Lousin Moumdjian.

ABSTRACT

Background

Gait disturbances and fatigue are two of the most prevalent symptoms in persons with multiple sclerosis (PwMS). Metronome cueing and music could have a positive effect on these because of an entrainment process.

Objectives

Assess the possible effects of prolonged entrainment in different conditions – music, metronome and silence – on gait parameters, synchronisation, fatigability during walking in PwMS compared with healthy controls.

Participants

31 PwMS and 30 healthy controls were recruited.

Measurements

During the experimental session, participants had to walk on an optimal tempo during three different conditions, e.g. silence, metronome and music, each condition lasted 12 minutes. Data was recorded through APDM sensors and the D-jogger system. Primary outcome measures were phase angle, resultant vector length and the spatiotemporal parameters of gait – speed, stride length and cadence.

Results

PwMS had a significantly lower resultant vector length in the metronome condition compared to healthy controls ($p=0.0078$). This difference was not found during the music condition. During the metronome condition, the phase angle was significant more directed towards zero degrees within PwMS ($p\leq.0001$) compared to the music condition. The resultant vector length was significantly higher within PwMS ($p=0.0253$) during the music condition compared to the metronome condition. In PwMS, cadence was significantly increased ($p\leq.0001$) and stride length was significantly decreased ($p=0.0141$) with music compared to silence.

Conclusion

Synchronisation occurs more in music than in metronome. Also, perceived cognitive fatigability would be lower with music. For the perceived motor fatigability, the type of stimuli implies not to be important. In contrast to performance motor fatigability, here a metronome should be used during a trial shorter than six minutes. In trials longer than six minutes, the type of stimuli seems not important anymore. Auditory stimuli appear to have no influence on speed and a negative influence on cadence and stride length in PwMS.

INTRODUCTION

Multiple Sclerosis (MS) is an immune-mediated demyelinating and/or inflammatory disease in focal areas of the brain and spinal cord (Trapp & Nave, 2008). Gait disturbances and fatigue are the most common symptoms in PwMS, with a prevalence of 85% for gait disturbances and 83% for fatigue (Kelleher et al., 2010; MacAllister & Krupp, 2005; Minden et al., 2006). A reduced velocity, stride and step length, ankle plantar flexion, propulsive force and increased double-support time are the most common impaired gait parameters in PwMS (Conklyn et al., 2010; Givon et al., 2009; Kelleher et al., 2010; Leone et al., 2016; Martin et al., 2006). Fatigue is described as: "a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" (MacAllister & Krupp, 2005; Severijns et al., 2017). One category of fatigue is fatigability, which is an unstable feeling of "weariness" and occurs according to changes in activities (Kluger, Krupp, & Enoka, 2013). When fatigability is present, it will affect walking endurance and walking distance. Together with the gait impairments this influences daily activities, emotional health, work –and social life (Larocca, 2011).

To increase walking distance and improve spatial-temporal gait parameters and fatigability, auditory stimulation can be hypothesized as a rehabilitation strategy. Music is assumed to activate the dopaminergic mesolimbic system, which is connected to fatigue and improves attention, executive functions, memory, motivation, and mood (Zatorre, Chen, & Penhune, 2007). Also cardiovascular and endocrine responses are induced by the use of music (Sihvonen et al., 2017). The dopaminergic mesolimbic system is not the only system activated by music, a strong connection between auditory areas and motor areas is suggested (Rossignol & Jones, 1976; Thaut et al., 1996; Thaut, McIntosh, McIntosh, & Hoemberg, 2001). Especially rhythm activates the basal ganglia, cerebellum, dorsal lateral premotor cortex, supplementary motor area, the right primary auditory cortex, bilateral superior temporal gyrus, the right inferior temporal gyrus, somatosensory areas and several subcortical limbic areas (Alluri et al., 2012; Sarkamo, Tervaniemi, & Huotilainen, 2013; Zatorre et al., 2007). So music interventions could have an impact on fatigue and gait disturbances, because there is a stimulation of impaired pathways, such as the dopaminergic, histaminergic, serotonergic and motor pathways.

In rehabilitation, metronome cueing is used through rhythmic neurologic music techniques such as rhythmic auditory stimulation. With metronome cueing, movements are synchronized to a fixed beat provided by auditory stimuli (Sihvonen et al., 2017). Synchronisation refers to two oscillating bodies, which move in stable rhythmic cycles and is measured through the phase angle and resultant vector length (Moumdjian, 2018; Thaut, 2015). For example, while walking, each step

would be placed closer to the fixed beat. When synchronisation occurs, a mental representation of movement timing develops by auditory stimuli. Through this mental representation, tempo deviations could be fine-tuned (Schaefer, 2014). However, research has shown that there are more affected spatial-temporal parameters in PwMS (Conklyn et al., 2010; Kelleher et al., 2010; Leone et al., 2016). For an affect on more gait parameters, a more abundant stimulus, such as music, is needed. More mental representations would arise and more spatial-temporal gait parameters, e.g. stride length, velocity, cadence, and double support time, could be related to different aspects of the music, e.g. rhythm. Activating and adjusting these mental representations occurs through entrainment, which is the process to synchronisation (Leman et al., 2013).

Previous studies have reported that the application of metronome or music in stroke and Parkinson Disease results in an improvement of the participant's gait parameters, such as gait velocity, stride time, etc. (Cha, Kim, Hwang, & Chung, 2014; Conklyn et al., 2010; de Bruin et al., 2010; Sarkamo et al., 2008; Schauer & Mauritz, 2003; Thaut et al., 2007). In PwMS, the application of metronomic cueing could have a positive influence on stride length, stride time, double support time, cadence and gait speed (Conklyn et al., 2010; Shahraki, Sohrabi, Taheri Torbati, Nikkhah, & NaeimiKia, 2017). Musical feedback appears to increase force and decrease perceived exertion during the performance in healthy controls (Fritz et al., 2013). Music interventions appear to be promising for PwMS to decrease fatigue and fatigability. Until recently, this intervention has not been applied on trials that last longer than six minutes and no comparison between music and metronome for the influence in PwMS was made.

Therefore, the aim of this study is to assess possible effects of prolonged entrainment in different conditions – music, metronome and silence – on gait parameters, synchronisation, fatigability during walking in PwMS compared with healthy controls.

METHODOLOGY

Participants

A random sample of PwMS were recruited from REVAL Diepenbeek, MS Centre Overpelt and National MS Centre Melsbroek in Belgium and healthy controls were recruited through social media, friends, relatives and colleagues of the researchers and participants from February 2017 till November 2017. None of the participants were blood relatives in first line. PwMS were screened by the following inclusion criteria: diagnosis of MS for more than one year, no relapse in the last one or two months, ability to walk for six minutes, a walking speed between ranges of 0.4 and 1.2 m/s (Lord, McPherson, McNaughton, Rochester, & Weatherall, 2004). Exclusion criteria included

cognitive impairment hindering the understanding and execution of the experimental procedures, not speaking Dutch and hearing impairment.
In total 66 participants were screened, from this group 31 PwMS and 30 age and gender matched healthy controls were included. Five PwMS and two healthy controls dropped out over the different sessions. Finally, 27 PwMS and 28 healthy controls participated in the study (figure 1).

Procedure

This observational study was part of a larger project, of which the descriptive and one experimental session will be discussed. Assessments and measurements were conducted at three different locations: REVAL Diepenbeek, MS Centre Overpelt and National MS Centre Melsbroek. To increase the reliability of the measures, experimental tests were standardised across the different locations. Therefore, a room without external disturbances was used for all sessions, where participants had to walk in a rectangle of six by four and a half meters. Tests for descriptive and experimental data were collected on different days. The procedure during the sessions is described below.

Descriptive session

During the first session, descriptive characteristics and an anamnesis of the participants were collected.

Cognitive functions A series of cognitive tests were taken, different researchers with a physiotherapeutic background performed the assessments. The 7/24 Spatial Recall Test was assessed to measure visual learning and recall, word-list generation for verbal fluency, Paced Auditory Serial Addition Test for sustained attention and information processing speed, Single Digit Modality Test for information processing speed, Stroop task for executive function and the Buschke Selective Reminding Test for verbal learning and memory. With these cognitive testings, a level of cognitive impairment was determined. A classification of cognitive impairment was made conform following conditions (Fischer et al.):

- Performing 1.5/2 standard deviations below normative means in 20-30% of the battery.
- Impairment in two cognitive domains (using the standard deviation criteria).

Motor functions One researcher assessed all different motor functions. Manual Muscle Testing was used to test the muscle weakness of the dorsiflexors of the ankle, the knee extensors and the hip flexors, the Modified Ashworth Scale for spasticity, rapid alternating movements (pro- and

supination) with the hands for dysdiadochokinesis, finger-to-nose test for dysmetria, Timed Up and Go (s) and Timed 25-Foot Walk (s) for mobility, 6 Minute Walk Test (m) for walking endurance and Dynamic Gait Index for gait, balance and fall risk.

Dual task Two different dual tasks were taken according to a dual task cost protocol in random order (Leone, Patti, Moumdjian, Zappia, & Feys, 2015). The Word List Generation (15s) and the Digit Span (60s) were used as cognitive single tasks. The motor single tasks were a 15 seconds walk and a 60 seconds walk. Then, the dual tasks combined these two tasks simultaneously, e.g. Word List Generation combined with the 15 seconds walk and the digit span with the 60 seconds walk. With the results of the single tasks and the dual tasks, the cognitive dual task cost and the motor dual task cost were calculated according to the following formula:

$$Dual\ Task\ Cost = \frac{single\ task - dual\ task}{single\ task} \times 100$$

Patient reported outcomes Questionnaires were provided at the beginning of the first session. Participants were asked to take this home and bring them filled out the next session. The patient reported outcomes consisted of different questionnaires, these were: the Twelve item MS Walking Scale which questioned walking abilities from the patients' perspective, Falls Efficacy Scale for the fear of falling, Modified Fatigue Impact Scale for the impact of their fatigue, Hospital Anxiety and Depression Scale for the levels of anxiety and depression. Music abilities were measured with the Montreal Battery of Evaluation of Amusia.

Experimental session

In the experimental session, participants had to walk under three conditions - silence, metronome or music - in a randomised order. Each condition lasted 12 minutes, with 15 minutes rest between the conditions (figure 2). Participants were instructed to step on the beat – e.g. synchronising – during both metronome and music.

Optimal tempo An optimal walking tempo was individually selected through a standardised procedure based on results obtained in a previous session. This tempo was determined by analysing the highest stable synchronisation level in combination with a maintained or increased stride length compared to the baseline. The baseline tempo was measured at the beginning of

each experimental session and participants were asked to walk on their comfortable walking speed. To measure the average comfortable walking speed, participants had to walk three times for one minute without stimuli. This was measured with the D-jogger and was transported to D-jogger software.

Equipment Participants were equipped with five APDM sensors (OPAL, APDM, INC., Portland) and the D-jogger system, which consisted of an iPod touch (Apple, USA) strapped at each ankle and headphones (Thaut, 2015). With the D-jogger system, it was possible to measure if people synchronised to the rhythm and thus performed entrainment. It measured the timing difference between the beats of the metronome or music and the steps of the feet (Moens, 2010).

The conditions

Metronome: An isochronous metronome with an individualised beat per minute, based on the optimal tempo of the participant.

Music: There were six music genres available (table 1). Participants had the freedom to choose their preferred music style. The beats per minutes were determined in the same way as with the metronome condition. D-jogger software adapted the beats per minute of the songs in such a way that the optimal tempo of the participant could be obtained.

Silence: Participants were not stimulated to walk at their optimal tempo, thus without any auditory stimuli.

Outcome measures:

Primary outcome measures Phase angle, resultant vector length, and the spatiotemporal parameters of gait – speed, stride length, and cadence – were primary outcome measures. Phase angle was defined as the degree/time a person stepped next to the beat, e.g. the nearer to zero, the closer the step occurred to the beat. With the phase angle, it is possible to calculate the resultant vector length: the more stable the results of the phase angle, the higher the value of the resultant vector length. The resultant vector length showed the degree of stable synchronisation, e.g. zero out of one meant that there was no synchronisation and one out of one meant that there was a perfect synchronisation. The cut off for synchronisation was set on a score of more than 0.7 (Moumdjian, 2018). Both the resultant vector length and phase angle were measured with the D-jogger system. A delta of the speed, stride length, and cadence was used to compare the different parameters of gait. The formula to calculate delta was as followed:

$$Delta = Average\ Experimental\ data\ minute\ x - Average\ baseline\ data$$

Secondary outcome measures were performance motor fatigability, perceived motor fatigability and perceived cognitive fatigability. Performance fatigability was measured by the distance walked index. Where the percentage change in distance walked was calculated between minutes six and one. If there was a decrease of 15% or more the participant has walking-related motor fatigability (Leone et al., 2016).

$$Distance\ walked\ index = \frac{Distance\ walked\ minute\ n - Distance\ walked\ minute\ 1}{Distance\ walked\ at\ minute\ 1} \times 100$$

Perceived fatigability was measured by using the visual analogue scale (VAS) for cognitive and motor fatigability. To compare the VAS, a delta was calculated by subtracting the post-VAS from the pre-VAS.

Data analysis

Data analysis was done with JMP®, Version <13>, SAS Institute Inc., Cary, NC, 1989-2007. For the descriptive values a t-test was used for normally distributed data, Wilcoxon Signed Rank Test for variables which were not normally distributed and Pearson for variables which were not continuous, but ordinal or nominal. A mixed model ANOVA was used (backwards model fitting) for the experimental data. Multiple comparisons (Tukey) were used to analyse the differences between and within the groups, stimuli, time points, and cognitive impairment. Intention to treat analyses was used.

Correlations were analysed for the resultant vector length and phase angle. When variables were normally distributed, the pairwise correlations were used and Spearman's ρ correlation was used when variables were not normally distributed.

Ethic committee

The ethic committee approved the study on 23-11-2016, with the Belgian registration number: B670201629797

RESULTS

Descriptive data

Mean age of PwMS and healthy controls was respectively 53.45 (SD 10.61) and 51.77 (SD 11.40). In both PwMS and healthy controls were females were more represent compared to males, namely 23 females in PwMS and 22 in healthy controls. For the type of MS, relapsing remitting was the most present in the MS group, with 20 out of 30. No significant differences were found for age, gender, height, weight, and education years between PwMS and healthy controls as shown in table 2. There was a significant difference between PwMS and healthy controls for almost all motor tests. PwMS scored significantly lower on all motor tests, expect for spasticity in the right leg, where no difference was found (table 3). Table 4 shows comparable scores for the cognitive tests, with the exception of the Paced Auditory Serial Addition Test, Single Digit Modality Test and dual task cost. Healthy controls scored significantly higher on the Paced Auditory Serial Addition Test and Single Digit Modality Test and PwMS had a significantly higher dual task cost with the digit span. PwMS had a significantly higher impact of fatigue on activities in daily live, more difficulties with dual tasking, and a higher risk of falling as found by patient reported measures (table 5).

Experimental data

Groups: Healthy controls vs. PwMS (table 6)

Within the metronome condition, the resultant vector length was significantly higher in healthy controls compared to PwMS ($p=0.0078$). There were no significant differences between groups in the music condition (figure 3). It was shown that healthy controls had a significant higher delta in cadence compared to PwMS in the metronome condition ($p=0.00035$) and the music condition ($p\leq.0001$)(figure 4). For the perceived fatigability, there was a significant higher delta of motor fatigability ($p=0.0002$) and delta of cognitive fatigability ($p\leq.0001$) in healthy controls compared to PwMS (figure 5 & 6). No significant differences between groups were revealed for the phase angle, delta of speed, delta of stride length, performance motor fatigability or motivation.

Stimuli: Music vs. metronome vs. silence (table 7)

Phase angle During the metronome condition, the phase angle was significant more directed towards the neutral (0°) within PwMS ($p\leq.0001$) and within cognitive impaired persons ($p=0.0003$) compared to the music condition (figure 7).

Resultant vector length The resultant vector length was significantly higher in PwMS ($p=0.0253$) and cognitive impaired participants ($p=0.008$) during the music condition compared to the metronome condition. There was no significant difference in healthy controls.

Gait parameters Strong evidence of a significant difference between stimuli was present in PwMS and healthy controls, cadence was significantly more increased during the metronome ($p\leq.0001$) and music ($p\leq.0001$) condition compared to silence. Cadence even decreased during the silence condition for PwMS compared to the baseline. There was a significant difference between the conditions for participants with cognitive impairment. The silence condition resulted in a decrease in cadence, while the music and metronome condition had an increase in cadence ($p\leq.0001$). As shown in figure 8, the metronome condition had a significantly higher decrease in stride length in PwMS compared to the music ($p=0.0484$) and silence ($p\leq.0001$) condition (figure 8). Furthermore, the music condition had a significantly higher decrease of stride length than the silence condition ($p=0.0141$). There were similarities in cognitive impaired persons were silence also gave a lower decrease in stride length in comparison with the metronome condition ($p\leq0.001$). Healthy controls demonstrated a significant higher speed during the metronome ($p\leq.0001$) and music ($p\leq.0001$) condition compared to the silence condition (figure 9). For speed, no differences between stimuli were found in PwMS.

Other parameters From the data of the PwMS in Figure 10, it was apparent that the Distance Walked Index differed significantly and was lower in minute one till six in the music ($p=0.0070$) and silence ($p=0.0032$) condition compared to the metronome condition. For all participants together this significant difference was only seen between metronome and silence ($p=0.0067$). In figure 9, the significant difference between the stimuli for all participants can clearly be seen. Metronome ($p=0.0676$) and silence ($p=0.0212$) condition had a significant higher increase in perceived cognitive fatigability compared to the music condition. Comparable results were present for motivation where all participants were significantly more motivated in the music condition compared to the metronome ($p\leq.0001$) and silence condition ($p\leq.0001$). No significant differences were found for the performance motor fatigability measured between minutes six and twelve.

Changes during 12 minutes walking

Phase angle A significant increase was found between minute one and nine (p=0.0077) and minute one and twelve (p=0.0135) for the phase angle in all participants during all conditions. There was no difference of the phase angle associated with the control group, PwMS, stimuli (music or metronome) or cognitive impaired.

Resultant vector length Within PwMS, the resultant vector length was significantly decreased in minute eleven compared to minute two (p=0.0007), minute three (p=0.0053) and minute four (p=0.0344). Minute twelve was only significantly decreased when compared to minute two (p=0.015). Overall, time did not affect healthy controls, stimuli (music or metronome) or cognitive impaired differently in these measures.

Gait parameters Significant differences were found within all participants. Cadence was significantly higher in minute one (p=0.0188) and two (p=0.0168) compared to minute twelve. There was a significant decrease in speed for minute one (p=0.0028) and two (p=0.0199) compared to minute twelve. Lastly, stride length had a significant decrease in minutes eight (p=0.0271), nine (p=0.0359) and twelve (p=0,0087) compared to minute one.
No significant difference was observed for healthy controls, PwMS, stimuli, and cognitive impaired.

Correlations in music and metronome

Music In PwMS, positive significant correlations were observed between the resultant vector length and the six-minute Walk Test (p=0.021), the dynamic gait index (p=0.0407) and motivation (p=0.0158). Negative significant correlations were present between the phase angle and Falls Efficacy Scale (p=0.0074) and between the phase angle and Modified Fatigue Impact Scale the physical (p=0.0166), and physiological (p=0.0476) subscales. No significant correlations were observed in healthy controls for the resultant vector length. However, correlations were observed between the phase angle and motivation (p=0.0397) and Distance Walked Index between minute 12 and six (p=0,00166) in healthy controls.
When all participants were taken together, a significant negative correlation was found between the resultant vector length and speed (p=0.0068) and Timed 25-Foot Walk (p=0.0091). Positive correlations were present with the Six-Minutes Walk Test (p=0.0002), Dynamic Gait Index (p=0.001) and, muscle strength left (p=0.0323). For the phase angle

significant negative correlations with the Twelve Item MS Walking Scale (p=0.0449) and motivation (p=0.0385) were found.

Metronome During the metronome condition no significant correlations could be noted for the phase angle. In PwMS, positive correlations were found between the resultant vector length and the Six-Minutes Walk Test (p=0.0289), Dynamic Gait Index (p=0.0133) and motivation (p=0.0313). A negative correlation was seen for the Timed 25-Foot Walk (p=0.0333). Last, in all participants significant positive correlations were detected between the resultant vector length and the delta of perceived motor fatigability (p=0.0084) and the Dynamic Gait Index (p≤.0001). Negative correlations were obtained for the Timed Up and Go Test (p=0.0131) and Timed 25-Foot Walk (p=0.0012).

DISCUSSION

The aim of this study is to consider the effect of prolonged entrainment in persons with MS compared to healthy controls and which relationship with synchronisation, gait, and fatigability during the different conditions is noted.

An initial objective of the project is to identify the effect of prolonged entrainment on synchronisation. A strong relationship between synchronisation and fatigability seems to be apparent in this study. An interesting finding is therefore, that the resultant vector length decreases overtime in PwMS and remains stable in healthy controls. This result may be explained by the fact that perceived motor and perceived cognitive fatigability is increased in PwMS and not in healthy controls. There is not only a difference between groups, but also between both auditory conditions. During the metronome condition the resultant vector length is significantly higher in healthy controls compared to PwMS. This difference is not found in the music condition, it can therefore be assumed that PwMS are able to synchronise as good as healthy controls during the music condition, which is not possible during the metronome condition. This finding is supported by the results within the PwMS who achieved a higher resultant vector length during the music condition compared to the metronome condition, which thus also suggest that PwMS are able to synchronise better during the music condition.

The results of this study show a negative phase angle during both auditory conditions, it can thus be suggested that action-perception and anticipation is present. Participants predict the beat and this prediction gets closer to zero over time. During the metronome condition, PwMS

are stepping closer to the beat compared to the music condition, which also occurs in cognitive impaired participants. There are two potential causes for the difference between the music and metronome condition in PwMS. It is possible that music is too complex to interpret for PwMS. Another explanation could be that patients are paying more attention to the beat of the metronome than to the beat of music. This may relate to overall perceived fatigue, as revealed by the negative correlation between the phase angle and the two subscales of the Modified Fatigue Impact Scale, physical and psychological. It is likely therefore that the more fatigued PwMS are, the lower the phase angle will be. In PwMS is seen that the Distance Walked Index was significantly different between conditions. A positive Dynamic Walked Index was apparent in the metronome condition compared to a negative result during the music and silence condition in the first six minutes. One can state that during the metronome condition no slowing down is observed in contrast to music and silence condition, which means that performance motor fatigability is only present during the music and silence condition. This difference disappears during the last six minutes, when performance motor fatigability stabilised in all stimuli. However, the perceived motor fatigability is not different between stimuli and the perceived cognitive fatigability is lower during the music condition. These rather contradictory results may be due to the significant higher motivation during the music condition compared to the metronome condition in PwMS, which could decrease the cognitive fatigability.

The last objective in this study sought to determine the effect of entrainment on the spatiotemporal parameters of gait. Healthy controls have an increase in speed, which probably is caused by an increase of stride length and cadence during the sessions with auditory stimulation. Opposed to the healthy control group, speed decreases equally during all three conditions in PwMS. Contrary to the expectations, this study shows a decrease in stride length in the PwMS group, especially in the conditions with auditory stimuli. A possible explanation for this might be that PwMS try to follow the beat by making smaller steps. It is possible, that it also has an influence on the increased cadence. It can thus be suggested that walking to auditory stimuli at an optimal tempo has no beneficial effect on the walking parameters compared to the silence condition for PwMS.

Previous research shows that rhythmic auditory stimulation has a positive effect on gait velocity, cadence and stride length in stroke patients and PwMS (Cha et al., 2014; Conklyn et

al., 2010; Sarkamo et al., 2008; Schauer & Mauritz, 2003; Shahraki et al., 2017). However, the findings in the current study do not completely support this previous research for PwMS. The metronome condition has a positive effect on cadence, but there is no effect on speed and even a negative effect on stride length. When looking at the music condition, *Thaut et al., (2017)* shows a positive effect on gait velocity and cadence for patients with Parkinson Disease. Findings in this study are consistent for cadence, but are unable to demonstrate the improvement of speed in PwMS. The present findings of perceived cognitive fatigability during the music condition in PwMS supports the previous research of *Fritz et al., (2013),* where music is proven to decrease the perceived fatigability during walking. *Leow et al., (2017)* suggests that young healthy individuals have a less variable synchronisation with music than with a metronome. This study is unable to demonstrate this for the healthy controls, however the PwMS group shows the same results. *(Seebacher, Kuisma, Glynn, & Berger, 2017)* applies a four-week intervention, which compares motor imagery together with verbal feedback and auditory cues, music or metronome, in PwMS. There is also a control group, which does not receive any therapy at all. Music and metronome conditions improve walking speed compared to the control group. However, this result is not described in this study there is no significant effect for speed between conditions in PwMS. Cognitive fatigue improves significantly in the intervention groups compared to the control group and physical fatigue improved significantly, but only after the music intervention. This study is unable to demonstrate these results were only significant improvements in cognitive fatigability are present during the music condition.

Finally, a number of limitations need to be considered. First, APDM data is missing for an unknown reason from minute six to 12 for 10 different participants, which could have affected the measurements of the spatiotemporal parameters of gait. The analysis software JMP takes this in account during analyses, but caution must be taken, when interpreting the spatiotemporal parameters of gait. Secondly, the study does not take in account the possible impact of medication on prolonged walking and synchronisation abilities. There are patients who take Fampridine, which can improve the walking speed with an average of 25,7% on the Timed 25-Foot Walk (Goodman et al., 2010). It is possible that this medication also has an effect on prolonged walking and synchronisation abilities. Finally, there is a small sample size of cognitive impaired persons. Future research including cognitive impaired patients is advocated in order to judge the robustness of the currently obtained findings.

CONCLUSION

The present study is designed to determine the effect of entrainment on synchronisation, gait parameters and fatigability in PwMS. Findings suggest in general that synchronisation occurs more in music than in metronome. Also, perceived cognitive fatigability would be lower with music. For the perceived motor fatigability, the type of stimuli implies not to be important. In contrast to performance motor fatigability, here a metronome should be used during a trial shorter than six minutes. In trials longer than six minutes, the type of stimuli seems not important anymore. Auditory stimuli appear to have no influence on speed and a negative influence on cadence and stride length in PwMS. In practice, auditory motor coupling could be used in PwMS when fatigability is present. However, the type of fatigability should be taken in account when choosing the stimuli. More research in a larger sample is needed to determine the clinical implications and to understand the effects according to motor and cognitive impairment level.

REFERENCES

Alluri, V., Toiviainen, P., Jaaskelainen, I. P., Glerean, E., Sams, M., & Brattico, E. (2012). Large-scale brain networks emerge from dynamic processing of musical timbre, key and rhythm. *Neuroimage, 59*(4), 3677-3689. doi:10.1016/j.neuroimage.2011.11.019

Arias, P., & Cudeiro, J. (2010). Effect of rhythmic auditory stimulation on gait in Parkinsonian patients with and without freezing of gait. *PLoS One, 5*(3), e9675. doi:10.1371/journal.pone.0009675

Cha, Y., Kim, Y., Hwang, S., & Chung, Y. (2014). Intensive gait training with rhythmic auditory stimulation in individuals with chronic hemiparetic stroke: a pilot randomized controlled study. *NeuroRehabilitation, 35*(4), 681-688. doi:10.3233/nre-141182

Conklyn, D., Stough, D., Novak, E., Paczak, S., Chemali, K., & Bethoux, F. (2010). A home-based walking program using rhythmic auditory stimulation improves gait performance in patients with multiple sclerosis: a pilot study. *Neurorehabil Neural Repair, 24*(9), 835-842. doi:10.1177/1545968310372139

de Bruin, N., Doan, J. B., Turnbull, G., Suchowersky, O., Bonfield, S., Hu, B., & Brown, L. A. (2010). Walking with music is a safe and viable tool for gait training in Parkinson's disease: the effect of a 13-week feasibility study on single and dual task walking. *Parkinsons Dis, 2010*, 483530. doi:10.4061/2010/483530

Fischer, M., Kunkel, A., Bublak, P., Faiss, J. H., Hoffmann, F., Sailer, M., . . . Kohler, W. - How reliable is the classification of cognitive impairment across different. - *J Neurol Sci. 2014 Aug 15;343(1-2):91-9. doi: 10.1016/j.jns.2014.05.042. Epub*(- 1878-5883 (Electronic)), T - ppublish.

Fritz, T. H., Hardikar, S., Demoucron, M., Niessen, M., Demey, M., Giot, O., . . . Leman, M. (2013). Musical agency reduces perceived exertion during strenuous physical performance. *Proc Natl Acad Sci U S A, 110*(44), 17784-17789. doi:10.1073/pnas.1217252110

Givon, U., Zeilig, G., & Achiron, A. (2009). Gait analysis in multiple sclerosis: characterization of temporal-spatial parameters using GAITRite functional ambulation system. *Gait Posture, 29*(1), 138-142. doi:10.1016/j.gaitpost.2008.07.011

Goodman, A. D., Brown, T., Edwards, K., Krupp, L., Schapiro, R., Cohen, R., . . . Blight, A. (2010).

In Mo Park, D. W. O., Suhn Yeop Kim, Jong Duk Choi. (2010). Clinical feasibility of integrating fasttempo auditory stimulation with self-adopted walking training for improving walking function in poststroke patients. *Journal of Physical Therapy Science, 22*, 295-300.

Kelleher, K. J., Spence, W., Solomonidis, S., & Apatsidis, D. (2010). The characterisation of gait patterns of people with multiple sclerosis. *Disability and Rehabilitation, 32*(15), 1242-1250. doi:10.3109/09638280903464497

Kluger, B. M., Krupp, L. B., & Enoka, R. M. (2013). Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology, 80*(4), 409-416. doi:10.1212/WNL.0b013e31827f07be

Koch-Henriksen, N., & Sorensen, P. S. (2010). The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol, 9*(5), 520-532. doi:10.1016/s1474-4422(10)70064-8

Larocca, N. G. (2011). Impact of walking impairment in multiple sclerosis: perspectives of patients and care partners. *Patient, 4*(3), 189-201. doi:10.2165/11591150-000000000-00000

Leman, M., Moelants, D., Varewyck, M., Styns, F., van Noorden, L., & Martens, J. P. (2013). Activating and relaxing music entrains the speed of beat synchronized walking. *PLoS One, 8*(7), e67932. doi:10.1371/journal.pone.0067932

Leone, C., Patti, F., Moumdjian, L., Zappia, M., & Feys, P. (2015). The effects of different cognitive and motor tasks on the dual task cost of walking in multiple sclerosis: a case-control study. *Multiple Sclerosis Journal, 21*, 416-417.

Leone, C., Severijns, D., Dolezalova, V., Baert, I., Dalgas, U., Romberg, A., . . . Feys, P. (2016). Prevalence of Walking-Related Motor Fatigue in Persons With Multiple Sclerosis: Decline in Walking Distance Induced by the 6-Minute Walk Test. *Neurorehabil Neural Repair, 30*(4), 373-383. doi:10.1177/1545968315597070

Lim, I., van Wegen, E., de Goede, C., Deutekom, M., Nieuwboer, A., Willems, A., . . . Kwakkel, G. (2005). Effects of external rhythmical cueing on gait in patients with Parkinson's disease: a systematic review. *Clin Rehabil, 19*(7), 695-713. doi:10.1191/0269215505cr906oa

Lord, S. E., McPherson, K., McNaughton, H. K., Rochester, L., & Weatherall, M. (2004). Community ambulation after stroke: how important and obtainable is it and what measures appear predictive? *Arch Phys Med Rehabil, 85*(2), 234-239.

MacAllister, W. S., & Krupp, L. B. (2005). Multiple Sclerosis–Related Fatigue. *Physical Medicine and Rehabilitation Clinics of North America, 16*(2), 483-502. doi:https://doi.org/10.1016/j.pmr.2005.01.014

Martin, C. L., Phillips, B. A., Kilpatrick, T. J., Butzkueven, H., Tubridy, N., McDonald, E., & Galea, M. P. (2006). Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Mult Scler, 12*(5), 620-628. doi:10.1177/1352458506070658

Minden, S., Frankel, D., Hadden, L., Perloffp, J., Srinath, K., & Hoaglin, D. (2006). - The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample. - *Mult Scler. 2006 Feb;12(1):24-38. doi: 10.1191/135248506ms1262oa.*(- 1352-4585 (Print)), T - ppublish.

Moens, B., van Noorden, L., & Leman, M. (2010). D-Jogger: Syncing Music with Walking. *Proceedings of SMC Conference 2010, Barcelona, Vol. online, pp. 451-456*.

Moumdjian, L. B., J.; Willems, I.; Feys, P.; Leman, M. (2018). Entrainment and synchronisation to auditory stimuli during walking in healthy and neurological populations: A methodological systematic review. *Frontiers of Human Neuroscience in review*.

Rossignol, S., & Jones, G. M. (1976). Audio-spinal influence in man studied by the H-reflex and its possible role on rhythmic movements synchronized to sound. *Electroencephalogr Clin Neurophysiol, 41*(1), 83-92.

Sarkamo, T., Tervaniemi, M., & Huotilainen, M. (2013). Music perception and cognition: development, neural basis, and rehabilitative use of music. *Wiley Interdiscip Rev Cogn Sci, 4*(4), 441-451. doi:10.1002/wcs.1237

Sarkamo, T., Tervaniemi, M., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., . . . Hietanen, M. (2008). Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain, 131*(Pt 3), 866-876. doi:10.1093/brain/awn013

Schaefer, R. S. (2014). Auditory rhythmic cueing in movement rehabilitation: findings and possible mechanisms. *Philos Trans R Soc Lond B Biol Sci, 369*(1658), 20130402. doi:10.1098/rstb.2013.0402

Schauer, M., & Mauritz, K. H. (2003). Musical motor feedback (MMF) in walking hemiparetic stroke patients: randomized trials of gait improvement. *Clin Rehabil, 17*(7), 713-722. doi:10.1191/0269215503cr668oa

Seebacher, B., Kuisma, R., Glynn, A., & Berger, T. (2017). - The effect of rhythmic-cued motor imagery on walking, fatigue and quality of life. - *Mult Scler. 2017 Feb;23(2):286-296. doi: 10.1177/1352458516644058. Epub 2016 Jul*(- 1477-0970 (Electronic)), T - ppublish.

Severijns, D., Zijdewind, I., Dalgas, U., Lamers, I., Lismont, C., & Feys, P. (2017). The Assessment of Motor Fatigability in Persons With Multiple Sclerosis: A Systematic Review. *Neurorehabil Neural Repair, 31*(5), 413-431. doi:10.1177/1545968317690831

Shahraki, M., Sohrabi, M., Taheri Torbati, H. R., Nikkhah, K., & NaeimiKia, M. (2017). Effect of rhythmic auditory stimulation on gait kinematic parameters of patients with multiple sclerosis. *J Med Life, 10*(1), 33-37.

Sihvonen, A. J., Sarkamo, T., Leo, V., Tervaniemi, M., Altenmuller, E., & Soinila, S. (2017). Music-based interventions in neurological rehabilitation. *Lancet Neurol, 16*(8), 648-660. doi:10.1016/s1474-4422(17)30168-0

Thaut, M. H. (2015). The discovery of human auditory-motor entrainment and its role in the development of neurologic music therapy. *Prog Brain Res, 217*, 253-266. doi:10.1016/bs.pbr.2014.11.030

Thaut, M. H., Leins, A. K., Rice, R. R., Argstatter, H., Kenyon, G. P., McIntosh, G. C., . . . Fetter, M. (2007). Rhythmic auditory stimulation improves gait more than NDT/Bobath training in near-ambulatory patients early poststroke: a single-blind, randomized trial. *Neurorehabil Neural Repair, 21*(5), 455-459. doi:10.1177/1545968307300523

Thaut, M. H., McIntosh, G. C., Rice, R. R., Miller, R. A., Rathbun, J., & Brault, J. M. (1996). Rhythmic auditory stimulation in gait training for Parkinson's disease patients. *Mov Disord, 11*(2), 193-200. doi:10.1002/mds.870110213

Thaut, M. H., McIntosh, K. W., McIntosh, G. C., & Hoemberg, V. (2001). Auditory rhythmicity enhances movement and speech motor control in patients with Parkinson's disease. *Funct Neurol, 16*(2), 163-172.

Trapp, B. D., & Nave, K. A. (2008). Multiple sclerosis: an immune or neurodegenerative disorder? *Annu Rev Neurosci, 31*, 247-269. doi:10.1146/annurev.neuro.30.051606.094313

WHO, M. S. I. F. (2013). Atlas of MS 2013.

Zatorre, R. J., Chen, J. L., & Penhune, V. B. (2007). When the brain plays music: auditory-motor interactions in music perception and production. *Nat Rev Neurosci, 8*(7), 547-558. doi:10.1038/nrn2152

Appendices

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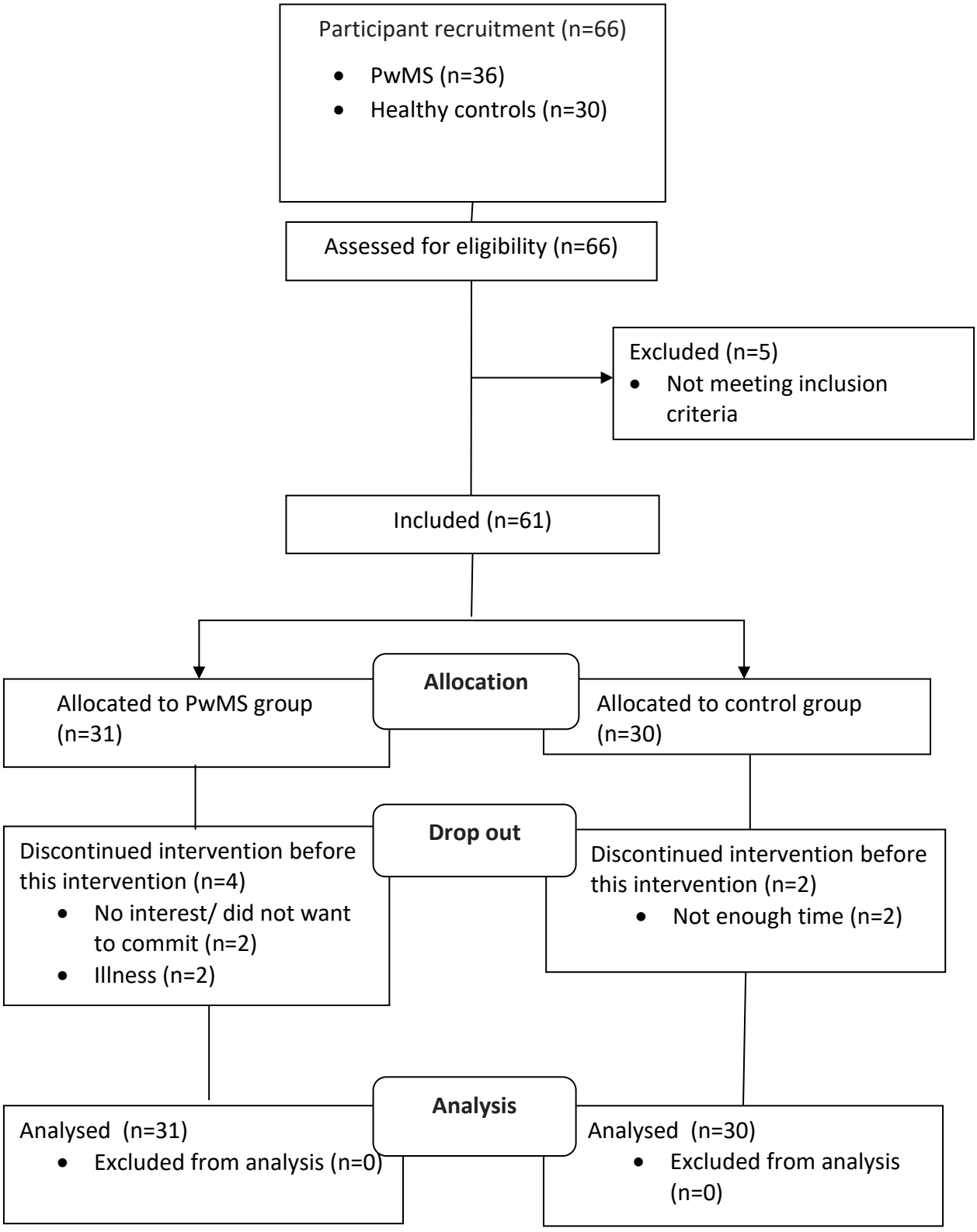

Figure 1: Flowchart of participants

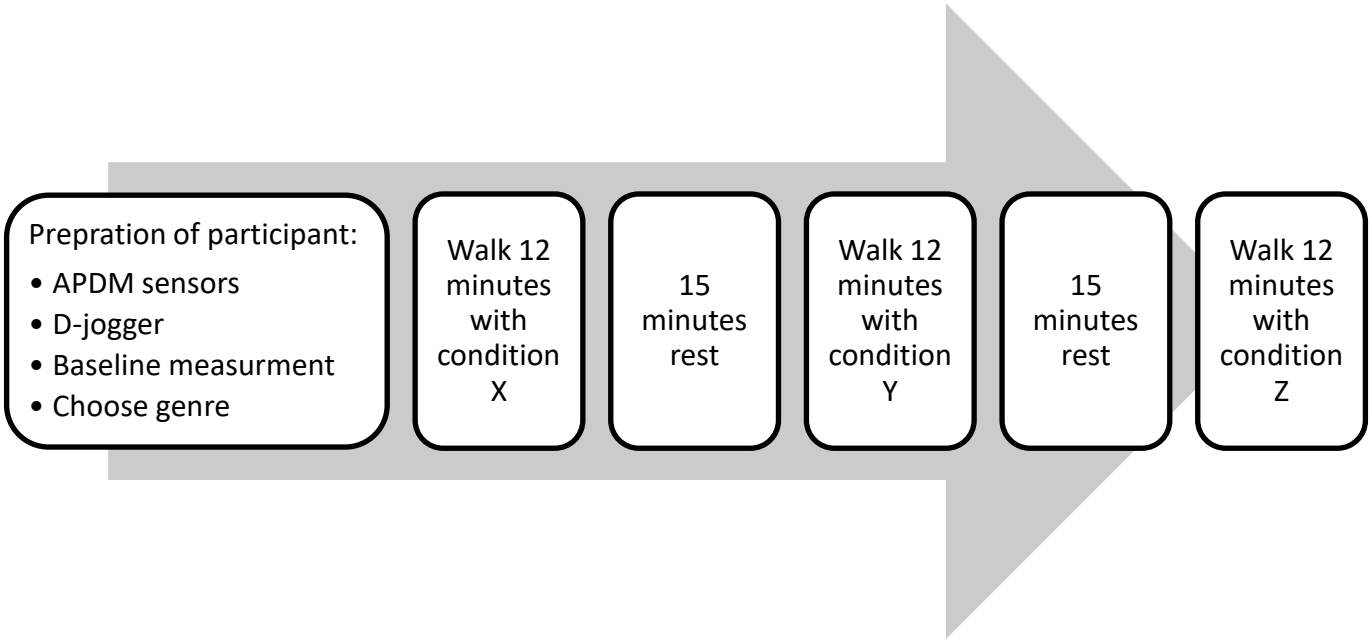

Figure 2: Experimental session

Condition X, Y and Z are with music, metronome or silence. The order of the different conditions is dependent on the randomisation.

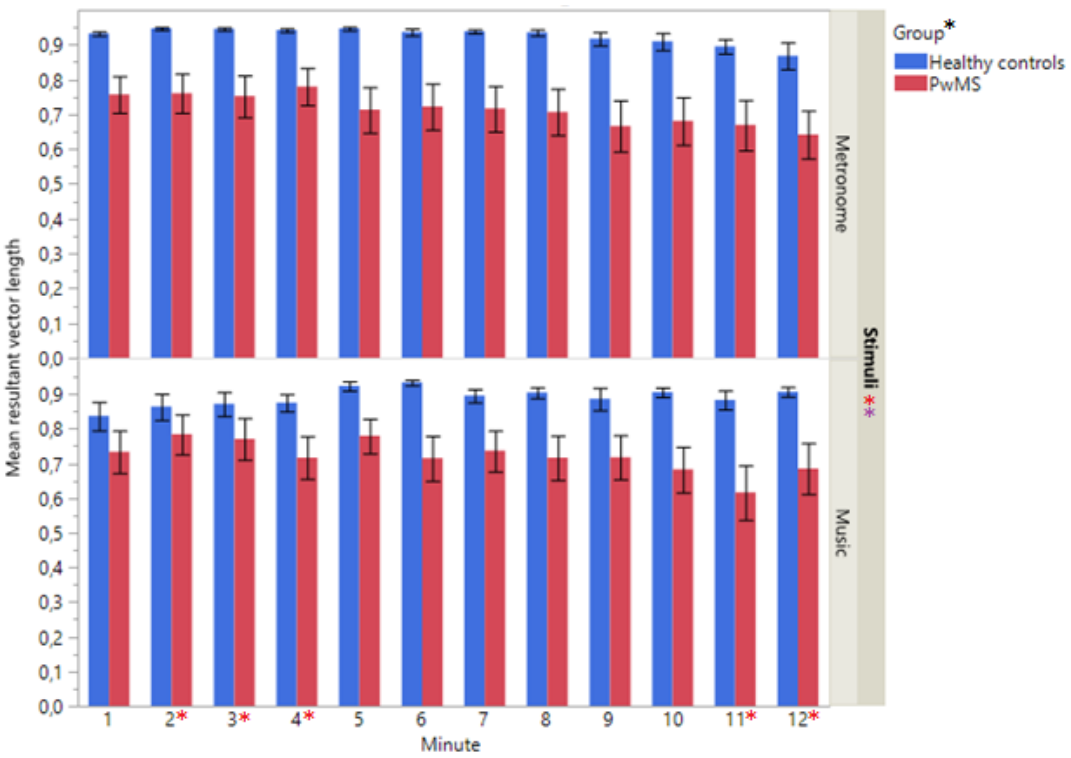

Figure 3: Mean resultant vector length over 12 minutes in conditions metronome and music

With standard error; PwMS: Persons with Multiple sclerosis significant difference all participants *PwMS *Between healthy controls and PwMS*

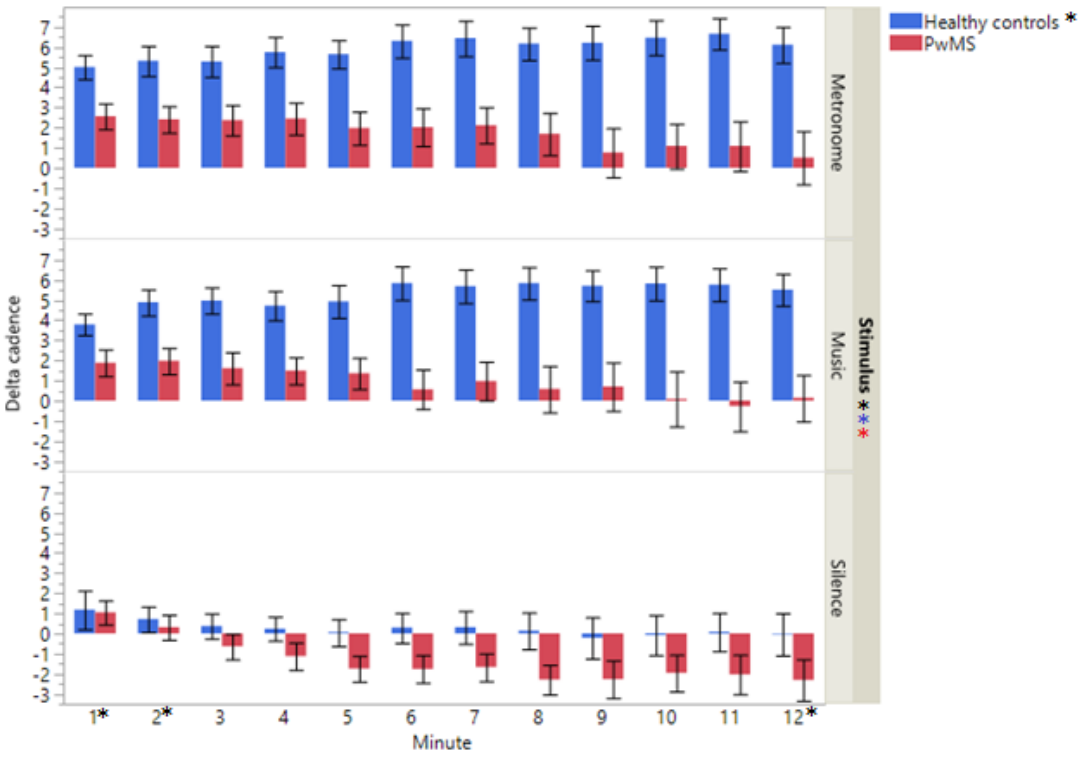

Figure 4: Delta cadence over 12 minutes in conditions metronome, music and silence

With standard error; PwMS: Persons with Multiple sclerosis significant difference all participants *Healthy controls *PwMS*

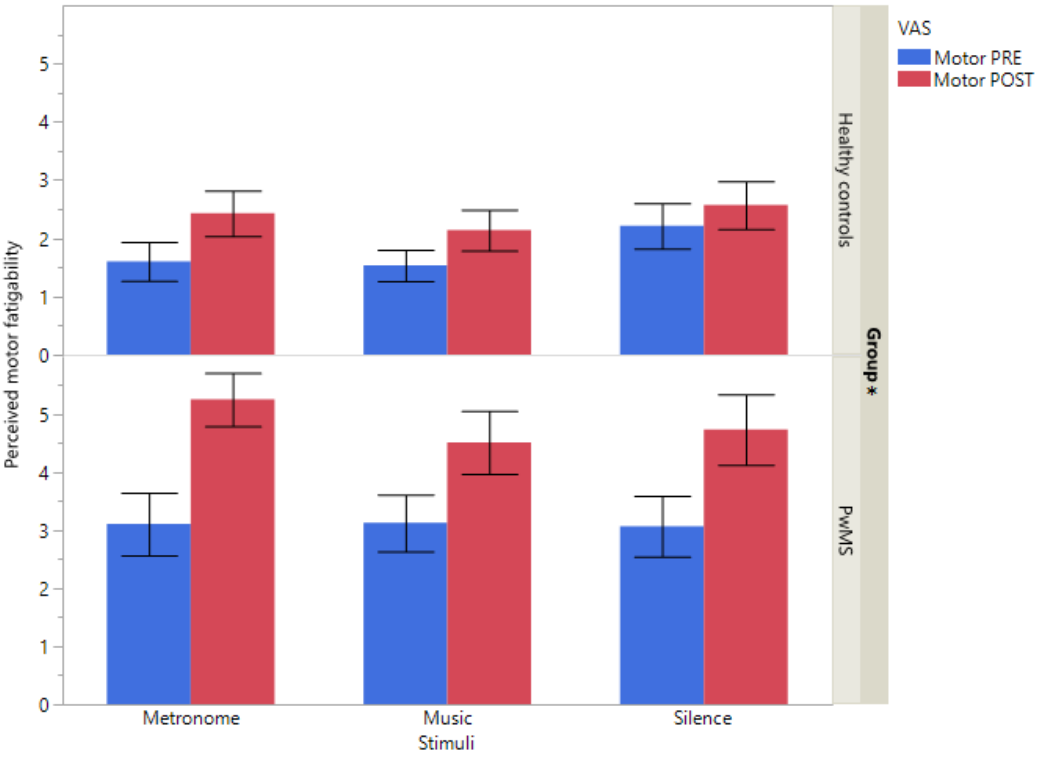

Figure 5: Perceived motor fatigability in conditions metronome, music and silence

With standard error; PwMS: Persons with Multiple sclerosis significant difference all participants*

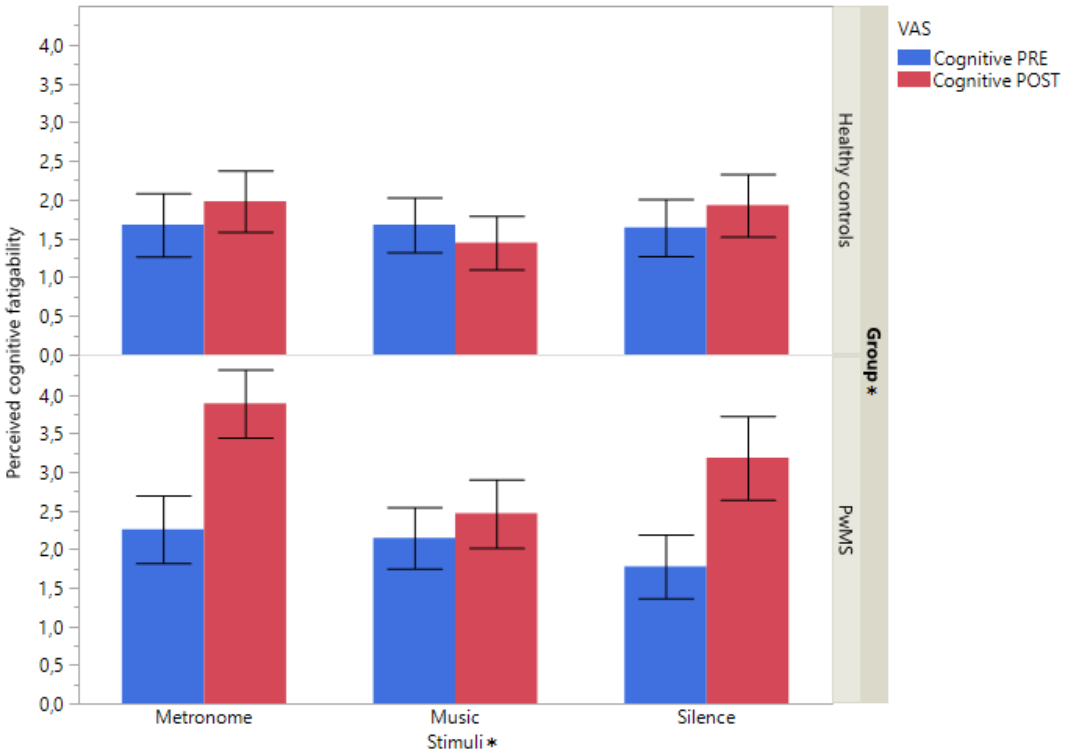

Figure 6: Perceived cognitive fatigability in conditions metronome, music and silence

With standard error; PwMS: Persons with Multiple sclerosis significant difference all participants*

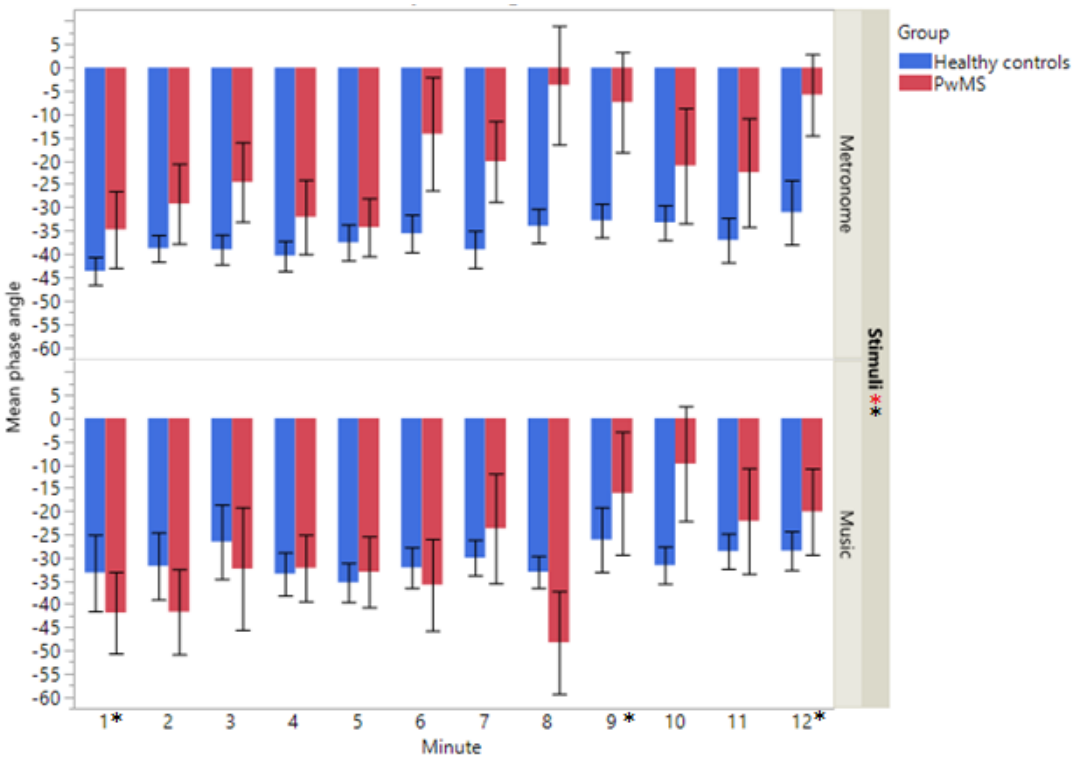

Figure 7: Mean phase angle over 12 minutes in conditions metronome and music

With standard error; PwMS: Persons with Multiple sclerosis significant difference all participants *PwMS*

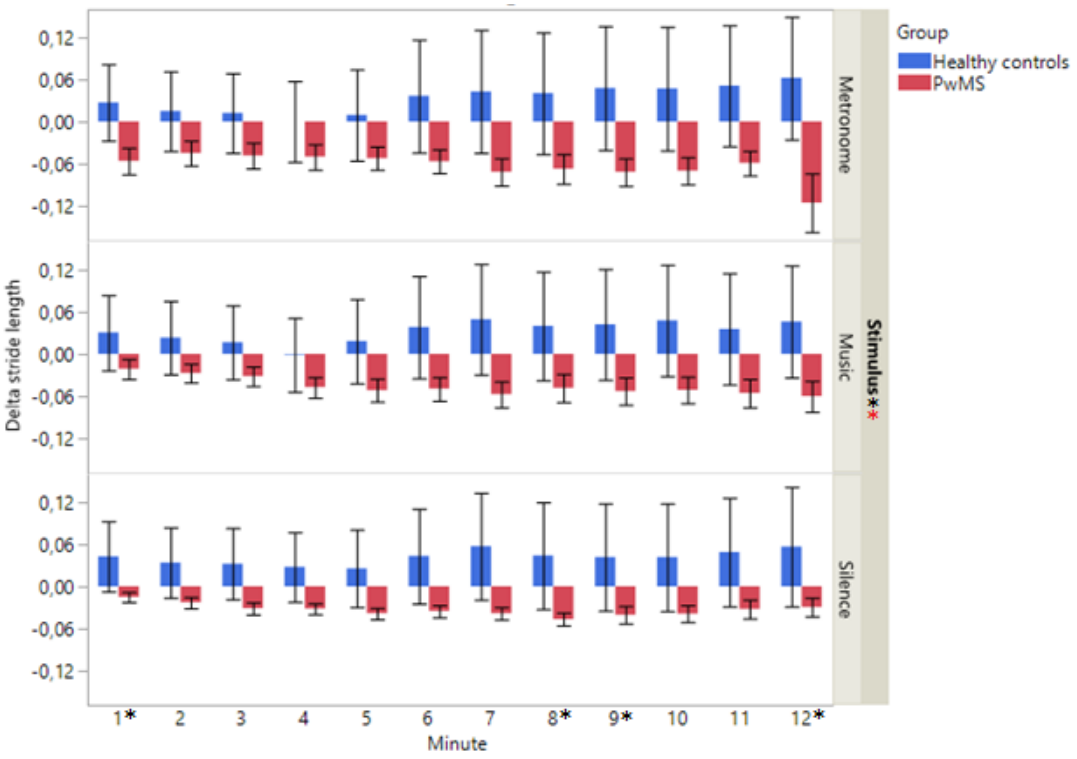

Figure 8: Delta stride length over 12 minutes in conditions metronome, music and silence

With standard error; PwMS: Persons with Multiple sclerosis significant difference all participants *PwMS*

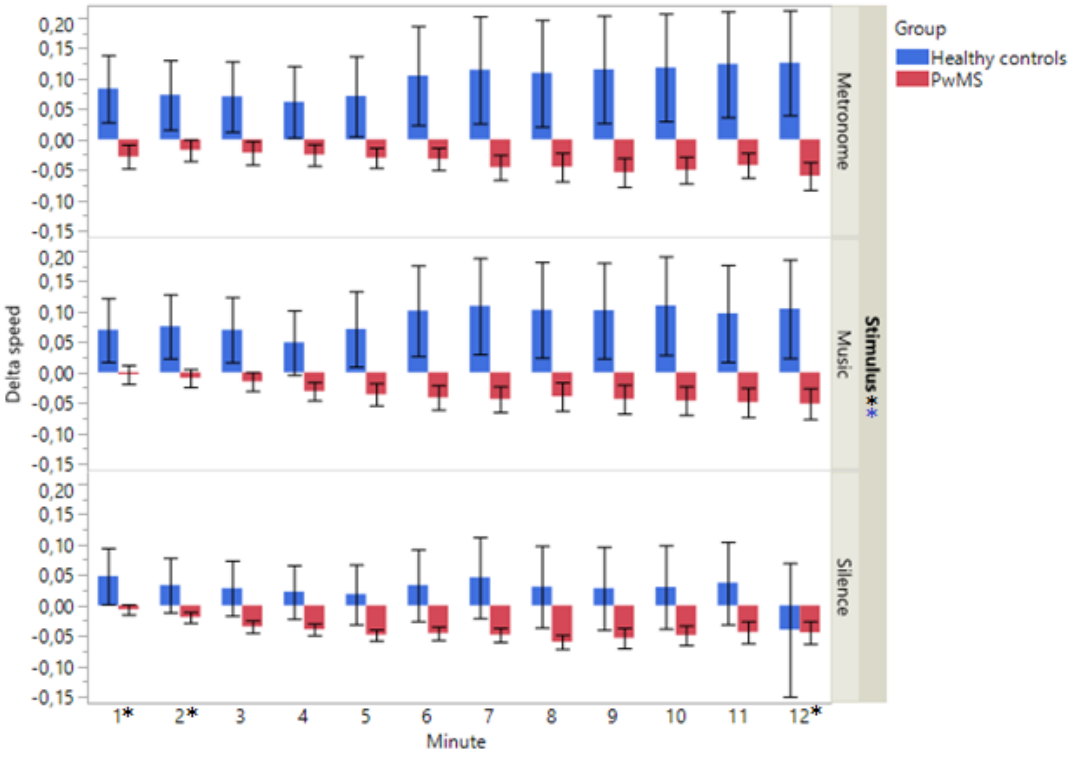

Figure 9: Delta speed over 12 minutes in conditions metronome, music and silence

With standard error; PwMS: Persons with Multiple sclerosis significant difference all participants *Healthy controls*

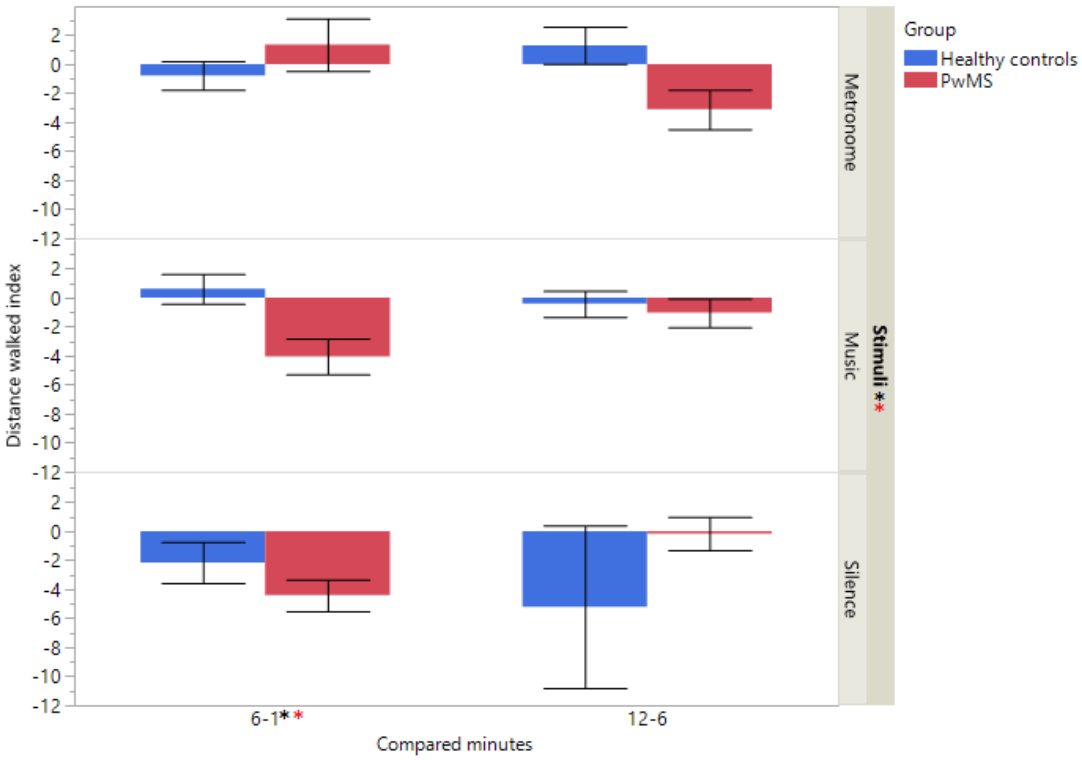

Figure 10: Distance walked index over 12 minutes in conditions metronome, music and silence

With standard error; PwMS: Persons with Multiple sclerosis significant difference all participants *PwMS*

Table 1: Music genres

Genres	*Examples of songs*	*Link to songs*
Disco	Oleta Adams - Rhythm of Life	spotify:track:3jOwA8XZplvTVsV0SdLWhc
	Lindstrom - Music in My Mind	spotify:track:27qOyDFfbZZgbmPFeS2j5V
	Caserta - Heaven	spotify:track:1GFlnW8ZEWlwuPQCOncYl6
Instrumental	Samvel Yervinyan - Allegro	spotify:track:0f4BS4GTj5qGyVW36ug1g7
	Enigma - The Alchemist	spotify:track:1iZ9jvWC5bw8meJbOsw1YZ
	Dead Can Dance - Avatar	spotify:track:7IYtS82lwGx5eemdG2LxOL
Pop	Sean Paul - We Be Burnin	spotify:track:79Ot5mE1cG9Ge4YQKAJT1d
	MIKA - Relax Take it Easy	spotify:track:2UmIV6L2kavGpZnti5YIrL
	Michael Jackson - Thriller	spotify:track:1D9KEXIrlmPUkMTdYzqgX4
Pop-Rock	Muse - Psycho	spotify:track:383QXk8nb2YrARMUwDdjQS
	Supertramp - It's Raining Again	spotify:track:5tEWG2w3eCJAleGxvZGm8p
	Hoobastank - The Reason	spotify:track:6Gn02ZC8juXwQ10Xk7ACXx
Variete	Thomas - Sur la Route	spotify:track:29sQCUJYAR4UWj6PEAsxt2
	Serge Gainsbourg - Mon Legionnaire	spotify:track:746mi2BnPXki6ERpCBtm3L
	Debut De Soiree - Nuit de Folie	spotify:track:7zhmazCm877yScXIQfeMh0

Table 2: Descriptive characteristics - general information

General	Average		t-test[1]	WSRT[2]	Pearson[3]
	PwMs	HC			
Age (years)	53,45	51.77		0.5734	
Gender (M/F)	8/23	8/22			0.9391
Height (cm)	170.81	170.1 (7.95)	0.7390		
Weight (kg)	69.10	71.15	0.5418		
Education (Years)	13.84 (1.92)	14.17 (2.39)		0.5940	
Music experience (Yes)	8	12			0.2378
Type of MS (RR/PP/SP)	20/6/4	n.a.		n.a.	
Smoker (yes) [4]	8	3			0.0953
Number of					
Ortheses	3	0		n.a.	
Assistive device[5]	9	0		n.a.	

[1] *(Prob>|t|)*

[2] *Wilcoxon Signed Ranked Test; (Prob>|Z|)*

[3] *(Prob>ChiSq)*

[4] *Smokes at the moment*

[5] *Assistive device is a rollator or a cane*

(..) = Standard deviation

RR: Relapsing remitting; PP: Primary progressive; SP: Secondary progressive; MS: Multiple sclerosis

Table 3: Descriptive characteristics - motor tests

Motor	Average		t-test[1]	WSRT[2]	Pearso
	PwMs	HC			
6MWT (meters)					
Minute 1	64.70 (17.30)	94.95 (13.68)	<.0001*		
Minute 6	377.56	559.46	<.0001*		
	(105.43)	(78.13)			
Gait speed (m/s)	0.97 (0.25)	1.25 (0.14)	<.0001*		
With assistive device[4]	0.81 (0.11)	/		n.a.	
Without assistive device[4]	1.03 (0.26)	1.25 (0.14)		0.0015*	
TUG (seconds)					
Rollator (n=6)	14.98 (4.41)	/		n.a.	
Without rollator(n=25)	10.17 (4)	6.62 (1.17)		<.0001*	
DGI (max 24)	18.13 (4.75)	24 (0)		<.0001*	
T25FW (seconds)	7.81 (2.11)	5.58 (0.80)		<.0001*	
Muscle weakness (max)					
Left	92.16 (9.28)	100 (0)		<.0001*	
Right	88.29 (18.44)	100 (0)		<.0001*	
Spasticity					
Left leg	no (n=27)	no (n=30)			0,0418
Right leg	no (n=30)	no (n=30)			0,3212

[1] (Prob>ltl)

[2] Wilcoxon Signed Ranked Test; (Prob>|Z|)

[3] (Prob>ChiSq)

[4]Asstistive device is a rollator or a cane

(..) = Standard deviation

* = significant

6MWT: Six-Minute Walk Test; TUG: Timed Up & Go test; DGI: Dynamic Gait Index; T25FW: Timed 25-Foot Walk; PwMS: Persons with Multiple Sclerosis

Table 4: Descriptive characteristics - cognitive tests

Cognitive test	Average		t-test[1]	WSRT[2]
	PwMs	HC		
7/24 SRT				
Visual learning	29.84 (5.15)	31.27 (3.4)		0.4783
Recall (short term)	6.29 (1.15)	5.5 (2.05)		0.1987
Recall (long term)	6.2 (0.83)	5.46 (2.18)		0.7233
WLG	33.79 (12.01)	35.16 (8.64)	0.6675	
PASAT	43.24 (13.36)	48.93 (10.38)		0.0485*
SDMT	48.10 (11.04)	59.01 (8.86)	0.0001*	
Buschke selective	23.52 (17.70)	23.52 (12.91)	0.9998	
STROOP 1	51.91 (13.06)	54.38 (21.58)		0.7183
2	63.82 (19.19)	64.36 (17.63)		0.8698
3	99.44 (50.59)	92.4 (20.11)		0.7427
Dual Task Cost (%)				
15s phonemics	-0.70 (23.60)	-3.95 (25.30)		0.9172
15s speed (m/s)	8.65 (25.06)	8.98 (11.59)		0.4557
60s digit span	25.17 (32.69)	11.05 (25.24)		0.0164*
60s speed (m/s)	9.60 (10.11)	6.18 (8.68)		0.0891

[1] *(Prob>ltl)*

[2] *Wilcoxon Signed Ranked Test; (Prob>|Z|)*

(..) = Standard deviation

* = significant

7/24 SRT: 7/24 Spatial Recall Test; WLG: Word List Generation; PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test; PwMS: Persons with Multiple Sclerosis

Table 5: Descriptive characteristics - patient reported outcomes (PRO)

PRO (max. score)		Average (SD) PwMs	Average (SD) HC	t-test[1]	WSRT[2]
[3]**MSWS-12** (100%)		32.45	/	n.a.	
[4]**FES** (64)		35.96	18.97 (3.10)		<0.0001*
[5]**MFIS**	**Total** (84)	35.77	15.93		0.0002*
	Physical (36)	18.37 (9.39)	6.83 (7.12)		<0.0001*
	Cognitive (40)	15.59	8.18 (6.66)		0.0049*
	Psychological (8)	3.17 (2.07)	1.47 (1.59)		0.0010*
[6]**HADS**	**Total** (42)	9.42(7.38)	6.77 (4.99)		0.2057
	Anxiety (21)	5 (4.15)	4.4 (3.49)		0.6955
	Depression (21)	4.42 (4.03)	2.37 (2.24)		0.0671
[7]**MMB**	**Scale** (15)	12.11 (1.74)	12.66 (1.76)		0.2042
	Rhythm (15)	13.15 (1.77)	13.59 (1.45)		0.3718

[1] (Prob>ltl)

[2] Wilcoxon Signed Ranked Test; (Prob>|Z|)

[3] Higher scores indicate a greater impact on walking than lower scores

[4] Higher scores indicate a greater fear of falling than lower scores

[5] Higher scores indicate a greater influence of fatigue on daily life

[6] Higher scores indicate more complaints. 0-7: no depression / anxiety disorder

[7] Higher scores indicate a better perception of scale or rhythm

(..) = Standard deviation

MSWS-12: Twelve Item MS Walking Scale; FES: Falls Efficacy Scale; MFIS: Modified Fatigue Impact Scale; HADS: Hospital Anxiety and Depression Scale; BMRQ: Barcelona Music Reward Questionnaire; PwMS: Persons with Multiple Sclerosis; MMB: Montreal Music Battery

Table 6: Significant levels between groups

		PwMS	Healthy controls	[1]p-value	Lower 95%	Upper 95%
PA	Music	-31.82 (5.2)	-28.34 (5.8)	0,9637	-15,18	22,13
	Metronome	-16.88 (5.1)	-28.42 (5.8)	0,3773	-30,08	6,99
RVL	Music	0,75 (0,0)	0,88 (0,0)	0,0704	-0,01	0,27
	Metronome	0,71 (0,0)	0,88 (0,0)	0,0078*	0,03	0,31
Speed[2]	Music	-0.02 (0.0)	0,07 (0,0)	0,5434	-0,06	0,24
	Metronome	-0.02 (0,0)	0,07 (0,0)	0,5696	-0,07	0,24
	Silence	-0,03 (0,0)	0,02 (0,0)	0,9684	-0,11	0,20
Stride	**length**[2]	-0,03 (0,0)	0,02 (0,1)	0,9354	-0,11	0,21
	Metronome	-0,05 (0,0)	0,01 (0,1)	0,9015	-0,10	0,22
	Silence	-0,05 (0,0)	0,01 (0,1)	0,9913	-0,13	0,19
Cadence[2]	Music	1.61 (0,6)	5.47 (0,7)	<,0001*	1,48	6,23
	Metronome	2.22 (0,6)	5.28 (0,7)	0,0035*	0,68	5,44
	Silence	-0,90 (0,6)	0,13 (0,7)	0,8163	-1,34	3,40
PMF	Music	-4.04 (1.2)	0.64 (1.5)	0.1475	-0.86	10.22
	Metronome	1.47 (1.3)	-0,78 (1.5)	0.8497	-7.89	3.37
	Silence	-4.40 (1.2)	-2.14 (1.4)	0.8241	-3.13	7.65

[1]significance level <0.05

[2]Data missing from minute 6 till 12 for 10 participants in all conditions

PA: Phase angle; RVL: Resultant vector length; PwMS: Persons with Multiple sclerosis; PMF: Performance motor fatigability

Table 7: Significant levels between stimuli

		Music (SE)	Metronome (SE)	Silence (SE)	[1]p-value	Lower 95%	Upper 95%
PA	PwMS	-31.82 (5.2)	-16.88 (5.1)	/	<0.0001*	8.14	21.73
	Healthy controls	-28.34 (5.8)	-28.42 (5.8)	/	1	-7.65	7.48
RVL	PwMS	0,75 (0,0)	0,71 (0,0)	/	0.0253*	-0.06	-0.00
	Healthy controls	0,88 (0,0)	0,88 (0,0)	/	0.9609	-0.03	0.04
Speed[2]	PwMS	-0.02 (0.0)	-0.02 (0,0)	/	1	-0.02	0.02
		-0.02 (0.0)	/	-0,03 (0,0)	0.9116	-0.01	0.02
		/	-0.02 (0,0)	-0,03 (0,0)	0.8983	-0.01	0.03
	Healthy controls	0,07 (0,0)	0,07 (0,0)	/	0.9999	-0.02	0.02
		0,07 (0,0)	/	0,02 (0,0)	<.0001*	0.03	0.08
		/	0,07 (0,0)	0,02 (0,0)	<.0001*	0.03	0.08
Stride length[2]	PwMS	-0,03 (0,0)	-0,05 (0,0)	/	0.0484*	-0.03	-0.00
		-0.03 (0,0)	/	-0,02 (0,0)	0.0141*	-0.03	-0.00
		/	-0,05 (0,0)	-0,02 (0,0)	<.0001*	-0.04	-0.02
	Healthy controls	0,02 (0,1)	0,01 (0,1)	/	0.8069	-0.02	0.01
		0.02 (0,1)	/	0,01 (0,1)	0.9634	-0.01	0.02
		/	0,01 (0,1)	0,01 (0,1)	0.9979	-0.02	0.01
Cadence[2]	PwMS	1.61 (0,6)	2.22 (0,6)	/	0.1398	-0.10	1.33
		1.61 (0,6)	/	-0,90 (0,6)	<.0001*	1.80	3.21
		/	2.22 (0,6)	-0,90 (0,6)	<.0001*	2.41	3.84
	Healthy controls	5.47 (0,7)	5.28 (0,7)	/	0.9916	-1.09	0.71
		5.47 (0,7)	/	0,13 (0,7)	<.0001*	4.45	6.23
		/	5.28 (0,7)	0,13 (0,7)	<.0001*	4.26	6.04
PMF	PwMS	-4.04 (1.23)	1.47 (1.3)	/	0.0070*	1.04	9.98
		-4.04 (1.23)	/	-4.40 (1.2)	0.9999	-3.99	4.72
		/	1.47 (1.3)	-4.40 (1.2)	0.0032*	1.40	10.35
	Healthy controls	0.64 (1.45)	-0,78 (1.5)	/	0.9659	-6.59	3.74
		0.64 (1.45)	/	-2.14 (1.4)	0.5941	-2.26	7.82
		/	-0,78 (1.5)	-2.14 (1.4)	0.9693	-3.68	6.39

[1]significance level <0.05

[2]Data missing from minute 6 till 12 for 10 participants in all conditions

PA: Phase angle; RVL: Resultant vector length; PwMS: Persons with Multiple sclerosis; PMF: Performance motor fatigability

Universitair Ziekenhuis Gent
Afz: Commissie voor Medische Ethiek (UZP074)

UNIVERSITEIT GENT
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	2016/1186	23-nov-16	Zie "CC"

BETREFT

DEFINITIEF ENIG (centraal) ADVIES voor studie met als titel:
Het effect van motorische synchronisatie met auditieve metronoomstimuli en muziek tijdens het wandelen op de stapkwaliteit van de beweging en de waargenomen vermoeidheid bij personen met multiple sclerose (PmMS).
Effect of motor entrainment to auditory cues and music during walking on quality of movement and perceived fatigue in persons with multiple sclerosis (PwMS).

Belgisch Registratienummer: B670201629797

* Begeleidende brief dd. 19/09/2016
* Protocol (E.)
* Verzekeringscertificaat dd. 1/09/2016
* Financiële overeenkomst dd. 7/07/2016 (BOF funding)
* Flyer
* Vragenlijsten
  - Equipment description
  - Dynamic gait balance
  - Neuropsychological batteries
  - Multiple sclerosis walking scale 12
  - Activities-specific balance confidence scale
  - Modified fatigue impact scale
  - Hospital anxiety and depression scale
  - Barcelona music reward questionnaire
  - Dual task questionnaire
  - Credibility and expectations questionnaire
  - BORG scale
  - Music liking and familiarity questionnaire
* CV Marc Leman, Beatrijs De Klerck, Peter Feys, Lousin Moumdjian
* Advies lokale EC's
  - Universiteit Hasselt - advies dd. 05/10/2016 (ontv. 10/10/2016)
  - Revalidatie & MS Centrum Overpelt - advies dd. 11/10/2016 (ontv. dd. 12/10/2016)
  - Nationaal Mutliple Sclerose Centrum Melsbroek - advies dd. 18/10/2016 (ontv. dd. 19/10/2016)
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* Adviesaanvraagformulier (versie 2, dd. 22/11/2016)
* (Patiënten)informatie- en toestemmingsformulier dd. 22/11/2016

Advies werd gevraagd door:
Prof. dr. P. FEYS ; Hoofdonderzoeker

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UW KENMERK	**ONS KENMERK**	**DATUM**	**KOPIE**
	2016/1186	23-nov-16	Zie "CC"

BOVENVERMELDE DOCUMENTEN WERDEN DOOR HET ETHISCH COMITÉ BEOORDEELD.
ER WERD EEN DEFINITIEF ENIG (CENTRAAL) POSITIEF ADVIES GEGEVEN OVER DIT PROTOCOL OP 23/11/2016. INDIEN DE STUDIE NIET WORDT OPGESTART VOOR 23/11/2017, VERVALT HET ADVIES EN MOET HET PROJECT TERUG INGEDIEND WORDEN.
Vooraleer het onderzoek te starten dient contact te worden genomen met Bimetra Clinics (09/332 05 00).

THE ABOVE MENTIONED DOCUMENTS HAVE BEEN REVIEWED BY THE ETHICS COMMITTEE.
A DEFINITIVE SINGLE POSITIVE ADVICE WAS GIVEN FOR THIS PROTOCOL ON, 23/11/2016. IN CASE THIS STUDY IS NOT STARTED BY 23/11/2017, THIS ADVICE WILL BE NO LONGER VALID AND THE PROJECT MUST BE RESUBMITTED.
Before initiating the study, please contact Bimetra Clinics (09/332 05 00).

THIS ADVICE APPEARS IN THE PROCEEDINGS OF THE MEETING OF THE ETHICS COMMITTEE OF 20/12/2016
DIT ADVIES WORDT OPGENOMEN IN HET VERSLAG VAN DE VERGADERING VAN HET ETHISCH COMITE VAN 20/12/2016

- *Het Ethisch Comité werkt volgens 'ICH Good Clinical Practice' - regels*
- *Het Ethisch Comité beklemtoont dat een gunstig advies niet betekent dat het Comité de verantwoordelijkheid voor het onderzoek op zich neemt. Bovendien dient U er over te waken dat Uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid enz., die het resultaat zijn van dit onderzoek.*
- *In het kader van 'Good Clinical Practice' moet de mogelijkheid bestaan dat het farmaceutisch bedrijf en de autoriteiten inzage krijgen van de originele data. In dit verband dienen de onderzoekers erover te waken dat dit gebeurt zonder schending van de privacy van de proefpersonen.*
- *Het Ethisch Comité benadrukt dat het de promotor is die garant dient te staan voor de conformiteit van de anderstalige informatie- en toestemmingsformulieren met de nederlandstalige documenten.*
- *Geen enkele onderzoeker betrokken bij deze studie is lid van het Ethisch Comité.*
- *Alle leden van het Ethisch Comité hebben dit project beoordeeld. (De ledenlijst is bijgevoegd)*

- *The Ethics Committee is organized and operates according to the 'ICH Good Clinical Practice' rules.*
- *The Ethics Committee stresses that approval of a study does not mean that the Committee accepts responsibility for it. Moreover, please keep in mind that your opinion as investigator is presented in the publications, reports to the government, etc., that are a result of this research.*
- *In the framework of 'Good Clinical Practice', the pharmaceutical company and the authorities have the right to inspect the original data. The investigators have to assure that the privacy of the subjects is respected.*
- *The Ethics Committee stresses that it is the responsibility of the promotor to guarantee the conformity of the non-dutch informed consent forms with the dutch documents.*
- *None of the investigators involved in this study is a member of the Ethics Committee.*
- *All members of the Ethics Committee have reviewed this project. (The list of the members is enclosed)*

Het Ethisch Comité UZ Gent heeft rekening gehouden met de adviezen van bovenvermelde lokale ethische commissies.
The Ethics Committee UZGent took into account the advice of the above mentioned non-leading EC's.

Het aangepaste patiënteninformatie- en toestemmingsformulier (versie en datum zoals boven vermeld) werd goed bevonden door het centraal EC UZGent.
Er wordt aangenomen dat dit door de andere lokale EC's aanvaard wordt, tenzij binnen de 5 dagen deelname geweigerd wordt./
The adapted patient informed consent form (version and date as mentioned above) has been acceptedby the leading EC UZGent
It is assumed to have been accepted by the non-leading EC's, unless they refuse to participate within 5 days.

Namens het Ethisch Comité / On behalf of the Ethics Committee
Prof. dr. D. MATTHYS
Voorzitter / Chairman

Bijlage: Aangepast(e) patiënteninformatie- en toestemmingsformulier(en)./
Encl.: Adapted informed consent form(s)

CC: De heer T. VERSCHOORE - UZ Gent - Bimetra Clinics
Nationaal Multiple Sclerose Centrum - Ethisch Comité; Vanheylenstraat 16 1820 Melsbroek
Revalidatie & MS Centrum - Ethisch Comité; Boemerangstraat 2 3900 Overpelt
Universiteit Hasselt - Ethisch Comité; Agoralaan Gebouw D 3590 Diepenbeek
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Informatiebrief voor de deelnemers aan experimenten

1 Titel van de studie:

Het effect van motorische synchronisatie met auditieve metronoomstimuli en muziek tijdens het wandelen op de stapkwaliteit van de beweging en de waargenomen vermoeidheid bij personen met multiple sclerose (PmMS).

2 Doel van de studie:

Men heeft u gevraagd om deel te nemen aan een studie.

Personen met MS (PmMS) hebben moeilijkheden met wandelen, hetgeen kan leiden tot een hoge graad van vermoeidheid. We denken dat synchronisatie met muziek, in hogere mate dan metronoomstimuli of de afwezigheid van auditieve stimuli, bij PmMS de kwaliteit van het wandelen zou kunnen bevorderen en dat het de waargenomen vermoeidheid zou kunnen doen afnemen. Bijgevolg willen we in deze studie onderzoeken a) of PmMS kunnen synchroniseren met muziek, waarbij hun stappen synchroniseren met de beats van de muziek en b) of die synchronisatie met muziek een effect heeft op de kwaliteit en de intensiteit van het wandelen en op de waargenomen vermoeidheid, dat groter is dan synchronisatie met metronoomstimuli of de afwezigheid van auditieve stimuli.

We hypothetiseren dat het onderzoek bepaalde theraptische voordelen met zich mee zou kunnen brengen. We denken bijvoorbeeld dat PmMS door externe auditieve stimuli aan een hogere intensiteit en met een verminderde waargenomen vermoeidheid zouden kunnen trainen. Een ander voordeel zou kunnen worden verwacht voor PmMS met cognitieve problemen, aangezien we zullen onderzoeken of muziek (en metronoomstimuli) haalbare trainingsmiddelen zijn voor deze doelgroep door een statistische analyse uit te voeren. We willen graag benadrukken dat het om een onderzoekstudie gaat met zekere onderzoeksvragen, waarbij de resultaten nog onderzocht dienen te worden.

3 Beschrijving van de studie:

Dit onderzoek zal uitgevoerd worden op gezonde controlepersonen (50) en op personen met MS (50).
Er zullen in totaal vier sessies plaatsvinden (een descriptieve sessie om de referentiewaarden te bepalen en drie experimentele sessies). Alle sessies zullen plaatsvinden in MS centers waarmee we een samenwerkingsverband onderhouden.

De studie wordt uitgevoerd op basis van drie experimentele sessies die elk verschillende onderzoeksvragen hebben:

- In de eerste sessie zullen we descriptieve eigenschappen documenteren en zullen we een interview afnemen om de muziekselectie te personaliseren.
- In de tweede sessie zullen we onderzoeken welk effect spontane synchronisatie (en meer bepaald het proces in de richting van synchronisatie)

met muziek gekarakteriseerd door verschillende tempi, heeft op de wandelkwaliteit.
- In de derde sessie zullen we onderzoeken welk effect bewuste synchronisatie met muziek en met metronoomstimuli heeft op de wandelkwaliteit.
- In de vierde sessie zullen we het effect van drie condities (namelijk stilte, muziek en geluid aan een gepersonaliseerd, optimaal tempo) onderzoeken op de wandelkwaliteit en de waargenomen vermoeidheid.

De verwachte totale duur van de studie is 1 maand.

Figuur 2 in paragraaf 6.2 toont het studieverloop, inclusief de tijd die tussen de verschillende sessies voorzien wordt.

4 Wat wordt verwacht van de deelnemer?

Voor het welslagen van de studie, is het uitermate belangrijk dat u volledig meewerkt met de onderzoeker en dat u zijn/haar instructies nauwlettend opvolgt.

Bovendien moet u onderstaande items respecteren:

- Breng de onderzoeker alsjeblieft tijdig op de hoogte indien u niet aan de geplande sessie kunt deelnemen, zodat een nieuw tijdstip kan worden afgesproken.
- Wees alsjeblieft aanwezig op de afgesproken plaats tien minuten voor de eigenlijke afspraak om een vlotte opeenvolging te verzekeren.

5 Deelname en beëindiging:

De deelname aan deze studie vindt plaats op vrijwillige basis.
Deelname aan deze studie brengt voor u mogelijkerwijze therapeutisch voordeel. We hypothetiseren dat deelnemers therapeutische voordelen zouden kunnen ondervinden, maar de studie zelf zal nog moeten uitwijzen of dat een correcte aanname is. Uw deelname in de studie kan helpen om in de toekomst patiënten beter te kunnen helpen.
U kan weigeren om deel te nemen aan de studie, en u kunt zich op elk ogenblik terugtrekken uit de studie zonder dat u hiervoor een reden moet opgeven en zonder dat dit op enigerlei wijze een invloed zal hebben op uw verdere relatie en/of behandeling met de onderzoeker of de behandelende arts.
Uw deelname aan deze studie zal worden beëindigd als de onderzoeker meent dat dit in uw belang is. U kunt ook voortijdig uit de studie worden teruggetrokken als u de in deze informatiebrief beschreven procedures niet goed opvolgt of u de beschreven items niet respecteert.
Als u deelneemt, wordt u gevraagd het toestemmingsformulier te tekenen.

6 Procedures:

6.1 Procedures:

De inclusiecriteria voor PmMS zijn de volgende:
- Gediagnosticeerd met MS sinds een jaar of langer
- Geen aanval (relapse) in de laatste 1 à 2 maanden
- Vermogen om te wandelen gedurende 12 minuten tegen een snelheid van minimum 0,8 m/s en maximum 1,2 m/s.

De exclusiecriteria voor PmMS zijn de volgende:
- Cognitieve problemen die ervoor zorgen dat de persoon de procedures van het experiment niet verstaat of niet kan uitvoeren
- Gehoorbeschadiging
- Amusia
- Beatdoofheid

Op gezonde controlepersonen zijn dezelfde criteria van toepassing, met uitzondering van de criteria die direct aan MS gelinkt kunnen worden.

De studie zal in totaal een maand duren. Gedurende die maand zullen we vier sessies inplannen, met telkens een week tussen de verschillende sessies.

Sessie een: totale duur van drie uur
- Documentatie van descriptieve eigenschappen (2 uren en 50 minuten)
- Interview met de deelnemer ter personalisatie van de muziekselectie (10 minuten)

Een week later

Sessie twee: totale duur van een uur
- Aanwijzingen en apparatuur (20 minuten)
- Uitvoering van de studie (40 minuten, inclusief rusttijd)

Een week later

Sessie drie: totale duur van twee uur
- Aanwijzingen en apparatuur (20 minuten)
- Uitvoering van de studie (1 uur en 40 minuten, inclusief rusttijd)

Een week later

Sessie vier: totale duur van twee uur
- Aanwijzingen en apparatuur (20 minuten)
- Uitvoering van de studie (1 uur en 40 minuten, inclusief rusttijd)

Er zullen in totaal 100 personen aan deze studie deelnemen (namelijk 50 personen met MS en 50 gezonde controlepersonen).

Hieronder kunt u een gedetailleerde beschrijving vinden van wat elke sessie zal inhouden.

Sessie een (totale duur van drie uur)
- Documentatie van descriptieve eigenschappen
  We zullen u vragen om ons de volgende gegevens te verschaffen:

- Persoonlijke informatie (naam, geslacht, geboortedatum, lengte, gewicht, contactinformatie);
- Opleidingsniveau (aard en duur van de gevolgde opleidingen);
- Informatie gerelateerd aan MS (datum van het eerste symptoom, datum van de diagnosis, type MS, datum van de laatste aanval, vroegere en huidige MS medicatie, medicatie gerelateerd aan)
- Informatie gerelateerd aan muziek
  - Voer je de volgende activiteiten minstens eenmaal per week uit?
    - Dansen
    - Zingen
    - Een instrument bespelen

Vervolgens zullen we u vragen om de volgende tests uit te voeren:

a) Spierzwakte

Motricity Index in het onderste lidmaat

b) Spasticiteit

Modified Ashworth scale in het onderste lidmaat

c) Core stabiliteit

Trunk impairment scale

d) Ataxia

- Dysdiadochokinesia test
- Heel-to-shin test

e) Dynamisch lopen balans

- Time up and go test
- Dynamic gait index
- Sway measurement doon middle van APDM sensors

f) Looppatroon en uithoudingsvermogen

Six minute walking test

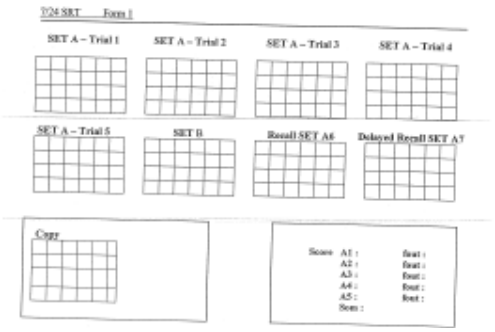
g) Ambulation

Hauser Ambulation index

h) Neuropsychologische batterij

Indien u deze testen reeds in de rekruteringscentra afgelegd heeft in het jaar dat u werd geincludeerd,kunnen de resultaten van de testen uit uw dossier overgenomen worden en zullen we u niet vragen om deze testen nogmaals te doen. Een voorbeeld van een van de betreffende testen voor cognitieve functies kunt u hieronder vinden.

- Brief Repeatable Battery of Rao
  - Buschke selective reminding test (verbal learning and memory)
  - 7/24 spatial recall test (visual learning and recall)
  - Paced auditory serial addition test (sustained attention and information processing speed)
  - World list generation (verbal fluency)
- Stroop test (executive function)
- Symbol digit modality test (information processing speed)



Figuur 1. Spatial recall test- Een voorbeeld van een test in de neuropsychologische testen batterij

i) Dubbele taak protocol

We zullen u vragen om te wandelen terwijl u een beker water vasthoudt en terwijl u cognitieve opdrachten gedurende respectievelijk vijftien seconden en een minuut uitvoert.

j) Vragenlijsten

- Hospital Anxiety and Depression Scale (angst en depressie)
- MS Walking Scale-12 (wandelen)
- Barcelona Music Reward Questionnaire (muziek)
- Modified Fatigue Impact Scale (vermoeidheid)
- Dual Task Questionnaire (dubbele taak)
- Activities-specific balance confidence scale (evenwicht)

Ontwikkeling van een gepersonaliseerde muziekdatabase: we zullen u vragen wat uw favoriete muziek is (genre, jaartal, artiest enzovoort). Vervolgens zullen we een playlist aanmaken van uw favoriete liedjes, gesorteerd per genre.

Sessie twee (totale duur van een uur)

We zullen u voorzien van de D-jogger software, hetgeen op een tablet geïnstalleerd is en in de vorm van een rugzak op uw rug bevestigd zal worden. We zullen u vragen om de rugzak te dragen terwijl u wandelt. Ook zullen we enkele Accelerometers (ook ‘APDM-sensoren’ genaamd) in de vorm van horlogebandjes bevestigen rondom uw polsen, enkels en taille. Vervolgens zullen we u vragen om te wandelen onder zes verschillende condities, telkens door een rustperiode gevolgd. Een voorbeeld van een dergelijke instructie luidt als volgt: ‘U mag beginnen te wandelen. Ondertussen zal u mogelijkerwijze enkele liedjes op de achtergrond horen.’

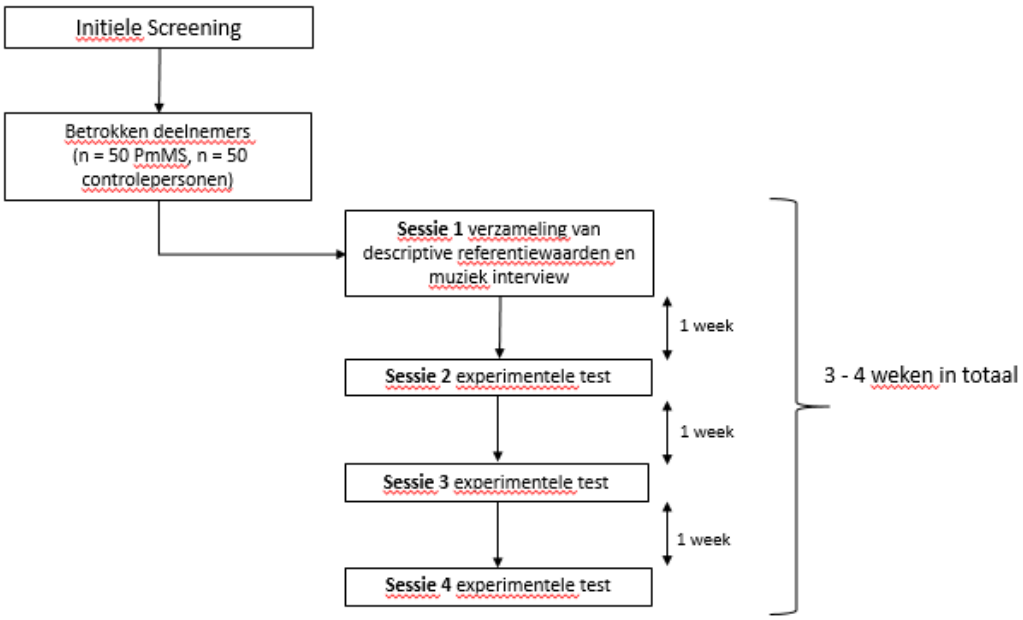
Sessie drie (totale duur van twee uur)
Opnieuw zullen we u vragen om een rugzak te dragen met de D-jogger software evenals de Accelerometers. Verder zal het experiment in deze sessie dezelfde structuur hebben als in de vorige, tweede sessie. Het enige verschil is dat we een andere reeks van zes condities zullen toevoegen. U zal dertig minuten kunnen rusten tussen de twee reeksen.

Sessie vier (totale duur van twee uur)
Opnieuw zullen we u vragen om een rugzak te dragen met de D-jogger software evenals de Accelerometers. Vervolgens zullen we u vragen om te wandelen in drie verschillende condities. Elke conditie zal twaalf minuten duren, met telkens een rustperiode van vijftien minuten tussen de verschillende condities.

In sessie vier zullen we u vragen om de volgende vragenlijsten te beantwoorden:
- Na elke reeks: de BORG-schaal, om uw waargenomen vermoeidheid aan te duiden.
- Na de muziekreeks: de 'Music Familiarity and Liking Questionnaire', een vragenlijst om de mate waarin u vertrouwd was met de beluisterde muziek en de mate waarin u de beluisterde muziek goed vond, na te gaan.
- Na het volledige experiment: de 'Credibility and Expectations Questionnaire', een vragenlijst om uw verwachtingen en indrukken over deze studie na te gaan.

Metingen die tijdens alle sessies uitgevoerd zullen worden: we zullen gegevens verzamelen van de D-Jogger software en van de Accelerometers gedurende de drie experimentele sessies.

6.2 Studieverloop:



Figuur 2 toont het studieverloop, inclusief de tijd die tussen de verschillende sessies voorzien wordt.

7 Risico's en voordelen:

Het risico bestaat dat de deelnemer valt tijdens het wandelen. Echter, om dit risico tot een absoluut minimum te herleiden, zullen onderzoekers met een medische achtergrond te allen tijde naast de deelnemer wandelen.

We denken dat er voordelen met betrekking tot het wandelen en de balans van de deelnemer zouden kunnen zijn. De resultaten van de studie zullen uitwijzen of dat een correcte aanname is.

U hebt het recht op elk ogenblik vragen te stellen over de mogelijke en/of gekende risico's, nadelen van deze studie. Als er in het verloop van de studie gegevens aan het licht komen die een invloed zouden kunnen hebben op uw bereidheid om te blijven deelnemen aan deze studie, zal u daarvan op de hoogte worden gebracht. Mocht u door uw deelname toch enig nadeel ondervinden, zal u een gepaste behandeling krijgen.

Deze studie werd goedgekeurd door een onafhankelijke Commissie voor Medische Ethiek verbonden aan het UZ Gent en wordt uitgevoerd volgens de richtlijnen voor de goede klinische praktijk (ICH/GCP) en de verklaring van Helsinki opgesteld ter bescherming van mensen deelnemend aan klinische studies. In geen geval dient u de goedkeuring door de Commissie voor Medische Ethiek te beschouwen als een aanzet tot deelname aan deze studie.

8 Kosten:

Uw deelname aan deze studie brengt geen extra kosten mee voor U.

9 Vergoeding:

Als vergoeding voor uw erg geapprecieerde deelname, zal u een cinematicket krijgen.

10 Vertrouwelijkheid:

In overeenstemming met de Belgische wet van 8 december 1992 en de Belgische wet van 22 augustus 2002, zal u persoonlijke levenssfeer worden gerespecteerd en zal u toegang krijgen tot de verzamelde gegevens. Elk onjuist gegeven kan op uw verzoek verbeterd worden.

Vertegenwoordigers van de opdrachtgever, auditoren, de Commissie voor Medische Ethiek en de bevoegde overheden hebben rechtstreeks toegang tot Uw medische dossiers om de procedures van de studie en/of de gegevens te controleren, zonder de vertrouwelijkheid te schenden. Dit kan enkel binnen de grenzen die door de betreffende wetten zijn toegestaan. Door het toestemmingsformulier, na voorafgaande uitleg, te ondertekenen stemt U in met deze toegang.
Als u akkoord gaat om aan deze studie deel te nemen, zullen uw persoonlijke en klinische gegevens tijdens deze studie worden verzameld en geanonimiseerd.Verslagen waarin U wordt geïdentificeerd, zullen niet openlijk beschikbaar zijn. Als de resultaten van de studie worden gepubliceerd, zal uw identiteit vertrouwelijke informatie blijven.

11 Letsels ten gevolge van deelname aan de studie:

De onderzoeker voorziet in een vergoeding en/of medische behandeling in het geval van schade en/of letsel tengevolge van deelname aan de studie. Voor dit doeleinde is een verzekering afgesloten met foutloze aansprakelijkheid conform de wet inzake experimenten op de menselijke persoon van 7 mei 2004. Op dat ogenblik kunnen uw gegevens doorgegeven worden aan de verzekeraar.

12 Contactpersoon:

Als er letsel optreedt tengevolge van de studie, of als U aanvullende informatie wenst over de studie of over uw rechten en plichten, kunt U in de loop van de studie op elk ogenblik contact opnemen met:

Uitvoerende onderzoeker
Naam: Lousin Moumdjian, GSM: 0032 (0) 476 63 86 16,
Email: lousin.moumdjian@uhasselt.be, lmoumddj@ugent.be.

Samenwerkende onderzoeker uit Revalitadie & MS Centrum Overpelt
Naam: Veronik Truyens, email: veronik.truyens@msreva.be

Samenwerkende onderzoeker uit Nationaal MS Centrum Melsbroek
Naam: Beatrijs De Klerck, email: beatrijs.deklerck@mscenter.be

Toestemmingsformulier

Ik, _____ heb het document "Informatiebrief voor de deelnemers aan experimenten" pagina 1 tot en met 8, gelezen en er een kopij van gekregen. Ik stem in met de inhoud van het document en stem ook in deel te nemen aan de studie.

Ik heb een kopij gekregen van dit ondertekende en gedateerde formulier voor "Toestemmingsformulier". Ik heb uitleg gekregen over de aard, het doel, de duur, en de te voorziene effecten van de studie en over wat men van mij verwacht. Ik heb uitleg gekregen over de mogelijke risico's en voordelen van de studie. Men heeft me de gelegenheid en voldoende tijd gegeven om vragen te stellen over de studie, en ik heb op al mijn vragen een bevredigend antwoord gekrege

Ik stem ermee in om volledig samen te werken met de toeziende onderzoeker Ik zal hem/haar op de hoogte brengen als ik onverwachte of ongebruikelijke symptomen ervaar.

Men heeft mij ingelicht over het bestaan van een verzekeringspolis in geval er letsel zou ontstaan dat aan de studieprocedures is toe te schrijven.

Ik ben me ervan bewust dat deze studie werd goedgekeurd door een onafhankelijke Commissie voor Medische Ethiek verbonden aan het UZ Gent en dat deze studie zal uitgevoerd worden volgens de richtlijnen voor de goede klinische praktijk (ICH/GCP) en de verklaring van Helsinki, opgesteld ter bescherming van mensen deelnemend aan experimenten. Deze goedkeuring was in geen geval de aanzet om te beslissen om deel te nemen aan deze studie.

Ik mag me op elk ogenblik uit de studie terugtrekken zonder een reden voor deze beslissing op te geven en zonder dat dit op enigerlei wijze een invloed zal hebben op mijn verdere relatie met de onderzoeker.

Men heeft mij ingelicht dat zowel persoonlijke gegevens als gegevens aangaande mijn gezondheid, worden verwerkt en bewaard gedurende minstens 20 jaar. Ik stem hiermee in en ben op de hoogte dat ik recht heb op toegang en verbetering van deze gegevens. Aangezien deze gegevens verwerkt worden in het kader van medisch-wetenschappelijke doeleinden, begrijp ik dat de toegang tot mijn gegevens kan uitgesteld worden tot na beëindiging van het onderzoek. Indien ik toegang wil tot mijn gegevens, zal ik mij richten tot de toeziende onderzoeker die verantwoordelijk is voor de verwerking.

Ik begrijp dat auditors, vertegenwoordigers van de opdrachtgever, de Commissie voor Medische Ethiek of bevoegde overheden, mijn gegevens mogelijk willen inspecteren om de verzamelde informatie te controleren. Door dit document te ondertekenen, geef ik toestemming voor deze controle. Bovendien ben ik op de hoogte dat bepaalde gegevens doorgegeven worden aan de opdrachtgever. Ik geef hiervoor mijn toestemming, zelfs indien dit betekent dat mijn gegevens doorgegeven worden aan een land buiten de Europese Unie. Ten alle tijden zal mijn privacy gerespecteerd worden.

Ik ben bereid op vrijwillige basis deel te nemen aan deze studie.

Naam van de vrijwilliger: _____

Datum: _____

Handtekening:

Ik bevestig dat ik de aard, het doel, en de te voorziene effecten van de studie heb uitgelegd aan de bovenvermelde vrijwilliger.

De vrijwilliger stemde toe om deel te nemen door zijn/haar persoonlijk gedateerde handtekening te plaatsen.

Naam van de persoon
die voorafgaande uitleg
heeft gegeven: _____

Datum: _____

Handtekening:

Naam van de persoon (een locale Belgische onderzoeker met het juiste diploma)
die voorafgaande uitleg
heeft gegeven: _____

Datum: _____

Handtekening:

Ethias
Zetel voor Vlaanderen
Prins-Bisschopssingel 73, 3500 Hasselt
Tel. 011 28 21 11 Fax 011 85 63 10

VERZEKERINGSATTEST

Ethias NV, Prins-Bisschopssingel 73 te 3500 Hasselt, bevestigt dat de waarborgen van polis nr. **45.197.381**, afgesloten door **Universiteit Hasselt**, Martelarenlaan 42 te 3500 Hasselt, binnen de grenzen der algemene en speciale voorwaarden én overeenkomstig de bepalingen van de Wet van 7 mei 2004 inzake de experimenten op de menselijke persoon, van toepassing zijn op de burgerlijke aansprakelijkheid welke, uit hoofde van schade veroorzaakt aan de deelnemers en / of hun rechthebbenden, ten laste gelegd kan worden van de opdrachtgever in het kader van de klinische studie:

"Effect of motor entrainment to auditory cues and music during walking on quality of movement and percieved fatigue in persons with multiple sclerosis".

Deze dekking wordt verleend onder voorbehoud van goedkeuring door de Commissie Medische Ethiek.

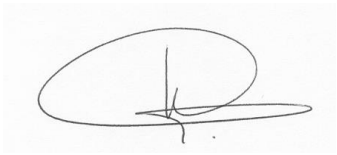
Waarborgbedragen

De waarborg wordt verleend tot beloop van 2.500.000,00 € per schadegeval inzake de lichamelijke, materiële en immateriële gevolgschade vermengd. Voornoemd bedrag maakt tevens de maximale waarborgtussenkomst uit voor de volledige duur van de studie.

Opgemaakt te Hasselt, 1 september 2016.

Voor Ethias,

Voor het Directiecomité



Katrien Germeys
Dienstverantwoordelijke

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Campus Diepenbeek | Agoralaan gebouw D | BE-3590 Diepenbeek
T + 32(0)11 26 81 11 | E-mail: info@uhasselt.be

UHASSELT
KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
25-09	Processing of the data	Promotor: Copromotor: Student(e): Student(e):
23-10	Processing of the data	Promotor: Copromotor: Student(e): Student(e):
06-11	Processing of the data	Promotor: Copromotor: Student(e): Student(e):
27-11	Processing of the data	Promotor: Copromotor: Student(e): Student(e):
06-02	Processing of the data + start writing of the introduction and methodology	Promotor: Copromotor: Student(e): Student(e):
26-02	Start writing of the introduction and methodology (tips, info and feedback)	Promotor: Copromotor: Student(e): Student(e):
13-03	Data organizing	Promotor: Copromotor: Student(e): Student(e):
27-03	Plan of the statistics	Promotor: Copromotor: Student(e): Student(e):
02-04	Discussing analysis	Promotor: Copromotor: Student(e): Student(e):
19-04	Discussing analysis	Promotor: Copromotor: Student(e): Student(e):

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
The effect of prolonged auditory motor coupling on gait and fatigability in persons with multiple sclerosis compared to healthy controls

Richting: **master in de revalidatiewetenschappen en de kinesitherapie-revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen**
Jaar: **2018**

in alle mogelijke mediaformaten, - bestaande en in de toekomst te ontwikkelen - , aan de Universiteit Hasselt.

Niet tegenstaand deze toekenning van het auteursrecht aan de Universiteit Hasselt behoud ik als auteur het recht om de eindverhandeling, - in zijn geheel of gedeeltelijk -, vrij te reproduceren, (her)publiceren of distribueren zonder de toelating te moeten verkrijgen van de Universiteit Hasselt.

Ik bevestig dat de eindverhandeling mijn origineel werk is, en dat ik het recht heb om de rechten te verlenen die in deze overeenkomst worden beschreven. Ik verklaar tevens dat de eindverhandeling, naar mijn weten, het auteursrecht van anderen niet overtreedt.

Ik verklaar tevens dat ik voor het materiaal in de eindverhandeling dat beschermd wordt door het auteursrecht, de nodige toelatingen heb verkregen zodat ik deze ook aan de Universiteit Hasselt kan overdragen en dat dit duidelijk in de tekst en inhoud van de eindverhandeling werd genotificeerd.

Universiteit Hasselt zal mij als auteur(s) van de eindverhandeling identificeren en zal geen wijzigingen aanbrengen aan de eindverhandeling, uitgezonderd deze toegelaten door deze overeenkomst.

Voor akkoord,

Beerens, Lisa **Geelen, Celine**