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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Unlocking the Rhythm of Steps: Auditory-Motor Coupling in Progressive Multiple Sclerosis

Birte Degens
Fenne Kinnaert

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen

PROMOTOR :
Prof. dr. Peter FEYS

BEGELEIDER :
Mevrouw Nele VANBILSEN

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www.uhasselt.be
Universiteit Hasselt
Campus Hasselt:
Martelarenlaan 42 | 3500 Hasselt
Campus Diepenbeek:
Agoralaan Gebouw D | 3590 Diepenbeek

2023
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Setting

This observational case-control study expands upon the data collected in an ongoing PhD project led by Nele Vanbilsen, entitled: *"Understanding the effect of variances on precision in predictive coding when walking to music and metronomes in persons with multiple sclerosis with progressive subtypes"*. The original study received approval from the Medical Ethical Committees of Hasselt University, the National MS Center Melsbroek, and the Noorderhart Rehabilitation and MS Center on January 20, 2021 (B1152020000019). Funding for this study was provided by the *Fonds Wetenschappelijk Onderzoek (FWO*), through two projects: one obtained by prof. dr. Peter Feys, grant number G082021N, and another obtained by dr. Lousin Moumdjian, grant number 1295923N. This study falls under the domain of research focusing on gait and balance, with the following research questions:

1. Can persons with progressive multiple sclerosis (PwPMS) synchronize at different tempi to music and metronomes compared to healthy controls (HCs)?
2. What tempi and type of auditory stimuli lead to the best synchronization for PwPMS compared to HCs?
3. What is the impact of different tempi and auditory stimuli on spatiotemporal parameters?

These research questions were formulated in consultation with our mentor, dra. Nele Vanbilsen. Our thesis aims to assess the feasibility of synchronization to music and metronomes among PwPMS and its impact on gait. The goal is to pave the way for the development of a novel therapeutic approach within the clinical setting, focused on functional therapy to enhance gait and physical activity among PwPMS. Clinical tests were conducted in various locations, including Hasselt University, the National MS Center Melsbroek, the library of Ghent (De Krook), and the Noorderhart Rehabilitation and MS Center. This study was authored by Birte Degens and Fenne Kinnaert. While Nele Vanbilsen mainly conducted the tests, both authors actively participated in patient recruitment and were involved in at least ten testing session. Statistics, data analysis, discussion, conclusion, and abstract were performed and written together. The introduction was originally drafted by Birte Degens and refined by Fenne Kinnaert, while for the methods, the roles were reversed. Additionally, both authors contributed to the creation of figures and tables, presented in this thesis.

Abstract

Background. Persons with progressive multiple sclerosis (PwPMS) often experience severe walking difficulties. Exercise training studies for PwPMS are scarce and have small effects, so functional training like auditory-motor coupling (AMC) is proposed. AMC involves walking to beats in music and metronomes at different tempi. Both high and low tempi are explored, as the effects of low tempi are unstudied in this population.

Objectives. Investigating if PwPMS, compared to healthy controls (HCs), can synchronize their gait to music and metronomes at different tempi and the effects of the tempi and auditory stimuli on spatiotemporal parameters.

Methods. 19 PwPMS and 16 HCs, completed the experimental session. Participants walked 3 minutes to each tempo (-4%, -8%, 0%, 4%, 8%) to music and metronomes. Statistical analysis used mixed-model ANOVA, Tukey's test, linear regression, and one-way ANOVA in SAS JMP Pro.

Results. A higher synchronization consistency can be seen for metronome conditions compared to music and for HCs compared to PwPMS. Highest synchronization consistency for PwPMS was at -4% and 0% compared to the high tempo 8%. Gait speed and cadence was adapted to various tempi. Greater variability in gait parameters was seen for PwPMS compared to HCs.

Conclusion. PwPMS can synchronize steps to beats in music and metronomes, with the highest consistency at comfortable speed and -4% to the metronome condition. However, the metronome condition resulted in more variability in gait parameters and a less persistent gait compared to music.

Keywords. Auditory-motor coupling, synchronization, music, metronome, gait, progressive multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease affecting the central nervous system (CNS), characterized by demyelination and axonal degeneration (Klineova & Lublin, 2018). Relapsing-remitting MS (RRMS) shows recovery after episodes, secondary progressive MS (SPMS) progresses after RRMS, and primary progressive MS (PPMS) entails continuous deterioration from onset (Klineova & Lublin, 2018). Recently, there has been recognition of a continuum within MS. Progressive subtypes can be characterized within the continuum as a failure of compensatory mechanisms accompanied by extensive inflammation and neurodegeneration (Kuhlmann et al., 2023). MS symptoms exhibit considerable heterogeneity (Klineova & Lublin, 2018). Progressive multiple sclerosis (PMS) manifests in the deterioration of various symptoms such as cognition, fatigue, muscle weakness, visual symptoms, bladder symptoms, walking, and balance (Pozzilli et al., 2023). These manifestations in PMS are significantly more pronounced, leading to a more substantial impact on the individual (Pozzilli et al., 2023). About 4 in 5 people with MS develop problems with walking within 10-15 years after onset of the disease (Feinstein et al., 2015). These walking problems affect physical activity (PA), since walking is a major component of PA (Pedullà et al., 2023). The Expanded Disability Status Scale (EDSS) describes MS progression and assesses treatment effectiveness in clinical trials, using a scale from 0 (normal) to 10 (MS-related death) in 0.5 increments after reaching EDSS 1 (Meyer-Moock et al., 2014). Understanding constraints in this population aids in developing tailored interventions, treatment plans, and assistive technologies, improving overall quality of life.

Prior studies mainly addressed exercise training for enhancing walking in MS, primarily focusing on (RRMS). While exercise training may affect walking in PMS, evidence supporting this remains insufficient (Baird et al., 2018). Many studies examine auditory stimuli in neurological diseases like Parkinson's and RRMS, but the benefits of synchronization for PMS-related issues are unclear. This study aims to explore how synchronization may reduce walking symptoms and positively impact steps in persons with progressive multiple sclerosis (PwPMS). Synchronization involves aligning steps to the beats in music or metronomes based on error prediction correction (Leman, 2007). Once they lock in time, synchronization is established (Moumdjian et al., 2018). Auditory-motor-coupling (AMC) involves individuals with gait disorders synchronizing their steps with either music or metronome signals as a form of intervention (Leow et al., 2021). A study by Moumdjian et al. (2019) explored synchronization in RRMS using different fast tempi and various types of music or metronomes. They used both stimuli because they expected a difference, with music experiencing less perceived fatigue. Their findings suggest that coupling walking to music at an individualized pace (min. +2%, max. +8%) can be used for functional gait training in RRMS, although this study was a case control study (Moumdjian et al., 2019).

In this study, we focus on PMS, this includes SPMS and PPMS, as little research has been done on this to date. This study investigates a task-oriented approach strategy focused on walking with music or metronomes specifically for PwPMS. This approach involves repeated practice of functional tasks, such as walking, which has shown promise by providing intensive multisensory input (vision, vestibular, proprioceptive) (Baird et al., 2018). The input facilitates reorganization in the CNS and improves task performance (Baird et al., 2018). This study examines gait dynamics in relation to music and metronome coupling by analyzing temporal correlations in step intervals. The distinction between music and metronomes lies in the alpha values, with music exhibiting higher alpha values than metronomes (Moumdjian et al., 2020). The study employed both metronomes and music, with findings indicating that metronomes are easier to follow than music due to their less complex rhythm (Schaefer, 2014). Both fast and slow tempi were used to test adaptability. This could be important because neurological patients often process auditory sounds with longer tendencies, indicating that slow tempi with longer inter-beat intervals might be more helpful (Vanbilsen et al., 2023).

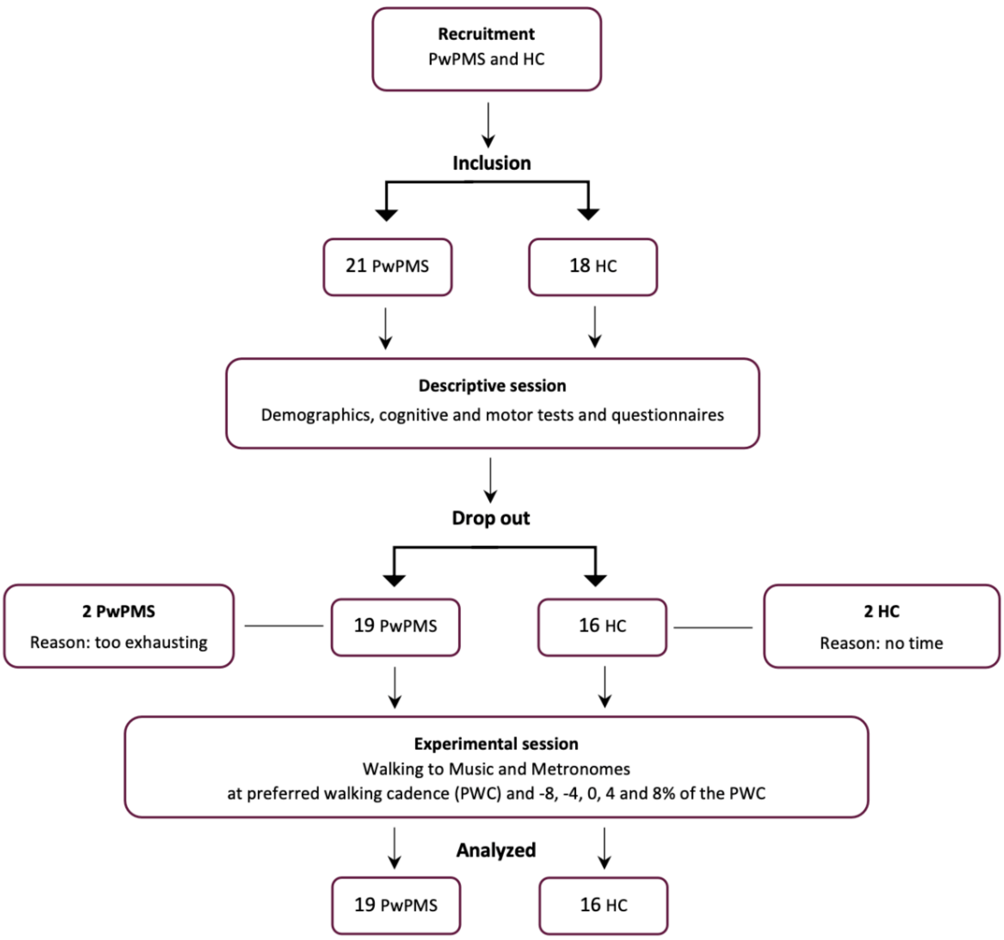
This study aims to investigate the potential of AMC in aiding rehabilitation to improve walking-related problems in PwPMS, focusing on its feasibility. To achieve this, the following questions are answered. Can PwPMS synchronize at different tempi to music and metronomes compared to healthy controls (HCs)? What tempi and type of auditory stimuli lead to the best synchronization for PwPMS compared to HCs? What is the impact of different tempi and auditory stimuli on spatiotemporal parameters? Within these research questions, we will also explore whether the EDSS score, cognition and balance have an influence. We predict that PwPMS will show poorer synchronization abilities than HCs, especially with music versus metronomes. Higher tempi are expected to reduce synchronization consistency and increase gait parameter variability.

Methods

This observational case-control study was approved by the Medical Ethical Committees of Hasselt University, the National MS Center Melsbroek, and the Noorderhart Rehabilitation and MS Center on January 20, 2021 (B1152020000019). Participants were recruited using study flyers in the MS centers and advertisements on MS-related social media platforms such as the University MS Center (UMSC). Prior to commencing the experimental sessions, participants agreed to, and signed the informed consent form, while also receiving detailed information about the sessions. Inclusion criteria comprised a diagnosis of MS (> 1 year), absence of exacerbation in the preceding month, an average comfortable walking speed of 0.4 m/s during 3 minutes of walking and being older than 18 years. Exclusion criteria included pregnancy, amusia, hearing impairment, or cognitive impairment hindering the understanding of the study instructions.

Figure 1

Flowchart



Note. Flowchart illustrating the study selection process, participant flow and experimental procedure; PwPMS, persons with multiple sclerosis progressive subtype; HC, healthy controls.

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

Session 1: Descriptive demographic and clinical information

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

Motor functions. Assessments included the 6-Minute Walking Test (6MWT) (Goldman et al., 2008), Dynamic Gait Index (DGI) (Shumway-Cook et al., 1997), Timed 25-Foot Walk (T25FW) (Hauser et al., 1983), and Timed Up and Go (TUG) (Podsiadlo & Richardson, 1991) to measure mobility and dynamic balance. The Modified Ashworth Scale (MAS) (Ashworth, 1964) assessed muscle tone in the hamstrings and quadriceps, while the Motricity Index (MI) (Demeurisse et al., 1980) evaluated muscle strength in the lower extremities.

Cognitive functions. Participants underwent assessments such as the Buschke Selective Reminding Test (BSRT) (Hannay & Levin, 1985) for verbal learning and memory, the 7/24 Spatial Recall Test (Gontkovsky et al., 2004) for visual learning and recall, and the Controlled Oral Word Association Test (COWAT) (Ruff et al., 1996) for verbal fluency. The Paced Auditory Serial Addition Test (PASAT) (Gordon & Zillmer, 1997) evaluated sustained attention, auditory information processing speed, and flexibility, and the Symbol Digit Modalities Test (SDMT) (Smith, 1973) for information processing speed. The Stroop Color Test (Stroop, 1935) focused on executive function and inhibitory control.

Self-reported questionnaires. Walking ability was further analyzed using the twelve-item Multiple Sclerosis Walking Scale (MSWS-12) (Hobart et al., 2003). The Activities Specific Balance Confidence Scale Dutch-version (ABC-NL) (Powell & Myers, 1995) was used to measure participants' confidence in avoiding falls during specific activities and the Modified Fatigue Impact Scale (MFIS) (Mills et al., 2010) to assess the impact of fatigue on daily living. The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) detects symptoms of depression or anxiety and the Barcelona Music Reward Questionnaire (BMRQ) (Mas-Herrero et al., 2013) provided insight into global sensitivity to music reward.

Session 2: Experimental session

Participants were equipped with APDM sensors (OPAL, USA, Figure 2) to measure spatiotemporal gait parameters. Three portable sensors were used, with two attached to the participants' feet and one to their sternum. Additionally, they were equipped with the D-jogger (Figure 3). The D-jogger consisted of headphones, two ankle sensors, and a laptop equipped with specialized software (Moens et al., 2014). This apparatus delivered auditory stimuli at varying tempi through the headphones, simultaneously assessing gait-music synchronization and gait dynamics. A personalized music database was utilized, encompassing songs with tempi ranging from 80 to 130 beats per minute. The songs were categorized into six genres: disco, pop, soft pop, pop rock, instrumental, and variety. Participants were asked to select one of these genres to walk to, accordingly, the system selected a song matched to each specific tempo within the chosen genre. The experiment was conducted in a room, and participants were asked to walk for 3 minutes to each tempo in a big rectangle. For standardization, we measured a rectangle of 6 by 8 meters in each testing location.

Figure 2

APDM Sensors

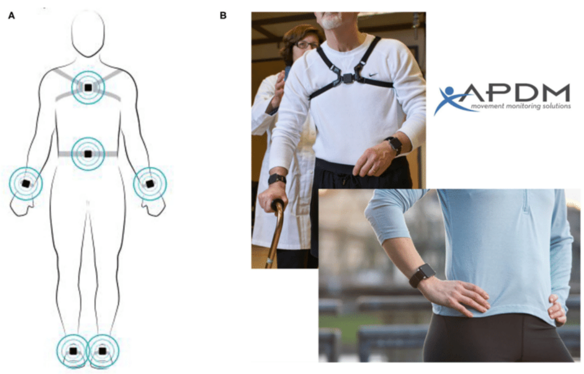
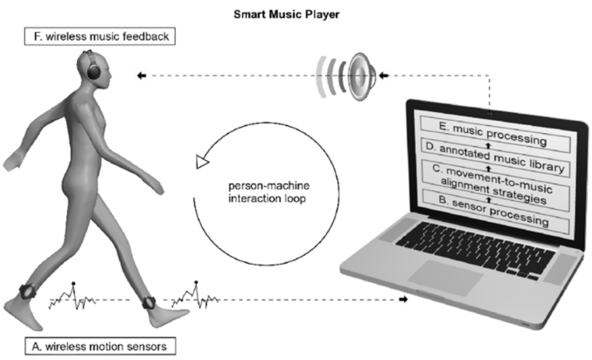


Figure 3

The D-jogger



Prior to conducting the experimental conditions, participants were asked to walk 3 minutes on the 'walking path' to quantify cadence, stride length and gait speed. Participants then underwent a familiarization task involving the song "Sanctum" by the artist "Shades of the Abyss". This task was administered to instruct participants to synchronize their steps with the beat of the music. Participants were asked to walk to five conditions for 3 minutes each in two blocks of music and metronomes. The conditions were -8%, -4%, 0%, 4%, and 8% of their individual baseline cadence. The order of administration of blocks and conditions within blocks were randomized. Each condition entailed walking for 5 seconds in silence, followed by 3 minutes with the auditory stimuli, and concluding with 4 minutes of rest.

Primary outcome measures

The primary outcome measures are related to synchronization accuracy and consistency. For a detailed overview please see Moumdjian (2018).

Relative Phase Angle (rPA). A measure for the accuracy of the synchronization expressed in degrees, measuring the timing of the footfall relative to the beat. This can be either negative, footfall before the beat, or positive, footfall after the beat.

Resultant Vector Length (RVL). The RVL is a measure from 0-1 and measures the stability of the rPA over time. A steep distribution of the rPAs over time results in a high RVL (maximum value of 1) and would indicate that all footfalls coincide with the beat. Conversely, a low RVL (minimum value of 0) suggests an inconsistent synchronization with a broad and multimodal distribution of the rPA over time. A cut-off score of 0.7 was established, a score greater than or equal to 0.7 represents consistent synchronization (Moumdjian et al., 2019).

Secondary outcome measures

Secondary outcome measures include the mean and coefficient of variation (CoV) of the following spatiotemporal gait parameters: cadence (steps/min), gait speed (m/s) and stride length (m).

Alpha. A metric to quantify the anti-persistence of the gait pattern in terms of gait dynamics (Hausdorff et al., 1995). It is delineated by a numerical value within the range of 0 to 1. A value above 0.5 signifies reduced variability in the gait cycle, indicating greater persistence in the steps taken. Detrended fluctuation analysis was applied to compute this outcome, replicating the methodological approach conducted in our previous work (Moumdjian et al., 2020).

Statistical analysis

The descriptive data was tested for normality using the Shapiro-Wilk test. Subsequently, normally distributed data were subjected to analysis using a t-test to explore inter-group differences. For non-normally distributed data, analysis was performed using the Wilcoxon signed-rank test. The secondary outcome measures are reported as a percentage changes for subsequent analytical procedures. A mixed model analysis of variance (ANOVA) was applied to the primary (RVL and rPA) and the secondary (cadence, speed, stride length and alpha) outcome measures, with group (HCs vs PwPMS), condition (music vs metronomes) and experimental tempi (-8%, -4%, 0%, 4%, 8%) as between-subjects factors. A multiple comparisons Tukey's test was further performed as a post hoc test when interactions were present. In order to be certain that the results found in the gait dynamics (alpha) were not due to random processes observed within the experimental data, surrogate time series were created by shuffling each original time series collected for each participant and experimental condition 50 times. Thereafter, the same statistics were calculated on alpha shuffled and compared with the statistical results of alpha.

Additionally, a linear regression analysis was performed on the effect of TUG, EDSS, SDMT and PASAT on synchronization consistency (RVL). For significant outcomes, an additional one-way ANOVA was performed on the group with poor and the group with good TUG scores, the cut-off was based on the median scores. All analyses were performed using SAS JMP Pro. To choose the right analysis, a decision tree was consulted (see Appendix 1 and 2).

Results

Participants

As seen in Figure 1, in total, 21 PwPMS and 18 age and gender-matched HCs were included in the study. Two participants from both groups dropped out, and thus experimental data was analyzed on 19 PwPMS and 16 HCs.

No significant differences were found in age, gender, and education between HCs and PwPMS. A t-test was not conducted for the motor functions and self-reported questionnaires as they were only assessed for PwPMS.

Table 1 illustrates notable differences in the mean baseline cadence ($t = -3.11$, $p = 0.0040$), mean stride length ($t = -2.71$, $p = 0.0109$), and mean gait speed ($t = -3.30$, $p = 0.0024$) between HCs and PwPMS. Furthermore, significant differences are observed in the CoV for baseline cadence ($t = 3.06$, $p = 0.0053$), stride length ($t = 4.09$, $p = 0.0003$), and gait speed ($t = 2.82$, $p = 0.0070$) between HCs and PwPMS. Significant differences are evident in the cognitive functions, with notable differences observed in Buschke ($t = 5.19$, $p = <.0001$), PASAT ($t = -5.46$, $p = <.0001$), SDMT ($t = -5.52$, $p = 0.0096$), Stroop Color Test I (seconds) ($t = 3.42$, $p = 0.0017$), and Stroop Color Test III (seconds) ($t = 1.47$, $p = 0.0160$).

Primary outcome measures

Resultant Vector Length. Figure 4A. Overall, all participants demonstrated the ability to synchronize to the different tempi. Significant main effects were observed for group ($F(1,43) = 5.87$, $p = 0.0188$), condition ($F(1,280) = 19.45$, $p < .0001$), and tempi ($F(4,280) = 3.66$, $p = 0.0064$). Overall, HCs synchronized significantly more consistently (mean RVL over all tempi and condition = 0.85) than PwPMS (mean RVL over all tempi and condition = 0.56) ($t = 2.44$, $p = 0.0188$). More consistent synchronization was found for metronomes (RVL = 0.75) compared to music (RVL = 0.63) in both groups across tempi.

For tempi, post hoc testing showed a significantly higher RVL for tempo -4% compared to tempo 8% ($t = 2.94$, $p = 0.0036$) and tempi 0% ($t = 3.49$, $p = 0.0006$) compared to tempo 8%.

Significant interactions were found between group*condition*tempi ($F(4,280) = 2.92$, $p = 0.0217$). Post-hoc analyses indicate a significantly higher RVL for HCs compared to PwPMS when walking to a) the metronome condition at all tempi except for -8% (tempi -4%: $t = 2.19$, $p = 0.0328$; 0%: $t = 2.60$, $p = 0.0118$; 4%: $t = 3.68$, $p = 0.0005$; 8%: $t = 3.55$, $p = 0.0008$),

b) the music condition, at tempi -4% (t = 3.22, p = 0.0021); 0% (t = 2.98, p = 0.0042) and 4% (t = 3.15, p = 0.0026). Within the PwPMS group the combination of metronome with tempi -4% (RVL mean = 64.71, t = 3.54, p = 0.0005) or 0% (RVL mean = 63.50, t = 2.78, p = 0.0058) resulted in the best synchronization consistency.

Table 1

Demographic, MS-Specific, Motor and Cognitive Characteristics and Self-Reported Questionnaires of the Study Participants

Descriptive Information	PwPMS (n= 19)	HC (n = 16)	t Test (Prob > ltl)
Demographic			
Age (years)	52.42 ± 2.13	56.50 ± 2.32	ns
Gender (M/F)	13/6	6/10	ns[a]
Education (years)	7.11 ± 0.57	8.63 ±0.62	ns
EDSS (1-10))	4.24 ± 1.13	/	N/A
Motor functions			
6MWT (m)	362.70 ± 108.26	/	N/A
DWI (%)	1.05 ± 25.03	/	N/A
DGI (24)	20.17 ± 5.73	/	N/A
T25WT (s)	8.43 ± 2.24	/	N/A
TUG (s)	11.45 ± 5.25	/	N/A
MAS LEFT (LL)	1.26 ± 0.93	/	N/A
MAS RIGHT (LL)	1.53 ± 0.90	/	N/A
MOTRICITY LEFT (LL)	28.47 ± 6.31	/	N/A
MOTRICITY RIGHT (LL)	23.37 ± 4.80	/	N/A
Spatiotemporal parameters / baseline			
Gait CADENCE MEAN (steps/min)	96.29 ± 3.32	111.61 ± 3.64	.0040
Gait STD (steps/min)	3.06 ± 0.25	2.23 ± 0.28	.0179[a]
Gait CADENCE COV (steps/min)	0.03 ± 0.003	0.02 ± 0.003	.0053[a]
Gait stride length MEAN (m)	1.05 ± 0.04	1.22 ± 0.05	.0109
Gait stride length STD (m)	0.04 ± 0.003	0.03 ± 0.003	.0044
Gait stride length COV (m)	0.04 ± 0.002	0.03 ± 0.003	.0003
Gait speed MEAN (m/s)	0.86 ± 0.05	1.14 ± 0.06	.0024
Gait speed STD (m/s)	0.05 ± 0.004	0.04 ± 0.004	ns[a]
Gait speed COV (m/s)	0.06 ± 0.005	0.04 ± 0.006	.0070[a]
Cognitive functions			
Buschke SRT (a.u.)	37.47 ± 2.11	21.25 ± 2.30	<.0001
7 / 24 SRT(a.u.)	29.32 ± 0.95	31.13 ± 1.03	ns[a]
COWAT	35.16 ± 1.96	35.75 ± 2.13	ns
PASAT (a.u.)	36.42 ± 1.50	48.50 ± 1.63	<.0001[a]
SDMT (N)	50.89 ± 2.20	59.06 ± 2.39	.0096
Stroop Color Test I (seconds)	56.68 ± 1.35	49.88 ± 1.47	.0017
Stroop Color Test II (seconds)	67.16 ± 1.48	64.00 ±1.61	ns
Stroop Color Test III (seconds)	97.68 ± 2.32	92.63 ± 2.53	0.0160[a]
Self-reported questionnaires			
MSWS-12 (100)	61.20 ±20.37	/	N/A
MFIS total score (84)	46.44 ± 14.04	/	N/A
MFIS physical part (36)	21.44 ± 5.32	/	N/A
MFIS cognitive part (40)	18.89 ± 8.14	/	N/A
MFIS psychological part (8)	4.17 ± 1.42	/	N/A
ABC-NL (160)	94.94 ± 45.10	/	N/A
BMRQ (100)	68.67 ± 9.89	/	N/A
HADS (42)	13.83 ± 7.43	/	N/A

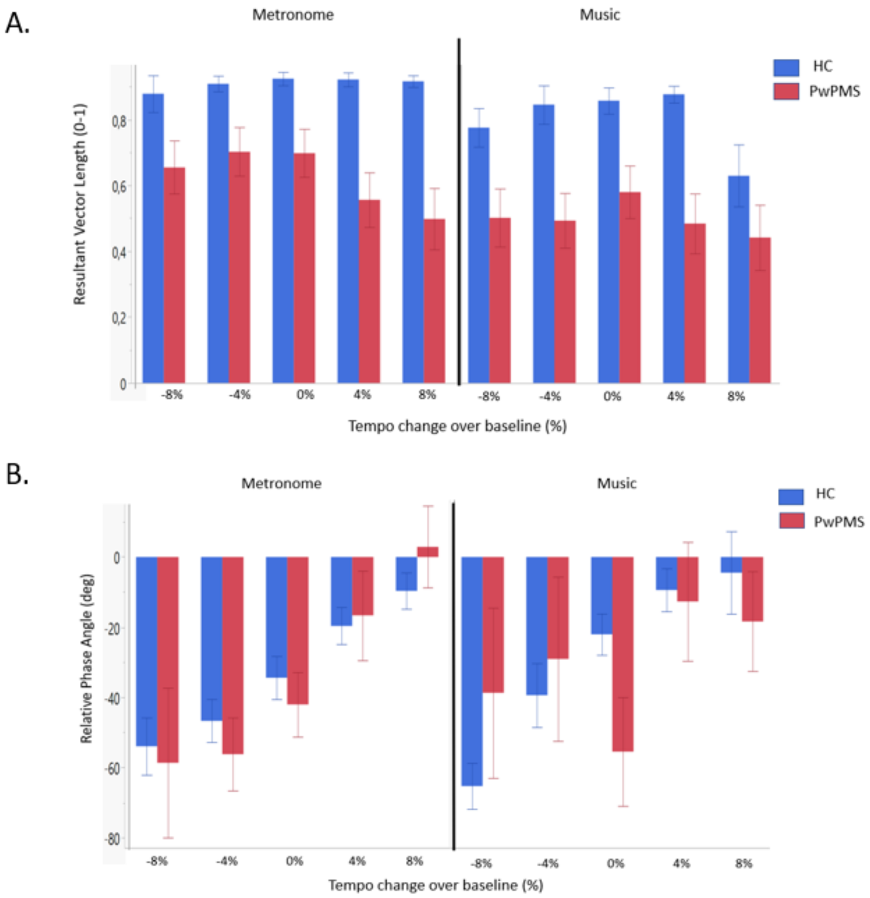
Note. PwPMS, persons with progressive multiple sclerosis; HC, healthy controls; M, male; F, female; EDSS, Expanded Disability Status Scale; 6MWT, 6-minuten walking test; DWI, distance walking index; DGI, Dynamic Gait Index; T25FW, Time 25 Foot Walk; TUG, Timed Up and Go; a.u., arbitrary units; STD, Standard deviation; CoV, Covariance; MAS, Modified Ashworth Scale; Buschke SRT, Buschke Selective Reminding Test; 7/24 SRT, Spatial Recall Test; COWAT, Controlled Oral Word Association Test; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modality Test; MSWS-12, Multiple Sclerosis Walking Scale–12; MFIS, Modified Fatigue Impact Scale; ABC-NL, Activities-Specific Balance Confidence; BMRQ, Barcelona Music Reward Questionnaire; HADS, Hospital Anxiety and Depression Scale; ns, not significant; N/A, not applicable. [a] Signifies the use of the nonparametric Wilcoxon signed rank test (Prob > |Z|), for the non-normally distributed data.

Relative Phase Angle. In general, all participants anticipated the beat (Figure 4B). Significant main effects were observed for tempi ($F(4,269) = 11.00$, $p < .0001$). No significant interactions were found. The initial post hoc analysis revealed that participants have a significantly lower rPA at negative tempi and at tempo 0% compared to positive tempi, indicating an earlier anticipation to these slow tempi. (tempi -8% vs. -4%, $t = -1.33$, $p < .0001$; -8% vs. 8%, $t = -5.56$, $p < .0001$; -4% vs. 4%, $t = -3.40$, $p = 0.0008$; -4% vs. 8%, $t = -4.24$, $p < .0001$; tempi 0% vs. 4%, $t = -2.79$, $p = 0.0057$; 4% vs. 8%, $t = -0.84$, $p = 0.0004$).

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

Figure 4

Primary Outcome Measures in Relation to Group, Condition and Tempi



Note. Synchronization consistency and relative phase angle of persons with progressive multiple sclerosis (PwPMS) and healthy controls (HC) walking to metronomes and music at different tempi, -8%, -4%, 0% and 4% and 8% of preferred walking cadence. (A) Resultant vector length and (B) Relative phase angle. Mean standard errors are shown.

Table 2

Experimental Results of Walking to Music and Metronomes

		Experimental conditions tempi																			
		-8%				-4%				0%				4%				8%			
		PwPMS		HC		PwPMS		HC		PwPMS		HC		PwPMS		HC		PwPMS		HC	
Outcomes measure	Auditory stimuli	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Resultant vector lenght (0-1)	Music	0.50	0.38	0.78	0.23	0.49	0.36	0.85	0.23	0.58	0.34	0.86	0.15	0.48	0.39	0.88	0.10	0.44	0.42	0.63	0.36
	Metronome	0.66	0.34	0.88	0.22	0.70	0.31	0.91	0.09	0.70	0.31	0.92	0.08	0.56	0.35	0.92	0.08	0.50	0.40	0.92	0.07
Relative phase angle (degrees)	Music	0.61	0.23	0.55	0.28	0.54	0.28	0.43	0.28	0.56	0.30	0.42	0.24	0.58	0.32	0.42	0.21	0.54	0.29	0.65	0.39
	Metronome	0.45	0.24	0.28	0.18	0.35	0.20	0.38	0.35	0.36	0.27	0.26	0.19	0.46	0.25	0.24	0.15	0.47	0.22	0.38	0.20
Cadence (percentage change from baseline)	Music	-7,28	26.52	-5,8	4.03	-2,38	6.82	-4,15	1.46	-5,86	16.77	0.14	0.55	-1,33	11.87	3.18	2.25	-0,8	12.27	4.91	4.38
	Metronome	-6,82	17.10	-7,12	2.44	-7,83	14.15	-3,75	1.62	-4,21	12.95	0.10	1.61	-2,66	14.93	3.52	1.50	0.33	10.38	7.39	1.25
Speed (percentage change from baseline)	Music	-8,52	20.78	-8,61	10.72	-5,52	18.13	-5,54	8.56	-5,91	13.87	-1,46	8.60	-4,68	18.13	2.97	8.56	-2,58	18.24	2.62	10.72
	Metronome	-15,1	18.76	-12,2	8.46	-10,7	13.41	-6,65	5.29	-9,03	17.49	-1,67	5.65	-6,97	20.46	2.07	6.18	-6,25	18.83	6.18	6.09
Stride length (percentage change from baseline)	Music	-5,92	21.35	-3,02	8.15	-2,33	5.88	-1,46	6.47	-1,76	7.20	-1,28	8.55	-5,27	13.20	-0,15	8.44	-5,18	18.12	-2,3	7.54
	Metronome	-9,30	14.79	-5,88	7.84	-4,08	9.00	-3,05	4.42	-4,67	7.68	-1,72	5.28	-6,04	13.18	-1,45	5.77	-5,16	11.35	-1,11	5,73
Cadence CoV	Music	0.04	0.02	0.02	0.01	0.03	0.02	0.02	0.01	0.03	0.01	0.02	0.01	0.03	0.01	0.02	0.01	0.03	0.01	0.03	0.01
	Metronome	0.04	0.02	0.02	0.02	0.03	0.02	0.02	0.01	0.03	0.02	0.02	0.01	0.03	0.01	0.02	0.01	0.03	0.02	0.03	0.01
Speed CoV	Music	0.07	0.02	0.05	0.03	0.07	0.03	0.04	0.02	0.06	0.02	0.04	0.02	0.06	0.03	0.04	0.03	0.06	0.03	0.05	0.02
	Metronome	0.09	0.08	0.05	0.05	0.07	0.03	0.04	0.01	0.06	0.03	0.04	0.02	0.06	0.03	0.04	0.02	0.08	0.05	0.04	0.02
Stride length COV	Music	0.05	0.02	0.04	0.02	0.05	0.02	0.03	0.02	0.05	0.02	0.03	0.02	0.05	0.02	0.03	0.02	0.05	0.02	0.04	0.02
	Metronome	0.07	0.05	0.04	0.01	0.05	0.03	0.03	0.01	0.05	0.03	0.04	0.02	0.05	0.03	0.03	0.01	0.07	0.07	0.03	0.01
Alpha	Music	0.61	0.23	0.55	0.28	0.54	0.28	0.43	0.28	0.56	0.30	0.42	0.24	0.58	0.32	0.42	0.21	0.54	0.39	0.65	0.29
	Metronome	0.45	0.24	0.28	0.18	0.35	0.20	0.38	0.35	0.36	0.27	0.26	0.19	0.46	0.25	0.24	0.15	0.47	0.22	0.38	0.20

Note. PwMS, persons with progressive multiple sclerosis; HC, healthy controls; SD, standard deviation.

Secondary Outcome Measures

Data presented below are percentage change of the parameters during the experimental condition compared to the individual baseline condition.

Cadence. Significant main effects were identified for tempi ($F(4,277) = 26.80$, $p < .0001$). No significant interactions were found. Post hoc comparisons showed that both PwPMS and HCs adjust their cadence by taking less steps to lower tempi and more steps per minute at higher tempi (Figure 5A).

Speed. Significant main effects were observed for condition ($F(1,277) = 9.82$, $p = 0.0019$) and tempi ($F(4,277) = 31.25$, $p < .0001$), indicative that persons walked with a significantly lower speed with metronomes compared to the music condition and that speed was adjusted to the different tempi. An interaction effect of group*tempi was found ($F(4,277) = 3.72$, $p = 0.0058$). Additionally, post hoc analysis revealed that HCs showed significantly reduced gait speed at lower tempi and increased speed at higher tempi. However, PwPMS showed fewer disparities in gait speed across different tempi, particularly at higher speeds (Figure 5C).

Stride length. A significant main effect of tempi ($F(4,277) = 2.46$, $p = 0.0455$) was found indicating that participants decreased their stride length when walking to 0% ($t = -2.95$, $p = 0.0035$), as well as when walking at tempo -8% compared to tempi -4% ($t = -2.25$, $p = 0.0252$), 4% ($t = -2.17$, $p = 0.0307$) and 8% ($t = -2.01$, $p = 0.0453$) (Figure 6A).

Variability in spatiotemporal gait parameters. No significant interactions were identified. Higher variability in gait parameters were observed for PwPMS compared to HCs as well as for metronomes compared to music conditions.

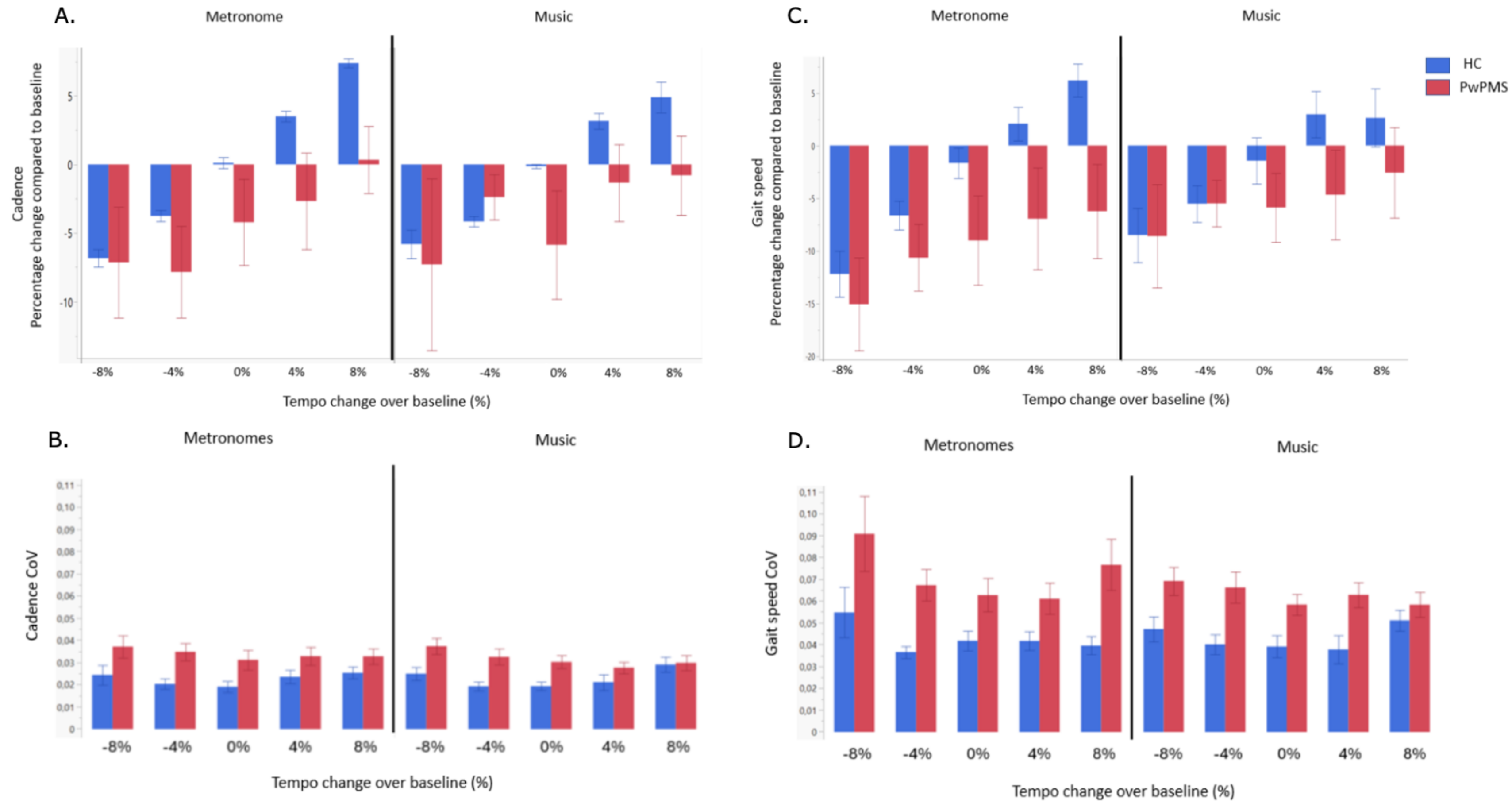
Speed CoV. A significant effect of group ($F(1,74) = 9.92$, $p = 0.0024$), session ($F(1,290) = 5.89$, $p = 0.0158$) and tempi ($F(4,290) = 4.08$, $p = 0.0031$) can be identified (Figure 5D). No significant interactions were found. Post hoc testing shows that there is a significantly lower variability in speed for HCs compared to PwPMS ($t = -3.15$, $p = 0.0024$), but a significantly higher variability in speed for metronomes compared to music ($t = 2.43$, $p = 0.0158$). Post hoc testing for tempi showed only significant differences between tempo -8 compared to tempo -4 (t = 3.15, p = 0.0018), 0 (t = 3.44, p = 0.0007), 4 (t = 3.17, p = 0.0017) and 8, but only a small effect (t = 2.06, p = 0.0404).

Cadence CoV. Significant primary effects (Figure 5B) were identified for group (F(1,72) = 8.84, p = 0.0040) and tempi (F(4,290) = 3.20, p = 0.0136). No significant interactions were found. The first post hoc examination showed that the PwPMS show a higher variability in cadence when compared to HCs (t = -2.97, p = 0.0040). The second post hoc analysis showed that there is a significantly higher variability in cadence at tempo -8 compared to tempo -4 (t = 2.27, p = 0.0237), tempi -8 and 0 (t = 3.10, p = 0.0021) and tempi -8 and 4 (t = 2.30, p = 0.0224). At tempo 0 there is a significantly lower variability in cadence compared to tempo 8 (t = -2.32, p = 0.0212).

Stride length CoV. Significant main effects (Figure 6B) were found for group (F(1, 84) = 5.42, p = 0.022) and session (F(1,290) = 4.49, p = 0.035). No significant interactions were found. Post-hoc analysis shows a higher stride length variability for PwPMS compared to HCs (t = -2.33, p = 0.022) and more variability for metronomes compared to music conditions (t = 2.12,p = 0.035).

Figure 5

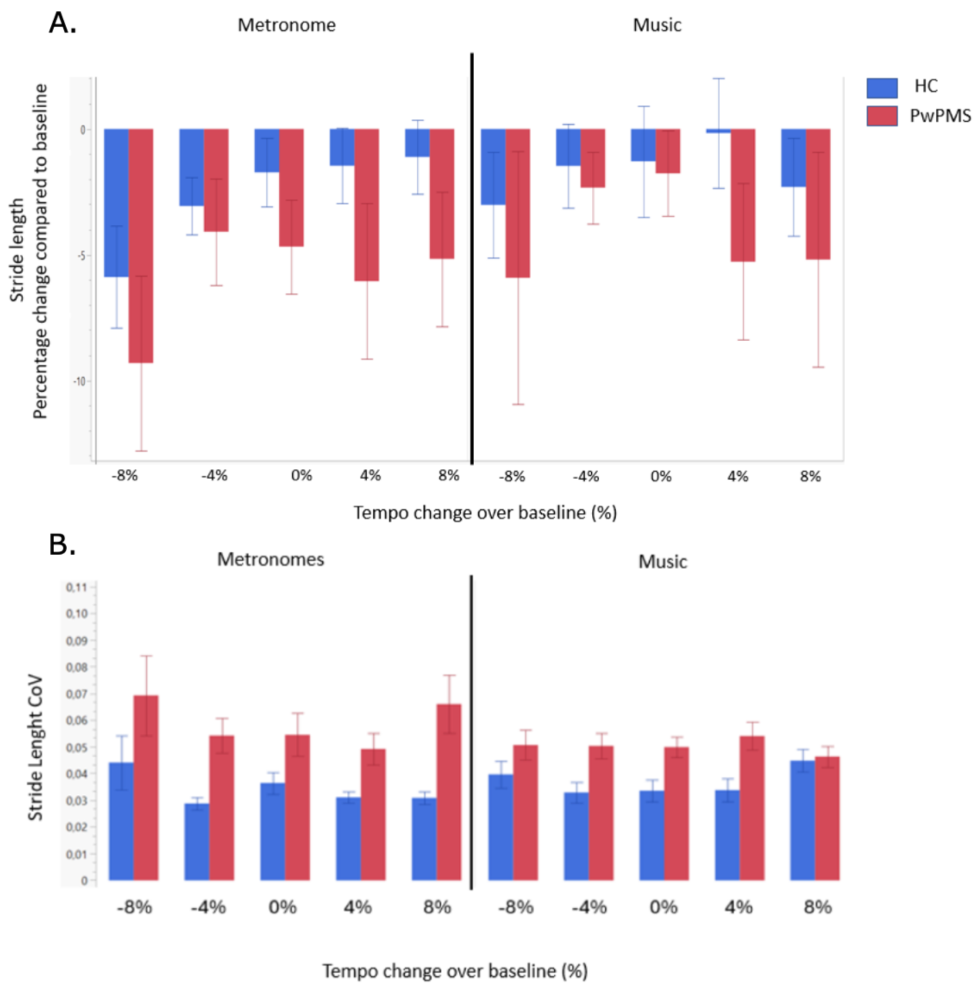
Secondary Outcome Measures in Relation to Group, Condition and Tempi



Note. Results of persons with multiple sclerosis (PwMS) and healthy controls (HC) walking to metronomes and music at different tempi, -8%, -4%, 0% and 4% and 8%. (A) Cadence, (B) Cadence CoV, (C) Gait Speed, and (D) Gait Speed CoV. Mean standard errors are shown.

Figure 6

Stride Length in Relation to Group, Condition and Tempi

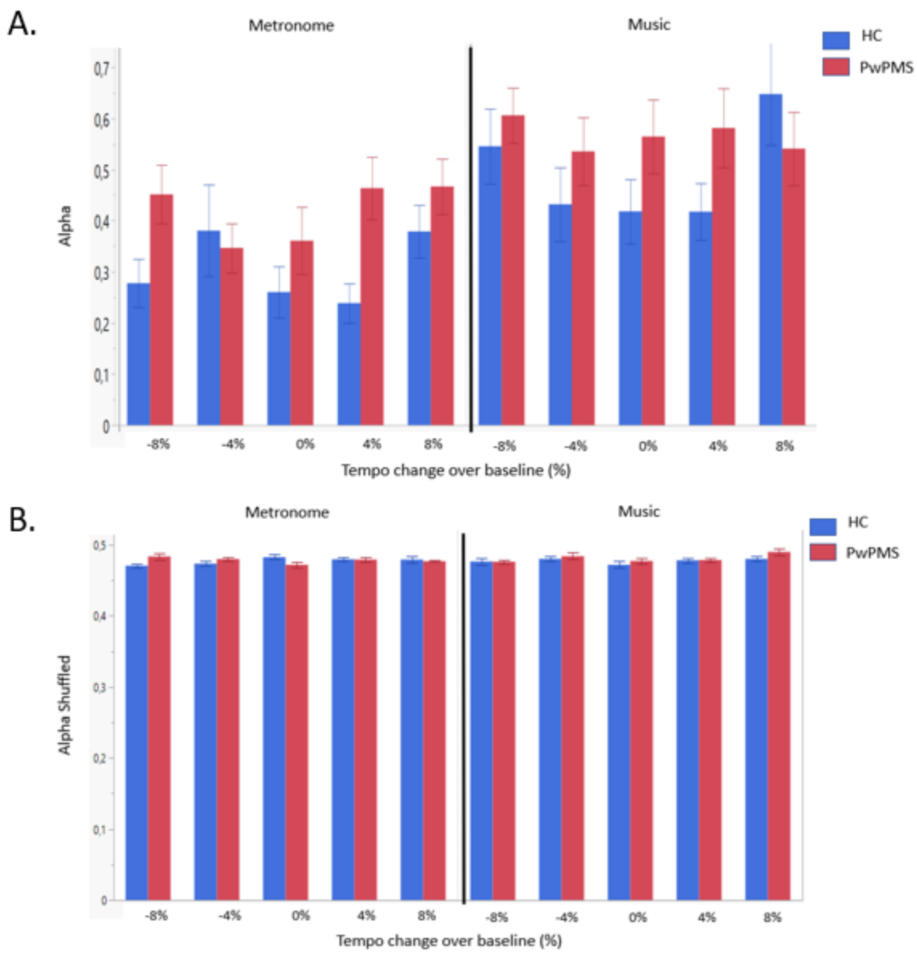


Note. Results of persons with multiple sclerosis (PwMS) and healthy controls (HC) walking to metronomes and music at different tempi, -8%, -4%, 0% and 4% and 8%. (A) Stride Length and (B) Stride length CoV. Mean standard errors are shown.

Alpha. Significant main effects of session (F(1, 269) = 16.91, p < .0001) and tempi (F(4, 269) = 2.59, p = 0.0373) were observed. No significant interactions were found. There is significantly higher alpha for music (alpha = 0.53) compared to metronome (alpha = 0.37) conditions (t = -4.11, p < .0001), indicating a higher persistent gait pattern for music compared to metronome conditions. Post hoc tests of tempi showed a significantly lower alpha for tempo -4% compared to 8% (t = -2.33, p = 0.0206), tempo 0% compared to 8% (t = -2.83, p = 0.0050) and tempo 4 compared to 8 (t = -2.19, p = 0.0292) (Figure 7A). Additionally, the same statistical procedure was performed on the alpha shuffled data (Figure 7B). No significant results could be observed. We can thus conclude that the results found in alpha were not due to random processes.

Figure 7

Alpha and Alpha Shuffled in Relation to Group, Condition and Tempi



Note. Reports on the results on gait dynamics between persons with multiple sclerosis (PwMS) and healthy controls (HC) walking to metronomes and music at different tempi, -8%, -4%, 0% and 4% and 8%. (A) alpha (B) alpha shuffled. Mean standard errors are shown.

A summary of the main effects and interactions observed in the statistical mixed model can be found in Table 3.

Table 3

Walking to Music and Metronomes at Different Tempi on Auditory-Motor Coupling and Gait Parameters Main Effects and Interactions of the Statistical Mixed Model ANOVA Test

Outcomes measures	Group	Condition	Tempi	Significant Interaction P < .05
Resultant vector lenght (0-1)	0.0188	<.0001	0.0064	Group *Condition*Tempi
Relative phase angle (degrees)	ns	ns	<.0001	ns
Cadence (percentage change from baseline)	ns	ns	<.0001	ns
Cadence CoV	0.0040	ns	0.0136	ns
Speed (percentage change from baseline)	ns	0.0019	<.0001	Group*Tempi
Speed CoV	0.0024	0.0158	0.0031	ns
Stride length (percentage change from baseline)	ns	ns	0.0455	ns
Stride length CoV	0.0223	0.0350	ns	ns
Alpha	ns	<.0001	0.0373	ns

Note. Ns, not significant; CoV, covariance.

Factors impacting RVL

Regression analysis. A regression analysis was performed on the 0% tempo between RVL and TUG, EDSS, SDMT and PASAT. A significant effect for TUG was found ($F(1, 8660) = 4.51$, $p = 0.044$). No significant effect of EDSS (Figure 7), SDMT or PASAT was found.

Additionally, two groups within the TUG score were delineated based on the median average TUG score which was 10.47 seconds. Group 1 exhibited higher scores on the TUG (indicating poorer performance), while the other (group 0) demonstrated lower scores on the TUG (indicating better performance). There is a significant difference ($t = -2.72$, $p = 0.0101$) in RVL between group 0 (RVL = 0.69) and group 1 (RVL = 0.45) (Figure 8).

Figure 7

Effect of Expanded Disability Status Scale (EDSS) on Synchronization Consistency (RVL) within PwPMS

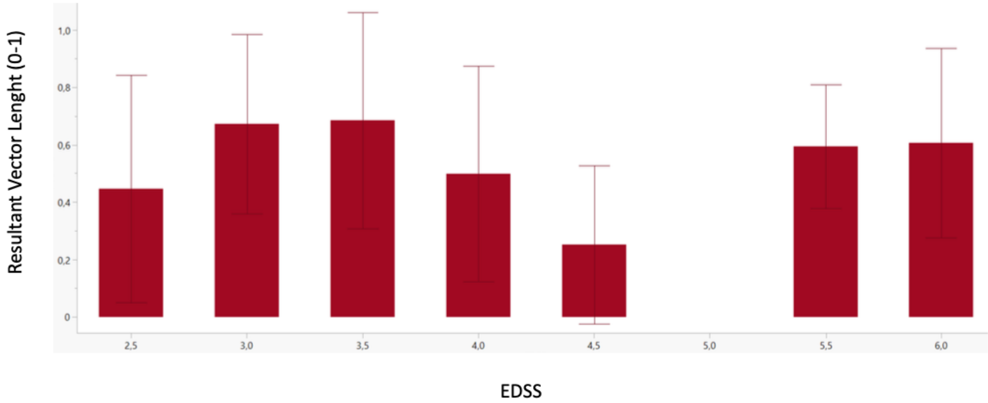
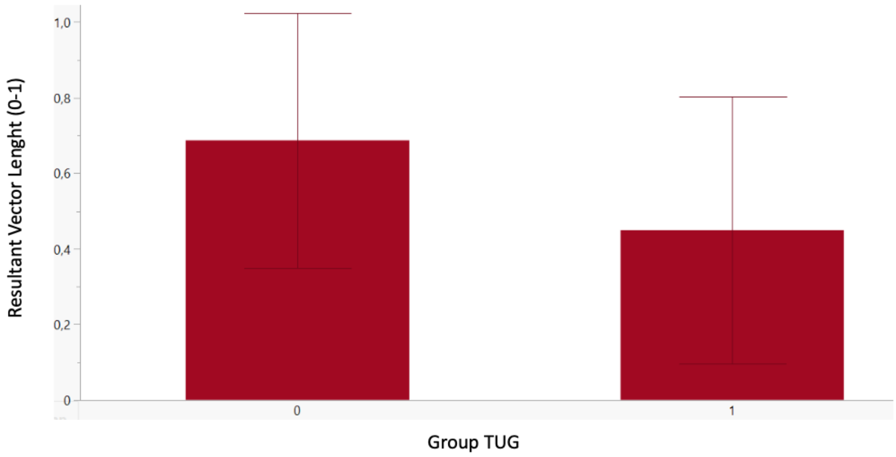


Figure 8

Effect of Timed Up and Go (TUG) on Synchronization Consistency (RVL) within PwPMS



Note. Two subgroups of the PwPMS based on the median average TUG score (group 0 = TUG scores < 10.47 seconds; group 1 = > 10.47 seconds TUG scores).

Discussion

This study aimed to investigate the potential synchronization capacities of HCs and PwPMS at different tempi to both music and metronomes. The effects of these tempi and conditions on spatiotemporal parameters were further assessed. In addition, the impact of the EDSS score, balance, and cognitive function on the synchronization ability was examined.

In total, 19 PwPMS and 16 HCs completed the experimental session. In response to the initial research question, the findings generally demonstrated that synchronization is possible in both groups for the different conditions and various tempi. However, the results show a significant difference in the ability to synchronize between HCs and PwPMS, with HCs synchronizing more overall. Nevertheless, PwPMS show signs of consistent synchronization when looking at their adaptation to the tempi, with the highest synchronization consistency at tempi -4% and 0%. PwPMS exhibit higher variability in their baseline gait parameters than HCs, possibly demonstrating fewer motor capacities to show a consistent synchronization. Very low tempi (-8%) and high tempi (4% and 8%) are showing less synchronization consistency, in both groups. Employing very slow tempi may not be advantageous for PwPMS, as synchronization consistency was lower under the -8% conditions. This could be explained by the study of Almarwani et al. (2016) showing that walking slowly results in greater variability in gait which presents a heightened demand of motor control. PwPMS experience less cognitive and motor abilities, making walking to slow tempi even harder (Pozzilli et al., 2023). Conversely, slow tempi may serve as a method to train the cognitive aspect in terms of adaptability of gait in everyday situations. The challenges encountered with high tempi can be linked to the observed differences in corticospinal excitability among individuals with MS, characterized by higher thresholds for excitability, delayed latency of motor evoked potentials (MEPs), delayed onset of cortical silent period, and prolonged MEP durations contributing to slower processing of auditory sounds (Neva et al., 2016). Consequently, PwPMS adapt more slowly to presented stimuli, particularly with very rapid stimuli, because signals are transmitted more slowly through the nerves and take longer to reach the limbs. Moreover, rapid tempi may place increased cognitive demands that exceed the cognitive capacity of PwMS who have cognitive impairment (Moumdjian et al., 2019). A better synchronization consistency is seen in the metronome condition, in both groups. This aligns with the earlier findings in the study of

Schaefer (2014) clarifying that music contains multiple rhythms, making it more complex than the stable rhythms produced by a metronome.

The participants anticipated to the beat in all tempi and both conditions, meaning coupling occurred. This characteristic is a common indication of action prediction and anticipation mechanisms at play during auditory-motor coupling (Repp & Su, 2013). The rPA showed a significant earlier anticipation to the beat in slower tempi compared to the faster ones. This observation aligns logically with the understanding that lower tempi feature longer inter-beat intervals (i.e. duration between one beat and the next), allowing for more time to process each sound (Vanbilsen et al., 2023).

The spatiotemporal parameters reveal an adjustment in cadence and gait speed in response to varying tempi. The participants were able to adapt their cadence to the different tempi and demonstrate increased gait speed when walking to music in contrast to metronomes. Music elicits a notably greater gait speed along with a longer stride length, enhancing its effectiveness for gait pattern training. There is a limited difference observed in gait speed across different tempi among PwPMS, potentially attributable to a diminished capacity for faster walking (Martin et al., 2006). Nonetheless, there is an evident adaptation to the different tempi, proving the ability of PwPMS to follow the presented tempi. Higher tempi result in a reduction in stride length in combination with an increase of cadence in PwPMS. This leads to a slower gait speed, a factor worth noting due to its afunctional consequences, with the observed greater variability in stride length among PwPMS compared to HCs serving as a clear illustration.

Participants walked with a more persisted gait pattern when walking to music compared to metronome conditions, as evidenced by increased structure in inter-step intervals over time, consistent with findings from previous research (Moumdjian et al., 2020). This difference may be attributed to the task-related demands as metronomes prompt rapid gait corrections, leading to non-structured intervals (Moumdjian et al., 2020). Whereas music, with its continuous inter-beat-interval structure, allows for less immediate error correction but fosters greater structural consistency over time. Moreover, gait patterns were more persistent at high tempi compared to comfortable and slow tempi, with a decline in persistence at a very low tempo (-8% of baseline cadence). The decline is possibly due to decreased precision in beat coupling. Importantly, no significant differences were observed between PwPMS and HCs.

These results suggests that auditory-motor processes vary with musical cues and tempi, confirming the prior findings in research (Moumdjian et al., 2020). Variability measures in gait parameters further supported these results, revealing greater variability in gait speed and stride length during metronome conditions compared to music. With acknowledge of this, music seems to have a better impact on the gait pattern even though synchronization consistency is more difficult.

Upon further analysis of balance, a significant influence of balance on the synchronization ability was found, with PwPMS exhibiting better synchronization abilities when demonstrating superior dynamic balance performance on the TUG test. This contributes to the hypothesis that motor impairments impact the synchronization consistency. However, EDSS and cognition showed to have no significant effect on synchronization capacities, while one might expect a decrease in synchronization ability with an increasing EDSS score and a higher cognitive impairment. A closer examination of the data reveals noticeable differences between the different EDSS scores. An explanation for not exposing this effect of EDSS could be the small size of the subgroups within the PwPMS group; each EDSS category only includes one or two patients for comparison. The same reasoning could apply to the non-significant impact of cognition. Nevertheless, further exploration of these factors could be important to identify which specific patients may benefit from an AMC training in a clinical setting.

Guidelines indicate that PwMS should do at least 150 minutes of PA per week. However, studies show that only 60% of participants met these guidelines (EDSS mild: 64.43%; moderate: 51.53%; severe: 39.34%) (Pedullà et al., 2023). By applying AMC, the reduced physical activity of PwPMS may increase. Research shows that music has an inherent motivational component, leading PwMS to walk longer and thereby meet the guidelines for physical activity more effectively (Moumdjian et al., 2019). Music is associated with a significant higher persistent gait pattern resulting in a less mechanistic, rigid gait. This trait holds greater functional relevance as it necessitates adaptation to the dynamic environmental demands encountered during everyday walking and community ambulation.

The strengths of this study lie in the extensive dataset obtained through conducting numerous tests, enabling profound insights. Objective measurements were prioritized to reduce subjective bias. The sessions were all administered by the same individual, ensuring reliability.

Moreover, there were no significant differences in the demographic data between groups, making them suitable for comparison enhancing the validity of our findings.

However, a few limitations are present. Firstly, there was no consideration about the musicality of the participants, underlying synchronization abilities. Additionally, there was no training provided to induce a learning effect. Repetition of the synchronization protocol might have led to more consistent synchronization, offering an understanding of its effects on spatiotemporal gait parameters. Fatigue and fatigability commonly manifest as symptoms in MS, potentially affecting the performance during the experimental session (Enoka et al., 2021). This could be a potential direction for further research. Moreover, not all baseline tests were performed in both groups, limiting the ability to fully test all hypothesis regarding the observed differences.

Finally, this current study was unable to quantify gait quality. A proposal to add parameters of gait quality in future research is appropriate to make thorough recommendations for the use of auditory-motor strategies in clinical practice.

Conclusion

The results show the feasibility of the use of auditory-motor strategies in PwPMS. Although the influence of EDSS and cognition on synchronization consistency could not be determined, it is advisable to consider the disability score and information processing speed, along with the motor impairments of individuals with PwPMS, given the small sample size in this study.

The use of metronomes combined with tempi 0% or -4% demonstrates the most effective condition for achieving high synchronization consistency in both groups. Slower walking is associated with increased motor control demands and greater gait variability. Therefore, if the aim is to train this cognitive aspect of the gait, the use of slower tempi with a steady rhythm, like that provided by a metronome, may be proposed.

Music correlates with efficient spatiotemporal parameters, better motivation, and a heightened persistent gait pattern, contributing to functional walking. A higher tempo (4%) is associated with an increase in walking speed with the overall gait exhibiting a more persistent walking pattern. This persistence observed in both music and higher tempi proves to be the most optimal strategy to promote community walking. A recommendation for the use of music and comfortable to high tempi is made as it shows less variability in gait parameters and a more persistent gait pattern. To confirm the findings of this study and assess the effectiveness of AMC in optimizing the walking pattern in PwPMS, further research with larger sample sizes is required.

Reference list

Almarwani, M., VanSwearingen, J. M., Perera, S., Sparto, P. J., & Brach, J. S. (2016). Challenging the motor control of walking: Gait variability during slower and faster pace walking conditions in younger and older adults. *Arch Gerontol Geriatr*, *66*, 54-61. https://doi.org/10.1016/j.archger.2016.05.001

Ashworth, B. (1964). PRELIMINARY TRIAL OF CARISOPRODOL IN MULTIPLE SCLEROSIS. *Practitioner*, *192*, 540-542.

Baird, J. F., Sandroff, B. M., & Motl, R. W. (2018). Therapies for mobility disability in persons with multiple sclerosis. *Expert Rev Neurother*, *18*(6), 493-502. https://doi.org/10.1080/14737175.2018.1478289

Demeurisse, G., Demol, O., & Robaye, E. (1980). Motor evaluation in vascular hemiplegia. *Eur Neurol*, *19*(6), 382-389. https://doi.org/10.1159/000115178

Enoka, R. M., Almuklass, A. M., Alenazy, M., Alvarez, E., & Duchateau, J. (2021). Distinguishing between Fatigue and Fatigability in Multiple Sclerosis. *Neurorehabil Neural Repair*, *35*(11), 960-973. https://doi.org/10.1177/15459683211046257

Feinstein, A., Freeman, J., & Lo, A. C. (2015). Treatment of progressive multiple sclerosis: what works, what does not, and what is needed. *Lancet Neurol*, *14*(2), 194-207. https://doi.org/10.1016/s1474-4422(14)70231-5

Goldman, M. D., Marrie, R. A., & Cohen, J. A. (2008). Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Mult Scler*, *14*(3), 383-390. https://doi.org/10.1177/1352458507082607

Gontkovsky, S. T., Vickery, C. D., & Beatty, W. W. (2004). Construct validity of the 7/24 spatial recall test. *Appl Neuropsychol*, *11*(2), 75-84. https://doi.org/10.1207/s15324826an1102_2

Gordon, A., & Zillmer, E. A. (1997). Integrating the MMPI and neuropsychology: A survey of NAN membership. *Archives of Clinical Neuropsychology*, *12*(4), 325-326. https://doi.org/10.1093/arclin/12.4.325b

Hannay, H. J., & Levin, H. S. (1985). Selective reminding test: an examination of the equivalence of four forms. *J Clin Exp Neuropsychol*, *7*(3), 251-263. https://doi.org/10.1080/01688638508401258

Hausdorff, J. M., Peng, C. K., Ladin, Z., Wei, J. Y., & Goldberger, A. L. (1995). Is walking a random walk? Evidence for long-range correlations in stride interval of human gait. *J Appl Physiol (1985)*, *78*(1), 349-358. https://doi.org/10.1152/jappl.1995.78.1.349

Hauser, S. L., Dawson, D. M., Lehrich, J. R., Beal, M. F., Kevy, S. V., Propper, R. D., Mills, J. A., & Weiner, H. L. (1983). Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. *N Engl J Med*, *308*(4), 173-180. https://doi.org/10.1056/nejm198301273080401

Hobart, J. C., Riazi, A., Lamping, D. L., Fitzpatrick, R., & Thompson, A. J. (2003). Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology*, *60*(1), 31-36. https://doi.org/10.1212/wnl.60.1.31

Klineova, S., & Lublin, F. D. (2018). Clinical Course of Multiple Sclerosis. *Cold Spring Harb Perspect Med*, *8*(9). https://doi.org/10.1101/cshperspect.a028928

Kuhlmann, T., Moccia, M., Coetzee, T., Cohen, J. A., Correale, J., Graves, J., Marrie, R. A., Montalban, X., Yong, V. W., Thompson, A. J., & Reich, D. S. (2023). Multiple sclerosis

progression: time for a new mechanism-driven framework. *Lancet Neurol*, *22*(1), 78-88. https://doi.org/10.1016/s1474-4422(22)00289-7
Leman, M. (2007). *Embodied Music Cognition and Mediation Technology.* . MIT Press.
Leow, L. A., Watson, S., Prete, D., Waclawik, K., & Grahn, J. A. (2021). How groove in music affects gait. *Exp Brain Res*, *239*(8), 2419-2433. https://doi.org/10.1007/s00221-021-06083-y
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. https://doi.org/10.1177/1352458506070658
Mas-Herrero, E., Marco-Pallares, J., Lorenzo-Seva, U., Zatorre, R. J., & Rodriguez-Fornells, A. (2013). Barcelona Music Reward Questionnaire. Music Perception.
Meyer-Moock, S., Feng, Y. S., Maeurer, M., Dippel, F. W., & Kohlmann, T. (2014). Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol*, *14*, 58. https://doi.org/10.1186/1471-2377-14-58
Mills, R. J., Young, C. A., Pallant, J. F., & Tennant, A. (2010). Rasch analysis of the Modified Fatigue Impact Scale (MFIS) in multiple sclerosis. *J Neurol Neurosurg Psychiatry*, *81*(9), 1049-1051. https://doi.org/10.1136/jnnp.2008.151340
Moens, B., Muller, C., van Noorden, L., Franěk, M., Celie, B., Boone, J., Bourgois, J., & Leman, M. (2014). Encouraging spontaneous synchronisation with D-Jogger, an adaptive music player that aligns movement and music. *PLoS One*, *9*(12), e114234. https://doi.org/10.1371/journal.pone.0114234
Moumdjian, L., Buhmann, J., Willems, I., Feys, P., & Leman, M. (2018). Entrainment and Synchronization to Auditory Stimuli During Walking in Healthy and Neurological Populations: A Methodological Systematic Review. *Front Hum Neurosci*, *12*, 263. https://doi.org/10.3389/fnhum.2018.00263
Moumdjian, L., Maes, P. J., Dalla Bella, S., Decker, L. M., Moens, B., Feys, P., & Leman, M. (2020). Detrended fluctuation analysis of gait dynamics when entraining to music and metronomes at different tempi in persons with multiple sclerosis. *Sci Rep*, *10*(1), 12934. https://doi.org/10.1038/s41598-020-69667-8
Moumdjian, L., Moens, B., Maes, P. J., Van Nieuwenhoven, J., Van Wijmeersch, B., Leman, M., & Feys, P. (2019). Walking to Music and Metronome at Various Tempi in Persons With Multiple Sclerosis: A Basis for Rehabilitation. *Neurorehabil Neural Repair*, *33*(6), 464-475. https://doi.org/10.1177/1545968319847962
Neva, J. L., Lakhani, B., Brown, K. E., Wadden, K. P., Mang, C. S., Ledwell, N. H., Borich, M. R., Vavasour, I. M., Laule, C., Traboulsee, A. L., MacKay, A. L., & Boyd, L. A. (2016). Multiple measures of corticospinal excitability are associated with clinical features of multiple sclerosis. *Behav Brain Res*, *297*, 187-195. https://doi.org/10.1016/j.bbr.2015.10.015
Pedullà, L., Santoyo-Medina, C., Novotna, K., Moumdjian, L., Smedal, T., Arntzen, E. C., van der Linden, M. L., Learmonth, Y., Kalron, A., Güngör, F., Nedeljkovic, U., Kos, D., Jonsdottir, J., Coote, S., & Tacchino, A. (2023). Physical Activity in Multiple Sclerosis: Meeting the Guidelines at the Time of the COVID-19 Pandemic. *Journal of Neurologic Physical Therapy*, *47*(2), 112-121. https://doi.org/10.1097/npt.0000000000000430
Podsiadlo, D., & Richardson, S. (1991). The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*, *39*(2), 142-148. https://doi.org/10.1111/j.1532-5415.1991.tb01616.x

Powell, L. E., & Myers, A. M. (1995). The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol A Biol Sci Med Sci*, *50a*(1), M28-34. https://doi.org/10.1093/gerona/50a.1.m28

Pozzilli, C., Pugliatti, M., Vermersch, P., Grigoriadis, N., Alkhawajah, M., Airas, L., & Oreja-Guevara, C. (2023). Diagnosis and treatment of progressive multiple sclerosis: A position paper. *Eur J Neurol*, *30*(1), 9-21. https://doi.org/10.1111/ene.15593

Repp, B. H., & Su, Y. H. (2013). Sensorimotor synchronization: a review of recent research (2006-2012). *Psychon Bull Rev*, *20*(3), 403-452. https://doi.org/10.3758/s13423-012-0371-2

Ruff, R. M., Light, R. H., Parker, S. B., & Levin, H. S. (1996). Benton Controlled Oral Word Association Test: reliability and updated norms. *Arch Clin Neuropsychol*, *11*(4), 329-338.

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. https://doi.org/10.1098/rstb.2013.0402

Shumway-Cook, A., Baldwin, M., Polissar, N. L., & Gruber, W. (1997). Predicting the probability for falls in community-dwelling older adults. *Phys Ther*, *77*(8), 812-819. https://doi.org/10.1093/ptj/77.8.812

Smith, A. (1973). Symbol Digit Modalities Test. Los Angeles, CA: Western Psychological Services

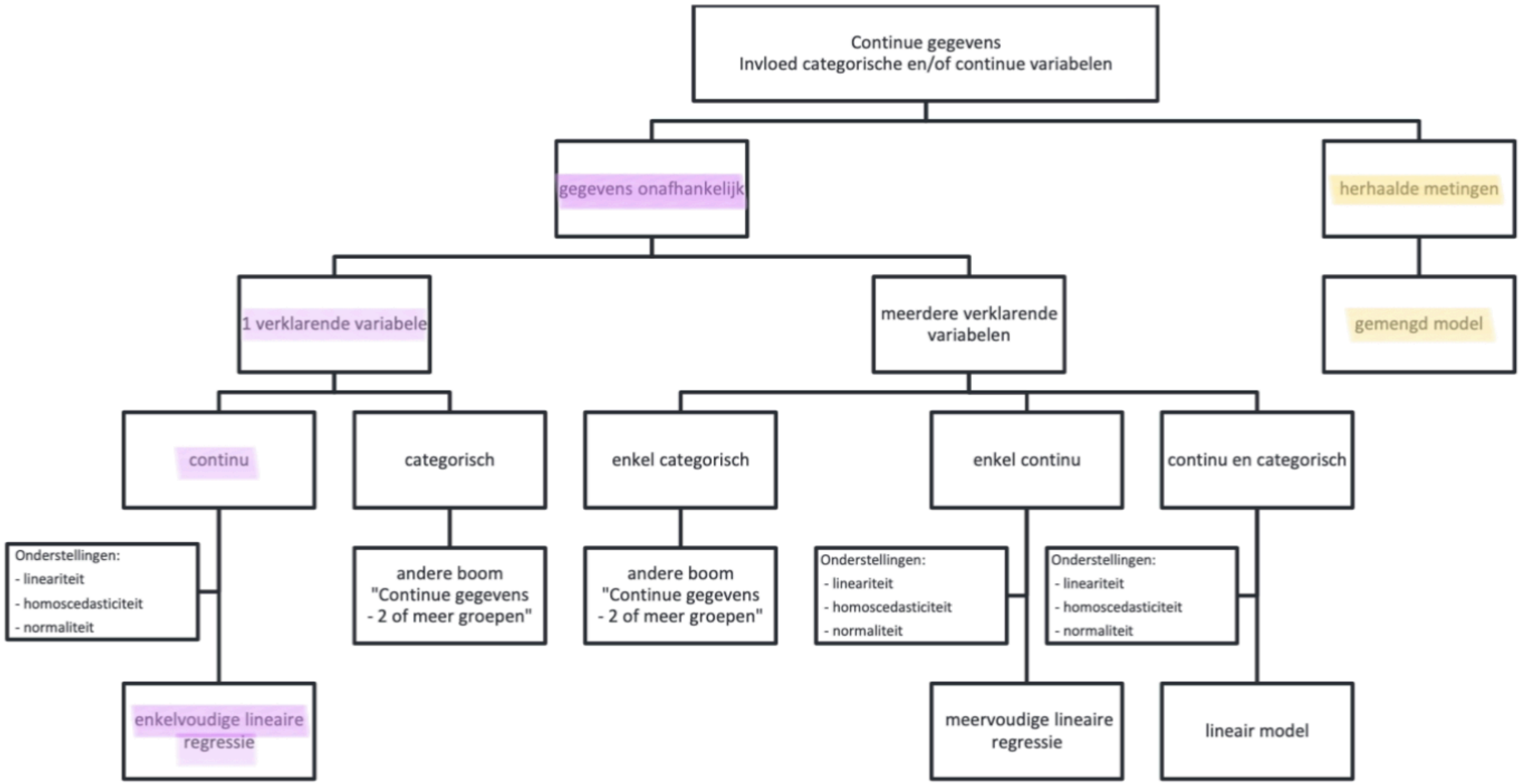
Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643-662. https://doi.org/10.1037/h0054651

Vanbilsen, N., Kotz, S. A., Rosso, M., Leman, M., Triccas, L. T., Feys, P., & Moumdjian, L. (2023). Auditory attention measured by EEG in neurological populations: systematic review of literature and meta-analysis. *Sci Rep*, *13*(1), 21064. https://doi.org/10.1038/s41598-023-47597-5

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr Scand*, *67*(6), 361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Appendix 1

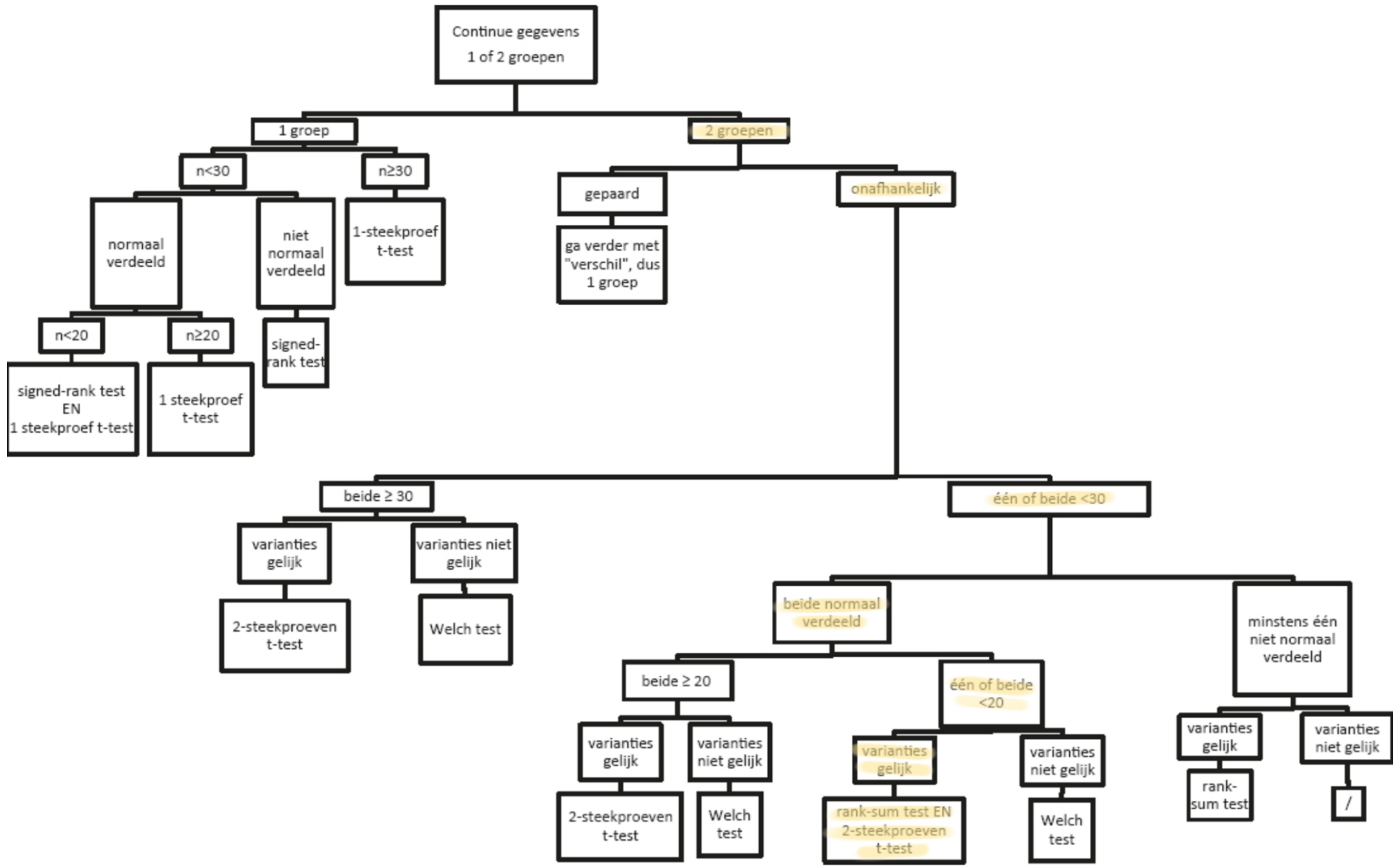
Decision Tree of Continuous Data with the Influence of Categorical and/or Continuous variables



Note. (Yellow) path to use a mixed-model ANOVA. (Purple) path to use a linear regression analysis.

Appendix 2

Decision Tree of Continuous Data



Note. (Yellow) path to use a one-way ANOVA.