Effects and mechanisms of differently cued and non-cued motor imagery in people with multiple sclerosis: A randomised controlled trial

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Abstract

Background: Walking impairment and fatigue are prevalent symptoms in people with multiple sclerosis (PwMS). Motor imagery (MI) with rhythmic-auditory cueing improved walking in PwMS, but so far, the underlying mechanisms are not fully explored.

Objective: This study investigated the effects and mechanisms of differently cued and non-cued MI on walking, fatigue and quality of life (QoL) in PwMS.

Methods: Sixty PwMS with mild to moderate disability were randomised to music- and verbally cued MI (MVMI), music-cued MI (MMI) or MI. Participants practised cued or non-cued MI of walking for 17 minutes, 6 times per week for 4 weeks at home. Primary outcomes were walking speed (Timed 25-Foot Walk) and walking distance (6-Minute Walk Test).

Results: Fifty-nine participants completed the study. All interventions induced significant improvements in walking speed and distance, while MVMI was superior. After cued MI, fatigue and QoL significantly improved, with greatest changes seen after MVMI. All participants showed high MI ability. Post-intervention, sensorimotor synchronisation was significantly more accurate after cued MI.

Conclusion: All interventions significantly improved walking. MVMI was superior in improving walking, fatigue and QoL. Results suggest that MI and sensorimotor synchronisation were mechanisms of action.

Trial registration: ISRCTN Registry, ISRCTN92351899 (http://www.isrctn.com/)

Original Research Paper

Introduction

Between 75% to 88% of people with multiple sclerosis (PwMS) have walking impairment and fatigue, crucially affecting their quality of life (QoL)[1]. Pyramidal, cerebellar, brain stem and sensory symptoms[2] are associated with reduced walking speed and increased gait variability[3]. Specific physiotherapy approaches such as motor imagery (MI) have been shown to benefit motor function and fatigue in people with MS[4]. MI development was based on the notion that motor representations, which are related to the intention and preparation of movements, can be consciously accessed via MI[5, 6]. MI is the mental rehearsal of movements without actual execution, involving similar spatial and temporal characteristics and brain area activation to executed movements[5, 7]. Internal, first-person perspective refers to a MI experience from within the body and external MI to a third-person perspective[5]. The visual MI mode concerns the visualisation of a movement, whereas the kinaesthetic mode refers to bodily movement perception[7, 8].

One study was identified that investigated the effects of MI on walking, fatigue and quality of life (QoL) in twenty PwMS and found significant improvements in

fatigue and QoL but not walking at six-month follow-up[4]. Another study in people with stroke compared the effects of metronome-cued (visual and kinaesthetic) MI against non-cued MI on walking and found that metronome-cued kinaesthetic MI was more effective[9]. Our previous study results showed improvements in walking, fatigue and QoL after rhythmic- cued MI in PwMS when compared to controls[10]. However, underlying mechanisms of action are currently unknown. People with cognitive dysfunction[11] and depression[12] have a lower capacity to practise MI and were excluded from the studies. Studies suggested to assess MI ability using two different approaches because, while some people may have problems generating vivid images and intense sensations or describing their imageries, others may struggle with the duration of their MI, in relation to executed movements[5, 13].

Cueing of the MI may provide a temporal framework, leading to activation of the auditory-motor circuit and rhythmic entrainment, which is the temporal synchronisation of neural rhythm processes with regular external cues[14]. Previous findings demonstrate that cues synchronise the motor response so that people unconsciously adapt their movement to an external rhythm[15]. Indeed, participants in our study improved their walking, but a further study was required to evaluate whether gait synchronisation with the cues (sensorimotor synchronisation, SMS) occurred. Therefore, the purpose of this study was to

investigate the effects and mechanisms of differently cued and non-cued MI on walking, fatigue and QoL in PwMS and assess their MI ability and SMS.

Methods

Study design and participants

This was a prospective three-group single-centre randomised parallel trial conducted at the MS-Clinic of the Department of Neurology, Medical University of Innsbruck, Austria, from 28 April to 16 August, 2016. Ethical approval was received from the Ethic Committees of the Universities of Brighton, UK (no approval number, 17 December, 2015) and Innsbruck, Austria (AN2014-0052 334/4.14-358/5.13(3743a). Information brochures and invitations for study participation were displayed in the MS-Clinic and on the Austrian MS Society website. Additionally, during their regular visits, PwMS were notified about the study by MS-Clinic staff. Upon approval, study participants provided written informed consent and were reimbursed for travel expenses only. A CONSORT flow diagram is shown in Figure 1 and a CONSORT checklist in Supplementary File 2. Research data are available on request (barbara.seebacher@i-med.ac.at).

All eligible and accessible patients were selected for recruitment (consecutive sampling). Sixty participants were randomised into one of three groups with a 1:1:1 allocation ratio using a computer-generated random number sequence and sealed, opaque envelopes. Stratified blocked randomisation with allocation concealment was performed by an independent researcher, according to pertinent predictive factors for a change in walking, specifically age (<40, ≥40), gender (female, male) and disability (Expanded Disability Status Scale, EDSS[2] 1.5-3.0, 3.5-4.5).

[Insert-Figure-1]

Inclusion Criteria were: PwMS with mild to moderate disability (EDSS 1.5-4.5), aged ≥18 years, clinically definite MS according to revised McDonald´s criteria[16], any MS phenotype or ethnicity, German speaking.
Exclusion Criteria were: Concomitant diseases potentially affecting the interventions or walking, relapse of MS within the last three months, recent change of treatment (physiotherapy, medication) within the last two months known to affect walking, pregnancy, clinical symptoms of depression or cognitive dysfunction. A relapse or medication change during the intervention period necessitated the exclusion of the participant.

Outcome measures

Demographic (gender, age) and MS disease specific data (current EDSS) were obtained from patients' files, study data were collected in the MS-Clinic Innsbruck pre and post the 4-week intervention. Current depression (state of low mood, loss of activity, sadness, anxiety, awkwardness, loss of appetite, insomnia, suicidal thoughts) and/or cognitive dysfunction (impairment in orientation, memory, attention, learning, language, visuospatial skills, calculating, planning or any other executive function) were clinically evaluated by the treating neurologist (TB) before study enrolment. Adverse events were recorded during or after a MI session. Withdrawals or other reasons for exclusion from the study were recorded.

Primary outcomes were walking speed and walking distance. Walking speed was measured by the Timed 25-Foot Walk (T25FW), a component of the Multiple Sclerosis Functional Composite[17]. Walking distance was assessed by the 6-Minute Walk Test (6MWT)[18]. Consistent with evidence and clinical judgement, improvements in walking speed[3] and walking distance[19] were considered clinically significant if they improved by ≥20%.

Secondary outcomes were fatigue as assessed by the Modified Fatigue Impact Scale (MFIS)[20, 21] which evaluates the effects of subjective fatigue on physical, cognitive and psychosocial functioning. QoL was measured by the MS Impact

Scale-29 (MSIS-29)[22, 23]. Further secondary outcomes were MI ability and SMS. MI ability was assessed by the German short version of the Kinaesthetic and Visual Imagery Questionnaire (KVIQ-10)[24], the KVIQ-G-10[25], and the Time-Dependent Motor Imagery screening test (TDMI)[26], a mental chronometry test; it requires recording the number of imagined stepping movements over 15, 25, and 45 seconds. A cut-off score of 3 out of 5 was used to indicate adequate MI ability[27]. SMS was assessed during gait, with fast and slow music at 110 and 75 beats per minute (BPM) using a 2-dimensional video-based gait analysis system, which was previously described in detail and had been found to be reliable and accurate[28]. Steps were recorded on the central 4.5 metres while participants walked 4-6 times on a 30 metre hallway. SMS parameters were step time and step length variability and stepwise synchronisation[15]. Assessments were performed at the same time of day, to account for daytime fluctuations in fatigue. Blinding was not possible because interventions and assessments were performed by one physiotherapist and participants were aware of their group allocation.

Intervention

The intervention consisted of home-based music- and verbally cued MI (MVMI group), music-cued MI (MMI group) and non-cued MI (MI group). A description

of the PETTLEP model[6] and rhythmic auditory stimulation[14] based intervention is provided in Figure 2 and Supplementary File 1 and was previously published in detail[10, 28]. The study and intervention duration were based on a review of MI interventions[8]. Four comparable Audio-Mixes were on one CD and changed weekly, to maintain attention to the MI[14] and facilitate compliance. Participants were called once weekly to support their use of MI.

[Insert-Figure-2]

Sample size

The study sample size was based on the pilot study[28] between-group differences of 20% in walking distance. Using the HyLown Consulting LLC Power and Sample Size Calculator (2013), a 5% type I error rate and 80% power, the true difference in the three intervention means was expected to be 20%. Hence, including a 10% attrition rate, 60 participants were required to enable the detection of a significant between-group difference.

Statistical analysis

SPSS software, release 24.0 (IBM Corporation, Armonk, NY, USA) were used for all statistical analyses. Statistical significance was defined as two-tailed p-value <0.05. Intention-to-treat analysis was performed for all cases with

complete follow-up data which were analysed by original assigned groups. Descriptive statistics were used to summarise baseline demographic variables.

Paired T-tests were performed on split file (for group) to detect differences in T25FW and 6MWT data between pre- and post-intervention measures. On split file, MFIS, MSIS-29, KVIQ-10 and TDMI data, Wilcoxon Signed Ranks tests were computed. Bonferroni corrections for multiple comparisons were executed as appropriate. Two-Factor Mixed ANOVA was used to test for continuous data, with groups as between-subjects factor and time as within-subject factor. ANOVA effect size measures were calculated as partial eta squared values (η^2). For all relevant analyses, significant violations of ANOVA were tested for and where appropriate, standard correction procedures were applied. For categorical data, Kruskal Wallis test from the differences between post-intervention and baseline values was calculated, and Dunn´s multiple comparisons test conducted. If the overall interaction was significant, Chi-Square test was used to detect clinically significant changes.

Adequate MI ability, as assessed by the TDMI screening test, was pre-defined: a) there must not be a significant difference between the numbers of imagined stepping movements with the left or right lower extremities within the same time periods; b) the numbers of imagined movements significantly increase with the

duration (Friedman's ANOVA); and c) the numbers of imagined movements and durations are moderately to strongly correlated and the correlations are significant. Bivariate Spearman´s correlation coefficients (range) were used.

Due to non-normal step time data distribution, stepwise synchronisation was determined by calculating the ratio of the music beat frequency (BPM) over the median cadence[15]. Assuming normality, the within-subjects gait variability is evaluated by the Coefficient of Variation (CV), using the equation CV(%)=((SD/Mean)*100). As robust analogues to the SD and CV, the Median Absolute Deviation (MAD)[29] and the Coefficient of Mean Deviation about the Median (CV MAD) were used[30]. The MAD was calculated analogously to the SD, MAD=median($|x_i - \text{median}(x)|$), where the median(X) is the median of the sample. X_i are the absolute differences between the sample values and their median values; the MAD is the median of these absolute differences[30]. The CV MAD was calculated analogously to the CV.

Results

Of 60 randomised participants, 59 completed the study and their data were analysed (MVMI group 19, MMI group 20, MI group 20), corresponding with a 1.7 % attrition rate. One participant was excluded due to a relapse from MS. There were no missing data.

Baseline characteristics

As shown in Table 1, 47 females and 12 males completed the study, and their mean age was 44.4 (95% CI 41.7, 47.0) years. The median EDSS was 2.5 (range 1.5, 4.5). There were no significant differences in outcome measures at baseline, except lower QoL was observed in the MVMI group. All participants were able to perform MI (Supplementary Table 1).

[Insert-Table-1]

Safety, adverse events and adherence

No adverse events were reported. Participants reported that the home-based intervention was safe and convenient and they appreciated the phone call support. They recorded their practice sessions in a diary and reported median practice of 5 (4-6) times per week.

Primary outcomes

Within-group comparisons showed that all three interventions significantly improved walking speed and walking distance (Figure 3).

[Insert-Figure-3]

Between-group analyses demonstrated an overall significant group difference from baseline to post-intervention: T25FW: $F(2,56)=4.65$, $p=0.013$, with a medium effect size of $\eta^2=0.143$. MVMI was superior to MI in effectiveness ($p=0.024$). There was an overall significant group difference in walking distance from baseline to post-intervention: $F(2,56)=3.53$, $p=0.036$, $\eta^2=0.112$. The effect of MVMI ($p=0.001$) versus MI was significant. Walking improvements were similar in participants irrespective of disability level (Supplementary Figure 3). Intervention effects on walking are shown in Table 2.

[Insert-Table-2]

Secondary outcomes

Intervention effects on subjective fatigue and QoL for all groups are shown in Table 3 and Supplementary Figures 1-2.

Within-group analyses showed that physical, cognitive and total fatigue and physical QoL significantly improved only after cued MI (MVMI, MMI) and psychosocial fatigue significantly improved in all groups (all p-values <0.01). Psychological QoL improved only after MVMI ($p=0.030$).

Between-group comparisons in psychosocial fatigue showed a significant superiority of MVMI over MI ($p=0.041$). Post-intervention, an overall

improvement in physical QoL was observed (p=0.007). Post-hoc analyses showed that only the MVMI group contributed to this improvement (p=0.005). Thirty-two out of 59 participants reached a clinically significant improvement in physical QoL of whom significantly more participants were in the MVMI group (p=0.030).

[Insert-Table-3]

Intervention effects on MI ability are shown in Figure 4 and Supplementary Table 1. Post-intervention, overall, participants improved their MI ability, as evidenced by median KVIQ-G-10 values of 4.1 (range 2.9-5.0) out of 5.0. In all groups, the medians were higher than the cut-off value of 3 points for adequate visual and kinaesthetic MI ability. There was no group X time interaction in MI capability.

Post-intervention, improvement in MI abilities was also shown by the TDMI screening test. The numbers of imagined stepping movements and durations were strongly correlated and significant, as indicated by a median Spearman's ρ of 0.91 (range 0.88, 0.95).

[Insert-Figure-4]

Intervention effects on SMS are presented in Figure 5 and Supplementary Table 2. With fast music, significant improvements in step length variability were only seen after music-cued MI (p=0.045) while group X time interactions were significant (MVMI p=0.031; MMI p=0.015). Step time variability even worsened in the MI group (p=0.030).

With slow music, following MVMI (p=0.003) and MMI (p<0.001) but not MI, step length variability improved while interactions were still significant (MVMI p=0.030; MMI p=0.006). Step time variability improved solely after MMI (p=0.018) and the group comparison was still significant (p=0.008). Stepwise synchronisation worsened after MI (p=0.036). Group interaction analyses showed significant differences in stepwise synchronisation, in favour of MVMI (p=0.001) and MMI (p=0.008) compared with MI.

[Insert-Figure-5]

Discussion

Results showed that cued and non-cued MI improved walking speed and walking distance in PwMS, represented by medium effect sizes, but MVMI was more effective than MI in improving walking, subjective fatigue and QoL. Overall, these results agree with our previous study[10] and a gait training study in

PwMS, where walking significantly improved after metronome-cued versus non-cued gait training[31]. Consistent with our findings, people with stroke improved their walking mainly after cued kinaesthetic MI when compared to visual or non-cued kinaesthetic MI[9].

The effects of non-cued MI on walking were greater than those seen by a small non-controlled study, demonstrating significant improvements in fatigue and QoL, but not in walking speed, after five weeks of MI in PwMS[4]. We observed improvement in fatigue and QoL only after cued MI, with MVMI being superior. The discrepancy in results could be related to the difference in intervention, which included various executed movements alongside MI whereas our study used MI of walking only. In absence of a control group we acknowledge that natural fluctuations in fatigue and walking speed could also have been a factor.

In our study, music-cued MI but not MI alone improved fatigue and QoL while MVMI was most effective, suggesting these findings are related to the effects of music and verbal cueing. Studies have evidenced effects of music on mood, motivation, arousal, perceived effort[32] and cognitive performance[14], and so music could impact on MI. Verbal cueing could have intensified the cueing and directed the attention towards relevant movement aspects.

MI capability was measured to test whether it could, at least partially, explain any changes seen. At baseline, all participants were found to be able to perform MI. KVIQ-10 scores were consistent with those from another study in thirty PwMS[11]. TDMI screening test results were suggestive of high MI capability[26]. It is likely that the MI familiarisation facilitated participants' understanding of MI and enhanced their performance during the assessments and practice[6, 8]. MI was, thus, considered a potential mechanism of action.

SMS was explored during gait with fast and slow music. Overall, cued MI was found to be significantly more effective for SMS than MI alone. In all likelihood, the rhythmic-cued walking imagery practice positively impacted on the spatiotemporal gait variability, comparable to rhythmic auditory simulation (RAS) during real walking. In agreement with this, a study in twelve people with Parkinson's disease and healthy controls showed significantly improved variability of step time and step length, but only in patients who followed cueing while walking cued gait training did not change the gait variability in healthy controls[33]. Another recent study has compared the effects of four weeks of cued versus un-cued gait training on gait parameters in people with stroke. Significantly improved gait was observed only when RAS was used[34].

There are several limitations to this study. Data were collected before and after the four-week intervention period, but there is no follow-up data. No phone calls were made after the intervention period. Therefore, no statement can be made regarding long-term effects of the MI. Screening for cognitive impairment and depression was performed clinically, but no validated assessments were used. Therefore, some impairment could have been overlooked in some participants. There were significant between-group differences in baseline QoL, with poorer QoL in the MVMI group, who might have had a greater potential for improvement. Although pretested in our pilot study, the stride-to-stride variability measurement could have been confounded by the variability between trials and the inability to capture at least 10 consecutive steps for every participant. Further, biomechanical differences between walking with and without shoes during the testing could have influenced the results[35]. Blinding was not possible as one physiotherapist was responsible for instructions and assessments however a script was used for consistency. Participants realised their group allocation although there was a true uncertainty regarding the results.

Conclusions

Study results demonstrated that four weeks of cued and non-cued MI with weekly phone calls significantly improved walking in PwMS with mild to

moderate disability. MVMI was most effective in improving walking, fatigue and QoL. After familiarisation with MI, participants were able to perform MI. SMS was significantly more accurate after cued MI when compared to MI alone. Therefore, the improvements in walking may be attributed to the MI and SMS. This contributes to the growing evidence base supporting the use of MI and SMS to improve gait in PwMS.

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Conflicts of interests

The authors declare that there is no conflict of interest.

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Table 1: Participant baseline characteristics.

Parameter	MVMI group N=19	MMI group N=20	MI group N=20	p-value
Gender [a] (F/M)	N=15:4	N=16:4	N=16:4	0.996
Age (years) [b]	45.3 (39.8, 50.8)	44.5 (40.5, 48.5)	43.3 (38.3, 48.3)	0.826
EDSS total [c]	3.0 (1.5, 4.5)	2.5 (1.5, 4.5)	2.5 (1.5, 4.5)	0.925

Abbreviations: MVMI: music and verbally cued motor imagery; MMI: music-cued MI; N: number of participants; F/M: Females/Males; EDSS: Expanded Disability Status Scale.

[a]Number of participants, analysed with Chi-Square test.

[b]Mean (95% CI), analysed with One-Way ANOVA.

[c]Median (range), analysed with Kruskal-Wallis test.

Table 2: Effect of interventions on primary outcomes and clinically significant improvement.

Parameter	MVMI group N=19	MMI group N=20	MI group N=20	Overall p-value
T25FW (seconds)				
Baseline[a]	6.1 (5.2, 7.0)	6.1 (4.9, 7.3)	5.6 (4.7, 6.4)	0.602
Post-intervention[a]	5.3 (4.5, 6.1)	5.2 (4.4, 6.0)	5.3 (4.4, 6.1)	
Change from baseline[a]	-0.8 (-1.0, -0.6)*	-0.9 (-1.4, -0.4)	-0.3 (-0.5, 0.06)	0.013
Clin. sig. improvement (≥20%)[b]	N=3 (21.1%)	N=3 (15.0%)	N=0 (0.0%)	0.110
6MWT (metres)				
Walking aid use during 6MWT[a]				
No/uni-/bilateral aid	N=16/2/1	N=19/0/1	N=18/0/2	
Baseline[a]	457.3 (394.3, 520.3)	461.7 (395.5, 528.0)	461.7 (395.5, 528.0)	0.937
Post-intervention[a]	510.3 (450.5, 570.2)	499.1 (433.8, 564.3)	491.7 (424.0, 559.5)	
Change from baseline[a]	53.0 (38.2, 67.7)**	37.3 (12.4, 62.3)	19.1 (4.8, 33.5)	0.036
Clin. sig. improvement (≥20%)[b]	N=5 (26.3%)	N=2 (10.0%)	N=1 (5.0%)	0.128

Abbreviations: MVMI: music- and verbally cued motor imagery; MMI: music-cued MI; T25FW: Timed 25-Foot Walk; 6MWT: 6-Minute Walk Test; Clin. sig. improvement: clinically significant improvement; N: number of participants.

With walking speed (T25FW), improvement is indicated by a minus and worsening by a plus; with walking distance (6MWT), improvement is indicated by a plus and worsening by a minus.

[a]Mean (95% CI); significance of group differences analysed with Mixed Design ANOVA; if overall p-value significant, post hoc pairwise comparisons between groups with Bonferroni correction for 3 comparisons: *$p<0.05$, **$p\leq0.001$

[b]Analysed with Chi-Square test.

Table 3: Effect of interventions on fatigue and quality of life and clinically significant improvement.

Parameter	MVMI group N=19	MMI group N=20	MI group N=20	Overall p-value
MFIS total score				
Baseline[a]	43.0 (11.0, 72.0)	28.5 (2.0, 69.0)	33.0 (2.0, 54.0)	0.209
Post-intervention[a]	27.0 (1.0, 55.0)	19.5 (0.0, 45.0)	23.5 (2.0, 52.0)	
Change from baseline[a]	-12.0 (-31.0, 5.0)	-10.0 (-37.0, 7.0)	-4.0 (-40.0, 11.0)	0.197
Clin. sig. improvement[b]	N=6 (31.6%)	N=7 (35%)	N=6 (30%)	0.942
MSIS-29 physical subscore				
Baseline[a]	47.5 (12.5, 76.2)	25 (6.2, 56.2)	21.9 (3.7, 63.7)	0.010
Post-intervention[a]	25.0 (5.0, 61.2)	21.2 (2.5, 37.5)	16.2 (2.5, 51.2)	
Change from baseline[a]	-15.0 (-38.7, -1.2)*	-7.5 (-28.7, 8.7)	-3.1 (-41.2, 8.7)	0.007
Clin. sig. improvement[c]	N=15 (78.9%)*	N=10 (50%)	N=7 (35%)	0.020
MSIS-29 psychological subscore				
Baseline[a]	33.3 (2.8, 66.7)	19.4 (0.0, 47.2)	13.9 (0.0, 66.7)	0.005
Post-intervention[a]	25.0 (2.8, 50.0)	11.1 (0.0, 36.1)	8.3 (0.0, 52.8)	
Change from baseline[a]	-11.1 (-50.0, 16.7)	-2.3 (-19.4, 13.9)	-1.4 (-38.9, 19.4)	0.233
Clin. sig. improvement[c]	N=12 (63.2%)	N=9 (45%)	N=8 (40%)	0.317

Abbreviations: MVMI: music and verbally cued motor imagery; MMI: music-cued MI; Clin. sig. improvement: Clinically significant improvement; MFIS: Modified Fatigue Impact Scale; MSIS-29: Multiple Sclerosis Impact Scale-29.

[a]Median (range); significance of group differences analysed with Kruskal Wallis test; if overall p-value significant, post hoc pairwise comparisons between groups with Dunn´s multiple comparisons test: *p<0.05.

[b]Improvement in fatigue was regarded clinically significant when there was a reduction of 16.2 points on the total MFIS score, 8.9 points on the physical subscale, 8 points on the cognitive subscale, and 2.3 points on the psychosocial subscale (Rietberg, Van Wegen and Kwakkel 2010, reference number 21).

[c]Changes in QoL were considered clinically significant if the reduction on the MSIS-29 physical subscale was 7.5 points and on the psychological subscale 5.56 points (Van der Linden et al. 2005, reference number 22).

[b, c]Analysed with Chi-Square test; if overall p-value significant, analysed with Fisher´s Exact test and corrected for multiple comparisons: *p<0.05.

Figure 1: CONSORT Flow Chart.

Figure 2: Intervention.

Abbreviations: MI: Motor Imagery.

Familiarisation with MI was used according to a review (Schuster et al. 2011, reference number 8). The PETTLEP approach to MI was developed by Holmes and Collins 2001, reference number 6)

Figure 3: Effect of intervention on walking speed and walking distance.

Figure legend: Abbreviations: MVMI: music- and verbally cued MI; MMI: music-cued MI; MI: motor imagery; T25FW: Timed 25-Foot Walk Test; 6MWT: 6-Minute Walk Test. (A) Walking speed and (B) walking distance; small square brackets above the figure indicate significant within-group comparisons between baseline and post-intervention; h-beams indicate significant group X time interactions. Grey circles and black squares show means, and error bars indicate 95% confidence intervals; *p-value <0.05; **p-value <0.01; ***p-value <0.001.

Figure 4: Effect of intervention on total motor imagery ability and motor imagery ability, as assessed by mental chronometry.

Figure legend: Abbreviations: MVMI: music- and verbally cued MI; MMI: music-cued MI; MI: motor imagery; KVIQ-10: Kinaesthetic and Visual Imagery Questionnaire-10; TDMI: Time-Dependent Motor Imagery screening test. Motor imagery ability: (A) vividness of images and intensity of sensations (KVIQ-10); (B) mental chronometry; correlations between the number of imagined stepping movements within three time periods of 15, 25 and 45 seconds, with the right and left lower extremities (all correlations are significant at the 0.01 level). Medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and the range by the whiskers. Dashed lines represent the cut-off value for acceptable to high MI ability: (A) 30 points on the KVIQ-10; (B) very strong significant correlation, rho between 0.8 and 1.0. Square brackets on top of the figures show significant within-group comparisons between baseline and post-intervention; *p-value <0.05.

Figure 5: Effect of intervention on sensorimotor synchronisation.

Figure legend: Abbreviations: MVMI: music- and verbally cued MI; MMI: music-cued MI; MI: motor imagery. (A) Step length variability, (B) step time variability and (C) stepwise synchronisation with music at 110 beats per minute (BPM); (D; E; F) corresponding parameters with music at 75 BPM. Grey circles and black squares show medians and interquartile ranges. Small square brackets on top of the figures show significant within-group comparisons between baseline and post-intervention; h-beams indicate significant group X time interactions. (C, G) Dashed lines show the optimum synchronisation ratio at 1.0; *p-value <0.05; **p-value <0.01; ***p-value <0.001.

CONSORT
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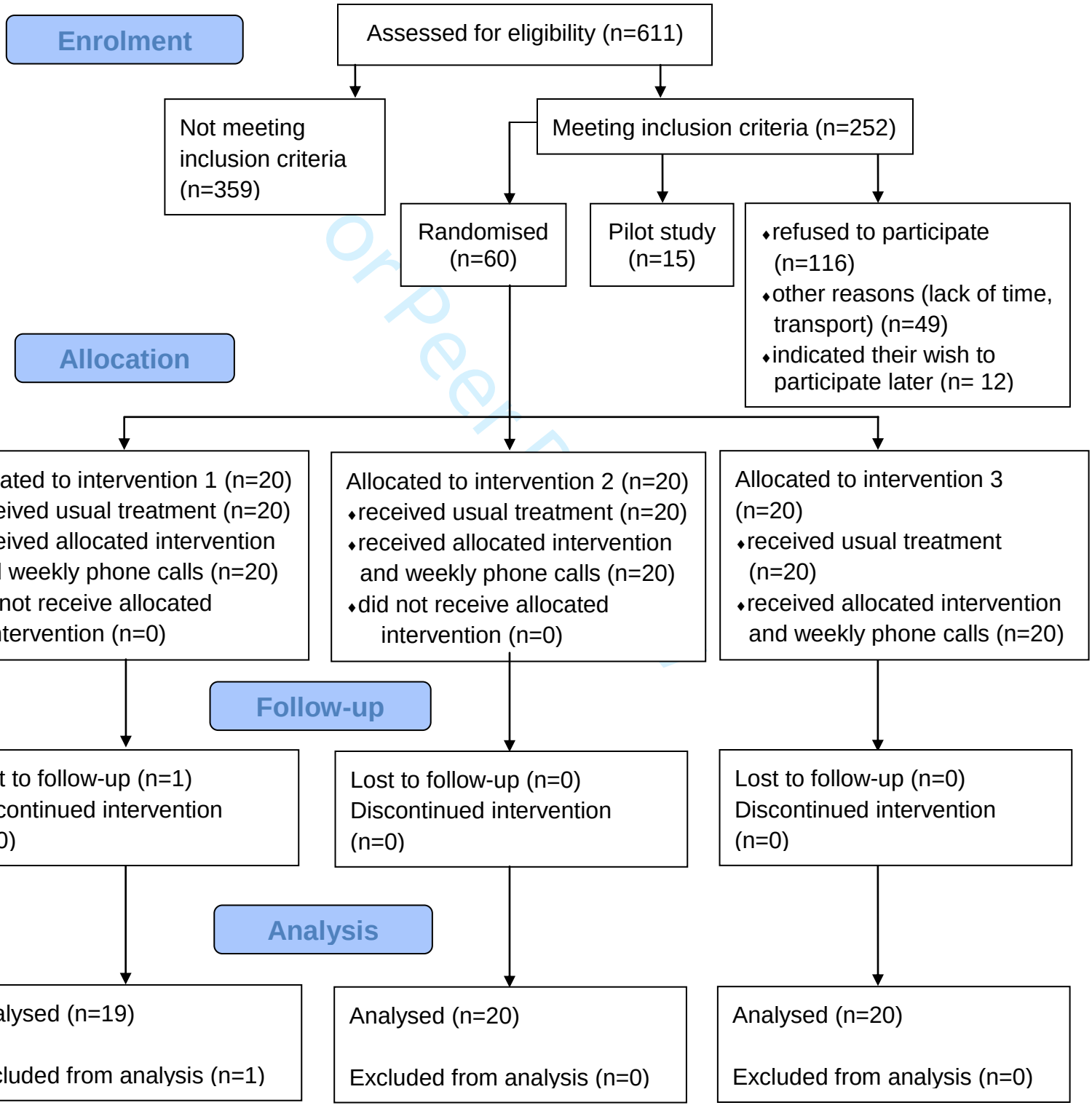
CONSORT 2010 Flow Diagram



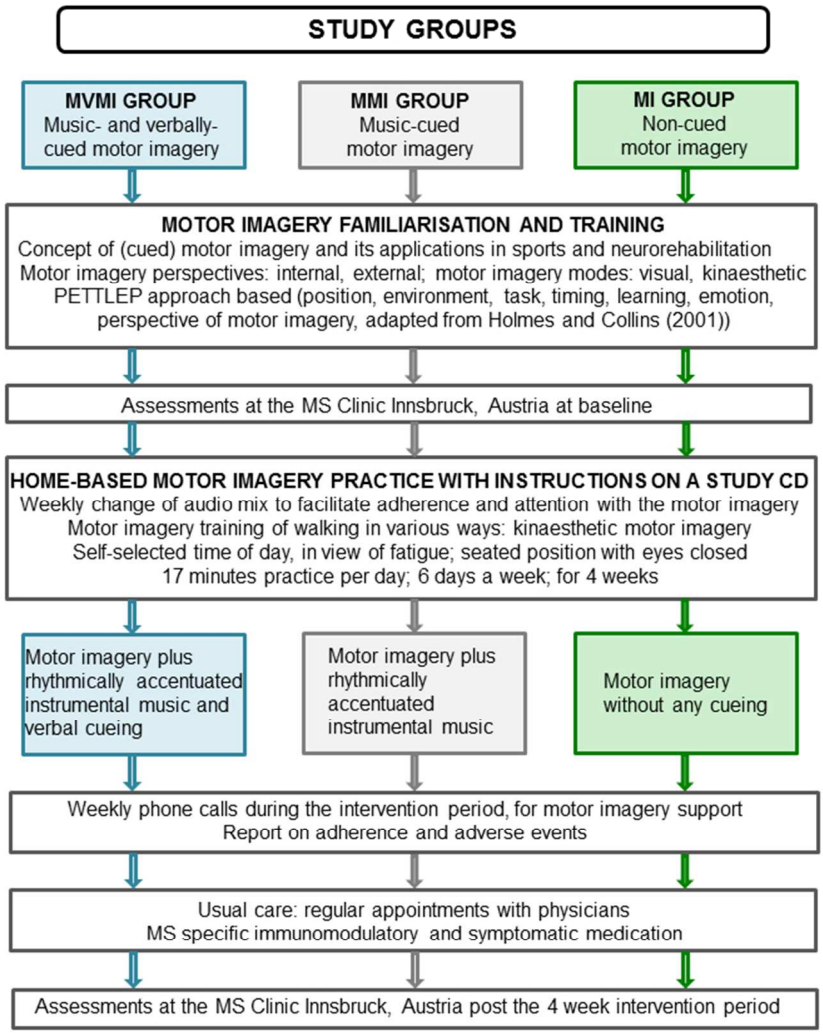


Figure 2

190x254mm (96 x 96 DPI)

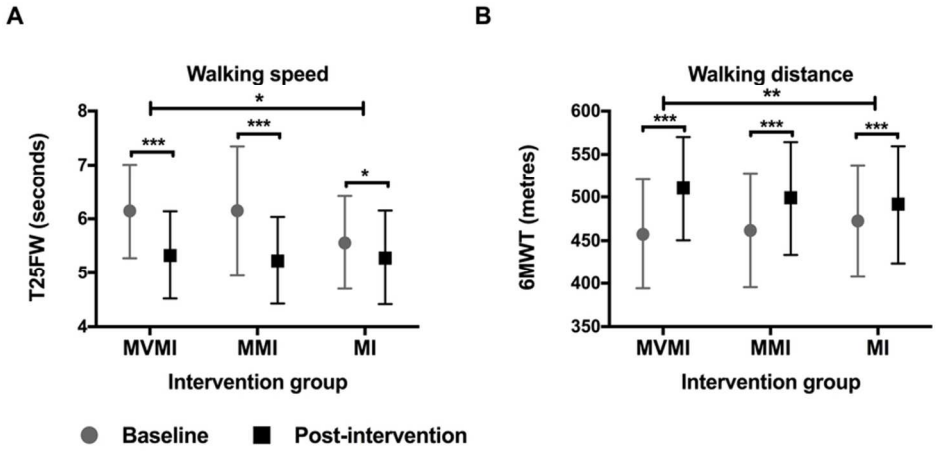


Figure 3

82x38mm (300 x 300 DPI)

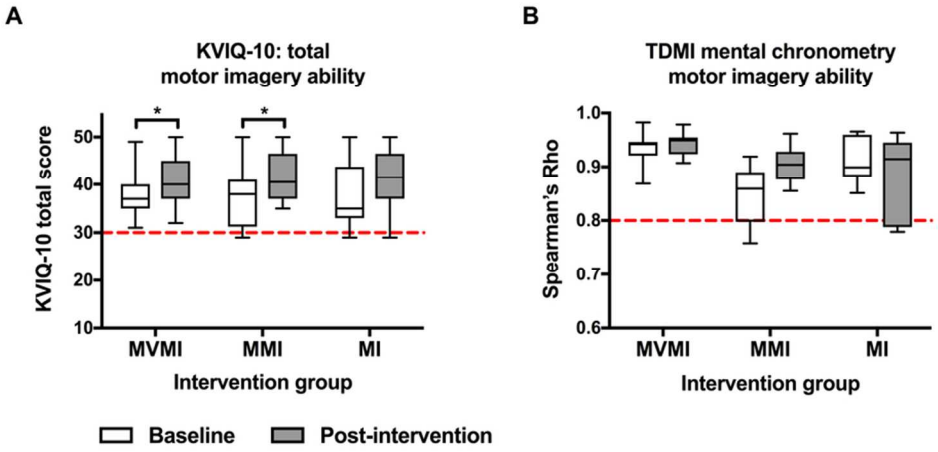


Figure 4

82x38mm (300 x 300 DPI)

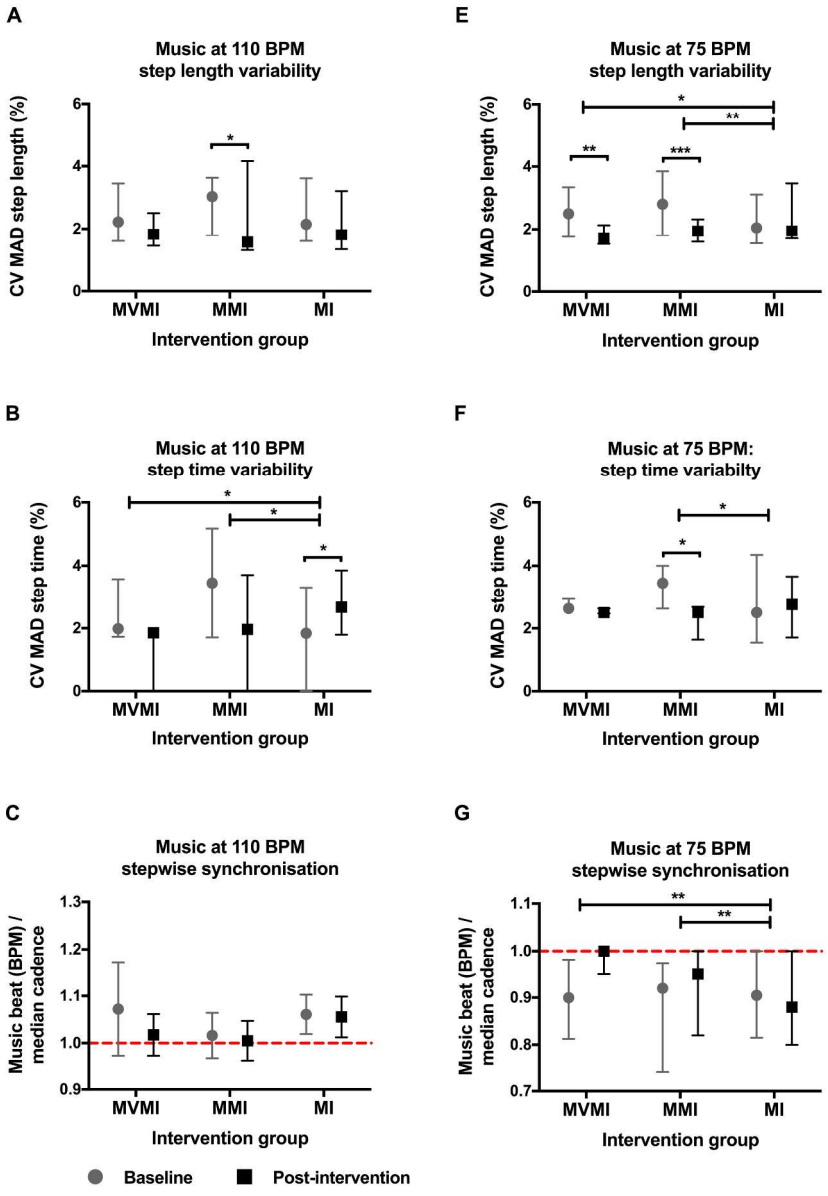


Figure 5

243x328mm (300 x 300 DPI)

Supplementary File 1: Intervention.

The intervention consisted of home-based music- and verbally cued MI (MVMI group), music-cued MI (MMI group) and non-cued MI (MI group). After the randomisation and prior to the intervention, study participants were individually familiarised with (cued) MI, as suggested in previous studies[1]. The PETTLEP approach was used as an interventional MI model, involving the "**P**hysical, **E**nvironmental, **T**ask, **T**iming, **L**earning, **E**motional, and **P**erspective" components of MI[2]. The PETTLEP elements relate to the physical, or bodily, position of the practitioner including arousal, the imagined environment, the imagined task, the MI timing, the learning or changes induced by the MI, the emotions or affective states, which refer to the MI task, and the MI perspective. These elements were applied to the current study.

The participants were informed in lay language about the concept of MI and its application in sports and neurorehabilitation. The new approach of rhythmic-cued MI was introduced. Examples of Rhythmic Auditory Stimulation[3] were described, that is, music cues with gait training, plus their use in neurorehabilitation. In addition, participants were educated about the two perspectives (internal, first-person and external, third-person) and the modes of MI (kinaesthetic and visual). After that, under the supervision of the researcher, participants practised MI and became aware of their preferred mode or perspective. The researcher highlighted internal, kinaesthetic MI, which was adopted for this study. Participants were asked for MI content features such as the mode and perspective they were using, for the environment or for movement aspects they were imagining. Moreover, to receive information about the temporal coupling of the actual and imagined movements, the duration of actual and imagined walking along a marked 6-metre pathway was compared[4]. The time was measured and reported back to the participants who were allowed to repeat the imagery tasks several times.

Based on the PETTLEP approach, the MI script included different elements:

1. Position (Physical): Participants were asked to practise at any time of the day when they were alert. They were frequently reminded to keep their eyes closed and breath normally, sit in an upright body position and relax their shoulders. They were informed that they should avoid tightening their muscles or moving.

2. Environment: Participants were asked to practice in a quiet place at home. They were instructed to imagine themselves walking indoors (long hallway similarly to that in the MS Clinic) and walking outdoors (on a straight path participants are familiar with).

3. Tasks: The imagery scripts slightly changed weekly and remained the same throughout the week. The instructions were: “take long/giant strides; roll your feet on the ground and feel your body weight on your soles; touch the ground with your heels first; raise the front of your feet/your knees; pace; place/feel your weight on your feet/legs; stamp your feet while walking; walk effortlessly, almost as if you were floating; walk forcefully and energetically as if you were an athlete; march as if you were in the army; walk in an extremely upright posture such as when balancing a sachet, filled with rice, on your head; feel the swinging of your arms/legs while walking.”

4. Timing: In the MVMI group, external timing was provided: “imagine yourself walking in time with the music and verbal cues”. In the MMI group, external timing was provided: “imagine yourself walking in time with the music”. In both cued MI groups, the cueing tempo was between 80 and 120 BPM and slow, medium and fast music pieces alternated, with a general progression in the tempo. The cueing tempo was consistent with an imagined walking tempo at 80 to 120 steps per minute. In the MI group, timing was internal and depended on the tempo and intensity of the walking tasks

5. Learning: See familiarisation; additionally, weekly phone call support was individually provided for participants in all groups.

6. Emotion: In the music-verbal-MI group, motivational instrumental music was used with the MI whilst in the metronome-verbal-MI group, simple metronome cues were employed. In all groups, the MI instructions and cues included motivational and arousal enhancing aspects (e.g. walk forcefully and energetically as if you were an athlete; stamp-stamp). See instructions under Tasks.

7. Perspective: Participants were asked to use kinaesthetic MI from an internal, first-person perspective.

In the MVMI and MMI groups, cueing of the MI was provided by instrumental (karaoke) music. A selection of the music type and beat was based on a published summary of practical guidelines and recent publications[3]: rhythmic cueing was in a 2/4 or 4/4 metre with strong ON and OFF beat patterns, which means that every first or every first and third beats were stressed.

Additional verbal cueing was used in the MVMI group. The literature shows that three to four different verbal cues are useful in early learning stages and seven to nine cues improve more advanced motor learning stages. By contrast, a higher number of cues might confuse participants and detract them from the motor task[5]. In the current study, the verbal cueing was applied accordingly. For part one of the CDs, four verbal cues were used ("step-step", "stamp-stamp", "large-step" and "toe-off"). These cues were reused in parts two to four with gradually added new cues ("upright", "strike-heel", "roll-foot", "pace-pace" and "swing-swing")[5]. The verbal emphasis was placed on the beats accordingly such that with a 4/4 metre, every first and third beat were stressed, and with a 2/4 metre, every first beat was emphasised. At the same time, every first beat was dedicated to one leg, such as the right leg, and every second beat was for the other leg.

In the MI group, no cueing was employed.

The MI instructions with or without music or verbal cues were on a CD prepared for this study by the researcher (using GarageBand, Apple Inc.), as the intervention was home-based. If no CD player was available, participants could access the audio mix via a Dropbox link and download it on their smartphones, laptop, tablet or MP3-player. The audio mix should be clearly audible for participants, who were allowed to use headphones or earphones, if desired.

After the familiarisation and verbal instructions, participants received the CD consistent with their group allocation. They were asked to practice kinaesthetic MI of walking 6 times a week and once a day for 17 minutes over 4 weeks. Weekly phone calls were provided also as a reminder on the practice. After each week, the audio mix was changed to enhance attention towards the MI[3] and to facilitate adherence, so that four mixes, designed in the same way, were on one CD. The duration of both the practice and the study were based on the current literature on MI, showing an average study duration of thirty-four days; however, with a practice intensity of three

times a week, for seventeen minutes[1, 6]. The actual practice frequency was noted in a diary but could not be directly assessed. Weekly participant reports on their practice frequency were recorded.

References:

1. Schuster C, Hilfiker R, Amft O, et al. Best practice for motor imagery: a systematic literature review on motor imagery training elements in five different disciplines. *BMC Med*. 2011; 9: 75.
2. Holmes PS and Collins DJ. The PETTLEP approach to motor imagery: A functional equivalence model for sport psychologists. *J Appl Sport Psychol*. 2001; 13: 60-83.
3. Thaut MH. *Rhythm, music and the brain. Scientific foundations and clinical applications*. Oxon: Routledge, 2005.
4. Malouin F, Richards CL, Durand A and Doyon J. Reliability of mental chronometry for assessing motor imagery ability after stroke. *Arch Phys Med Rehabil*. 2008; 89: 311-9.
5. Edwards WH. *Motor learning and control: from theory to practice*. Belmont: Wadsworth, 2011.
6. Catalan M, De Michiel A, Bratina A, et al. Treatment of fatigue in multiple sclerosis patients: a neurocognitive approach. *Rehabilitation research and practice*. 2011: 670537.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	4-5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	5; 7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-9; Figure 2; Supplementary File 1
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	8
	11b	If relevant, description of the similarity of interventions	8-9; Supplementary File 1
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9-11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1; 11
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	11
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Figure 1; 9-10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Tables 2-4 Figures 3-5 Supplementary Tables 1-2 Supplementary Figures 1-3 Pages 12-15
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18-19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15-19
Other information			

Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Corresponding author
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Supplementary Table 1: Effect of interventions on visual, kinaesthetic and total motor imagery ability and motor imagery ability, as assessed by mental chronometry.

Parameter	MVMI group N=19	MMI group N=20	MI group N=20	Overall p-value
KVIQ-G-10 visual subscale				
Baseline [a]	18.0 (14.0, 25.0)	18.0 (13.0, 25.0)	20.0 (14.0, 25.0)	0.386
Median visual subscale [a]	3.6 (2.8, 5.0)	3.6 (2.6, 5.0)	4.0 (2.8, 5.0)	
Post-intervention [a]	19.0 (15.0, 25.0)	20.0 (14.0, 25.0)	22.0 (13.0, 25.0)	
Median visual subscale [a]	3.8 (3.0, 5.0)	4.0 (2.8, 5.0)	4.4 (2.6, 5.0)	
Change from baseline [a]	1.0 (-2.0, 9.0)	1.5 (-4.0, 8.0)	1.5 (-4.0, 10.0)	0.923
KVIQ-G-10 kinaesthetic subscale				
Baseline [a]	19.0 (13.0, 25.0)	20.0 (12.0, 25.0)	18.0 (13.0, 25.0)	0.438
Median visual subscale [a]	3.8 (2.6, 5.0)	4.0 (2.4, 5.0)	3.6 (2.6, 5.0)	
Post-intervention [a]	21.0 (13.0, 25.0)	21.0 (14.0, 25.0)	21.0 (16.0, 25.0)	
Median kinaest subscale [a]	4.2 (2.6, 5.0)	4.2 (2.8, 5.0)	4.2 (3.2, 5.0)	
Change from baseline [a]	1.0 (-2.0, 6.0)	2.0 (-4.0, 7.0)*	2.0 (-3.0, 6.0)*	0.336
KVIQ-G-10 total score				
Baseline [a]	37.0 (31.0, 49.0)	38.0 (29.0, 50.0)	35.0 (29.0, 50.0)	0.925
Median visual subscale [a]	3.7 (3.1, 4.9)	3.8 (2.9, 5.0)	3.5 (2.9, 5.0)	
Post-intervention [a]	40.0 (32.0, 50.0)	41.0 (35.0, 50.0)	42.0 (29.0, 50.0)	

Median total score [a]	4.0 (3.2, 5.0)	4.1 (3.5, 5.0)	4.2 (2.0, 5.0)	
Change from baseline [a]	1.0 (-2.0, 12)*	2.5 (-5.0, 13.0)*	3.0 (-6.0, 16.0)	0.745
Time-Dependent Motor Imagery screening test (TDMI) at baseline				
25 seconds right [a]	14.0 (9.0, 25.0)	15.0 (9.0, 23.0)	14.0 (9.0, 22.0)	
15 seconds left [a]	9.0 (6.0, 18.0)	10.0 (6.0, 16.0)	8.0 (5.0, 14.0)	
45 seconds right [a]	27.0 (18.0, 41.0)	28.0 (18.0, 41.0)	25.0 (15.0, 39.0)	
15 seconds left [a]	10.0 (6.0, 17.0)	10.0 (7.0, 15.0)	9.0 (5.0, 14.0)	
25 seconds left [a]	16.0 (9.0, 26.0)	16.0 (9.0, 23.0)	14.0 (8.0, 21.0)	
Spearman's ρ [a, b]	0.94 (0.87, 0.98)	0.86 (0.76, 0.92)	0.90 (0.85, 0.87)	
TDMI at post-intervention				
25 seconds right [a]	16.0 (12.0, 30.0)	19.0 (12.0, 26.0)	19.0 (11.0, 25.0)	
15 seconds left [a]	11.0 (8.0, 19.0)	12.0 (8.0, 18.0)	12.0 (7.0, 16.0)	
45 seconds right [a]	27.0 (18.0, 41.0)	28.0 (18.0, 41.0)	25.0 (15.0, 39.0)	
15 seconds left [a]	10.0 (6.0, 17.0)	10.0 (7.0, 15.0)	9.0 (5.0, 14.0)	
25 seconds left [a]	17.0 (12.0, 29.0)	18.0 (13.0, 26.0)	18 (11.0, 25.0)	
Spearman's ρ [a, b]	0.95 (0.91, 0.98)	0.90 (0.85, 0.96)	0.91 (0.78, 0.96)	

Abbreviations: KVIQ-G-10: Kinaesthetic and Visual Imagery Questionnaire-10, German short version; N: number of participants; kinaest: kinaesthetic; sub: subscale;

[a]Median (range); significance of group differences analysed with Kruskal Wallis test; if overall p-value significant, post hoc pairwise comparisons between groups with Dunn´s multiple comparisons test: *p<0.05. Median motor imagery vividness scores were calculated by dividing

the median KVIQ-G-10 scores by the number of items, that is, 5 for the visual and kinaesthetic subscales, and 10 for the total score.

[b]10 pairwise correlations; all correlations were significant at ≤0.01 (two-tailed).

Supplementary Table 2: Effect of interventions on gait variability and stepwise synchronisation.

Parameter	MVMI group N=19	MMI group N=20	MI group N=20	Overall p-value
Fast music trial, 110 BPM				
Step length variability				
Baseline[a]	2.22 (0.85, 6.33)	3.03 (1.20, 5.66)	2.14 (1.28, 6.52)	0.610
Post-intervention[a]	1.72 (0.78, 3.74)	1.93 (0.00, 4.17)	1.94 (1.54, 4.95)	
Change from baseline[a]	-0.80 (-2.13, 1.50)	-0.75 (-2.71, 1.46)	-0.06 (-3.16, 1.67)	0.462
Step time variability				
Baseline[a]	1.92 (0.00, 6.60)	3.45 (0.00, 8.77)	1.83 (0.00, 8.77)	0.169
Post-intervention[a]	1.85 (0.00, 6.67)	1.96 (0.00, 6.76)	2.67 (0.00, 10.34)	
Change from baseline[a]	-1.38 (-3.57, 1.88)*	-1.82 (-6.90, 3.85)*	1.71 (-3.33, 3.85)	0.008
Stepwise synchronisation				
Baseline[a]	1.03 (0.90, 1.94)	1.02 (0.81, 1.28)	1.04 (0.93, 1.37)	0.358
Post-intervention[a]	0.99 (0.97, 1.37)	0.99 (0.92, 1.36)	1.04 (0.95, 1.37)	
Change from baseline[a]	-0.04 (-0.57, 0.07)	-0.02 (-0.11, 0.15)	0.00 (-0.06, 0.04)	0.131
Slow music trial, 75 BPM				
Step length variability				
Baseline[a]	2.61 (0.96, 5.22)	2.80 (1.59, 7.77)	2.04 (1.27, 7.87)	0.308
Post-intervention[a]	1.72 (0.78, 3.74)	1.93 (0.00, 4.17)	1.94 (1.54, 4.95)	
Change from baseline[a]	-0.89 (-2.36, 0.86)*	-0.76 (-5.79, 0.25)**	0.03 (-3.32, 1.58)	0.004

Step time variability				
Baseline[a]	2.70 (0.00, 5.00)	3.39 (1.37, 9.33)	2.50 (0.00, 17.24)	0.490
Post-intervention [a]	2.50 (0.00, 4.29)	2.50 (0.00, 8.11)	2.76 (0.00, 18.97)	
Change from baseline [a]	-0.13 (-3.33, 3.80)	-1.31 (-3.66, 3.50)**	0.07 (-4.62, 3.23)	0.011
Stepwise synchronisation				
Baseline[a]	0.90 (0.72, 1.98)	0.92 (0.65, 1.02)	0.91 (0.75, 1.02)	0.563
Post-intervention [a]	1.00 (0.77, 1.22)	0.95 (0.69, 1.01)	0.88 (0.72, 1.01)	
Change from baseline [a]	0.05 (-0.76, 0.26)**	0.03 (-0.10, 0.24)**	-0.02 (-0.08, 0.04)	<0.0001

Abbreviations: BPM = Beats per Minute; stepwise synchronisation = music beat (BPM) / median cadence; step length and step time variability were expressed by the Coefficient of Mean Deviation about the Median (%).

[a]Median (range); significance of group differences analysed with Kruskal Wallis test; if overall p-value significant, post hoc pairwise comparisons between groups with Dunn´s multiple comparisons test: *p<0.05; **p<0.01.

Supplementary Figure 1: Effect of intervention on physical, cognitive, psychosocial and total fatigue.

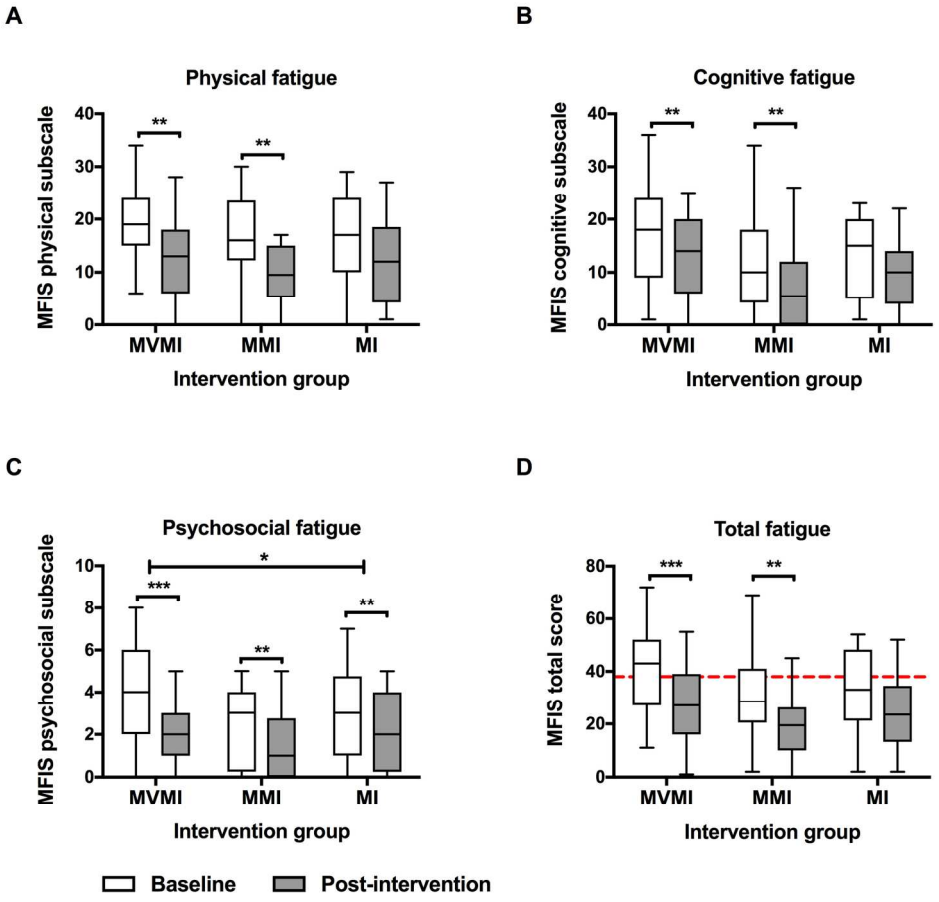
Figure legend: Abbreviations: MVMI: music- and verbally cued MI; MMI: music-cued MI; MI: motor imagery; MFIS: Modified Fatigue Impact Scale. (A) Physical, (B) cognitive, (C) psychosocial and (D) total fatigue; medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and the range by the whiskers. Square brackets on top of the figures show significant within-group comparisons between baseline and post-intervention; h-beams indicate significant group X time interactions. (D) The dashed line indicates the cut-off score for fatigue at 38 points on the total MFIS; *p-value <0.05; **p-value <0.01; ***p-value <0.001.

Supplementary Figure 2: Effect of intervention on physical and psychological quality of life.

Figure legend: Abbreviations: MVMI: music- and verbally cued MI; MMI: music-cued MI; MI: motor imagery; MSIS-29: Multiple Sclerosis Impact Scale-29. (A) Physical and (B) psychological quality of life; medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and the range by the whiskers. Square brackets on top of the figures show significant within-group comparisons between baseline and post-intervention; h-beams indicate significant group X time interactions; *p-value <0.05; **p-value <0.01; ***p-value <0.001.

Figure 3: Effect of intervention on walking speed and walking distance in participants with low (EDSS 1.5-3.0) and higher disability levels (EDSS 3.5-4.5).

Figure legend: Abbreviations: MVMI: music- and verbally cued MI; MMI: music-cued MI; MI: motor imagery; T25FW: Timed 25-Foot Walk Test; 6MWT: 6-Minute Walk Test. (A) Walking speed and (B) walking distance; small square brackets above the figure indicate significant within-group comparisons between baseline and post-intervention. Between-group comparisons yielded nonsignificant results. Grey and black symbols show means and error bars indicate 95% confidence intervals; *p-value <0.05; **p-value <0.01; ***p-value <0.001.



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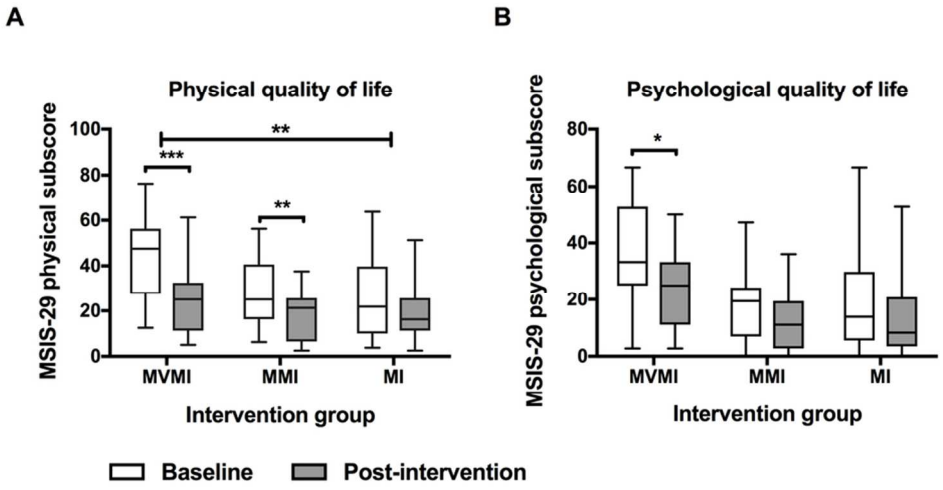

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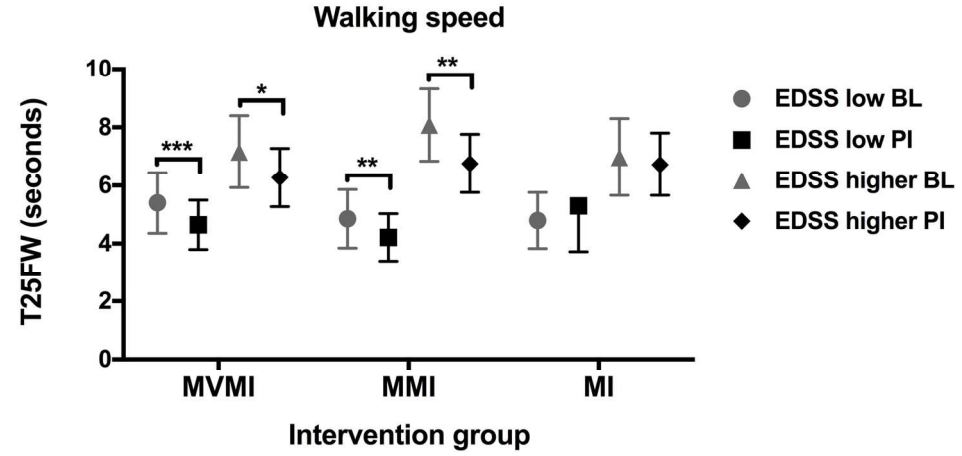

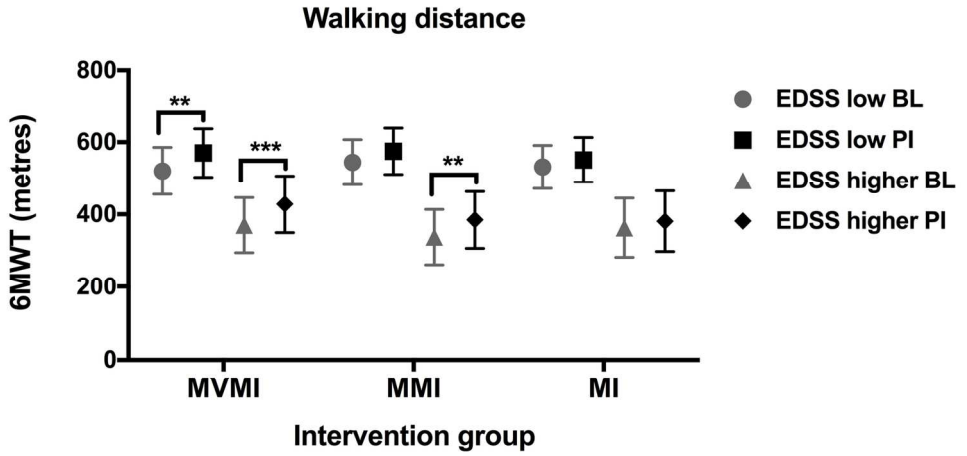

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