BMJ Open Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: protocol of a randomised parallel multicentre trial

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ABSTRACT

Introduction Motor imagery (MI) refers to the mental rehearsal of a physical action without muscular activity. Our previous studies showed that MI combined with rhythmic-auditory cues improved walking, fatigue and quality of life (QoL) in people with multiple sclerosis (pwMS). Largest improvements were seen after music and verbally cued MI. It is unclear whether actual cued gait training achieves similar effects on walking as cued MI in pwMS. Furthermore, in pwMS it is unknown whether any of these interventions leads to changes in brain activation. The purpose of this study is therefore to compare the effects of imagined and actual cued gait training and a combination thereof on walking, brain activation patterns, fatigue, cognitive and emotional functioning in pwMS.

Methods and analysis A prospective double-blind randomised parallel multicentre trial will be conducted in 132 pwMS with mild to moderate disability. Randomised into three groups, participants will receive music, metronome and verbal cueing, plus MI of walking (1), MI combined with actual gait training (2) or actual gait training (3) for 30 min, 4× per week for 4 weeks. Supported by weekly phone calls, participants will practise at home, guided by recorded instructions. Primary endpoints will be walking speed (Timed 25-Foot Walk) and distance (2 min Walk Test). Secondary endpoints will be brain activation patterns, fatigue, QoL, MI ability, anxiety, depression, cognitive functioning, music-induced motivation-to-move, pleasure, arousal and self-efficacy. Data will be collected at baseline, postintervention and 3-month follow-up. MRI reference values will be generated using 15 matched healthy controls.

Ethics and dissemination This study follows the Standard Protocol Items: Recommendations for Interventional Trials-PRO Extension. Ethical approval was received from the Ethics Committees of the Medical Universities of Innsbruck (1347/2020) and Graz (33-056 ex 20/21), Austria. Results will be disseminated via national and international conferences and published in peer-reviewed journals.

Trial registration number DRKS00023978.

Strengths and limitations of this study

- This is the first prospective double-blind randomised parallel multicentre trial to investigate the effects of imagined and actual gait training with music, metronome and verbal cueing versus a combination thereof in people with multiple sclerosis (MS).
- The intervention of this study was informed by previous study results and involvement of patients with MS.
- Study participants with MS will receive close individual telephone support of their home-based training to facilitate their motor learning and adherence.
- Semi-structured telephone interviews will assist in gaining insight into participants' perspectives of the intervention.
- Subjective and objective assessments and functional MRI will be used as outcome parameters.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system leading to disability accumulation. People with MS (pwMS) frequently have impairment in motor, sensory, visual and other functional systems.¹ Walking impairment and fatigue contribute to a limitation in quality of life (QoL).^{2–4} Motor imagery (MI)⁵ and rhythmic-auditory stimulation, or cueing^{6–9} are specific physiotherapy interventions. Rhythmic-auditory cues facilitate cyclical movements, predominantly gait,⁶ which can be provided either by a metronome or music beat,^{7,8} a combination thereof,⁹ or by rhythmic verbal cues.^{10,11} Cued walking training has been found to improve walking in people with neurological diseases including MS.^{12–16} The stimulation leads

to interactions between sensory and motor processes, referred to as sensorimotor interaction.¹⁷

MI is the mental execution of a movement without its actual performance¹⁸ and MI of walking activates brain areas similar to those in actual walking.^{19 20} Different imagery models exist and include individual and group MI, with or without physical practice.²¹ Jeannerod has distinguished between an internal and an external MI perspective.²² Further, a visual and a kinaesthetic MI mode have been described.²³ Persons imagine watching themselves moving with visual MI, with the kinaesthetic mode, they feel themselves moving.²⁴

Few small studies have explored rhythmic-cued gait training^{15 16} or MI of walking^{25 26} in pwMS, showing promising preliminary results. Results from our previous work showed superior effects of music and verbally cued MI over non-cued MI on walking, fatigue and QoL.^{27 28} So far, no studies have compared the effects of cued MI on walking and cued gait training or a combined cued MI and gait training in pwMS. Building on the promising results of our previous studies, we furthermore want to learn whether observed behavioural changes are reflected by changes in brain activation patterns. MRI has been suggested to contribute to the understanding of mechanisms behind motor deficits and functional recovery in pwMS.^{29 30} So far, functional MRI (fMRI) studies on motor rehabilitation in pwMS are scarce and,^{29 31} to our knowledge, brain activation changes due to specific walking training need to be further explored in pwMS. Extending the study by Tavazzi *et al*,²⁹ who showed a reduced extent of the widespread brain activation during a motor task (plantar dorsiflexion) after gait rehabilitation in pwMS, we will assess potential changes in brain activation associated with cued MI and/or cued gait training. In line, beneficial training might be associated with an increased activation of the primary motor areas, along with decreased activation outside the sensorimotor network (eg, frontal areas).^{29 32 33} We expect that MI training leads to similar neural reorganisation patterns as actual practice.³⁴

Therefore, the purpose of this study is to determine the effects of actual and imagined rhythmic-cued gait training vs their combination on walking, cognitive and emotional functioning in pwMS. Further aims are to compare brain activation changes during a motor or MI task between groups and determine which changes are specifically associated with improvements in gait function.

ALTERNATIVE HYPOTHESES

H1: All trainings will significantly improve walking, fatigue, QoL, emotional and cognitive functioning, and normalise brain activation (ie, a more focal activation of the sensorimotor network as observed in healthy controls) in pwMS.

H2: The effects of cued MI combined with cued gait training are superior to those of cued MI and cued gait training alone.

METHODS AND ANALYSES

Study design, setting and timeline

This study is designed as a multicentre, randomised, parallel, double-blind trial in pwMS with mild to moderate disability and follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 and SPIRIT-PRO Extension Checklist (online supplemental file 1). Study results will be reported in accordance with the Consolidated Standards of Reporting Statement.³⁵ The study will be conducted at the Clinical Department of Neurology, Medical Universities of Innsbruck (centre 1) and Graz (centre 3) and Clinic for Rehabilitation Muenster (centre 2), Austria. The expected recruitment phase is from 01 February 2021 to 31 March 2023.

Patient and public involvement

The study intervention was developed based on previous study results^{27 28 36 37} and patient involvement. An MS advisory group was consulted to clarify any questions, for example, with respect to their music preference and suggestions for the duration of the imagined and actual gait training. Semi-structured telephone interviews will be used to gain insight into patients' problems with and acceptability of the intervention. Patients' acceptance of the intervention is essential for adherence.

Sample size and participants

The sample size for this study was calculated using previous study data²⁷ and Cohen's d effect sizes of the walking distance endpoint, with 95% CI and corrected estimates of pooled SD. Based on 80% power ($\beta=0.2$), $\alpha=0.025$ and conservative effect sizes of $d=0.74$, a sample size of 37 participants per group is required to detect a between-group difference. Including 15% attrition and making the number divisible by 3, a total sample size of 132 participants results. Thereof, 36 patients will also undergo MRI scanning, while 15 healthy controls will be enrolled to provide reference values for the MRI analyses. Study procedures including screening for eligibility are presented in online supplemental figure 1 (flow diagram).

Eligibility criteria for this study are listed in table 1.

Recruitment, randomisation and blinding

Information brochures and invitations for study participation will be displayed in the study centres 1–3 and on the Austrian MS Society website, with pwMS notified about the study by clinical department staff. Written informed consent will be obtained from all participants (see online supplemental file 2 for an English version of the patient information sheet and informed consent form). Healthy controls will be enrolled at centre 3 only.

Patients fulfilling the eligibility criteria will be randomised into one of three groups with stratified blocked randomisation performed by an independent researcher at centre 1 using an online software-based random number generator (Sealed Envelope, London, UK), blocks of prespecified size and 1:1:1 allocation.

Table 1 Eligibility criteria

People with MS	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ▶ Any MS phenotype according to the revised McDonald's criteria^{123 124} ▶ Aged 18 years or older ▶ Any ethnicity ▶ Disability status score on the Expanded Disability Status Scale (EDSS)⁴¹ of 2.0–5.0 ▶ Stable disease; no clinical evidence of disease activity ▶ Ability to speak and understand German language <p>Exclusion criteria</p> <ul style="list-style-type: none"> ▶ Significant concomitant diseases (such as malignant diseases, other neurological or psychiatric disorders, musculoskeletal problems affecting walking, pain, uncorrected visual or hearing impairment) ▶ Cognitive impairment as defined by a MoCA cut-off score of 26/30 (<26=impaired cognition)⁸⁷ ▶ Anxiety or depression as signified by a HADS anxiety⁸² or depression subscale score of 11/21⁸³ or suicidality as evaluated by a narrative screening⁷⁹ ▶ Pregnancy ▶ Relapse of MS within the last 3 months before the study ▶ Any medication initiation or change (including corticosteroids) or any physiotherapy change or inpatient rehabilitation within 3 months prior to the study ▶ Any change of symptomatic treatment affecting walking (medication or physiotherapy) or of disease modifying treatment during the study will lead to an exclusion of the participant from further analysis
Healthy controls	<ul style="list-style-type: none"> ▶ Age-matched and gender-matched ▶ Without any history of neurological, psychiatric or orthopaedic disorders
MRI/fMRI contraindications	<ul style="list-style-type: none"> ▶ Metallic or electricity conducting implants or prostheses (cardiac pacemaker, insulin pump, middle-ear implants, heart valve or hip prostheses, artificial teeth, hearing aid, etc) in or on the body ▶ Non-removable metal parts (coil, braces, etc) or metal shrapnel in or on the body ▶ Tattoos in the head or neck area, nicotine plasters or cosmetic eye modifications ▶ Pregnancy ▶ Epilepsy ▶ Claustrophobia

fMRI, functional MRI; HADS, Hospital and Anxiety and Depression Scale; MoCA, Montreal Cognitive Assessment; MS, multiple sclerosis.

Stratification will be performed according to relevant predictive factors for a change in walking that is, ³⁸ age (<40, ≥40), gender (female, male)^{39 40} and disability (Expanded Disability Status Scale⁴¹ 2.0–3.5, 4.0–5.0). Sequentially numbered sealed opaque envelopes including group allocation numbers for groups 1–3 will be fabricated for each stratum. Allocation concealment will be performed to avoid allocation bias, assessors blinded to participants' group allocation and participants unaware of the study hypotheses.

Intervention

Three intervention groups will receive home-based kinaesthetic MI and/or gait training with music, metronome and verbal cueing for a total of 30 min, 4 times per week, for 4 weeks. Participants will receive cued MI (group 1), combined cued MI and gait training (group 2) or cued gait training (group 3).

An audio-mix has been created specifically for this study (Audacity. V.3.0.0)⁴² for download on participants' electronic devices or available as study CDs (group 1). Instrumental motivational music at a regular beat in a 2/4 or 4/4 m and strong ON and OFF beat patterns (ie, with every first or first and third music beats stressed) will be utilised.^{6 43 44} Additionally, metronome cues will accentuate the music beat and tempo and support gait synchronisation with the beat. Verbal cueing will be employed as a reminder of the task to practise and aid participants' focus on the respective body parts, for example, the feet.

Suitable rhythmical sequences at 80–120 beats/min will be cut and mixed with instructions on MI or gait training. Rhythmic-verbal cues will accentuate the cueing intermittently, for example using 'step-step' or 'toe-off',⁴⁵ with different walking tasks used. Familiarisation will occur individually with the rhythmic-cued MI and gait training as previously recommended.^{21 46} The audio mix will be changed weekly to gradually increase the tempo and facilitate adherence. The PETTLEP approach to MI will be applied, involving the 'Physical, Environmental, Task, Timing, Learning, Emotional, and Perspective' components of MI.⁴⁷ Using the Template for Intervention Description and Replication checklist,⁴⁸ detailed information on the PETTLEP approach and intervention is provided in online supplemental table 1. In [figure 1](#), key aspects of the intervention are presented.

Practice frequency will be noted in a diary with weekly reports on participants' practice frequency prepared. Weekly phone calls will be used in the home-based training support of all participants, additionally at 4 weeks postintervention. Additional phone call support will be provided on request by the intervention providers. The content of the semi-structured telephone interviews during and postintervention is presented in [figure 2](#) and online supplemental file 3.

Data collection

Demographic and disease specific data will be collected as detailed in [table 2](#). Three categories of disease modifying

Figure 1 Key elements of the intervention in the three groups.

treatment (DMT) will be operationalised according to the disease activity and course (1) no DMTs; (2) moderately effective and (3) highly DMTs (active substances are detailed in [table 2](#)). DMTs will be recorded and handled as a covariate in the data analysis because they may affect the primary and secondary outcomes. Clinical data will be collected by trained and blinded assessors (physiotherapists, occupational therapists, sports scientists and psychologists), with the order of the patient-reported outcome measures being randomised for each participant and visit to minimise order effects. A schedule of the study procedures is provided in [table 2](#).

Primary outcomes

Primary outcomes are walking speed as assessed by the Timed 25-Foot Walk (T25FW)⁴⁹ and walking distance as assessed by the 2-Minute Walk Test (2MWT).^{50 51} For the T25FW, patients will be asked to walk a marked distance of 25 feet (7.62 m) as quickly as possible, though safely, with an assistive device as required.⁵² Scoring is achieved by taking the average of two trials. Excellent psychometric properties of the T25FW have been demonstrated.^{53 54} A 20% change in the T25FW is interpreted as a clinically significant difference in walking speed.⁵⁵

Figure 2 Content of semi-structured interviews.

Table 2 Schedule of study procedures

	Study period					
	Enrolment	Allocation	Postallocation			Follow-up
	Screening		Baseline test Day 1	Postintervention test Week 4	Follow-up phone call Week 8	test Month 3
Timepoint	$-T_1$	0	T_1	T_2	T_3	T_4
<i>Enrolment</i>						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
<i>Interventions</i>						
Music-cued MI group			⬅————➡			
Music-cued MI and gait training group			⬅————➡			
Music-cued gait training group			⬅————➡			
Outcomes (assessments)						
<i>Baseline variables</i>						
Demographics (age, gender)	X					
Clinical characteristics (EDSS, MS phenotype, disease duration, disease modifying treatment*)	X					
Global cognitive impairment (MoCA test)	X			X		X
Anxiety and depression (HADS)	X			X		X
Suicidality (narrative screening)	X			X		X
<i>Primary outcomes</i>						
Walking speed and distance (T25FW, 2MWT)			X	X		X
<i>Secondary outcomes</i>						
Brain activation patterns (fMRI)			X	X		
MS related fatigue (NFI-MS)			X	X		X
Health-related QoL (MusiQoL)			X	X		X
MI ability (KVIQ-10, mental chronometry test)			X	X		X
Cognitive functioning (SDMT)			X	X		X
Music-induced motivation in exercise (BMRI-2)			X	X		X
Music-induced pleasure & arousal (SAM)				X		
MS specific self-efficacy (USE-MS)						
Adverse events and adverse reactions (log)				X	X	X
Falls (log)				X	X	X
Acceptability of the intervention, adherence and coping (checklist, weekly semi-structured phone interviews)			⬅————➡			
Self-report health status and feedback on the study intervention (follow-up semi-structured phone interviews)					X	

*Three categories of disease modifying treatment (DMT): (1) no DMTs; (2) moderately effective DMTs: interferon-b 1a and 1b, pegylated interferon-b 1a, glatiramer acetate, dimethyl fumarate, teriflunomide, azathioprine, intravenous immunoglobulins; (3) highly effective DMTs: alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, cyclophosphamide, mitoxantrone, rituximab, siponimod, ofatumumab and ozanimod.¹²⁵

BMRI-2, Brunel Music-Rating Inventory-2; EDSS, Expanded Disability Status Scale; fMRI, functional MRI; HADS, Hospital Anxiety and Depression Scale; KVIQ-10, Kinaesthetic and Visual Imagery Questionnaire, short version; MI, motor imagery; MoCA, Montreal Cognitive Assessment; MS, multiple sclerosis; MusiQoL, Multiple Sclerosis International Quality of Life; 2MWT, 2 min Walk Test; NFI-MS, Neurological Fatigue Index-Multiple Sclerosis; SAM, Self-Assessment Manikin; SDMT, Symbol Digit Modalities Test; T25FW, Timed 25-Foot Walk; USE-MS, Unidimensional Self-Efficacy Scale for Multiple Sclerosis.

The 2MWT will be performed as outlined in the American Thoracic Society Guidelines, which were developed for the 6 min Walking Test⁵⁶ and adapted by international experts from the NIH Toolbox.⁵⁷ For the 2MWT, excellent validity^{50 58} and test-retest reliability have been found.⁵⁹ A 20% change represents a clinically significant difference in walking distance.⁶⁰

Secondary outcomes

Brain activation patterns

MRI data will be acquired at T_1 and T_2 on a 3 Tesla scanner (Siemens PRISMA, Siemens Healthcare Erlangen) using a 20-channel head coil. The MRI protocol includes a high-resolution structural three-dimensional (3D) T1-weighted MPRAGE sequence with 1 mm isotropic resolution

(repetition time (TR)=1900 ms, echo time (TE)=2.7 ms) and a T2-weighted sequence (1 mm isotropic, TR=2800 ms, TE=405 ms). A 3D fluid-attenuated inversion recovery (FLAIR) sequence (1 mm isotropic, TR=5000 ms, TE=393 ms) is administered to assess hyperintense T2-LL in patients. Additionally, diffusion tensor imaging (DTI; 1.5 mm isotropic, TR=3318 ms, 64 directions), task-related fMRI (2 mm isotropic; TR=2500 ms; TE=30; 198 volumes, field of view=192×192 mm², acquisition time=8.31 min) and resting-state fMRI (2 mm isotropic; TR=1000 ms; TE=35; field of view=256×256 mm², acquisition time=5.20 min) will be performed. The scans will take approximately 35 min in total.

Task-related fMRI: experimental stimuli and procedure

The block-fMRI task will comprise a music-cued bipedal ankle movement on a treadmill that is, alternating dorsiflexion and plantarflexion of both feet,⁶¹ a corresponding music-cued MI, and a listen-to-music-only condition. Four instrumental music-excerpts were selected as cues based on the same criteria used in the interventions.⁶ Pace is held constant at 110 beats /min for all cues. Each condition is repeated four times, and presented in a pseudo-randomised order, so that no condition or music-cue occurs twice in a row, and identical music-cues never run successively.

Before each condition, a coloured symbol cue appears in the centre of the screen for 2.5 s, indicating the subsequent condition (orange feet for movement, blue think bubble for MI, violet ear for music-only condition; [figure 3A](#)). At the start of each condition, a fixation cross in the corresponding colour appears and the music starts. Participants are instructed to perform the ankle movement at the pace of the music, starting with the right foot and concentrate on the music beat during the music-only condition. After 22.5 s, the fixation cross turns black, indicating a period of total rest for 15 s ([figure 3B](#)).

Prior to entering the scanner, participants will practice the paradigm. Throughout the whole paradigm, participants are instructed to fixate on the cross, not to move their heads, to relax their entire body, except their feet

during the movement condition. To decrease stimulus-correlated motion, participants' heads are fixed with foam-cushions and their knees flexed to approximately 135° using a soft roll and cushion beneath their knees ([figure 3A](#)).⁶¹ Vision is corrected with prism lenses if necessary. During the paradigm, participants are observed with correct and incorrect movements recorded. After the scan, participants are asked to complete a short questionnaire on whether they recognised the songs (yes/no), liked the music-cues and found them motivating to move (both items: 7-point Likert scales). Three items will ask about the MI conditions (7-point Likert scale): the perceived MI difficulty and the extent to which they have 'seen' or 'felt' the MI (similar to the KVIQ-10 response format).

Fatigue

The Neurological Fatigue Scale-Multiple Sclerosis (NFI-MS) will be used to assess fatigue, including subscales of physical and cognitive fatigue, relief through daytime sleep or rest and abnormal nighttime sleep and sleepiness.^{62 63} A summary score of items 1–7, 9 and 11–12 is generated. A 4-point Likert scale is used, from 0='strongly disagree' to 3='strongly agree', where higher scores represent more severe fatigue. The NFI-MS displayed good validity⁶³ and reliability.⁶³

Health-related QoL

The 31-item Multiple Sclerosis International Quality of Life questionnaire (MusiQoL)^{64 65} has been chosen to record patient-reported health-related QoL (HRQoL). Nine dimensions of HRQoL are assessed: everyday activities, psychological well-being, symptoms, relationships with friends, family and the healthcare system, emotional and sex life, coping and rejection. A 5-point Likert scale from 1='never/not at all' to 5='always/a lot' is used with reverse scoring of negatively worded items. Nine domain scores and the global index are standardised on a 0–100 scale, where 100 represents the best HRQoL. A good validity⁶⁶ and reliability have been shown for the MusiQoL.^{64 65}

Figure 3 Schematic representation of the block functional MRI-paradigm.

MI ability

MI ability should be assessed using at least two different approaches,⁶⁷ hence the Kinaesthetic and Visual Imagery Questionnaire,^{68 69} using a German short version (KVIQ-G-10)⁶⁸ and a mental chronometry (MC) test.^{70–72}

The KVIQ-G-10 is patient-reported and assessor-administered and measures visual and kinaesthetic MI ability in neurological patients using five items.⁶⁹ Scoring is achieved using a 5-point Likert scale from 1='no image' to 5='image as clear as seeing' (visual subscale) and from 1='no sensation' to 5='as intense as executing the action' (kinaesthetic subscale). The KVIQ-G-10 has excellent psychometric properties.⁶⁸

MC tests are based on the theory of functional equivalence between MI and actual movement.^{47 73 74} Excellent temporal equivalence has been found for corresponding imagined and real movements.^{72 75} MC evaluation will be at a comfortable tempo on a marked 6-metre path.^{70–72} The 'index of deviation from isochrony' will be calculated to quantify the discrepancy between imagined and real walking: deviation index=absolute value (1–(MI/motor execution)).⁷⁶ Values close to zero are indicative of high MI ability.⁷⁶

Depression, anxiety and suicidality

The German version⁷⁷ of the Hospital Anxiety and Depression Scale (HADS)⁷⁸ and narrative screening for suicidality⁷⁹ adapted from item 9 of the Beck Depression Inventory⁸⁰ and a suicidality screening checklist⁸¹ will be employed for screening. The 14-item HADS assesses patient-reported anxiety and depression during the previous 2 weeks. Anxiety or depression will be signified by a HADS anxiety⁸² or depression subscale score of 11/21 points⁸³ or suicidality as evaluated by a narrative screening.⁷⁹ Good validity, reliability⁸⁴ and a bifactorial structure has been shown for the German HADS.⁷⁷

Overall cognitive impairment

Overall cognitive impairment (attention and concentration, executive functions, memory, language, visuo-constructive abilities, conceptual thinking, arithmetic and orientation) will be assessed using the German Montreal Cognitive Assessment (MoCA).^{85 86} The highest possible score is 30 points; values ≥ 26 are considered normal,⁸⁷ with good psychometric properties demonstrated.^{87–89}

Motivational qualities of music in exercise settings

The 6-item Brunel Music Rating Inventory-2 (BMRI-2)⁹⁰ has been chosen to assess the music-induced motivation to move on a 7-point Likert scale. Music pieces selected from the audio-mix will be played to participants (in relevant 90 s excerpts).⁹⁰ Motivational properties of the musical rhythm, style, melody, tempo, instrumentation and beat during physical exercise will be patient-rated. The BMRI-2 has shown good validity and reliability.^{90 91}

Music-induced pleasure and arousal

The Self-Assessment Manikin (SAM) will be used to measure the emotional responses of pleasure and arousal

to the music selected for the study intervention.^{92 93} The SAM consists of two series of pictograms, each of which displays a dimension on a 9-point scale.^{92 93} SAM validations have demonstrated good to excellent validity^{93 94} and reliability.⁹⁵

Self-efficacy

The validated German version⁹⁶ of the Unidimensional Self-Efficacy Scale for MS (USE-MS)⁹⁷ will be used to assess self-efficacy. For this patient-reported 12-item questionnaire using a 4-point Likert scale, excellent psychometric properties have been seen.^{96 97}

Cognitive function

Cognitive function including attention, visual scanning, working memory and psychomotor speed will be measured using the Symbol Digit Modalities Test (SDMT).⁹⁸ Patients will be asked to assign the numbers 1 through 9 to nine different symbols within 90 s. The number of maximum possible substitutions is 110. Excellent construct,⁹⁹ predictive¹⁰⁰ and discriminatory validity¹⁰¹ and test-retest reliability¹⁰² for the SDMT is demonstrated in pwMS.

Falls, adherence, and acceptability of the intervention

Falls and adverse events will be recorded in structured logs, the relationship with the intervention evaluated and treatment provided if necessary, which is covered by an indemnity insurance policy. Semi-structured telephone interviews will gain information on adherence and acceptability. Adherence will be monitored using a self-report checklist (figure 2).

Data management

As for confidentiality, the Austrian, Tyrolean and Styrian Data Protection Acts will be adhered to, and personal data codified by a participant ID. Only the research team will have access to the data. Data will be only used for the purposes for which they were collected and saved on a password-protected computer. Data will be digitised in double entry with double coding of interview data performed. Quality assurance measures such as spot checks of value ranges and field types and logical checks will be performed.

Data analyses

Statistical data analyses

All statistical analyses employ IBM SPSS software, release V.27.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism V.9, San Diego, California, USA. A two-tailed p value < 0.05 will signify statistical significance. Using Little's test of missing completely at random (MCAR) the assumption of MCAR will be tested, signified by a p value > 0.050 .¹⁰³ With data missing (completely) at random, multiple imputation will be used for handling missing data, or other strategies as appropriate.¹⁰⁴ Including all cases as originally allocated, intention-to-treat analysis will be performed. Descriptive statistics will be used as appropriate and continuous data tested for normal distribution using the Shapiro-Wilk test, Q-Q-plots and histograms.

For between-group comparisons at baseline, One-way analysis of variance (ANOVA), Kruskal-Wallis and χ^2 tests will be used.

Mixed design ANOVA test assumptions will be tested for, for example, sphericity (Mauchly's test) and homogeneity of variance (Levene's test), and standard correction procedures applied where appropriate. For continuous variables (T25FW, 2MWT, MC and SDMT), a 2-way mixed design ANOVA will be conducted, using time as within-subject factor and group as between-subject factor, and the three DMT categories as covariates (no DMT; moderately effective DMT; highly effective DMT).¹⁰⁵ Post-hoc Bonferroni adjustment performed as appropriate. For categorical data (NFI-MS, MusiQoL, KVIQ-10, HADS, MoCA, BMRI-2, SAM and USE-MS), calculation of differences between postintervention and baseline values will be followed by Kruskal-Wallis and Dunn's multiple comparisons tests.

Structural MRI analyses

Using the Statistical Parametric Mapping—Lesion Segmentation Toolbox, T2-lesion load (T2-LL) will be assessed on T2-FLAIR images by the lesion prediction algorithm¹⁰⁶ controlled by a single experienced rater. Individual binarised T2-LL masks will be registered to MNI and lesion probability mapping performed to identify the lesion locations, using FSL randomise. After lesion filling with the FSL lesion filling toolbox, brain volumes will be assessed from T1-weighted MPRAGE images using SIENAX.

fMRI analyses

Individual resting state and task-fMRI data will be preprocessed using FEAT (FMRIB's Expert Analysis Tool, V.6.0, part of FSL V.6.0).¹⁰⁷ Preprocessing includes: motion correction using MCFLIRT, brain extraction, spatial smoothing using a Gaussian kernel of FWHM (full width at half maximum) of 5 mm,¹⁰⁸ high pass temporal filtering using a cut-off of 150 s (0.007 Hz), linear registration to main structural image (BBR) and non-linear registration warp resolution of 10 mm. High-resolution T1 scans are used for image registration.

First-level task fMRI analyses will be performed for each participant, assessing activation patterns of the three conditions (movement, MI, music-only) and related contrasts. Higher-level analyses will be used to examine potential differences between intervention groups. Independent component analysis will be performed for rs-fMRI data (FSL-MELODIC, V.3.12). The resulting denoised functional images will be resampled to standard space (MNI152 template 2 mm). Dual-regression analyses on the denoised, registered functional images of each subject will be performed to obtain individual spatial maps of the resting-state networks, focusing on the sensorimotor and salience network. Group functional connectivity maps for timepoints 1 and 2 and longitudinal change will be computed for each subject (using FSL Randomise).

Qualitative data analysis

A thematic analysis, understood as a 'method for identifying, analysing, and reporting patterns or themes within data'¹⁰⁹ of the interview material will be performed.^{110 111} Semantic and latent themes will be identified, summarised and interpreted,¹⁰⁹ with data coded, segmented and extracted. From this data, broader themes will be developed. Themes will be reviewed, refined and validated in an iterative and reflexive process,¹¹² data recoded as appropriate, and subthemes identified. Subthemes or categories will be judged by the criteria of internal homogeneity (meaningful coherence within a category) and external heterogeneity (clear differences between categories).¹¹³ The Consolidated criteria for Reporting Qualitative research will be followed to enhance rigour, credibility and reliability.¹¹⁴

DISCUSSION

This study will investigate the effects of three variants of home-based cued gait training interventions on walking, fatigue, emotional and cognitive function, and brain activation. Music will be included to both provide a temporal cueing to the real or imagined walking and potentially induce pleasure in practitioners. Pleasurable, motivating music is known to induce highly enjoyable emotions, motivation and arousal.¹¹⁵ Music-based interventions have been found to improve motor performance, mood and cognition in healthy people and patients with neurological disorders including MS.^{116 117} This may be relevant because studies have further shown that depression¹¹⁸ and cognitive or higher levels of motor impairment^{119 120} reduce the MI ability in pwMS. Therefore, it seems relevant to include screening for anxiety, depression and cognitive impairment in the planned study. Moreover, other aspects, such as music-induced motivation, pleasure or arousal have not been previously measured in pwMS.

fMRI is a state-of-the-art method for assessing potential underlying mechanisms of motor impairment and rehabilitation. Despite the paucity of recent literature, we expect a training-induced decrease of the widespread activation, leading to a more focal activation of the primary sensorimotor network during the motor tasks.¹⁻³ This would also be in line with previous research indicating a rehabilitation-induced 'normalisation' in brain activation, that is, activation patterns more similar to those observed in healthy controls.³ In accordance with previous studies, we expect that pwMS recruit similar brain areas during MI and actual movement, although sensorimotor regions might be activated to a lesser and premotor and parietal regions recruited to a higher extent during MI.^{121 122} Additionally, cued MI training may lead to similar reorganisation patterns compared with training of the actual movement.³⁴

The absence of a physiotherapist during the home-based intervention could be a potential limitation of this study. Using a thorough familiarisation to the music-supported MI and gait training, as well as regular telephone support,

this limitation should be overcome. A further limitation could be a lack of motivation and adherence in participants, which we aim to counterbalance using weekly support phone calls and further support calls on request. A potential limitation in achieving the study objectives may be patients' hesitancy to undergo two extra MRI investigations at centre 3. Patients will be explained that they will be provided with the examination results at their request, which their treating doctors may include in their consultation and treatment planning.

Advantages of a home-based intervention are that pwMS can practise independently, provided that specifically trained physiotherapists familiarise them with the programme and guide their initial training phases. Depending on the results from this study, the most effective music-cued gait intervention can easily be put into practice.

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