Effects and Mechanisms of Rhythmic-Cued Motor Imagery on Walking, Fatigue and Quality of Life in People with Multiple Sclerosis

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ABSTRACT

BACKGROUND: walking impairment, fatigue and reduced (health-related, HR) quality of life (QoL) are key problems for people with multiple sclerosis (pwMS). Motor imagery (MI) and rhythmic cueing have been shown to improve motor function. It is unclear whether a combined rhythmic-cued MI treatment is effective in pwMS.

AIMS: the aims of this thesis were to investigate the effects and mechanisms of differently cued and non-cued MI on walking, fatigue, (HR)QoL, MI ability and gait synchronisation with music beat in pwMS. Two randomised controlled trials and a reliability study were conducted, to examine the gait analysis instruments.

METHODS: adults with mild to moderate MS were recruited at the MS-Clinic, Innsbruck Medical University, Austria and randomised to one of three groups. Participants practised MI of walking for 17 minutes, 6 times per week for 4 weeks. In Study 1, music-verbal-MI group participants performed music- and verbally-cued MI, metronome-verbal-MI group participants practiced metronome- and verbally-cued MI and participants in the control group received no intervention apart from their usual care, as all participants did. In Study 2, participants in the music-verbal-MI group practised music-cued MI with verbal cueing, participants in the music-MI group performed music-only cued MI and non-cued MI participants practised MI alone.

Primary outcomes were walking speed and walking distance. Secondary outcomes were walking perception, fatigue, (HR)QoL, MI ability and sensorimotor synchronisation, of gait to a music beat.

RESULTS: after rhythmic-cued MI, significant improvements in walking speed, distance and perception were observed when compared to no intervention or non-cued MI. The greatest and clinically most significant improvements in fatigue and (HR)QoL were seen after music- and verbally-cued MI. All participants were able to perform MI and showed improved MI ability after the 4 week intervention. The gait analysis instruments used were shown to be reliable. Post-intervention, sensorimotor synchronisation was significantly more accurate in participants in the rhythmic-cued MI groups, as compared to those in the non-cued MI group. There were no adverse events, full compliance was observed and 217 participated in the whole study.

CONCLUSIONS: as a stand-alone treatment, both non-cued and metronome- and verbally-cued MI significantly improved walking in pwMS. All types of rhythmic-cued MI significantly improved walking, fatigue and (HR)QoL in pwMS, but music- and verbally-cued MI was shown to be superior. After a familiarisation with rhythmic-cued MI, all participants showed high MI ability. This suggests that participants were undertaking MI and supports MI being a reasonable explanation for the improvements found. Sensorimotor synchronisation improved only after cued MI and might be another mechanism which contributed to participants’ walking improvements. This thesis, therefore, provides recommendations for physiotherapists on utilising rhythmic-cued MI, without physical practice, for the treatment of walking impairment and fatigue in pwMS.
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<td>Two-dimensional</td>
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<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
<tr>
<td>6MWT</td>
<td>6-Minute Walk Test</td>
</tr>
<tr>
<td>(\alpha)</td>
<td>Cronbach’s alpha; type I error probability</td>
</tr>
<tr>
<td>AKM</td>
<td>Society of authors, composers and music publishers</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<tr>
<td>ARAS</td>
<td>Ascending reticular activating system</td>
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<tr>
<td>A. T. S.</td>
<td>American Thoracic Society</td>
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<tr>
<td>(\beta)</td>
<td>Type II error probability</td>
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<tr>
<td>BL</td>
<td>Baseline</td>
</tr>
<tr>
<td>BPM</td>
<td>Beats per minute</td>
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<tr>
<td>CD</td>
<td>Compact disc</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
</tr>
<tr>
<td>CIS</td>
<td>Clinically isolated syndrome</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CONSORT</td>
<td>Consolidated Standards of Reporting Trials</td>
</tr>
<tr>
<td>CREC</td>
<td>College research ethics committee</td>
</tr>
<tr>
<td>CV MAD</td>
<td>Coefficient of mean deviation about the median</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of variation or curriculum vitae</td>
</tr>
<tr>
<td>(\delta)</td>
<td>Delta; true difference</td>
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<tr>
<td>ECTRIMS</td>
<td>European Committee for Treatment and Research in Multiple Sclerosis</td>
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<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
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<tr>
<td>FIS</td>
<td>Fatigue Impact Scale</td>
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<tr>
<td>FSS</td>
<td>Fatigue Severity Scale</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<td>FREGC</td>
<td>Faculty of Health and Social Science Research Ethics and Governance Committee</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>ICC</td>
<td>Intra-class correlation coefficient</td>
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<tr>
<td>ICD-10</td>
<td>International classification of diseases 10th revision</td>
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<tr>
<td>IOI</td>
<td>Inter-onset interval</td>
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<tr>
<td>KIVQ-10</td>
<td>Kinaesthetic and Visual Imagery Questionnaire-10</td>
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<tr>
<td>Log10</td>
<td>Logarithm with base 10</td>
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<tr>
<td>Ln</td>
<td>Natural logarithm</td>
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<tr>
<td>MAD</td>
<td>Median absolute deviation</td>
</tr>
<tr>
<td>MCID</td>
<td>Minimal clinically important difference</td>
</tr>
<tr>
<td>MDC</td>
<td>Minimal detectable change</td>
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<tr>
<td>MFIS</td>
<td>Modified Fatigue Impact Scale</td>
</tr>
<tr>
<td>m</td>
<td>Metre</td>
</tr>
<tr>
<td>MI</td>
<td>Motor imagery</td>
</tr>
<tr>
<td>M1</td>
<td>Primary motor cortex</td>
</tr>
<tr>
<td>min</td>
<td>Minute</td>
</tr>
<tr>
<td>min, max</td>
<td>Minimum, maximum</td>
</tr>
<tr>
<td>MIQ</td>
<td>Movement and Imagery Questionnaire</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>MSFC</td>
<td>Multiple Sclerosis Functional Composite</td>
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<tr>
<td>MSIS-29</td>
<td>Multiple Sclerosis Impact Scale-29</td>
</tr>
<tr>
<td>MSQLI</td>
<td>Multiple Sclerosis Quality of Life Inventory</td>
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<td>MSWS-12</td>
<td>Multiple Sclerosis Walking Scale-12</td>
</tr>
<tr>
<td>N</td>
<td>Number of participants</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<tr>
<td>η²</td>
<td>Partial eta squared</td>
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<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PETTLEP</td>
<td>Physical, Environmental, Task, Timing, Learning, Emotional, and Perspective of motor imagery</td>
</tr>
<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
</tr>
<tr>
<td>PI</td>
<td>Principal investigator; post-intervention</td>
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<tr>
<td>PIS</td>
<td>Participant information sheet</td>
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<tr>
<td>PPC</td>
<td>Posterior parietal cortex</td>
</tr>
<tr>
<td>PPI</td>
<td>Patient and public involvement</td>
</tr>
</tbody>
</table>
PMC  Premotor cortex
PPMS  Primary progressive multiple sclerosis
pwMS  People with multiple sclerosis
QoL   Quality of life
\( \rho \)  Spearman’s rho
\( r \)  Pearson’s correlation coefficient
RAS   Rhythmic auditory stimulation
RCT   Randomised controlled trial
RIMS  Rehabilitation in Multiple Sclerosis
RRMS  Relapsing remitting multiple sclerosis
s     Second
SAM   Self-Assessment Manikin
SD    \( \sigma \); standard deviation
SDC   Smallest detectable change
SEM   Standard error of measurement
SF-36  Short Form-36 Health Survey
SMA   Supplementary motor area
SMS   Sensorimotor synchronisation
SPIRIT Standard Protocol Items: Recommendations for Interventional Trials
SPMS  Secondary progressive multiple sclerosis
SRC   Smallest real change
T25FW Timed 25-Foot Walk
TDMI  Time-Dependent Motor Imagery screening test
UK    United Kingdom
V     Variance
VAS   Visual Analogue Scale
VMIQ  Vividness of Motor Imagery Questionnaire
WHO   World Health Organization
Preface

If you want to build a ship,
don’t herd people together
to collect wood
and don’t assign them tasks
and work,

but rather teach them
to long
for the endless immensity of the sea.

Antoine de Saint-Exupéry (1959)
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Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed____________________________________

Dated___________ 8 January 2018______________
1. Chapter 1 – Introduction to the Thesis

“Aged twenty three [he] was admitted into St. Bartholomew’s Hospital on account of a palsy of his limbs … in the course of six months his lower extremities became affected with occasional twitching, and he found that he could not distinguish their motions in walking: this increased to such a degree as to make him incapable of taking any exercise”.

Thomas Crichton, described above by Abernethy in 1809, cited by Compston et al. (2006).

1.1. Introduction

1.1.1 Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS), which leads to accumulating disability. People with MS (pwMS) have impairment in motor, sensory, visual and other body systems (Compston et al, 2006). Evidence shows that 50-80% of patients report fatigue (Induruwa, Constantinescu & Gran 2012; Krupp 2006) which, together with walking impairment, contributes to a limitation in their walking endurance (Phan-Ba et al, 2012) and quality of life (QoL) (Kamran et al, 2016). Around 50% of patients lose their mobility within fifteen years of disease onset, which in 80% of cases affects their ability to work; hence, many of them become unemployed within five years of disease onset (Green, Todd & Pevalin 2007). Depending on their age at the disease onset and its course, it is often necessary for pwMS to use a wheelchair after fifteen to thirty years following their diagnosis (Confavreux and Vukusic 2006).

1.1.2 Physiotherapy

Symptom management is a multidisciplinary team effort since pwMS require rehabilitation, with physiotherapy playing an important role. Even though physiotherapy strategies are not able to cure the effects of MS as it does not reverse CNS damage, physiotherapy can substantially help people achieve the best possible long-term outcomes (Rösler et al, 2010). A primary rehabilitation goal is to enhance the patients´ levels of activity, participation in society and independence which can be
achieved by physiotherapists applying different strategies to increase motor skills, mobility, speed, power, balance and endurance (De Souza-Teixeira et al, 2009; Wiles 2008).

1.1.3 Motor Imagery

Over the last two decades, specific physiotherapy approaches have been developed such as motor imagery (MI) (Guillot et al, 2012) and rhythmic auditory stimulation (RAS), which uses rhythmic auditory cues to facilitate cyclical movements, predominantly gait (Thaut 2005). MI is the mental execution of a movement without its actual performance (Jeannerod 1995). MI of walking activates brain areas similar to those in real walking (Decety 1996a; Kosslyn, Ganis & Thompson 2001). A literature search revealed only one study to investigate the effect of MI on walking, fatigue and QoL in pwMS. Their findings showed that fatigue and QoL significantly improved, but there was only a trend for a walking speed improvement, and this was not a controlled study (Catalan et al, 2011). A case study on a single patient with MS showed some balance improvement, but there was a lack of reliable outcome measures after the mental imagery and mental practice; only an abstract of this study is available in the literature (Fell 2000). Other research could not find any differences after the usual treatment compared to neurorehabilitation with an integrated MI programme (Bovend'Eerdt et al, 2010), and this study involved a heterogeneous study population with only one person with MS (Bovend'Eerdt et al, 2010).

Results from a cross-sectional study in pwMS showed that rhythmic cues facilitated MI by decreasing the excessive MI duration and increasing the spatial accuracy of the related eye movements; it evidenced a higher MI ability since at baseline, the MI duration was significantly increased in pwMS when compared to healthy controls (Heremans et al, 2012a). It had been found in a previous study that participants’ eye movements adapted to the MI task which was regarded as being a control parameter for accurate MI (Heremans, Helsen & Feys 2008). Similar results were shown by other studies where visual and auditory cues facilitated MI vividness and spatial accuracy of MI measures in healthy individuals (Heremans et al, 2009), and MI with rhythmic cueing also improved the mobility in people with stroke (Kim et al, 2011) or Parkinson’s disease (Heremans et al, 2012b). Therefore, it seemed that rhythmic cueing would improve the participants’ MI capacity.
1.1.4 Rhythmic Auditory Stimulation

RAS can be provided either by a metronome or music beat (Hove et al, 2012; Thaut et al, 2007), or by rhythmic verbal cues (Cason and Schon 2012; Hausen et al, 2013). RAS together with walking training has been found to improve walking in people with neurological diseases including MS (Baram 2013; Conklyn et al, 2010; Muto et al, 2012; Shahraki et al, 2017; Uchitomi et al, 2013). The stimulation leads to interactions between sensory and motor processes, referred to as sensorimotor interaction (Janata, Tomic & Haberman 2012). Only one study was identified to compare the effect on walking of both music and metronome cues in patients with neurological diseases (Thaut et al, 1999), and no studies were found that used additional verbal cues. Verbal cues employ ‘Patterned Sensory Enhancement’, which applies rhythmic auditory cues to provide a temporal framework for movements during functional exercises and daily life activities (Thaut 2014). Concise verbal cues, such as step right, step left, toe off, are also applied in sports to increase motivation, work output, skill learning and attention (Edwards 2011; Janelle et al, 2003).

Music has various beneficial influences during exercise, such as the ability to improve mood, to increase the amount of work performed and to enhance motivation (Karageorghis, Jones & Stuart 2008; Styns et al, 2007). Three small studies in pwMS used auditory feedback devices with either adapted metronome cues (Baram and Miller 2007; Shahraki et al, 2017) or music with embedded metronome cues which was 10% above the participants´ natural cadence (Conklyn et al, 2010). All but one (Baram and Miller 2007) studies showed significant improvements in walking speed and gait parameters. These findings confirmed the author’s suggestion that rhythmic cueing may improve walking performance in pwMS, and that it also might provide a temporal structure to MI of walking; this means that the cueing could facilitate the imagined steps during MI, similar to RAS during actual walking (Schaefer 2014b).

1.2 Professional Motivation

The author of this thesis is a physiotherapist with extensive experience in neurological physiotherapy and as a lecturer in neurological physiotherapy. During her Master´s studies, she performed a literature research in the area of MS. She reviewed studies that investigated the effect of physiotherapy on neural plasticity and found significant
changes in the CNS after specific training. The idea of investigating MI and rhythmic cueing as a combined intervention emerged from the author’s clinical practice. Although the basics of MI and RAS for walking rehabilitation in pwMS are known, a knowledge gap existed for rhythmic-cued MI and its effects on walking, fatigue and QoL. The author’s personal motivation was to devise and test a novel physiotherapy treatment for walking rehabilitation in pwMS.

1.3 Research Questions

The research question for Study 1 was: Does a rhythmic-cued MI change walking, fatigue and QoL in pwMS?

Study 2 was used to validate the results from Study 1 and to explore the mechanisms of the MI and rhythmic-cueing interventions and the research question was: Is there a difference between the effects of MI with music and verbal cueing, MI with music cueing and MI alone on walking, fatigue, QoL, MI ability and sensorimotor synchronisation (SMS) in pwMS?

1.4 Overview of the Studies

This thesis comprises two parts, Study 1 followed by Study 2. Both Study 1 and Study 2 included a pilot study (Pilot study1 and Pilot study 2) and Study 2 also included a reliability study. In Figure 1, all five studies are shown together with their main aims. Sections 1.5 to 1.7 will explain the detailed aims, objectives and null-hypotheses of the five studies.
1.5 Aims

The aims of the Pilot Study 1 were to explore the methods used and the feasibility of the main study. Further aims were to obtain preliminary information on changes in walking, fatigue and (health-related) quality of life following rhythmic-cued motor imagery in people with multiple sclerosis and to calculate the sample size for the main study.

The aims of the Main Study 1 were to investigate the impact of a rhythmic-cued motor imagery on walking, fatigue and quality of life in people with multiple sclerosis.

The aims of the Reliability Study were to establish the procedures and assess the relative and absolute reliability of the quantitative gait analysis instruments used to assess sensorimotor synchronisation in the Pilot and Main Study 2.
The aims of the Pilot Study 2 were to explore the methods used and the feasibility of the main study. Further aims were to obtain preliminary information on changes in walking, fatigue, quality of life, motor imagery ability and sensorimotor synchronisation following motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone in people with multiple sclerosis and to calculate the sample size of the main study.

The aims of the Main Study 2 were to investigate whether there is a difference between the effects of motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone on walking, fatigue, quality of life, motor imagery ability and sensorimotor synchronisation in people with multiple sclerosis.

1.6 Objectives

The objectives of the Pilot Study 1 were:

- Objective 1: The first objective of the study was to explore the methods planned for use in the main study.
- Objective 2: The second objective of the study was to explore the feasibility of a fully powered main study.
- Objective 3: The third objective of the study was to obtain preliminary information on changes in walking speed (related to the functional aspect of walking) following rhythmic-cued motor imagery in people with multiple sclerosis.
- Objective 4: The fourth objective of the study was to obtain preliminary information on changes in walking distance (endurance) following rhythmic-cued motor imagery in people with multiple sclerosis.
- Objective 5: The fifth objective of the study was to obtain preliminary information on changes in the perception of walking ability following rhythmic-cued motor imagery in people with multiple sclerosis.
- Objective 6: The sixth objective of the study was to obtain preliminary information on changes in fatigue following rhythmic-cued motor imagery in people with multiple sclerosis.
Objective 7: The seventh objective of the study was to obtain preliminary information on changes in (health-related) quality of life following rhythmic-cued motor imagery in people with multiple sclerosis.

Objective 8: The eighth objective of the study was to calculate the sample size for the main study using the between-group differences in walking performance.

The objectives of the Main Study 1 were:

Objective 1: The first objective of the study was to investigate whether a rhythmic-cued motor imagery changes walking speed (related to the functional aspect of walking) in people with multiple sclerosis.

Objective 2: The second objective of the study was to investigate whether a rhythmic-cued motor imagery changes walking distance (endurance) in people with multiple sclerosis.

Objective 3: The third objective of the study was to investigate whether a rhythmic-cued motor imagery changes the perception of walking ability in people with multiple sclerosis.

Objective 4: The fourth objective of the study was to investigate whether a rhythmic-cued motor imagery changes fatigue in people with multiple sclerosis.

Objective 5: The fifth objective of the study was to investigate whether a rhythmic-cued motor imagery changes (health-related) quality of life in people with multiple sclerosis.

The objectives of the Reliability Study were:

Objective 1: The first objective of the study was to establish and explore the procedures of the quantitative gait analysis used to assess sensorimotor synchronisation in the Pilot and Main Study 2.

Objective 2: The second objective of the study was to assess the relative (test-retest) reliability of the quantitative gait analysis instruments used to assess sensorimotor synchronisation in the Pilot and Main Study 2.
Objective 3: The third objective of the study was to assess the internal consistency reliability of the quantitative gait analysis instruments used to assess sensorimotor synchronisation in the Pilot and Main Study 2.

Objective 4: The fourth objective of the study was to assess the standard error of measurement (absolute reliability) for step length of the quantitative gait analysis instruments used to assess sensorimotor synchronisation in the Pilot and Main Study 2.

Objective 5: The fifth objective of the study was to assess the standard error of measurement (absolute reliability) for step time of the quantitative gait analysis instruments used to assess sensorimotor synchronisation in the Pilot and Main Study 2.

Objective 6: The sixth objective of the study was to assess the minimal detectable change (absolute reliability) for step length of the quantitative gait analysis instruments used to assess sensorimotor synchronisation in the Pilot and Main Study 2.

Objective 7: The seventh objective of the study was to assess the minimal detectable change (absolute reliability) for step time of the quantitative gait analysis instruments used to assess sensorimotor synchronisation in the Pilot and Main Study 2.

The objectives of the Pilot Study 2 were:

Objective 1: The first objective of the study was to explore the methods used planned for use in the main study.

Objective 2: The second objective of the study was to explore the feasibility of a fully powered main study.

Objective 3: The third objective of the study was to obtain preliminary information on changes in walking speed (related to the functional aspect of walking) following motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone in people with multiple sclerosis.

Objective 4: The fourth objective of the study was to obtain preliminary information on changes in walking distance (endurance) following motor
imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone in people with multiple sclerosis.

- **Objective 5:** The fifth objective of the study was to obtain preliminary information on changes in fatigue following motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone in people with multiple sclerosis.

- **Objective 6:** The sixth objective of the study was to obtain preliminary information on changes in quality of life following motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone in people with multiple sclerosis.

- **Objective 7:** The seventh objective of the study was to obtain preliminary information on changes in motor imagery ability following motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone in people with multiple sclerosis.

- **Objective 8:** The eighth objective of the study was to obtain preliminary information on changes in sensorimotor synchronisation following motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone in people with multiple sclerosis.

- **Objective 9:** The ninth objective of the study was to calculate the sample size for the main study using the between-group differences in walking performance.

**The objectives of the Main Study 2 were:**

- **Objective 1:** The first objective of the study was to investigate whether there is a difference between the effects of motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone on walking speed (related to the functional aspect of walking) in people with multiple sclerosis.

- **Objective 2:** The second objective of the study was to investigate whether there is a difference between the effects of motor imagery with music and
verbal cueing, motor imagery with music cueing and motor imagery alone on walking distance (endurance) in people with multiple sclerosis.

- **Objective 3:** The third objective of the study was to investigate whether there is a difference between the effects of motor imagery with music and verbal cueing, motor imagery with music cueing and MI alone on fatigue in people with multiple sclerosis.

- **Objective 4:** The fourth objective of the study was to investigate whether there is a difference between the effects of motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone on quality of life in people with multiple sclerosis.

- **Objective 5:** The fifth objective of the study was to investigate whether there is a difference between the effects of motor imagery with music and verbal cueing, motor imagery with music cueing and motor imagery alone on motor imagery ability in people with multiple sclerosis.

- **Objective 6:** The sixth objective of the study was to investigate whether there is a difference between the effects of motor imagery with music and verbal cueing, MI with music cueing and motor imagery alone on sensorimotor synchronisation in people with multiple sclerosis.

### 1.7 Null-Hypotheses

**The null-hypotheses of Study 1 were:**

- **H0₁:** A rhythmic-cued motor imagery will not change walking speed in people with multiple sclerosis as assessed by the Timed-25 Foot Walk.

- **H0₂:** A rhythmic-cued motor imagery will not change walking distance in people with multiple sclerosis as assessed by the 6-Minute Walk Test.

- **H0₃:** A rhythmic-cued motor imagery will not change walking perception in people with multiple sclerosis as assessed by the Multiple Sclerosis Walking Scale-12.

- **H0₄:** A rhythmic-cued motor imagery will not change fatigue in people with multiple sclerosis as assessed by the Modified Fatigue Impact Scale.
• H05: A rhythmic-cued motor imagery will not change (health-related) quality of life in people with multiple sclerosis as assessed by the Multiple Sclerosis Impact Scale-29, the EQ-5D-3L and the Short Form-36 Health Survey.

The null-hypotheses of Study 2 were:

• H01: Motor imagery with music and verbal cueing and motor imagery with music cueing are similarly effective for walking speed as opposed to motor imagery alone in people with multiple sclerosis, as assessed by the Timed-25 Foot Walk.

• H02: Motor imagery with music and verbal cueing and motor imagery with music cueing are similarly effective for walking distance as opposed to motor imagery alone in people with multiple sclerosis, as assessed by the 6-Minute Walk Test.

• H03: Motor imagery with music and verbal cueing and motor imagery with music cueing are similarly effective for fatigue as opposed to motor imagery alone in people with multiple sclerosis, as assessed by the Modified Fatigue Impact Scale.

• H04: Motor imagery with music and verbal cueing and motor imagery with music cueing are similarly effective for quality of life as opposed to motor imagery alone in people with multiple sclerosis, as assessed by the Multiple Sclerosis Impact Scale-29.

• H05: Motor imagery with music and verbal cueing and motor imagery with music cueing are similarly effective for motor imagery ability as opposed to motor imagery alone in people with multiple sclerosis, as assessed by the Kinaesthetic and Visual Imagery Questionnaire-10 and the Time-Dependent Motor Imagery screening test.

• H06: Motor imagery with music and verbal cueing and motor imagery with music cueing are similarly effective for sensorimotor synchronisation as opposed to motor imagery alone in people with multiple sclerosis, as assessed by a quantitative analysis of step time and step length variability, stepwise synchronisation and absolute accuracy.

1.8 Funding

A research grant for the material costs of the pilot study was approved by the Austrian MS Research Society in April, 2014. A funding extension of the material costs of the main study was approved on 26 January, 2015. Otherwise, the study was self-funded.
by the author. Costs amounting approximately to £96,000 (€ 115,200) were incurred by the study.

### 1.9 Ethics Approval and Governance

Full ethical and governance approval has been gained from the Faculty of Health and Social Science Research Ethics and Governance Committee (FREGC) of the University of Brighton, United Kingdom on 9 January, 2014 (reference number: 13 053; see Appendix 4) and the Ethics Committee of the Medical University of Innsbruck, Austria on 2 April, 2014 (reference number: AN2014-0052 334/4.14; see Appendix 5). As this is a PhD project registered with the University of Brighton, an annual monitoring procedure was in place.

### 1.10 Intellectual Property and Conflicts of Interest

There were no conflicts of interest. The intellectual property of other researchers and authors has been acknowledged, and their work has been cited carefully and precisely throughout this research project. If applicable, permission was asked for the use of copyright protected material. It will also be observed that the intellectual property gained by the results of this study will not be wrongfully claimed by other authors in order to profit academically or financially. It is recognised that all intellectual property related to this study belongs to the University of Brighton, according to the University of Brighton, Doctoral College (2015) research code of practice. The contribution of the advisory group members and of the study participants has been acknowledged within any presentations or publications in scientific journals.

### 1.11 Project Team

The pilot and main studies were conducted by Barbara Seebacher in partial fulfilment of her PhD. In Austria, a physiotherapist is not allowed to submit an ethics proposal; therefore, the project was led by Professor Thomas Berger (for his CV, see Appendix 6), the head of the MS Clinic Innsbruck, Clinical Department of Neurology, Medical University of Innsbruck, clinical lead of the study (PI) and member of the University of Brighton’s supervisory team. The project was supervised by the academic supervisors Dr Raija Kuisma and Dr Angela Glynn.
1.12 Overview of Thesis Chapters

The literature pertaining to MS including its various symptoms, diagnosis and treatment are presented in Chapter 2. MI and RAS are explained and potential advantages of a combined intervention are discussed. The evidence-based measurement of walking, fatigue and (HR)QoL used in these studies are considered in Chapter 3. The research methodology employed for this study is introduced in Chapter 4. Chapter 5 outlines how the ethical principles were adhered to in this research. Chapter 6 describes the study’s validity, reliability and objectivity.

Chapter 7 outlines the research methods of the first pilot study that explored the feasibility and preliminary effects of rhythmic-cued MI on walking, fatigue and QoL. The pilot results are presented in Chapter 8 and discussed in Chapter 9, together with their implications for the main study. Chapter 10 describes the first main study methods and Chapter 11 presents its results. The findings are interpreted in Chapter 12, including any limitations to the study. Based on this, Chapter 13 provides an introduction into the second pilot study and main study, which validated the first study’s results. Chapter 14 outlines the second pilot study investigation of feasibility, walking, fatigue and QoL. Chapter 15 describes the second main study which investigated the effects and mechanisms of differently cued and non-cued MI interventions on walking, fatigue and QoL in pwMS.

Chapter 16 describes the measurement of MI ability in the second study and the participants’ ability at baseline and after differently cued MI in the second pilot and main studies. Chapter 17 presents a study which explored the reliability of a gait analysis system. The gait analysis system was employed for the measurement of gait synchronisation with music beat in the second study. Chapter 18 describes the effects of differently cued and non-cued MI on SMS in the second pilot and main studies. Chapter 19 provides a general discussion of the results from the second study, concerning the effects of differently cued MI on walking, fatigue, QoL, MI ability and SMS. Chapter 20 summarises the overall findings of the studies in this thesis and discusses their limitations; it also draws attention to areas for future work and outlines the original contribution to knowledge.
Chapter 2 – Literature Review

2.1 Multiple Sclerosis

Figure 2 illustrates MS from a patient perspective.

"This kind of disease is frightening, it reminds me of red roulette, constantly evolving, sometimes everything okay and the next day a crisis occurs..."

Figure 2: Patients’ Multiple Sclerosis Drawing and Words, from Patient Commando (Dash 2011).

2.1.1 General Overview

In 1868, Charcot (1825-1893) was the first neurologist to describe MS, also known as disseminated sclerosis or encephalomyelitis disseminata. MS is a progressive demyelinating disease of the CNS (Compston et al, 2006). Disease mechanisms underlying the clinical course are inflammation in the CNS, mainly during relapses, and a degeneration of nerve axons, which contributes to MS progression (Rösler et al, 2010). Inflammatory demyelination and axonal injury mediated by immune cells occurs in the so-called MS plaques (lesions) (Compston et al, 2006). Remyelination takes place during the first years, leading to a remission of patient symptoms whereas later stages are characterised by an exhaustion of these repair mechanisms; from this process, a variety of symptoms and progressive accumulation of disability follow (Compston et al, 2006). The cause of MS has not yet been clarified, but it was found that genetics and environmental factors such as infections, geographic region of birth,
sun exposure and race interact with the development of the disease (Compston et al, 2006).

MS is more common among Caucasians living in northern and western Europe, North America, southeast Australia and New Zealand, than among any other ethnic groups (Compston et al, 2006). According to the World Health Organization’s (WHO) MS Atlas in 2008, globally, the median estimated prevalence of MS is 30 per 100,000 people. Across Europe, the prevalence rate of MS is about 83 in 100,000 people, and the mean annual incidence rate is about 4.3 in 100,000 people (Pugliatti et al, 2006). The MS prevalence in Austria is 98.2 per 100,000 people (Baumhackl et al, 2002). Studies in the UK have shown that the prevalence rate in England and Wales is between 100 and 140 per 100,000 people, about 170 in Northern Ireland and as high as 190 in Scotland (Compston et al, 2006). The total estimated number of people worldwide diagnosed with MS is approximately 1.3-2.5 million (World Health Organization and Multiple Sclerosis International Federation 2008).

MS mainly affects young adults with an onset peak at twenty to forty years of age (Rösler et al, 2010). Women are more than twice as often affected by MS (Compston and Coles 2008; Harbo, Gold & Tintore 2013). The female-to-male ratio in the UK is 2.4:1 (Mackenzie et al, 2014) whereas in Austria it is 2.7:1 (Trojano et al, 2012) with an increasing proportion of women over the last decade (Harbo, Gold & Tintore 2013). Life expectancy for patients with MS is seven to ten years lower than that of a healthy population (Kamm, Uitdehaag & Polman 2014).

Eighty percent of patients have an acute episode affecting one or more CNS areas, which is known as a clinically isolated syndrome (CIS) (Polman et al, 2011). A clinically definite MS is diagnosed with one or more further attacks of MS and/or new lesions in typical CNS regions with a dissemination in space and time, demonstrated by Magnetic Resonance Imaging (MRI) (Polman et al, 2011). A relapsing-remitting pattern is the most common and is characteristic for this disease: Relapsing Remitting MS (RRMS) is found in 80% of patients (Compston and Coles 2008). RRMS can occur with or without disease activity, which means inflammation and relapses (Lublin et al, 2014). After years of illness, 65% of these patients reach the secondary progressive stage (SPMS) with or without continuous progression (Lublin et al, 2014).
According to a new consensus, progressive relapsing MS, characterised by a progressive disease course with occasional relapses, is regarded as Primary Progressive MS (PPMS) with disease activity (Lublin et al, 2014). According to the 2010 Revised McDonald Diagnostic Criteria for MS, the diagnosis of MS requires the elimination of other more likely diagnoses and the demonstration of dissemination of lesions in space and time (Polman et al, 2011).

2.1.2 Clinical Symptoms

MS Symptoms are variable, depending on the location and extension of lesions, but typically motor and sensory functions are involved (Compston et al, 2006). These include ataxia, spasticity, paresis, spasms, clonus, tremor, impaired balance, paraesthesia, numbness and weakness (Gaby 2013). In addition, common symptom manifestations are visual, bowel, bladder and sexual dysfunction, fatigue, impaired speech, swallowing and respiration, pain, vertigo, cognitive and emotional symptoms, such as depression, or less often, euphoria (Compston et al, 2006). Mobility problems and fatigue are great concerns for pwMS because they contribute to their impairment in activities of daily living (Coote, Finlayson & Sosnoff 2014).

2.1.3 Expanded Disability Status Scale

The Expanded Disability Status Scale (EDSS) is introduced here because it is used to assess disability in pwMS in clinical studies generally and, in particular, at the MS Clinic, Innsbruck where the study took part. The scale is used by neurologists as part of their clinical assessment.

The EDSS is a standardised tool (Kurtzke 1983), used to quantify disability in pwMS, and which has been shown to be valid and reliable (Sharrack et al, 1999). However, Hobart, Freeman & Thompson (2000) applied psychometric methods to the EDSS, and they criticised its low responsiveness to changes, but found no floor or ceiling effects. Measures of concurrent validity showed a negative correlation with the SF-36, particularly with physical functioning ($r=-0.86$) (Nortvedt et al, 1999), and the EuroQoL Visual Analogue Scale (VAS) ($r=-0.69$), the SF-36 physical role limitation ($r=-0.50$), SF-36 social functioning ($r=-0.47$), SF-36 vitality ($r=-0.41$) and SF-36 general health perception ($r=-0.47$) (Sharrack et al, 1999). Balcer (2001) criticised the low sensitivity
of the scale in the mid and upper ranges of scores because of its ordinal scaling and absence of adequate cognitive and visual components. Despite this fact and according to the US National MS Society, “the EDSS has been used in virtually every major clinical trial that has been conducted in MS during the last four decades and in numerous other clinical studies” (LaRocca 2011). A recent systematic review recommends the EDSS for use in clinical studies to assess disability in pwMS despite some psychometric limitations (Meyer-Moock et al, 2014).

The MS Outcome Measure Taskforce provides a recommendation concerning the EDSS in clinical research: “the limited responsiveness data makes the EDSS an inappropriate measure by which to measure change; therefore, [it is] not recommended as an evaluative measure in research, but [it] might be useful to describe the sample studied” (Potter et al, 2014). Accordingly, the EDSS was not used as an outcome measure in this study, but participant selection was based on the EDSS as a measure of disability.

For EDSS scoring, results from the neurological examination are evaluated on a 6 point ordinal scale (from normal function to inability) with regard to the functional systems introduced below, and there are no subscales (Schädler et al, 2009). The administration time is 15-20 minutes (Potter et al, 2014). Based on the disease progression as reflected by the EDSS, disability milestones in pwMS were defined by Confavreux and Vukusic (2006) as shown in Table 1. Threshold values for people with mild, moderate and severe MS reported by internationally recognised authors (Confavreux et al, 2000; Rösler et al, 2010) are also shown in Table 1. These authors reported an EDSS of 4 to be the cut-off value between mild and moderate MS. In Appendix 7, Table A1, the EDSS is shown.
### Table 1: Disability Milestones in People with MS (created by the author, based on (Confavreux et al, 2000)).

<table>
<thead>
<tr>
<th>EDSS Score</th>
<th>Years from Disease Onset</th>
<th>Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3.5</td>
<td></td>
<td>Mild MS</td>
</tr>
<tr>
<td>4</td>
<td>5-15</td>
<td>Walking ability without aid or rest for more than 500 metres</td>
</tr>
<tr>
<td>4-6</td>
<td></td>
<td>Moderate MS</td>
</tr>
<tr>
<td>6</td>
<td>11-30</td>
<td>Ability to walk with unilateral support for no more than 100 metres with or without rest</td>
</tr>
<tr>
<td>6.5-10</td>
<td></td>
<td>Severe MS</td>
</tr>
<tr>
<td>7</td>
<td>17-33</td>
<td>Able to walk no more than 5 metres without rest, essentially restricted to a wheelchair</td>
</tr>
</tbody>
</table>

2.1.4 Treatment

Treatment strategies in pwMS are based on immunological and clinical aspects of the disease. Disease-modifying and immunosuppressive treatments target the patient immune system whereas symptomatic treatment addresses various symptoms (Henze, Rieckmann & Toyka 2006). Disease-modifying drugs are used to reduce the frequency and severity of relapses and the lesion accumulation within the CNS; immunosuppressive drugs are applied as a gold standard therapy to treat acute relapses (Compston et al, 2006). They are also used as ‘second line’ treatments when immune-modulating treatments have been ineffective and in more severe disease stages (Neuhaus, Kieseier & Hartung 2007).

Symptomatic treatment in pwMS involves symptomatic drugs and rehabilitation. Pharmacological treatment includes any drugs aimed at reduction of MS symptoms, such as spasticity, tremor, depression, urinary dysfunction, sleeping disorder, pain and many others (Tullman 2013; Windt, Glaeske & Hoffmann 2013). The primary goal of neurorehabilitation is to improve and maintain the individuals’ function, autonomy and QoL (Rösler et al, 2010). Evidence showed that rehabilitation strategies are
useful (Khan et al, 2008; Liberatore et al, 2014), and physiotherapy enhances walking performance (Kelleher et al, 2009; Wiles 2008), particularly in people with mild to moderate disease stages (Beer, Khan & Kesselring 2012; Latimer-Cheung et al, 2013; Toomey and Coote 2012). Reviews outlined the importance of rigorously designed physiotherapy randomised controlled trials (RCTs) including sample size calculations and stratification according to the relevant MS characteristics (Khan et al, 2008; Sa 2014).

2.2 Gait Control in Healthy People and in People with Multiple Sclerosis

2.2.1 The Gait Cycle

Gait is an exceptionally complex behaviour and a vital human skill involving coordination of a wide range of body parts, muscles and joints (Shumway-Cook and Woollacott 2012). Due to the complex mechanisms underlying gait control, understanding normal gait helps to comprehend walking problems in pwMS. Basically, there are three important requirements for locomotion, which are progression, postural control and adaptation (Das and McCollum 1988). Forward progression of the body is achieved by a basic gait pattern, which involves the production and coordination of cyclic muscle activation patterns in the upper body and legs; progression also includes a person’s ability to start and stop walking (Patla 1997). For locomotion to be possible, besides progression, an appropriate postural control is necessary. Postural control comprises the establishment of a stable and yet dynamic posture, and it preserves the body’s balance (Horak 1987). Finally, adaptation of the gait is necessary to navigate an ever-changing environment (Patla 1997). Adaptation refers to the alignment of gait patterns owing to changes in gait speed and gait direction, but also as a response to uneven ground and obstacles (Patla 1997). Normal gait speed has been defined as approximately 4 to 4.8 km per hour (Whittle 2002). Gait consists of repeated movement patterns, called the gait cycle. The gait cycle consists of four stance and four swing phases shown in Figure 3 (Perry 2001, 1992).
In pwMS, changes to the gait cycle and related parameters were observed in laboratory-based gait analysis studies. Studies have shown that pwMS walk at a reduced gait speed (Crenshaw et al, 2006; Kelleher et al, 2010; Remelius et al, 2012) and with a wider stride (base) width (Remelius et al, 2012). Their swing phases and step lengths are shorter than that of healthy people (Remelius et al, 2012). Even in pwMS at the earliest stages of the disease, decreased walking speed, shorter stride length and prolonged double support times were observed, as well as altered muscular recruitment (Benedetti et al, 1999). In summary, gait phases and parameters are shown to be impaired even in people with mild MS and are mainly associated with the neurological disability level (Kalron 2016).

2.2.2 Gait Parameters

Gait can be described with respect to temporal and spatial parameters (Shumway-Cook and Woollacott 2012). Relevant parameters are referred to in this section, such as step length, step time, and cadence (Perry and Burnfield 2010). Step length is the distance between the heel strike of one foot to the previous heel strike of the other foot, and the unit of measurement is centimetres (cm) (Perry 2001). In healthy individuals, the term heel strike is correct, but in some people with walking impairment or disability, the term ‘foot contact’ may be more appropriate as they touch the ground with the entire foot or forefoot rather than with the heel (Baker 2013). In young males, the mean step length at their preferred speed was 0.64 metres (m), and at high speed 0.73 m (Pietraszewski, Winiarski & Jaroszczuk 2012) whereas in another study in...
healthy individuals, the mean step length at a comfortable speed was 0.76 m (Craik 1989). Another study found step lengths between 0.5 m and 0.7 m in women from Sweden and Kuwait, demonstrating shorter step lengths at slower gait speeds (Al-Obaidi et al, 2003). These discrepancies in step lengths represented inter-individual differences in gait parameters, depending in part on body height and weight, age and culture (Al-Obaidi et al, 2003; Samson et al, 2001). In pwMS who have minimal disability, step lengths around 0.7 m were observed whereas in those with moderate disability, step lengths between 0.34 m and 0.59 m were seen (Preiningerova et al, 2015).

Step time is defined as the time passed from the first heel strike of one foot to the first heel strike of the opposite foot (Perry 2001) and is normally around 0.5-0.6 seconds (s) in older adults (Hollman, McDade & Petersen 2011) and 0.5 s in younger adults (Kodesh et al, 2012). Step times at 0.7±0.2 s were measured in pwMS with a moderate disability and aged 40-62 years (Motl et al, 2012), reflecting a substantial reduction in gait speed in this population.

Cadence is the number of steps per minute, calculated by dividing 60 seconds by a step time (s), and presented as steps per minute (Baker 2013; Tanawongsuwan and Bobick 2002). The natural cadence is known to be around 120 steps/minute (Götz-Neumann 2006). People with mild to moderate MS showed a mean cadence of 109.1±23.3 steps/minute (Wajda et al, 2013); pwMS and higher disability levels walked mean 98.97±19.95 steps/minute (Sandhoff et al, 2014). The cadence in pwMS with an EDSS of up to 5.7 was between 100.0±23.3 steps/minute and 112.1±11.3 steps/minute (Kalron and Givon 2016).

### 2.2.3 Brain Areas Associated with Motor Control of Gait

For normal walking to be possible, coordinated interaction of muscles and joints is necessary. However, this interaction would not work without the CNS motor command, a feature called motor control; motor control is defined as the ability to control or drive movement patterns (Cano-de-la-Cuerda et al, 2015). It involves the processing of sensory information to construct detailed and adjustable representations of the body and the environment to be able to select and regulate the desired movement (Cano-de-la-Cuerda et al, 2015; Takakusaki 2017). Moreover,
motor control enables individuals to be in a relationship with others and the environment, and thus it also involves multi-sensory information processing including somatosensory, visual, auditory and vestibular sensation (Cano-de-la-Cuerda et al, 2015; Takakusaki 2017). Highly automated stepping movements and postural reflexes are the basis for the performance of gait (Takakusaki 2017). Cognitive and emotional processes are essential since human gait requires intention, volition, planning, problem solving, attention and motivation; gait characteristics such as speed and coordination are influenced by emotions, located in the limbic system (Barliya et al, 2013). In response to various demands from the body, including those from chronic neurological disorders such as MS and from the environment, the CNS needs to be able to constantly adapt (Shumway-Cook and Woollacott 2012). A large brain network is, therefore, required, consisting of sensory and motor areas connected to the spinal cord and peripheral nervous system (Trepel 2012).

The brain's motor areas are organised both hierarchically and in parallel. Hierarchical processing of gait refers to motor circuits in which higher level brain areas deal with information abstraction, involving motor plans and action strategies. Lower level brain areas are responsible for monitoring and adaptation of gait execution (Cano-de-la-Cuerda et al, 2015; Takakusaki 2017). Simultaneously, parallel motor systems such as the brain stem, cerebellum, and thalamus process the same signals to fine-tune gait in terms of the muscle tone and coordination before they send them back to the motor cortex for action (Takakusaki 2017). Specifically, gait control is organised at four hierarchical levels, including the spinal cord, the brain stem, the motor cortex and the association cortex (Takakusaki 2017; Trepel 2012). It also contains two parallel processing side loops, the basal ganglia and the cerebellum, which interact with the four hierarchical levels via connections with the thalamus (Trepel 2012). As the name suggests, MS is a neurological disease with lesions in multiple brain areas and important pathways (Compston et al, 2006).

The spinal cord is at the lowest level of the hierarchy, being responsible for the initial reception and processing of somatosensory information from muscles, joints and skin (Takakusaki 2017). At the spinal cord level, gait control functions via motor neurons sending signals to muscles for gait execution, and using both stereotyped reflexes and voluntary movement (Cano-de-la-Cuerda et al, 2015; Takakusaki 2017). MS
lesions affecting the spinal cord lead to walking disability, mainly due to muscle weaknesses, balance problems, ataxia, sensory deficits, spasticity and postural instability (Compston et al, 2006). The pathways from the motor cortex to the spinal cord which control voluntary movement and reflex modulation are the upper motor neurons, also called the corticospinal pathways or pyramidal tracts; this tract, along with the corticobulbar tract, is the essential pathway responsible for voluntary movement (Trepel 2012). MS related lesions in the corticospinal and corticobulbar tracts lead to upper motor neuron signs such as spasticity, hyperreflexia, paresis or plegia, muscle weaknesses, loss in dexterity, spasms, clonus, cocontraction, pyramidal signs, loss in muscle flexibility and so on (Compston et al, 2006).

The brainstem is the next level of neural processing in gait control and is the primary structure for basic muscle tone (Trepel 2012). The brainstem receives somatosensory information from the vestibular and visual systems, and it contains the reticular formation responsible for arousal and awareness. Additionally, the brainstem comprises nuclei which are necessary for postural control and gait (Takakusaki 2017; Trepel 2012). MS plaques in the brainstem lead to vertigo, which causes walking impairment, but also severe imbalance, ataxia and muscle hypotonia (Compston and Coles 2008).

The motor cortex is the third level in the hierarchy, which consists of the primary motor cortex (M1), the premotor cortex (PMC) and the supplementary motor area (SMA) (Trepel 2012). The motor cortex is involved in gait planning and preparation, control of gait sequences and gait execution; hence, MS lesions to the motor cortex lead to coordination deficits and motor apraxia (Compston et al, 2006; Trepel 2012).

At the highest level of the hierarchy is the association cortex, primarily the prefrontal cortex (PFC) and the posterior parietal cortex (PPC). Strictly speaking, these areas are not motor areas, but they enable individuals to adapt their movements in accordance with the behavioural and environmental context (Cano-de-la-Cuerda et al, 2015; Trepel 2012). For example, pwMS who have lesions in the PPC experience problems overcoming obstacles during walking because this area is responsible for spatial processing of objects in the world (Ferreira 2010). In contrast, the PFC is responsible for appropriate actions in terms of social behaviour, but also for intention and motivation (Trepel 2012). In the context of this study, without the PFC being
properly functioning and activated, participants would not have been motivated to walk at all, and they would not have desired to improve their gait performance.

Parallel gait control systems are the basal ganglia, thalamus and cerebellum (Takakusaki 2017). The basal ganglia influences and modulates the activity of the motor cortex and the descending motor pathways (Trepel 2012). The basal ganglia nuclei are a major part of the extrapyramidal system, which are connected to the brainstem, cerebellum and corticospinal tract. As it is known from extrapyramidal impairment, such as in people with Parkinson’s disease, the basal ganglia are required to inhibit erratic movements, retain muscle tone and postural control (Takakusaki 2017; Trepel 2012). In practice, people with basal ganglia disorders walk with shorter, narrower and shuffling steps, experience a freezing of gait and problems turning and straightening their bodies (Bär et al, 2006). In rare cases of MS, the basal ganglia and extrapyramidal motor system can be affected (Batista et al, 2012; Vercellino et al, 2009).

The cerebellum is an extremely important brain structure that modifies the motor commands of the descending pathways to make gait more adjustable and precise (Takakusaki 2017). During walking, the cerebellum helps to retain balance, which is made possible by receiving input from the vestibular receptors and proprioceptors (Trepel 2012). Another role of the cerebellum is to coordinate the timing and power of the required muscles to produce smooth ambulation (Bares et al, 2007). Finally, the cerebellum is responsible for motor learning using the trial-and-error method; thus, motor programmes are adapted and fine-tuned to increase precision (Kimpo et al, 2014). In terms of the current study, this means that SMS with rhythmic auditory stimuli during gait is mainly controlled by the cerebellum (Molinari, Leggio & Thaut 2007). The cerebellum is frequently affected in pwMS, with 43–65% of patients having cerebellar impairment (Preziosa et al, 2014). Walking in these patients is characterised by ataxia, balance impairment, muscle weakness, clumsiness, action tremors (Compston and Coles 2008; McLoughlin et al, 2015) and reduced walking speed (Preziosa et al, 2014). Walking impairment and disability in pwMS may also be associated with damage to the cerebellar interconnections to literally all important motor and sensory brain areas and also essential non-motor areas such as the thalamus and PFC (O’Reilly et al, 2010).
The thalamus as a higher order brain area controls alertness, arousal and consciousness (Takakusaki 2017; Trepel 2012), which are mandatory preconditions for the ability to walk (Barliya et al, 2013). The thalamus plays an important role in motor control due to the transfer of sensory and motor signals from the basal ganglia and cerebellum to the motor cortex (Trepel 2012). The thalamus has been referred to as ‘the gateway to consciousness’ because it receives input from all modalities, apart from olfaction, and it is bi-directionally connected with the cortex (Scholpp and Shimogori 2013; Takakusaki 2017). In pwMS, thalamus lesions are seen frequently (Minagar et al, 2013; Vercellino et al, 2009), even in early disease stages (Calabrese et al, 2011). These patients show walking impairment due to sensory loss, fatigue and problems with postural control and awareness (Calabrese et al, 2010; Minagar et al, 2013); they also have difficulties with obstacle avoidance and attention during walking due to a reduced mental information processing speed (Batista et al, 2012).

To summarise, a variety of brain areas is involved in motor control of gait and movement in general, starting with motor programmes (Bernstein 1967) and leading to motor plans, movement execution, sensory feedback, motor adjustment and so forth (Sherrington 1906; Shumway-Cook and Woollacott 2012; Schmidt and Lee 2011). Both motor and higher order brain areas are necessary for gait control through an interaction of unconscious and conscious steering mechanisms (Cano-de-la-Cuerda et al, 2015; Takakusaki 2017). There are differences in progression, postural control and gait adaptation between pwMS and healthy persons, which are based on functional and structural damage to the brain centres responsible for gait control (Compston et al, 2006).

Figure 4 presents the widespread network which is responsible for motor control of gait. As outlined above, MS lesions can be located in any of these areas and affect their functions.
Figure 4: Systems Involved in Gait Control (created by the author using information from Trepel (2012) and Takakusaki (2017)).

Figure legend: blue = the hierarchy system of gait control; green = the parallel system of gait control; orange = the limbic system responsible for emotional processing; yellow = sensory input and afferent pathways; rose = efferent pathways and muscles generating motor output (gait).

2.3 Walking Impairment in People with Multiple Sclerosis

The purpose of walking is to safely, effectively and economically move oneself from one place to another (Carr and Shepherd 2010). Key elements of normal walking are the ability to change speed and direction whenever necessary, to avoid obstacles and to adapt the feet to the ground (Torres-Oviedo et al, 2011). In pwMS, due to CNS plaques in the aforementioned brain areas, impairment in walking can occur at any stage of the disease and most likely in people with progressive versus relapsing types of MS (Feys et al, 2015). Strikingly, both walking speed and distance are abnormal in
pwMS even in the absence of any disability, according to Kurtzke’s EDSS, and without patients being aware of any motor impairment (Kalron et al, 2014; Phan-Ba et al, 2012). Walking disability was found in 89% of people with moderate MS (EDSS 4.0-5.5), and walking impairment in as many as 43% of individuals with mild MS (EDSS 1.0-3.5) (Johansson et al, 2007). PwMS in general showed a larger gait variability when compared with healthy people (Sosnoff, Sandroff & Motl, 2012). Gait variability are the stride-to-stride fluctuations in walking (Hausdorff 2005) and have been related to increased falls (Socie et al, 2013b). Seventy percent of patients consider their walking difficulties to be the most challenging aspect of having MS (LaRocca 2011). Moreover, reduced walking speed seems to play an important role, leading to reduced physical activity and problems in daily life (Kohn et al, 2014a). Many people, therefore, adopt a sedentary lifestyle (Mayo et al, 2013), which contributes to a deterioration in their QoL (Lobentanz et al, 2004).

Following physiotherapy and training, walking would probably not change in the same way in pwMS as it would with healthy individuals due to various reasons. One reason might be that fatigue leads to impaired walking dynamics, in particular in long distance walking (Burschka et al, 2012). Another reason might be found in brain structural and functional changes, which generate walking patterns distinct to that of healthy persons (Burschka et al, 2012). PwMS have lesions mainly in the cerebellum, corticospinal tract and spinal cord (Cameron et al, 2008); associated symptoms might increase the energy cost of walking (Tantucci et al, 1996). For example, fatigue and weakness in leg muscles might impair long distance walking, spasticity might reduce step length and ataxia might increase base width and decrease velocity. However, many studies showed that physiotherapy, exercise and training improved walking performance also in pwMS even though it was to a smaller degree than in healthy persons (Kalron et al, 2015; Latimer-Cheung et al, 2013).

2.4 Fatigue in People with Multiple Sclerosis

Sixty percent of pwMS are affected by fatigue, and studies have shown that fatigue can even precede the disease onset (Berger et al, 2013). The aetiology of fatigue is poorly understood; however, it is most likely multifactorial (Braley and Chervin 2010). Primary and secondary fatigue is distinguished from each other; primary fatigue is
related to the disease process itself, including cerebral lesions, axonal damage, brain atrophy and immunological dysfunction. Secondary fatigue, by contrast, refers to symptoms associated with the consequences of the disease, such as sleeping and psychological disorders, medication use, pain, reduced activity, depression and infections (Johnson 2008; Kos et al, 2008). Due to its complex and subjective nature, MS fatigue is difficult to describe (Braley and Chervin 2010). Basically, it is useful to distinguish mental fatigue from motor fatigue (Compston et al, 2006). Motor fatigue is generated by biochemical changes within muscles (Kent-Braun et al, 1997), deficits in muscular excitation and contraction (Sharma et al, 1995) and axonal conduction block within the CNS (Cruz Gomez et al, 2013). Mental fatigue is usually understood as a lack of energy, and it is also called exhaustion, tiredness, asthenia (fatigue at rest), fatigability (fatigue with exercise) or lassitude (a subjective sense of reduced energy) (Kos et al, 2008; Krupp 2003). Fatigue leads to exhaustion following ordinary exertion such as a shopping trip, and it is one of the most disabling symptoms for 40-58% of pwMS (Fiest et al, 2016; Nagaraj et al, 2013). In summary, fatigue seems to substantially contribute to a decline in patients’ QoL (Flensner et al, 2013).

In the light of the complex entity of fatigue, a multi-professional approach is required for its treatment. Findings from a systematic review showed that rehabilitation interventions in pwMS led to greater improvements in fatigue as opposed to medication (Asano and Finlayson 2014). A recent review of other key reviews found strong evidence for physiotherapy and educational programmes to improve fatigue (Khan and Amatya 2017). In the current study, fatigue was a secondary outcome.

2.5 (Health-Related) Quality of Life in People with Multiple Sclerosis

The WHO defines health as "a state of complete physical, mental, and social well-being, not merely the absence of disease" (World Health Organization 1997). QoL is subjective and relates to a person’s well-being, satisfaction and happiness, entailing emotions, hopes, moods, mental health and resilience (Schulz 2000). QoL is a multidimensional construct involving physical, psychological, cognitive, job-related, sexual and social functioning and refers to an individual’s perceived wellbeing and health (Opara, Jaracz & Brola 2010). A person’s level of independence is closely linked to QoL, and it comprises mobility, activities of daily living, dependence on
medicinal substances, medical aids and work capacity (World Health Organization 1997).

For individuals, societies and governments, achievement and assessment of QoL has reached increasing importance (Vitali 2011). However, in medicine and healthcare, an individual’s QoL may be diminished due to chronic disease or disability; in relation to this, the phrase Health-Related-Quality-of-Life (HRQoL) was created (Bergner et al, 1981; Isaksson, Ahlstrom & Gunnarsson 2005; Miller and Dishon 2006). HRQoL refers to a person’s subjective perception of physical and mental health and its treatment (Bergner et al, 1981). Function is the key dimension attributed to HRQoL, including mainly physical, social and emotional role functions (Chen, Li & Kochen 2005). Other dimensions of importance are mental health and general health perception in addition to vitality, pain and cognitive function (Wilson and Cleary 1995). Evaluation of HRQoL should be subjective, involving a patient-rated health and wellbeing status (Bandari et al, 2010).

A review compared levels of HRQoL in people with different chronic diseases, one of them being MS. In physically disabled pwMS, a significant decrease in HRQoL was observed, particularly in younger women or people with high degrees of comorbidities (Hopman et al, 2009). These findings were in line with a survey showing that older persons with MS who were able to adapt to their situation reported higher HRQoL (Buhse, Banker & Clement 2014). As expected, reduced HRQoL in pwMS has also been related to increasing neurological disability, psychological distress (Kern et al, 2009), fatigue, anxiety, depression (Michalski et al, 2010), limitations in daily life and movement impairment (Lobentanz et al, 2004; Wood et al, 2013). Thereby, perceived walking deficits, particularly walking speed (Kohn et al, 2014a), fatigue, pain, coordination, sensory and cognitive problems were found to be associated with different domains of HRQoL (Isaksson, Ahlstrom & Gunnarsson 2005). In the current study, QoL and HRQoL were secondary outcomes as, from a clinical standpoint, walking improvement may not be helpful if (HR)QoL does not improve accordingly.

2.6 Physiotherapy in People with Multiple Sclerosis

Physiotherapists are trained to support their patients to improve their movement capacity. In the last two decades, an increasing number of studies have addressed
the effects of physiotherapy and rehabilitation interventions on functional outcomes in pwMS (Heine et al, 2015; Khan and Amatya 2017). A review elaborated guidelines for physiotherapy studies based on 50 RCTs in the field of physiotherapy. The author criticised non-standardised walking tests in certain studies and recommended the use of specific therapy approaches (Wiles 2008). A few years later, a meta-analysis showed that physiotherapy led to improved balance in pwMS despite methodological weaknesses of many studies, such as small sample sizes and a lack of randomisation, blinding, concealment of allocation and intention-to-treat analysis (Paltamaa et al, 2012). Another large meta-analysis demonstrated significant effects of endurance training and mixed exercise training on fatigue; however, it was based on moderate methodological study qualities. For example, a majority of the studies used nonspecific therapy approaches and non-validated fatigue assessments as a primary outcome (Heine et al, 2015). Recently, a systematic review investigated the effects of rehabilitation interventions in pwMS (Khan and Amatya 2017). The authors found high-quality evidence for specific physiotherapy strategies to improve mobility, muscle strength, aerobic capacity, fatigue and QoL whereas they reported moderate-quality or weak evidence for a range of other rehabilitation strategies. Physiotherapy effects in pwMS appear to be connected with neural plasticity (Prosperini et al, 2015) and depend also on the disability stage, with more improvement seen in people with mild or moderate MS (Dalgas et al, 2014; Latimer-Cheung et al, 2013; Paltamaa et al, 2012).

2.7 Existing Evidence on Motor Imagery and Rhythmic Auditory Stimulation in People with Multiple Sclerosis: Literature Search

A comprehensive literature search was performed to capture the key literature on the topic of motor imagery (MI) and rhythmic auditory stimulation (RAS) in pwMS. The literature was searched for the keywords “mental/motor imagery, mental representation, rhythmic auditory stimulation, rhythmic entrainment, sensorimotor synchronisation, auditory-motor coupling” and combinations thereof in the following databases: Medline (PubMed, OvidSP), CINAHL, Web of Science, EBSCOhost (AMED), Science Direct, Google Scholar, ClinicalTrials.gov. Additional articles were identified by references cited in the papers retrieved from this search.
Reference selection was based on the English or German language and availability of the full text. 7013 studies were identified. When used in conjunction with “multiple sclerosis AND/OR gait/ambulation/walk* AND/OR fatigue”, 4332 articles were discovered. After reading and evaluation, 6 papers were on the topic of MI/RAS interventions in pwMS (Bovend'Eerdt et al, 2010; Baram and Miller 2007; Catalan et al, 2011; Conklyn et al, 2010; Fell 2000; Heremans et al, 2012c). From these studies, one small cross-sectional study investigated the impact of rhythmic cueing on MI ability in pwMS (Heremans et al, 2012c).

The procedure and results from a literature search on MI and RAS in pwMS, adapted from a PRISMA 2009 Flow Diagram (Liberati et al, 2009) are shown in Figure 5.
In addition to the small number of studies which related MI or RAS to walking performance, fatigue and QoL, they reported different findings because of different outcome measures. Moreover, the studies are hampered by methodological issues.
mainly due to small sample sizes (e.g. n=1 (Fell 2000)), no sufficient description of the statistical analysis (Catalan et al, 2011) or heterogeneity of the study population (Bovend'Eerdt et al, 2010). The findings from these studies are described in the following chapters; they are discussed with reference to the current study results.

2.8 Motor Imagery

2.8.1 Background

Physiotherapy has been shown to play an important role in the rehabilitation of MS-induced impairment and disability. The use of specific approaches such as MI has also gained increasing interest in clinical settings (Gabbard and Fox 2013). MI is defined as the mental rehearsal of movements without their actual execution (Jeannerod 1995). As such, MI may be regarded as mental imagery in the motor modality (Jackson et al, 2001). In MI, the representation of one’s own body is activated by the use of motor memories (Decety and Boisson 1990; Decety and Jeannerod 1995; Jeannerod 1995); it, therefore, offers the opportunity to safely repeat imagined movements with the help of training (Malouin, Jackson & Richards 2013). In this research project, MI of walking was practised by the participants. The advantage of MI over other forms of physiotherapy is that it does not seem to cause motor fatigue (Rozand et al, 2014), and patients are not at risk of falling as it can be practised while seated. It was also recognised that MI might increase mental fatigue which was explored by using a fatigue measurement.

A literature search revealed only one study to investigate the effect of MI, combined with executed movement elements, on walking, fatigue and QoL in twenty pwMS; this study showed a significant improvement in fatigue and QoL even at a six-month follow-up (Catalan et al, 2011). However, there was only a trend for walking speed improvement, due to the small sample size of this non-controlled study. A case study in a single patient with MS showed some balance improvement due to mental imagery, but there was a lack of reliable outcome measures (Fell 2000). Another study could not find any differences after the usual neurorehabilitation compared to neurorehabilitation with integrated MI; nevertheless, it was a heterogeneous study population with only one person with MS (Bovend'Eerdt et al, 2010). In persons with neurological diseases other than MS, MI has been shown to improve motor

**2.8.2 Brain Activation during Motor Imagery**

During imagined walking, similar sensorimotor circuits are activated as with actual perception, motor planning and execution of walking (Land 2014; Park et al, 2015; Zhang et al, 2014); nonetheless, motor commands which activate gait patterns are typically inhibited (Guillot et al, 2012). This implies that typically there is no muscular activity in MI even if subliminal muscle activity was observed in some studies (Cesari, Pizzolato & Fiorio 2011; Fadiga et al, 1999). These studies found wide recruitment of motor-related areas during MI, such as the SMA, PFC and and PMC, cingulate motor areas, inferior and superior parietal cortex, the insula, striatum and cerebellum. There have been controversial results on the activation of M1 since some researchers found such an activation (Munzert, Lorey & Zentgraf 2009; Porro et al, 2000) even if it was weaker (Galdo-Alvarez and Carrillo-de-la-Pena 2004) while others did not (Park et al, 2015; Taube et al, 2015). The latter authors suggested that the lack of activation of M1 was associated with its inhibition, as the movement was not executed.

Unfortunately, there is scarce evidence on the recruitment of brain areas during MI in pwMS. At the Rehabilitation in MS (RIMS) Congress, Brichetto et al. (2014) presented their study on brain activation of participants with MS during MI of squeezing a ball. Compared to healthy individuals, persons with CIS showed no statistically relevant change in brain activation during MI whereas people with RRMS showed increased activation in sensorimotor brain areas, especially with more demanding tasks. In the current study, pwMS with mild to moderate disability were investigated. It was supposed that repetitive activation of the aforementioned brain areas may support skill acquisition similar to physical training (Kraeutner et al, 2014). Changes in brain plasticity are known to occur with physical practice, resulting in movement enhancement, and likewise, repetitive MI was hypothesised to improve corresponding movement (Grezes and Decety 2001; Miller et al, 2010).
2.8.3 Motor Imagery Modes and Perspectives

Different imagery models exist, such as individual and group MI, with eyes open or closed and with or without physical practice (Schuster et al, 2011). Researchers distinguished between implicit and explicit MI (Jeannerod 1994) and between an internal (first-person) and an external (third-person) MI perspective (Callow and Hardy 2004; Jeannerod 1997). According to Jeannerod’s definition, explicit MI is the conscious experience of imagining oneself walking whereas implicit MI is used in everyday situations, such as when one unconsciously estimates how large their next step needs to be to reach the first step of the stairway. Furthermore, two different modes have been described which can be adopted during MI: a visual or a kinaesthetic mode (Callow and Hardy 2004). In the visual mode, the people imagine watching themselves (first-person perspective) or other people (third-person perspective) moving, and in the kinaesthetic mode, they experience or feel themselves moving (Guillot, Collet & Dittmar 2004). For use of the kinaesthetic mode, motor representations are required to have been developed previously, and the corresponding motor skill to have already been acquired (Olsson et al, 2008). In other words, for MI of walking, individuals need to be ambulatory, since walking experience is the basis for the capacity of MI of walking (Jackson et al, 2001).

Studies have shown that the kinaesthetic mode corresponds more to walking than the visual mode (Bakker et al, 2007), and it is more effective (Jackson et al, 2001; Schuster et al, 2011; Slimani et al, 2016). Kinaesthetic MI involves sensory information such as proprioception of related body parts, and temporal features, such as duration, speed (Taktek, Zinsser & St-John 2008) and timing of motor actions (Fery 2003); therefore, it has been used in the current study. Kinaesthetic imagery is more effective in movements of which timing is an essential feature (Fery 2003). Obviously, timing is an essential characteristic of any movement, but particularly a cyclical movement such as walking (Thaut 2005). This was the rationale to choose kinaesthetic imagery for the current study, a decision which was also based on two other studies that supported the use of kinaesthetic MI in a neurological population (Rodrigues et al, 2010; Stinear et al, 2006). Stinear et al. (2006) demonstrated that kinaesthetic, but not visual, MI modulated the corticospinal excitability in a comparable way to physical practice. These authors, thus, recommended the use of
kinaesthetic imagery for rehabilitation in people with neurological disorders. In a similar study, kinaesthetic MI of a balance task changed the body sway, which was not the case with visual imagery (Rodrigues et al, 2010). As such, based on their findings, these authors recommended the application of kinaesthetic MI for motor rehabilitation.

In contrast to the studies discussed above, Callow and Hardy (2004) directly compared kinaesthetic MI in combination with two visual imagery perspectives in healthy individuals: an internal and an external perspective. It did not lead to a preference of any imagery modality and perspective. Their recommendation to researchers was to be specific and explicit in terms of the imagery content and modality. This was in line with other studies which suggested a specific introduction and familiarisation with MI (Schuster et al, 2011; Wondrusch and Schuster-Amft 2013). As a result, in the current study, detailed MI instructions were provided to the participants, described in Chapter 7.4. MI can be practised with or without verbal guiding and with additional visual or auditory cues (Schuster et al, 2011). Guiding might help the participants’ concentration on the task; hence, guided, that is directed, MI was applied, provided by a compact disc (CD) developed by the author specifically for this study.

2.8.4 Motor Imagery Characteristics and Ability

There are inter-individual differences in the abilities to imagine movement (Guillot, Collet & Dittmar 2004). Considering the complex nature of MI, certain studies targeted aspects of its accessible characteristics to measure MI ability in their participants. For example, studies found, that the duration of imagined and executed movements was similar, which is called mental chronometry (Decety and Jeannerod 1996; Decety, Jeannerod & Prablanc 1989). The authors explained this temporal congruence by similar motor representations in overt and covert movement. Similarly, in a pure MI task, the numbers of imagined stepping movements steadily increased with longer durations (for instance, higher number of imagined movements during 45 seconds than over 25 seconds), which also represented mental chronometry (Malouin et al, 2008b). Mental chronometry enables assessing the MI ability of a person by comparing the duration of their MI and movement execution (Decety 1996a; Guillot
and Collet 2005b, 2005a) or the numbers of movements over different time periods (Malouin et al, 2008b). In fact, Jeannerod became one of the first authors to describe measures of MI ability such as mental chronometry tests and self-report questionnaires (Jeannerod 1994, 1997). This approach was used to assess MI ability in pwMS (Heremans et al, 2012a; Tabrizi et al, 2014; Tacchino et al, 2013), stroke (Oostra et al, 2015), schizophrenia (Danckert et al, 2002), Parkinson’s disease (Dominey et al, 1995), parietal cortex damage (Sirigu et al, 1996), spinal cord injury (Decety and Boisson 1990) and apraxia (Sirigu et al, 1995).

Studies showed that there can be a distortion of the MI duration in relation to the overt movement duration even in healthy people (Collet et al, 2011; Decety and Jeannerod 1996). In an early study, persons were asked to either walk to a target or to imagine walking there (Decety, Jeannerod & Prablanc 1989). The time used for the actual walking was compared to the imagery time. Results showed that the actual and imagined walking times were very similar only if participants had received a detailed MI instruction. Similarly, other studies reported that short MI durations were often overestimated by individuals whereas long durations were frequently underestimated (Collet et al, 2011; Grealy and Shearer 2008). In other words, when the real movements involved longer durations, people tended to imagine these movements within excessive durations; when the actual movement duration was short, people needed less time to imagine the very movement than to execute it. The same authors showed that there was a linear increase in imagery times as tasks got more difficult, which was proportionate to the increase in mental effort. Therefore, in the present study, it seemed useful to employ rhythmic-auditory cueing with the MI to provide a temporal framework for participants.

Mental chronometry studies that assessed the MI ability in pwMS confirmed studies in people with other neurological disabilities, showing that the MI accuracy and its temporal organisation were impaired in pwMS versus controls; these deficits in MI ability were associated with cognitive impairment, but were independent of motor functioning (Azin et al, 2016; Heremans et al, 2012a; Tabrizi et al, 2014; Tacchino et al, 2013). Reduced MI accuracy and timing was also related to depression (Tabrizi et al, 2014); therefore, cognitively impaired or depressed patients were excluded from the current study. However, in healthy individuals, increased MI precision was shown
with increased movement familiarity, such as in walking (Parsons 1994). This might also apply to pwMS, as MI of walking was used in this study.

In the MS population, the MI duration was slightly longer even in individuals at early disease stages when they were compared to healthy controls (Nogueira et al, 2013). In contrast to these results, another study observed a shorter duration of imagined movements than with executed movements in pwMS, but not with healthy controls (Heremans et al, 2012a). These data suggest that pwMS might have deficits in the temporal organisation of their MI because, within the boundaries of motor control principles, MI cannot be performed faster than the execution of a corresponding movement (Jeannerod 1995; Sharma et al, 2008); this is because motor control involves the movement planning and preparation prior to its execution or the suppression of its execution during MI (Schmidt and Lee 2011). These results are not surprising as it has been argued that pwMS have impaired motor control due to MS lesions in the motor cortices and upper motor neurons (Rösler et al, 2010).

Additionally, pwMS may have structural damage in brain areas which are responsible for temporal organisation of MI, such as the frontal, prefrontal, and parietal cortices, the basal ganglia and the cerebellum (Decety 1996a; Sirigu et al, 1996). Apart from these differences in the MI ability, the type of movement influences the ability to perform MI. For example, it has been shown that motor performance and MI durations were fairly similar in both highly automatic and cyclical movements, such as walking (Papaxanthis et al, 2002), skating (Oishi, Kasai & Maeshima 2000) or rowing (Guillot, Collet & Dittmar 2004). These findings suggested a higher MI ability in the current study population, as MI of walking was used.

Bakker et al. (2007) and Stevens (2005) used walking pathways of different lengths and widths to measure the temporal congruence between executed and visually and kinaesthetically imagined walking. They found higher temporal congruence between kinaesthetic MI and real walking than with visual MI. This was another rationale for using kinaesthetic imagery in this study. Arguably, motor areas are damaged in pwMS, as discussed earlier, and that the approach of kinaesthetic MI, which is known to activate sensorimotor areas, might not be useful. Alternatively, visual MI could be used to compensate for the loss in sensorimotor areas. It should be noted, however, that also the visual cortex is frequently affected in pwMS, leading to manifold visual
impairment (Balcer et al, 2015). Twenty-one percent of patients suffer from optic neuritis at disease onset (Miller et al, 2005), and one third of pwMS have persistent visual impairment (Jasse et al, 2013). Thirty years after disease onset, as many as 50-80% of patients have visual impairment or disability (Kister et al, 2013). Thus, the MS lesion load in sensorimotor and visual brain areas seems to be comparable, so visual MI cannot be considered preferable to kinaesthetic MI.

2.9 Rhythmic Auditory Stimulation and Sensorimotor Synchronisation

Skilled walking involves precise timing mechanisms and perception of rhythm, both of which are processed in the distributed neural populations of our brain, which are believed to be simultaneously activated (Buhusi and Meck 2005; Filip et al, 2016). Neuroimaging research has provided insight into the connection of the auditory and sensorimotor circuits with neural areas relevant for both time perception and processing (Grahn 2012; Schubotz, Friederici & von Cramon 2000). Many studies have investigated the complex mechanisms of temporal processing and their neural correlates (Ashoori, Eagleman & Jankovic 2015; Beudel et al, 2008; Filip et al, 2016; Merchant et al, 2015).

In general, when talking about temporal processing, a distinction is made between implicit and explicit timing mechanisms (Ashoori, Eagleman & Jankovic 2015). Implicit timing refers to temporal prediction or expectation, as for example when we have to step aside for an approaching car, and which mainly leads to activation of the cerebellum (Bares et al, 2007; Beudel et al, 2008). Explicit timing refers to an estimation of movement speed and duration, and also to motor timing, such as during synchronisation tasks (Beudel et al, 2008) and recruits the basal ganglia, the SMA, the PMC and the cerebellum (Coull, Cheng & Meck 2011). The importance of the cerebellum in predictive motor timing processes, and its enhanced activation with increased movement speed and complexity, has been highlighted recently (Filip et al, 2016). Overall, there seems to be a cerebellar predominance in feedforward processing whereas the basal ganglia have an internal pacemaker function, and they are responsible for the estimation of movement speed and duration (Beudel et al, 2008). Cerebellar damage caused by atrophy or MS lesions may increase movement
variability (Petter et al, 2016) and affect the feedforward processing, which helps to predict future motor states using spatial and temporal cues (Broersen et al, 2016). For example, this could mean that patients have problems to coordinate their walking while navigating the environment.

The complex interconnectedness between motor, auditory and rhythmic areas might be responsible for the common urge to move to music (Schaefer 2014a). Based on this notion, in the 1990s, Thaut and his colleagues developed a walking rehabilitation strategy, using rhythmic auditory cues to provide a temporal structure for walking (Thaut 2005; Thaut and Rice 2014). They named the approach Rhythmic Auditory Stimulation (RAS) and showed that it can be successfully applied to facilitate movements which are intrinsically cyclical, primarily walking. In RAS, music, metronome and verbal cues, at a fixed or adaptive tempo, are used to guide walking (Thaut 2005). Abundant evidence has shown that RAS improves stride length, gait speed and walking distance, and it also reduces gait variability in various populations (Ellis et al, 2015; Hove and Keller 2015; Wright et al, 2016). An underlying mechanism of RAS is SMS, which leads to an alteration of gait patterns induced by rhythmic cueing (Repp 2005). In SMS, the brain’s beat processing networks and the auditory and motor systems adjust the gait tempo to the music tempo.

SMS would not be possible without rhythmic entrainment (Grahn 2012; Thaut 2005). Entrainment, broadly speaking, involves the interaction of two or more independent rhythmic processes, which gradually adjust to each other and eventually lock-in to a common phase (London 2002; Thaut and Schauer 1997). During entrainment, coordination of rhythmical and cyclical movement to auditory rhythms occurs spontaneously (Large and Snyder 2009). Moreover, entrainment to the beat is processed automatically, such that any perturbations are adjusted, even if the perturbation was not consciously noted (Wright and Elliott 2014). Timing in both executed and imagined motor actions refers to the duration of the total task, such as walking to a certain goal, whereas rhythmicity corresponds to the relative timing of individual movement sequences, as for example the gait phases (Smith and Wakefield 2013). Previous work demonstrated that movement synchronisation with external rhythms involves the adaption of the movement duration, or period, to the
rhythmic cue duration, rather than the coincidence of the movement response to the onset of the cue (Thaut and Kenyon 2003).

In relation to the current study, it is possible that such adjustments would occur between imagined walking and the cueing, inducing a potential gain in timing and coordination, which might then be transferred to actual walking. This hypothesis was supported by work from Oullier et al. (2005) who found activation of the same brain areas during executed and imagined index finger to thumb opposition movements with metronome cueing. For entrainment to function, the cues are required to be repetitive and continuous and to produce an impression of pulse, or rhythm (London 2004). However, should music be used for cueing, even high levels of musical complexity can induce entrainment (Phillips-Silver, Aktipis & Bryant 2010). It is important to note that synchronisation with auditory cues can be trained, which has been shown in students and even more so in musicians (Repp 2010). With practice, the synchronisation process becomes faster. It is worth mentioning that entrainment to rhythmic auditory cues also induced changes in motor planning and motor execution in people with stroke (Song and Ryu 2016), Parkinson’s disease (De Dreu et al, 2012) and MS (Baram and Miller 2007; Conklyn et al, 2010).

RAS has been investigated in combination with walking, usually while using an auditory feedback device to provide adaptive cueing. In these studies, people with neurological diseases other than MS showed improved walking patterns, in particular patients with stroke (Muto et al, 2012; Thaut et al, 2007), Parkinson’s disease (Lohnes and Earhart 2011; Lopez et al, 2014), spinal cord injury (De l'Etoile 2008), traumatic brain injury (Hurt et al, 1998) and Huntington’s disease (Thaut et al, 1999). A large study in people with Parkinson’s disease demonstrated that walking improvement decreased when auditory cueing was removed (Nieuwboer et al, 2007). A meta-analysis further showed that music-cued movement should be specific; it means that walking intervention should be performed for walking rehabilitation (De Dreu et al, 2012), which was the case with the current study.

A literature search revealed only three studies evaluating the effects of RAS for walking rehabilitation in pwMS; the latest was conducted after this PhD project (Baram and Miller 2007; Conklyn et al, 2010; Shahraki et al, 2017). Baram and Miller (2007) used an auditory feedback device that produced a tic according to the
participants’ steps. They found short-term effects in walking speed and stride length in pwMS, but not in healthy controls. Conklyn et al. (2010) used gait training with music and embedded metronome cues in which the beat was 10% above the participant’s spontaneous cadence. Gait parameters did not change, only double support time decreased; however, the sample size was very small (n=10). In eighteen pwMS, Shahraki et al. (2017) found significant improvements in stride length, stride time, cadence and gait speed after three weeks of metronome-cued gait training; the metronome tempo was also 10% above the participants’ preferred cadence. These results suggested that music or metronome cues, which have a slightly faster beat than the participants’ preferred cadence, induce rhythmic entrainment and effect on walking performance.

SMS during imagined walking was conjectured as a mechanism underlying any changes in walking, similar to those seen after cued walking (Thaut 2005; Thaut and Rice 2014). In other words, it was speculated that during cued MI, synchronisation of imagined gait with the external cueing would occur. Notably, for accurate synchronisation to be performed, the regular, and in the case of syncopation, regularly perceived beat sequences, are suggested to enable the brain to anticipate the occurrence of the next beat (Thaut 2005). By applying this feedforward mechanism, it could be possible to adapt one’s steps or imagined steps with the beat tempo (Thaut 2005). Healthy people are able to synchronise their walking with musical rhythms, both at fast and slow beat tempos, but there is an optimal range where synchronisation is easier (Styns et al, 2007). People walked faster while synchronising to a faster beat, but most optimally, this occurred at around 120 beats per minute (BPM) where the range was between 106 and 130 BPM (Styns et al, 2007). So far, there exists no evidence on optimal tempos for walking synchronisation in the MS population, but studies in pwMS with mild to moderate disability observed self-selected mean cadences between 94.4±2.1 (Givon, Zeilig & Achiron 2009) and 111.7±10.4 (Remelius et al, 2012) steps per minute. Thus, for the current study, instrumental songs with a beat between 80 and 120 BPM were selected. Following musicologist and neuroscientist Thaut (2005), to be suitable for the cueing of walking, the rhythmic cues need to be regular; RAS is best organised in a 2/4 or 4/4 metre, which is the music’s rhythmic structure, with strong ON and OFF beat patterns while every first or every first and third beats are stressed. In this study, the music beat and
tempo of metronome cues were selected accordingly, and the verbal cueing was used to emphasise the temporal structure of the beats and to enhance attention (see Chapter 2.13) (Edwards 2011; Janelle et al, 2003).

2.10 Effects of Music on Mental State and Movement Performance

2.10.1 Effects of Music Listening on Mental State and Brain Activation

Music and movement are used worldwide to express emotions, and both are processed by the brain in similar ways (Sievers et al, 2013). Music listening and experience involve activation of highly interactive sensorimotor, cognitive, emotional and auditory brain areas (Altenmüller and Schlaug 2013). Pleasurable music induces highly pleasurable emotions, accompanied by activation in brain areas which are responsible for reward processes, motivation, emotions and arousal (Blood and Zatorre 2001). Brain regions involved in this so-called reward network are part of the basal ganglia and the limbic system, ventral medial PFC, hypothalamus and dorsal midbrain areas (Blood and Zatorre 2001). Activation of this network also leads to increased dopamine release in the nucleus accumbens and is associated with an energy boost in the person concerned (Mavridis 2015). The reward network is strongly connected with the so-called arousal system (Mesulam 1999). The arousal system involves a large network within the posterior parietal lobe and the anterior frontal regions, with subcortical structures such as the thalamus and the ascending reticular activating system (ARAS) (Mesulam 1999), which innervates large cortical areas (Gadea et al, 2004). Arousal is regulated by the interaction of brain networks which are responsible for wakefulness, attention and consciousness (Hou et al, 2007), which are needed during MI. The arousal areas are strongly connected to the sensorimotor areas (Samuels and Szabadi 2008a, 2008b). However, pwMS are known to have problems with arousal regulation insofar as arousal levels are too low, which is associated with fatigue (Niepel et al, 2013). Their arousal dysfunction and fatigue might be related to immune-mediated CNS inflammation (Giovannoni 2006; Metz 2004). Evidence suggested that arousal and fatigue are negatively correlated so that fatigue results may be indicative of arousal (Niepel et al, 2013).

To address and overcome fatigue and reduced arousal in participants in the current study, and based on affluent evidence, the use of motivational music was considered
an appropriate tool (Elliott, Carr & Orme 2005; Karageorghis and Terry 2009). For example, physical activity was observed to be stimulated by motivational music (Karageorghis et al, 2006). The term ‘motivational music’ has been defined according to its measurable psychophysical effects on mood, arousal and reduced rating of perceived exertion (Simpson and Karageorghis 2006). The latter relates to the so-called ergogenic effect of music when it increases work output, endurance, power, productivity or strength (Karageorghis and Terry 2009). Apart from improvements in performance, motivational music also induces brain activity changes. Blood and Zatorre (2001) used highly pleasurable “shivers-down-the-spine” (Goldstein 1980; Krumhansl 1997; Witek et al, 2014) inducing music to assess levels of brain activations by a Positron Emission Tomography (PET). They found recruitment of reward network areas described above. Likewise, Menon and Levitin (2005) found recruitment of similar brain areas during music listening, and increased functional and structural connectivity between these areas, as measured by functional magnetic resonance imaging (fMRI). Activation of these brain areas is associated with high levels of pleasure and arousal in the listener (Csikszentmihalyi 1997; Koelsch 2014; Lehmann 1994). Other effects of music are related to emotional and cognitive benefits (Engh 2006), entertainment, coping, autonomy, self-identity, self-regulation (Laiho 2004) and enhancement of concentration and mood (Levitin 2007). In the current study, music in the music-cued MI group was suggested to induce some of these effects in participants. Nonetheless, it could not be known which effects would occur, if any, and whether this would contribute to improvements in walking, fatigue and QoL.

According to the British Association of Sport and Exercise Sciences, music with exercise should be appropriate for the motor activity in terms of its loudness, tempo and percussion, and involve marked rhythmic qualities in addition to pleasing melodic and harmonic structures (Karageorghis et al, 2012). During exercise and sports, music listening can both increase or reduce arousal, depending on the music type (loud, upbeat or soft, slow music) (Copeland and Franks 1991; Karageorghis, Drew & Terry 1996). In the current study, only motivating music was used because this type
of music has been shown to narrow attention and thus delay the perception of fatigue (Karageorghis and Priest 2012). Further, background music with lyrics has been found to decrease concentration in workers (Shih, Huang & Chiang 2012); therefore, instrumental (karaoke) music was used in the current study. To create an understanding of musical elements to consider for the music selection in this study, a description of the elements in music is given in Table 2.

<table>
<thead>
<tr>
<th>Musical element</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melody</td>
<td>Tune or voice; the foreground of a music piece</td>
<td>(Patel 2008)</td>
</tr>
<tr>
<td>Harmony</td>
<td>Accompanies and supports the melody; simultaneously played notes, pitches or chords</td>
<td>(Malm 1996)</td>
</tr>
<tr>
<td>Tempo</td>
<td>Music speed; measured in beats per minute</td>
<td>(Harnum 2013)</td>
</tr>
<tr>
<td>Dynamics</td>
<td>Gradual or sudden changes in music loudness, softness or tempo; the energy of a music piece</td>
<td>(Harnum 2013)</td>
</tr>
<tr>
<td>Timing</td>
<td>Duration of a note; pulse and metre occur as expected or with a time-shift to earlier or later</td>
<td>(Honing 2013b)</td>
</tr>
<tr>
<td>Rhythm</td>
<td>Consists of several elements: metre, pulse or beat; the rhythmic pattern, tempo and timing</td>
<td>(Large and Snyder 2009)</td>
</tr>
<tr>
<td>Metre</td>
<td>Temporal framework in music consisting of stressed and unstressed beats, of strong and weak elements; it leads to rhythmic expectations</td>
<td>(London 2004; Nozaran and al, 2011)</td>
</tr>
<tr>
<td>Pulse</td>
<td>Based on metre; a pattern of beats at regular or isochronous intervals</td>
<td>(Honing 2013b)</td>
</tr>
<tr>
<td>Rhythm pattern</td>
<td>Set of beats and rests that defines the tempo of a musical piece: periodic, regular, metric or non-periodic or irregular (such as syncopated); it consists of grouped patterns of pulse</td>
<td>(Patel et al, 2005, 2008)</td>
</tr>
</tbody>
</table>

**Table 2: Musical Elements.**

**2.10.2 Mental States with Groove Music**

Syncopation is characterised by an emphasis of weak pulses and a de-emphasis of strong beats in musical pieces, which leads to a violation of the metrical expectations.
of music listeners (Longuet-Higgins and Lee 1984). Syncopation further involves
displacement of accents from specific strong beats to weak beats (Temperley 1999).
These rhythmically complex music pieces do not meet with listeners’ expectations of
the way beats are organised (Huron 2006), which positively influences the enjoyment
of music (Keller and Schubert 2011). Surprise caused by syncopation might be a
reason for higher levels of pleasure and emotional arousal in listeners (Smith and
Honing 2006).

Syncopated music listening enhances SMS and creates the inclination to move some
part of one’s body, which is generally named ‘groove’ (Madison 2006; Witek et al,
2014). Groove has been referred to as the pleasure and happiness in which
movement becomes effortless and automatic (Janata, Tomic & Haberman 2012).
However, only optimal levels of syncopation increase the ability for movement
synchronisation with musical rhythm (Patel et al, 2005), which are dependent on the
context (North and Hargreaves 1997). Medium levels of syncopation increase groove
and SMS (Madison and Sioros 2014; Witek et al, 2014) while maximum levels of
syncopation reduce groove as the metre becomes disrupted (Sioros et al, 2014). In
pwMS, music therapy was shown to have similar effects to music listening in healthy
people, with improvements in individual coping strategies (Ostermann and Schmid
2006). Applied to the current study, this would mean that the participants in the
music-cued MI group enjoyed the practice and improved their SMS.

### 2.11 Music with Physiotherapy

As discussed above, music has a wide range of beneficial impacts on healthy
individuals and on people with various diseases. In this section, music applications in
physiotherapy settings are described, mainly in people with neurological disorders.

A review on the effects of music-based interventions found that rhythm-based music
interventions can improve gait speed and cadence in people with neurological
disorders including MS (Moumdjian et al, 2016). One study showed that people with
stroke improved their memory, attention and mood after having listened to their
favourite music for at least one hour per day for two months (Sarkamo et al, 2008).
Another study in people with stroke compared the effects of eight weeks exercise
therapy with and without music on upper limbs range of motion, muscle power,
activities in daily living and mood (Jun, Roh & Kim 2013). Significant improvements in range of motion and mood were found only in the music-supported group. In pwMS, a small pilot study failed to demonstrate significant effects of music therapy on self-esteem, depression and anxiety, but showed trends for improvement in subscales (Aldridge et al, 2005). This study used individualised music therapy in which patients are engaged by music therapists. In contrast to individualised music therapy, music interventions were defined as music medicine when patients listen to pre-recorded music (Bradt et al, 2011; Bradt, Dileo & Potvin 2013; Dileo and Bradt 2007). In the current study, pre-recorded music was used for the cueing of MI. As this study was an RCT, the music-cued MI intervention needed to be comparable within the group.

A six-month multitask exercise programme accompanied by piano-music improved walking under dual-task conditions and balance, and reduced fall rates in older people who were at increased risk of falling (Trombetti et al, 2011). This suggested that apart from the musical elements described above, the music’s temporal structure may improve motor learning. In addition, a summary of systematic reviews showed that music played alongside physiotherapy treatment was well received and reduced anxiety, depression (Kamioka et al, 2014) and pain (Cole and LoBiondo-Wood 2014; Lin et al, 2011). Prior to the music selection of the current study, an MS advisory group was consulted in terms of their music preference. Advisory group members emphasised their preference for music with a melodic sound and harmonic richness. Therefore, for this study, rhythmically accentuated and motivating music with pleasing melodies and harmonies was selected (Thaut 2005), with moderate levels of syncopation (Witek et al, 2014), allowing the music pulse to be perceived as being regular.

2.12 Metronome Cues with Physiotherapy

Physiotherapists successfully use metronome cues to influence walking (Pelton et al, 2010), running (Balasubramaniam et al, 2013) and arm reaching (McCombe Waller, Liu & Whitall 2008). In view of the complex nature of music and the simplicity of metronome cues, the question arises about which of the two cueing types may be more suitable for enhancing rhythmical movement. The key literature results are discussed in the following section.
Interestingly, the rhythm of motivational music increased running motivation in healthy individuals, but the consistent and simple cadence of a metronome led to more effective SMS and more economic running (Balasubramaniam et al, 2013). Only one study was identified which compared the effect on walking from both music and metronome cues in patients with neurological diseases. It showed improved walking speed in people with Huntington’s disease with simple metronome cues, but not with music (Thaut et al, 1999). These findings suggest that the group differences may have been induced by a deficit in cognition, sensory perception and temporal processing, which is known to be present in individuals with Huntington’s disease (Paulsen 2011). Three studies found that music, but not metronome cues, led to a significant improvement in walking speed in healthy individuals (Styns et al, 2007; Terry et al, 2012; Wittwer, Webster & Hill 2013a). It is likely that additional auditory elements in the music facilitated walking more than simple metronome cues.

Evidence has shown that three weeks of home-based, metronome-cued walking training significantly improved walking in individuals with Parkinson’s disease, but the functional gain was lost at the six-week follow-up (Lim et al, 2010). This study integrated the cueing into the participants’ daily life activities. Ambulation and any other static and dynamic activity were monitored by a wearable device. The loss of the functional gain at follow-up may be explained by the cessation of the rhythmic cueing after three weeks. The conclusion might be that, for this population, constant cueing is required. Another small study compared people with stroke against healthy individuals during treadmill walking to investigate their SMS. Walking was metronome-cued or non-cued while pacing occurred with either one or both footfalls. Stroke patients struggled to accelerate their steps, but increased their walking speed to a higher velocity with pacing of both steps (Roerdink et al, 2009). These results suggest that cueing is beneficial to improve walking speed in people with stroke. Unfortunately, in pwMS, only a small single study was conducted, to compare the effects of a two-week against a four-week, home-based rhythmic-cued walking training on gait parameters (Conklyn et al, 2010). For cueing, music was used with an embedded metronome beat tempo which was 10% above the participants’ spontaneous cadence. No significant group differences were found; however, trends for a gait improvement could be related to the small sample size (n=10). To summarise, metronome cues are simple, precise and consistent rhythmic auditory
cues which are suggested to enhance MI and so were used in the metronome-verbal-MI group of this study, together with verbal cues.

### 2.13 Rhythmic Verbal Cues

Music and speech share many aspects, such as melody, temporal patterns and rhythm, emotions and their relatedness to movement (Patel 2008). There are similarities of rhythm in music and speech, which help to justify the use of verbal cues in this study. In music, there is a rhythm which typically includes strong and weak elements, the ON and OFF elements (Thaut 2005). For example, in a march, strong and weak elements alternate in a simple metrical structure, such as, for instance, **1-2-1-2-1-2** (Cason and Schon 2012). It is easy to walk with a march, as with the first beat, the right heel strikes the ground and with the second beat the left heel. For this study, notions of rhythm refer to regular or periodical rhythm since walking can only be paced by regular rhythms.

Music cueing and metrical speech have relevant timing commonalities, such as repetition and modulation of temporal patterns, both of which lead to repeated rhythmic entrainment (Tierney and Kraus 2014). Research has shown that the ability for rhythmic entrainment and an improved motor performance, such as in walking, depends on the performer’s degree of attention (Thaut 2005); by contrast, the ability of a person to sustain attention during varied rhythmic elements is strongly connected to their ability to entrain to a metronome or piece of music (Tierney and Kraus 2014). Practically speaking, when a person is able to focus their attention on the tempo of the beat, entrainment to the beat is optimal (Tierney and Kraus 2015). Even with simple metronome cues, the attention of the listener is necessary, and studies suggested that music requires even more attention as the temporal structure increases in complexity (Tierney and Kraus 2014). Hence, the first rationale for the use of additional verbal cues in the current study was that concise verbal cues provide a simpler metrical structure for the music beat, which might enhance rhythmic entrainment in participants.

It is known that people with mild MS often have attention deficits even in the absence of overt cognitive impairment, mainly due to reduced information processing speed (Balsimelli et al, 2007; Kujala et al, 1994). Research has shown
that pwMS were able to solve cognitive tasks without errors, but they could not ever complete them within the time limit because of their reduced information processing speed (Balsimelli et al, 2007; Kujala et al, 1994). People with mild MS and an EDSS of <1.5 had a mild dysfunction on phased alertness and divided attention (Tinnefeld et al, 2005), selective attention and information processing speed, but not with verbal short-term memory (Schulz et al, 2006). This evidence suggested that some of the participants with mild to moderate MS, without any overt cognitive deficits, might have discrete information processing speed and attention dysfunction. Therefore, the second rationale for the use of verbal cues in this study was that for this study population, a strongly metrical beat, as provided with additional verbal cues, may enhance attention.

Verbal cues are frequently used to facilitate motor learning. Cues can enhance the learning of motor skills using an external learning focus while drawing a person’s attention to the performance results; it also employs an internal learning focus, with a person’s conscious attention on the movement of their body (Magill 2011; Schmidt and Lee 2011). In the current study, concise words were used which were designed to direct the participants’ attention to a specific aspect of their imagined movement, such as walking with large steps or raising the forefoot (Landin 1994). Verbal cues were used to prompt one specific component of (imagined) walking, as in walking in an upright position (Landin 1994) or taking large steps (Behrman, Teitelbaum & Cauraugh 1998). Researchers concerned with motor learning found that verbal instructions on the task and verbal cues should be related to each other (Edwards 2011). In this study, the verbal instructions on the MI were provided beforehand in some detail whereas related verbal cues were given during the practice. It has been recommended to frequently repeat verbal cues to support the practitioners aim to relate the cues with the corresponding motor task, particularly at the early stages of learning (Edwards 2011). Therefore, in this study, the different verbal cues were repeated frequently, and each cluster of cues was repeated several times.

The literature shows that three to four different verbal cues were found to be useful in early learning stages, and seven to nine cues were shown to improve more advanced motor learning stages. By contrast, a higher number of cues might
confuse participants and detract them from the motor task (Edwards 2011). In the current study, the verbal cueing was applied accordingly. It was suggested that the external cueing at some stage might lead to the participants’ self-cueing during actual walking, which could improve their self-efficacy.

2.14 Rhythmic-Cued Motor Imagery

On basis of the findings discussed in the previous sections, in this study, rhythmic and auditory cues were used in combination with MI. This combined intervention was chosen because, as this thesis conjectured, pwMS would be more attentive to MI when it was accompanied by rhythmic auditory cues. Based on a review on the impact of adding temporal patterns to MI (Schaefer 2014b), this study further suggested that rhythmic-auditory cueing would provide a temporal framework to the imagined walking. Moreover, music was effective in improving spatiotemporal gait parameters in healthy people, more than metronome cues (Styns et al, 2007; Wittwer, Webster & Hill 2013a), and so repetitive music cueing of the MI may be more motivating to participants than non-cued MI (Schaefer 2014a). In line with this, external auditory cues led to an enhanced vivid imagery and to more highly coordinated related eye-movements, most likely induced by SMS (Heremans et al, 2009). Both relaxing and stimulating music improved the MI vividness in healthy people; unfortunately, the author did not provide information on the music tempo used (Tham 1994). This could have been key information because SMS was significantly more pronounced during actual and imagined finger tapping when the music frequency was near the preferred tapping tempo, which is around 120 BPM (Moelants 2002). Thus, one might expect a more vivid MI when listening to a rather fast music beat than to relaxing music, which is typically slow (Bernardi, Porta & Sleight 2006). In contrast, impairment in healthy people’s MI ability of walking has been found when they listened to slow or fast music, as assessed by the temporal congruency during both actual and imagined walking (Debarnot and Guillot 2014). However, these authors used music published by work outside of the medical literature, which investigated the influence of slow (40-70 BPM) and fast (120-140 BPM) music on car driving performance; an so, the music metre was irregular (Brodsky 2001). It may be that with irregular music, real walking is easier than imagined walking, due to a
stronger proprioceptive feedback. In the current study, regular music in duple or quadruple metre was used.

Only a few researchers have evaluated the effects of external cueing on MI ability in people with neurological diseases, namely Parkinson´s disease (Heremans et al, 2012b), stroke (Kim et al, 2011) and MS (Heremans et al, 2012c). External cues reduced the MI duration and increased the vividness and temporal accuracy of imagined movements in individuals with Parkinson´s disease (Heremans et al, 2012b). In fifteen people with stroke, Kim et al. (2011) demonstrated significantly improved walking performance, mainly after kinaesthetic MI practice with auditory step rhythm when compared to visual MI practice without auditory cueing. So far, only Heremans et al. (2012c) have investigated the impact of external cues on MI ability in pwMS, showing increased temporal congruence between executed and imagined movements. The rationale for using external cueing to enhance the MI in the current study was, therefore, based on evidence provided by Heremans et al. (2012c).

For gait cueing, there seem to be substantial differences in efficacy between cueing modalities. For example, rhythmic auditory cues significantly improved gait variability when compared to visual, aural and tactile cues (Sejdic et al, 2012). In relation to imagined walking, recent work supports this study’s basic conjecture that SMS with rhythmic auditory stimuli may also apply to MI. Based on her research on temporal aspects of auditory and MI, Schaefer (2014b) suggests that the brain´s timing mechanisms are associated with expertise. In other words, MI of walking involves the temporal structure of walking. In pwMS, impairment of temporal processing and internal timekeeping is a common problem (Jones, Sprague & Vaz Pato 2002); therefore, timekeeping during MI was supported by the cueing.

Practice and repetition are widely known motor learning principles to improve movement coordination and to enhance motor control (Schmidt and Lee 2011). A supposition of this study was that frequent rhythmic-cued MI practice, that is six times a week, for four weeks, might induce neural plasticity-related CNS changes (Adkins et al, 2006) and improvement of the corresponding walking performance (Zeller et al, 2010). Moreover, the audio-mix used for the rhythmic auditory cueing, including various cueing tempos, and weekly changes thereof were based on Bernstein’s
(1967) well recognised motor learning principle “repetition without repetition”. This relates to movement variability while the performer aims at reaching a movement goal; it means that, due to motor redundancy, movements are never repeated in exactly the same way, which finally enables the performance of skilful motor actions (Bernstein 1967). Similarly, it has been shown that variety helps to maintain attention with a mental task; typically, during a task involving cognition, such as scholarly learning or MI, every novel stimulus interferes with the cognitive task (Raulerson 1973). Variety can be used as a means to redirect and retain attention to the content to be learned or the MI task to be practised. In this way, variety presents stimuli in diverse forms so that attention is directed towards the ever-changing stimulus (Raulerson 1973). In the current research, diverse MI tasks of walking were combined with different music types and tempos or metronome cues and varied verbal cues; this approach may have facilitated motor learning.

2.15 Summary

MS is a chronic and disabling disease of the CNS, and multidisciplinary therapy is required for its treatment. As part of the rehabilitation team, physiotherapists support patients to improve their mobility and QoL. During the disease course, a high percentage of pwMS have fatigue contributing to a decrease in their QoL.

Physiotherapy strategies such as MI and RAS have been found to be effective in people with neurological conditions including MS. Music and metronome cues, both with rhythmic-verbal cueing, were discussed to explain their role in rhythmic-cued MI. Finally, different MI models in terms of their application in the current study were referred to, aiming at a justification for the approach.

The following chapter will describe outcome measures to evaluate the effects of this study together with their justification.
Chapter 3: Measurement

Measures for this study were selected because they have high-grade psychometric properties, and they are safe, quick and easy to administer in order not to exhaust participants. All questionnaires were in German because it is the participants’ first language. All questionnaires, except the MSWS-12, were validated in German. A German MSWS-12 questionnaire from the Medical University of Innsbruck, Clinical Department of Neurology was used. This questionnaire had been frequently used in research studies. The validated German version of the EQ-5D-3L was used in this study because no Austrian version of the EQ-5D-3L was available. Index scores employed for this study are based on German values developed by Greiner et al. (2005).

The EDSS was not used as an outcome measure in this study, but participant selection was based on the EDSS as a measure of disability. Only persons with an EDSS from 1.5 to 4.5 were included in this study. Within the EDSS frame of reference, pwMS are considered to have mild, moderate or severe MS (Lobeck 2004).

3.1 Clinical Significance

“Not everything that can be counted counts, and not everything that counts can be counted” (Cameron 1963, page 13).

Statistical significance measures the probability that an effect observed in a research study is true and not occurring due to chance; however, clinical significance is the amount of difference in treatment effects which are important and relevant to the patient (Leung 2001). The minimal clinically important difference (MCID) is defined as the smallest treatment effect that will lead to a change in clinical practice (Make 2007). This has also been referred to as a meaningful change (Crosby, Kolotkin & Williams 2004) and (minimal) clinically significant difference (Hajiro and Nishimura 2002). From a physiotherapy standpoint, it is important to know what changes are relevant for pwMS; the measurement would employ a patient-reported outcome. A patient-reported outcome is a measure of patients' perception of their health status, the impact of the disease and its treatment, usually reported in a questionnaire
(Varma et al, 2010). In Chapters 3.1.1 and 3.1.2, results from the literature on (minimal) clinically significant changes of all outcome measures used for this study are shown.

3.1.1 Primary Outcomes

The primary outcomes of this study were walking speed and walking distance (endurance) as measured by the Timed 25-Foot Walk (T25FW) (Kaufman, Moyer & Norton 2000) and the 6-Minute Walk Test (6MWT) (Goldman, Marrie & Cohen 2008), respectively. All numbers described in this section are based on studies in pwMS, so that it is possible to compare them to the current study.

Several studies showed that a 20% change in walking speed exceeds the day-to-day differences in participants’ walking performance and the measurement errors (Coleman, Sobieraj & Marinucci 2012; Hobart et al, 2013; Hoogervorst et al, 2004a; Kaufman, Moyer & Norton 2000; Schwid et al, 2002). As a result, changes of more than 20% may be considered a clinically meaningful change. During daily living activities, walking very fast over short distances might enable patients to maintain their independence and to increase their range of action, such as when catching a bus.

Learmonth et al. (2013b) found that the minimal detectable change (MDC) in walking distance was 20% (88 metres). Notably, the MDC reflects the smallest real difference which exceeds the measurement error (Stratford, Binkley & Riddle 1996). In other words, this is a concept different from the minimal clinically significant change that reflects a change in functional status, which is based on the participants’ perceptions (Turner et al, 2010); the estimation of the clinically significant change requires use of an anchor-based method, which correlates the change in the test with a change in an external criterion such as a patient-rated questionnaire (Feys et al, 2014; Freeman et al, 2013). Based on their clinical judgement, Applebee et al. (2015) considered a 55 metre or 20% change in walking distance clinically meaningful in pwMS; such a change was comparable to the 6 MWT guidelines of the American Thoracic Society who reported a change of 50 metres or 20% as being clinically significant (A. T. S. Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002). In contrast, Baert et al. (2014) reported a change of 10% (21.6 metres) in the
6MWT measures to be sufficiently large for a clinically meaningful improvement. This large study used an anchor-based method in combination with a distribution-based method, which refers to the ability of an assessment of capturing real change. Therefore, it was surprising that their results showed smaller absolute values to represent a clinically meaningful improvement. From a clinical perspective, a 20% change seemed to be a relevant change that may exceed the within-day variability in walking (Feys et al, 2014), and so in the present study, a walking distance improvement of at least 20% was considered clinically significant.

3.1.2 Secondary Outcomes

For this study, the MS Walking Scale-12 (MSWS-12) (Hobart et al, 2003), the Modified Fatigue Impact Scale (MFIS) (Fisk et al, 1994), the Short Form-36 Health Survey (SF-36) (Bullinger 1995), the EQ-5D-3L (Brazier, Jones & Kind 1993; EuroQuol 2013) and the MS Impact Scale-29 (MSIS-29) (Hobart et al, 2001) were used as secondary outcomes.

The literature on the majority of MS population-based outcome measures is somewhat conflicting, with changes of -10.4 points (Baert et al, 2014), -6.84 points (Goodman et al, 2009), -10 points (Prugger and Berger 2013) and -15.5 points (Applebee et al, 2015) reported as representing a clinically significant change in walking perception (MSWS-12). Therefore, in this study, on the basis of conservative literature results, improvement in walking perception as assessed by the MSWS-12 was regarded clinically significant when the change exceeded -15 points. However, should there have been no clinically significant change in the primary outcomes, this decision needed to be questioned. This is because the goal of the study was primarily to improve walking performance to enhance QoL.

In this study, improvement in fatigue as measured by the MFIS was considered clinically significant if the change was -16.2 points on the total score, -8.9 points on the physical subscale, -8.0 points on the cognitive subscale and -2.3 points on the psychosocial subscale (Rietberg, Van Wegen & Kwakkel 2010). Their study used the Smallest Detectable Change (SDC), or MDC, reflecting a ‘true’ change which exceeds the measurement error (Beckerman et al, 2001). These numbers were chosen because the study population in the study from Rietberg and colleagues
(2010) was comparable to the current study while using EDSS-based disability measures. In addition, most studies only used the MFIS total score for their calculations of the minimal clinically significant change (-10 points (Kos et al, 2005, 2007), -10.3 points (Wingerchuk and Lipinski 2005)), yet the study by Rietberg, Van Wegen & Kwakkel (2010) also used the MFIS subscores and their results were the most conservative.

Improvement in HRQoL, as assessed by the SF-36, was considered clinically meaningful if the overall score increased by 5 or more points. This number was chosen because all studies on the topic and in an MS population consistently showed that such an improvement was to be considered clinically significant (Heessen and Cohen 2014; Kappos et al, 2014; Norman, Sloan & Wyrwich 2003; Rudick et al, 2007).

In the general population, differences of at least 0.03 points on utility measures such as the EQ-5D-3L are considered clinically meaningful (Kuspinar and Mayo 2013). In pwMS, minimal clinically significant changes in HRQoL, as assessed by the EQ-5D-3L Index Value, were evaluated by Kohn et al (2014b). They reported changes of at least 0.065 points to be clinically significant in people with mild impairment, 0.091 points in people with walking disability and 0.093 points in people with moderate walking disability. Disability measures were performed using the Patient Determined Disease Steps (Learmonth et al, 2013c), which is a similar instrument to the EDSS. For the current study, an improvement of 0.073* points in participants with an EDSS of 1.5-3.0 was regarded as clinically significant as was an improvement of 0.093 points in participants with an EDSS of 3.5-4.5. *The 0.073 were calculated using (0.065+0.082)/2.

To the author’s knowledge, so far, no studies were conducted to estimate the minimal clinically significant improvement in HRQoL as measured by the EQ-5D-3L VAS score. However, a recent study from Philipps et al. (2014) provided estimates of 5.5 units on the EQ-5D-3L VAS to represent a minimal clinically significant worsening in pwMS. This study retrospectively analysed data from a large multicentre trial (n=621). Hence, in the current study, 5.5 units’ improvement on the VAS score were considered clinically significant since no study was found to report clinically significant improvements.
Three studies provided estimations for a clinically significant improvement in QoL, as assessed by the MSIS-29. Van Linden et al. (2005) used the MSIS-29 for proxy use, so the results might not seem to be relevant for the current study. However, these authors provided similar estimates of clinically relevant changes in the physical subscore as opposed to the other two studies (-8.13 points compared to -7.8 and -7.5 points) (Costelloe et al, 2007; Phillips et al, 2014). In addition, their study was the only one to report estimates for the psychological subscore (-5.56 points). Therefore, in the current study, the improvement on the MSIS-29 was considered clinically significant on the physical subscore if it was ≤-7.5 points and on the psychological subscore if it was ≤-5.56 points.

3.1.3 Administration Time of Outcome Measures

All assessments were performed in accordance with the recognised guidelines, as discussed below. In Table 3, administration times of outcome measures used are shown.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Admin. Time</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-25FW</td>
<td>1–5 min</td>
<td>(LaRocca 2011; Kaufman, Moyer &amp; Norton 2000)</td>
</tr>
<tr>
<td>6-MWT</td>
<td>10 min</td>
<td>(Potter et al, 2014; Goldman, Marrie &amp; Cohen 2008)</td>
</tr>
<tr>
<td>MSWS-12</td>
<td>5–10 min</td>
<td>(Potter et al, 2014; Hobart et al, 2003)</td>
</tr>
<tr>
<td>MFIS</td>
<td>5–10 min</td>
<td>(LaRocca 2011; Fisk et al, 1994)</td>
</tr>
<tr>
<td>MSIS-29</td>
<td>10–15 min</td>
<td>(Potter et al, 2014; Hobart et al, 2001)</td>
</tr>
<tr>
<td>SF-36</td>
<td>10 min</td>
<td>(LaRocca 2011; Bullinger 1995)</td>
</tr>
<tr>
<td>EQ-5D-3L</td>
<td>3–5 min</td>
<td>(Brooks et al, 2003; Brazier, Jones &amp; Kind 1993)</td>
</tr>
<tr>
<td><strong>Total Time</strong></td>
<td><strong>44–65 min</strong></td>
<td><strong>(original in colour)</strong></td>
</tr>
</tbody>
</table>

**Table 3:** Administration Times of Outcome Measures for Study 1.

Table legend: Abbreviations: Admin. = administration; min = minutes; yellow = walking outcomes; green = fatigue outcomes; blue = (HR)QoL outcomes.
3.2 Walking Measurement

As shown in a recent multicentre study (Gijbels et al, 2012), standard instruments to assess walking are the T25FW and the 6MWT, both of which are recommended for research (Bennet et al, 2014; Hobart et al, 2003; Potter et al, 2014).

- Therefore, the T25FW (7.62 metres), the most commonly reported short walking test in pwMS, was chosen to measure walking speed (related to the functional aspect of walking).
- The 6MWT was used to measure walking distance (endurance).
- As a secondary outcome, the MSWS-12, a patient-rated measure of walking ability, was used. The MSWS-12 has been highly recommended by the MS consensus groups reported above.

To ensure scientific rigour, the psychometric properties of all outcome measures were critically scrutinised, particularly their reliability, validity, responsiveness, normative data if available, and both floor and ceiling effects.

3.2.1 Timed 25-Foot Walk

The T25FW was administered as follows (Cutter et al, 1999): for the baseline and post-intervention measures, participants were asked to walk 25 feet (7.62 metres), with or without their walking aid, on a marked hallway as quickly as possible, but safely. They were advised to start with “Ready? Go!” and to not slow down until they had passed the finish-line. The task was immediately and equally administered for a second trial. For scoring, the average was taken from the two measures. Any circumstances that may have affected the patients’ performance during the walk were recorded.

For the T25FW, excellent test-retest reliability was shown, as evidenced by Intra-class correlation coefficients (ICCs) of 0.96 (EDSS 0-6.5); excellent convergent validity was observed, as shown by Spearman’s $\rho$ of 0.8 with the EDSS and 0.7 with the MSWS-12; 0% floor and ceiling effects were found (Nieuwenhuis et al, 2006). Excellent responsiveness was reported, as indicated by high effect sizes when compared to the EDSS and MSIS-29 (Bosma et al, 2015). Normative data in pwMS showed that patients with an EDSS of 3.5 needed below 10 seconds to walk 25 feet.
whereas people with an EDSS of 0-6.5 needed 3.5-22.6 seconds for the same distance. The current study investigated people with an EDSS of 1.5-4.5.

3.2.2 6-Minute Walk Test

The 6MWT involved participants covering as much ground as possible in 6 minutes, with or without their assistive devices and without physical assistance, along a 30-metre hallway, with small cones at each end to mark the turnaround points. Warm-up was not allowed before the test, as recommended by the American Thoracic Society (A. T. S.) guidelines for the 6MWT (2002). Participants rested on a chair for at least 10 minutes, close to the starting line of the test. A second chair for rest was positioned close to the end of the hallway, but out of the walking way. Assistive devices could be used, but were kept consistent and documented from test to test. Participants were instructed to turn at each end; rests were allowed at any time, and the number and duration of rests during the 6 minutes were measured (Potter et al, 2014). Standard phrases of encouragement by use of an even voice were provided every minute, but no other words of encouragement or body language were used (A. T. S. Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002). The number of laps from the starting point was counted and recorded visible to the participant, and the number of metres in the final partial lap distance was marked after 6 minutes. The residual walking distance was measured with a digital measuring wheel¹.

For the 6MWT, excellent test-retest reliability was shown (EDSS 0-6.5; ICC=0.96) (Fry and Pfalzer 2006; Paltamaa et al, 2005), with both excellent inter-rater reliability (EDSS 0-6.5; ICC=0.91) (Goldman, Marrie & Cohen 2008) and convergent validity with the T25FW (EDSS 0-4; Pearson’s r=0.78) and the EDSS (EDSS 4.5-6.5; Spearman’s ρ=0.81) (Gijbels et al, 2012). 0% floor and ceiling effects were seen (Potter et al, 2014) and an excellent concurrent validity with the MSWS-12 (ρ=0.72), the MFIS physical subscale (ρ=0.66) and total score (ρ=0.59) (Goldman, Marrie & Cohen 2008). Healthy individuals walked approximately 530-883 metres in six minutes, with differences depending on gender, height and age (Gibbons et al, 2001).

In contrast, females and males with MS and an EDSS <4.0 walked mean (±SD) 380.1±156.0 m and 459.5±133.8 m, respectively; women and men with an EDSS of up to 6.5 walked 322.2±156.4 m and 362.8±169.2 m, with variations connected to age, cardiorespiratory function and balance (Wetzel, Fry & Pfalzer 2011). In this study, participants aged twenty-four to seventy were included.

3.2.3 Multiple Sclerosis Walking Scale-12

Participants were asked to complete the 12-item MSWS questionnaire. Using a 1 (not at all) to 5 (extremely) Likert scale; participants assessed their walking ability over the past two weeks (Potter et al, 2014). To score the scale, the numbers from the 12 items were summed up. To transform to a 0-100 scale, the minimum score possible (12) was subtracted from the sum. The result received was divided by 48 (the maximum score possible minus the minimum possible (60-12)), and then multiplied by 100 (Potter et al, 2014).

The concurrent validity of the MSWS-12 with the EDSS (Spearman’s ρ=0.65) is high (Hobart et al, 2003). Likewise, in pwMS and an EDSS of 0-6.5, the concurrent validity of the MSWS-12 with the 6MWT (r=0.73-0.84) (McGuigan and Hutchinson 2004a) is high. The concurrent validity with the T25FW (r=0.46) (Hobart et al, 2003) is moderate. This discrepancy between high and moderate concurrent validity may be explained by the fact that walking at a longer distance and the subjective walking ability reflect the actual walking ability more than a very short walking speed test.

Excellent internal consistency was shown, as indicated by Cronbach’s alphas of 0.94-0.97 (Hobart et al, 2003) and 0.97 (McGuigan and Hutchinson 2004a; Motl and Snook 2008). Very good responsiveness was demonstrated in comparison with the EDSS (McGuigan and Hutchinson 2004a) and after steroid treatment, with large effect sizes of 0.93 (Hobart et al, 2003). The MSWS-12 has small ceiling effects of 4.7% and larger floor effects of 13%, but both may be considered adequate as being below 15% (Terwee et al, 2007). Other authors considered floor and ceiling effects to be adequate if they are lower than 20% (McHorney and Tarlov 1995); however, from a clinical perspective, the responsiveness of a measure might be lower if the floor and ceiling effects are higher than 15%. Average MSWS-12 scores of 2.2±5.6 points were observed in healthy people and average scores of 28.2±25 points in pwMS (EDSS 0-
In consequence of the above, the scale was chosen for this study.

3.3 Fatigue Measurement

3.3.1 Modified Fatigue Impact Scale

The MFIS is a modified form of the Fatigue Impact Scale (FIS) (Fisk et al, 1994) and one part of the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Fischer et al, 1999). The MFIS was highly recommended by the expert groups, stated above, to assess fatigue in pwMS (Paul et al, 2014). It is a 21-item Likert scale that evaluates via self-report the effects of fatigue on physical, cognitive and psychosocial functioning in pwMS. All items can be answered by five categories (never, rarely, sometimes, often and almost always; min-max 0-4) resulting in a total score from 0-84 (Garrett 2011). For the current study, the total score and subscales were calculated with higher numbers indicating greater fatigue. The physical subscale ranges from 0-36 and was calculated by addition of the raw scores from items 4, 6, 7, 10, 13, 14, 17, 20 and 21. The cognitive subscale ranges from 0-40 to which raw scores from items 1, 2, 3, 5, 11, 12, 15, 16, 18 and 19 were added. The psychosocial subscale ranges from 0-8 by an addition of items 8 and 9 (Raad 2012). Overall MFIS scores of 38 or above (cut-off values) were indicative of MS-related fatigue, which demonstrated a highly effective discriminant validity (Flachenecker et al, 2002).

The MFIS has shown an excellent reliability (ICC= 0.86 (total score and physical subscale); 0.84 (cognitive subscale); ICC= 0.75 (psychosocial subscale) (Learmonth et al, 2013a)). The scale also demonstrated moderate to high convergent validity with the Fatigue Severity Scale (FSS; ρ<0.5 (Krupp et al, 1989)). The MFIS was found to be more responsive with the 6MWT (ρ=-0.61 (total score); ρ=0.68 (physical subscale); ρ=-0.43 (cognitive subscale); ρ=-0.61 (psychosocial subscale) (Kos et al, 2003; Learmonth et al, 2013a)) and with the MSWS-12 (ρ=0.76 (total score); ρ=0.85 (physical subscale); ρ= 0.55 (cognitive subscale); ρ=0.69 (psychosocial subscale) than the FSS (Learmonth et al, 2013a)). Moderate concurrent validity with the FSS was observed (ρ=0.68 (Krupp et al, 1989); ρ=0.66 (Rietberg, Van Wegen & Kwakkel 2010)), and excellent internal consistency (Cronbach’s α= 0.96 (total score and
cognitive subscale); $\alpha=0.94$ (physical subscale) (Amtmann et al, 2012); however, the psychosocial subscale was questionable with $\alpha=0.65$ (Kos et al, 2005).

In agreement with the latter results, it was found that the MFIS was able to fit a Rasch Model only when the psychosocial subscale was removed (Mills et al, 2010). These authors recommended using the physical and cognitive subscales separately, eliminating questions 4, 14, 17 from the physical and questions 1-3, 5 and 11. However, the MS Outcome Measure Taskforce advised being careful since no psychometric test results were available for this suggested version of the questionnaire. Kos et al. (2005) evaluated the MFIS in four European countries, and they found effective psychometric properties and recommended employing the scale in clinical trials, but that the interpretation of the psychosocial scale should be undertaken with caution. Therefore, in the current study, the MFIS standard version was used, with a cautious interpretation of the psychosocial subscale, which had the highest floor (7.4%) and ceiling (9%) effects when compared to the physical and cognitive subscales (0.7%; 1.1%) (Terwee et al, 2007).

### 3.4 (Health-Related) Quality of Life Measurement

Various patient-reported outcome measures have been developed to gain knowledge of patients’ perspectives of their QoL with regard to their treatment (Heesen and Cohen 2014). HRQoL is generally assessed using multidimensional patient-rated questionnaires to capture condition-specific and utility-based domains (Brazier, Jones & Kind 1993; Warren et al, 2009). In their review of generic (HR)QoL instruments, Coons et al. (2000) recommended using a combination of (HR)QoL instruments, as each of them has strengths and weaknesses over the others. For this study, both the generic instruments SF-36 and EQ-5D-3L were used to assess HRQoL. QoL was assessed using the MSIS-29. All questionnaires have been recommended for use in research by consensus groups described above (Cohen et al, 2015).

#### 3.4.1 Short-Form-36 Health Survey

The SF-36 is a generic self-reported outcome measure for health status (Morfeld, Kirchberger & Bullinger 2011). In people with mild MS, the use of the SF-36, in particular the physical functioning items, was recommended to detect deterioration in
HRQoL (De Groot et al., 2006). The SF-36 consists of eight subscales, which are the weighted sums of the questions in their section (the number of items is in brackets): physical functioning (10), physical role functioning (4), bodily pain (2), general health perceptions (5), vitality (4), social role functioning (2), emotional role functioning (3) and mental health (5). The scale also includes two questions for the estimation of health status changes over the past year (1). For scoring, each subscale is linearly transformed onto a scale from 0 (poor self-perceived health) to 100 (optimum health) (Brazier et al., 1992). Responses are on a nominal (yes/no) or ordinal scale. Five of the subscales are ‘unipolar’ (physical functioning, physical role functioning, bodily pain, social role functioning and emotional role functioning), which means that health status is associated with an absence of disability. The maximum score of 100 is consistent with no disability. The other scales (general health perception, vitality and mental health) are ‘bipolar’ scales, involving both good and poor health states. The maximum of 100 on these bipolar scales indicates not just the absence of disability, but the presence of a vital state of health. Each of the items are weighted and, therefore, software was used to calculate the scores (Morfeld, Kirchberger & Bullinger, 2011).

The second German version of the SF-36 was used for this study (Morfeld et al., 2005). In version 1, the form was translated using a forward-backward method with additional translation quality ratings and pilot testing in order to examine translation clarity and applicability (Bullinger, 1995). Version 2 contains the same response categories in the questions, but uses a more precise language. For this reason, it was used in this study.

Despite the broad range of subcategories, moderate to excellent test-retest reliability was shown for the SF-36 (ICC=0.65-0.93; the lowest were for bladder and vision scales) (Marrie et al., 2003); there was moderate to excellent internal consistency (Cronbach’s $\alpha=0.75-0.94$ (Freeman, Hobart & Thompson, 2001); $\alpha\geq0.8$ (overall); $\alpha>0.75$ (males); $\alpha=0.90$ (physical functioning, social functioning, emotional roles) (Morfeld et al., 2005)). Moderate convergent validity with the EQ-5D was observed (Spearman’s $\rho=0.50-0.75$; 8 subscales (Bullinger et al., 2003)), and high concurrent validity with the EDSS ($\rho=-0.86$ (physical functioning); $\rho=-0.32$ (mental health); $\rho=-0.26$ (vitality); $\rho=-0.18$ (emotional role functioning); $\rho=-0.48$ (social role functioning))
High construct and discriminant validity were found (Freeman, Hobart & Thompson 2001) since people with mild MS rated significantly higher than people with moderate and severe MS, and pwMS scored significantly lower than the general US population (particularly physical functioning and physical role functioning) (Vickrey et al., 1995). Acceptable floor (14.2% in ambulatory pwMS) and no ceiling effects (Riazi et al., 2003a) were demonstrated for the SF-36.

3.4.2 EQ-5D-3L

The EQ-5D-3L contains two distinct descriptive self-report elements, providing three approaches to analysis: the descriptive Likert-type system, the VAS score and the index values. The EQ-5D-3L descriptive element is a HRQoL instrument to evaluate health status across five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Revicki et al., 2009). Responses are rated on three levels: no problems, some problems and extreme problems. The digits for the five dimensions can be combined to a five-digit number which describes the participants’ health state, according to the patients’ self-reported health (from 11111 = perfect health to 33333 = worst health) (Devlin 2012). It is also named the EQ-5D profile. As this element was not used in the current study, it is not described in detail here.

The EuroQoL classification system (Krabbe et al., 1999) allows conversion of health state units of the EQ-5D-3L into index values or so-called ´value-sets´ (EuroQol Group 1990). A perfect health state would be represented as 11111 (health state) and 1.00 (index score); the worst health state would show 33333 and -0.59. For this study, SPSS syntax files were ordered from the EuroQoL Office2 to allow a faster conversion process. Parkin, Rice & Devlin (2010) showed that the use of the health-index generated by profile-weighting is the most common approach to the analysis of EQ-5D-3L data.

Part three of the scale is represented by the EQ VAS, which is similar to a thermometer, and records the participants’ own global rating of their overall health, on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

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Scoring is achieved by taking the value selected by the participant. This information can be used as a quantitative measure of HRQoL (EuroQuol 2013). The validated German EQ-5D-3L version was used in this study since no Austrian version was available. Index scores employed for this study were based on German values developed by Greiner et al. (2005).

Moderate to excellent test-retest reliability has been shown for the EQ-5D-3L (ICC=0.52; VAS: ICC=0.51 (Janssen et al, 2008); ICC=0.81 (Fisk et al, 2005)) and excellent convergent validity (VAS: \( \rho=0.88 \) (pain/discomfort) to \( \rho=0.99 \) (mobility and usual activities) (Janssen et al, 2008)). Moderate concurrent validity was found with the SF-6D (\( \rho=0.58 \) (Brazier, Roberts & Deverill 2002; Krabbe et al, 1999; Kuspinar and Mayo 2013; Walters and Brazier 2003)) and the MSWS-12 (\( \rho=-0.59 \) (Kohn et al, 2014b); \( \rho=-0.55 \) (Sidovar et al, 2013)), and moderate discriminant validity with the EDSS (\( \rho=-0.66 \)) and T25FW (\( \rho=-0.63 \) (Nunnally and Bernstein 1994)). Moderate internal consistency was demonstrated (\( \alpha=0.69 \) (Kohn et al, 2014b)) and high responsiveness because the health status as measured by the EQ-5D-3L reflected the walking perception, as assessed by MSWS-12 (Hawton et al, 2012a). Additionally, high EQ-5D-3L health states were associated with better health profiles (Jones et al, 2013a).

UK norm data in pwMS showed some or extreme problems in mobility and usual activities in \( \geq 90\% \) and pain in \( \geq 80\% \), particularly in people with a progressive disease course (Hemmett et al, 2004). Mean scores in pwMS with a median EDSS of 2 (1.0-3.5) were 0.69±0.18 (Kuspinar and Mayo 2013). PwMS with all disabilities scored a mean of 0.61±0.29 (Hawton et al, 2012b). Acceptable floor effects of 13.3\% and no ceiling effects were found (Kohn et al, 2014b). A critique concerned the absence of fatigue and cognitive dimensions in the scale (Brazier, Roberts & Deverill 2002; Walters and Brazier 2003). Balance, fatigue, social roles and relationships are not included, leading to a lack of content validity due to a mismatch between walking ability and self-reported walking ability in the mobility item (Kuspinar and Mayo 2013). In the current study, these domains were captured by other instruments, such as the MSWS-12, MFIS, SF-36 and MSIS-29, and the EQ-5D-3L was chosen to gain additional information about HRQoL.
3.4.3 Multiple Sclerosis Impact Scale-29

The MSIS-29 is a 29-item disease-specific, patient-reported questionnaire for measuring the impact of MS on individual lives, with 20 items associated with a physical subscale and 9 items with a psychological subscale (Hobart et al, 2001). For this study, version 1 of the MSIS-29 was used as version 2 was developed for use via the internet portal of the UK MS Register (Jones et al, 2013b). The MSIS-29 showed the strongest psychometric properties compared to other QoL scales (Hobart et al, 2005; Riazi 2006; Riazi et al, 2003b), and its use has been recommended by a recent multidisciplinary consensus meeting (Paul et al, 2014). The items ask about the impact of MS on day-to-day living over the past two weeks. Responses use a 5-point Likert scale, ranging from 1 “not at all” to 5 “extremely”. Both subscales were scored by summing the responses across all items, followed by a conversion to 0-100 scales where higher scores indicated a greater impact of MS on daily function. The number of items were subtracted from the sum and divided by the total possible, then multiplied by 100. Thus, for the physical items (1-20), assuming all items had a response, from the sum, 20 was subtracted, then divided by 80 and multiplied by 100. For the psychological items (21-29), based on an equal assumption, from the sum, 9 was subtracted, then divided by 36 and multiplied by 100. The minimum score received was 29 and the maximum score 145 (Garrett 2011).

Excellent test-retest reliability of the MSIS-29 has been found (ICC=0.94 (physical subscale); ICC=0.87 (psychological subscale) (Hobart et al, 2001)) in addition to excellent internal consistency (Cronbach’s $\alpha=0.88-0.96$ (physical subscale); $\alpha=0.87-0.92$ (psychological subscale) (Gray, McDonnell & Hawkins 2009; Hobart et al, 2001; McGuigan and Hutchinson 2004b; Riazi et al, 2002)). Moderate to high convergent and discriminant validity was demonstrated between the MSIS-29 and the SF-36 physical subscales (Pearson’s $r=-0.79$ to -0.70) and the MSIS-29 psychological subscale and the SF-36 mental health subscale ($r=-0.76$ to -0.73) (Hobart et al, 2001; Riazi et al, 2002). This was also shown between the MSIS-29 physical subscale and EQ-5D (mobility $r=0.61$; self-care $r=0.69$; usual activities $r=0.69$; pain/discomfort $r=0.44$; anxiety/depression $r=0.36$) and the MSIS-29 psychological subscale and EQ-5D (mobility $r=0.23$; self-care $r=0.37$; usual activities $r=0.42$; pain/discomfort $r=0.43$; anxiety/depression $r=0.68$) (Hobart et al, 2001). Moderate concurrent validity was
found between the MSIS-29 physical subscale and EDSS (Spearman’s $\rho=0.63-0.68$) and the MSIS-29 psychological subscale and EDSS ($\rho=0.22$) (Gray, McDonnell & Hawkins 2009; Hoogervorst et al, 2004b).

Medium to large effect sizes after treatment (physical scale $\geq 0.82$ (McGuigan and Hutchinson 2004b); psychological scale $=0.66$ (Hobart et al, 2001)) indicated high responsiveness. Mean MSIS-29 physical subscores of 38.35±25.3 and psychological subscores of 28.7±21.3 were observed in a large MS sample (EDSS 0-9.5) (McGuigan and Hutchinson 2004b). For the MSIS-29 physical subscale, floor effects of 0-9% were seen, and for the psychological subscale 1.4-7%; ceiling effects for the physical subscale were 0-3.9% and for the psychological subscale 1.3-9% (Hobart et al, 2001; McGuigan and Hutchinson 2004b; Riazi et al, 2002). According to a Rasch analysis, the two scales are strongly reliable and show excellent construct validity and responsiveness (Bacci et al, 2016), but they are different and should not be combined to a total score (Ramp et al, 2009). In the current study, the analysis was performed accordingly.
Chapter 4 – Research Methodology

4.1 Introduction

Methodology relates to the concepts and theory behind any research, representing the researcher’s way of thinking (Crotty 1998). The research methods employed should be grounded in the underlying methodology (Crotty 1998). In the current project, the author intended to engage herself in a rigorous, controlled, systematic, empirical and critical way (Blaikie 2007, 2010; Creswell 2009). This was undertaken with the further aim of producing valid, reproducible and sound results (Blaikie 2010; Creswell 2009).

However, nothing can ever be considered ‘truly true’ because, someday it may be revealed that it is false (Popper 1992). Thus, scientific judgements can be considered valid if they are grounded in factual evidence, argument and logical implication, that is justification (Black 1999). This is the approach which has been taken in the current study.

As this study was hypothesis-driven, research methods were required, which allowed a generation of numerical data to answer the research questions. Therefore, a post-positivist paradigm seemed to be an appropriate foundation to a quantitative approach.

4.2 Post-Positivist Paradigm

The research paradigm comprises the researcher’s stance within a study as it is an underlying theoretical framework and represents various assumptions about ontology and epistemology (Blaikie 2010). The theoretical and philosophical assumptions of Popper’s post-positivism met the author’s personal and professional knowledge, and so this research paradigm was chosen (Popper 1963).

After positivism, post-positivism is known to be ‘scientific’ due to its systematic approach and ability to generate reproducible results (Black 1999). In this regard, a scientific method is a multitude of strategies of inquiry, used not only to generate new knowledge, but also to revise and integrate existing knowledge (Reeve 2000).
Minimal requirements for methods to be scientifically sound are that they are based upon independent empirical and measurable evidence, and particular methods of reasoning (Newton 1966). In this context, such a method of reasoning would be deductive reasoning since it is concerned with the development of hypotheses, based on existing theory; it also employs quantitative methods to test these hypotheses (Newton 1966), as performed in this thesis.

4.3 Ontology

Ontology is the study of being, existence and reality (Teddlie and Tashakkori 2009). The ontological assumptions of the author correspond with a cautious realist worldview, comprising of a reality existing independently of human beings (Blaikie 2007, 2010; Popper 1963). Nevertheless, direct or accurate observation of phenomena, such as neural plasticity which might induce a change in walking capacity in pwMS, is not possible, as human senses and measures are imperfect (Blaikie 2007). Having been aware of these limitations and in line with Popper’s falsificationism, a cautious and critical stance was adopted by the researcher. The idea of falsificationism is to eliminate false theories by the process of conjecture and refutation (Popper 1963). Using this approach, conjectured theories which are proven to be false are rejected; conjectures are never proven to be true as there might be an alternative explanation or competing idea, but they continue to exist as long as they are not found to be wrongful. Research hypotheses of this study were either supported or refuted after their systematic investigation and statistical data analysis (Blaikie 2010).

4.4 Epistemology

Epistemology is the study of different forms of knowledge about reality, but also sources and limits of knowledge (Teddlie and Tashakkori 2009). The epistemological viewpoint of the author corresponds with critical rationalism, which is a modest and self-critical rationalism. Such a critical attitude employs deductive logical reasoning to discover weaknesses in a theory. In other words, critical rationalism is a method of trial and error; it is a tentative acceptance of a scientific theory, in connection with a rational enthusiasm to revise the theory, unless it is shown to be unable to pass the
tests it is subjected to (Popper 1963). These epistemological assumptions led to the study’s methodology.

4.5 Methodology – Quantitative

Methodology has been referred to as the strategy, principles, process or design of a research study, leading to selection and use of specific methods, and associating these methods with the results (Greene 2008). This study used a quantitative methodology by establishing a ‘true experiment’ in which all relevant factors that might have affected the parameters to be studied were controlled, and participants were randomly assigned to groups (Black 1999). A true experiment is any study where an effort is made to identify and impose control over all other variables except one. In this study, three groups were evaluated for the proposed dependent variable (e.g. walking speed) pre- and post-intervention. The intervention groups experienced the manipulated independent variable (intervention) whereas the control group for comparisons did not.

4.5.1 Purpose of Research

The purpose of this research was confirmatory. Confirmatory studies are those seeking to test a pre-specified relationship of variables (Field 2009). For illustration, the pathway from a theory to confirmation is shown: Theory → Hypotheses → Observation → Confirmation (Burney 2008).

4.5.2 Enquiry Logic

Within the selected research paradigm of post-positivism, the associated enquiry logic was deductive reasoning. Deductive reasoning works from the more general, such as a provisional notion, a conjecture, a hypothesis to the more specific, such as a conclusion (Blaikie 2010). In this study, a clearly stated theory on the impact of rhythmic-cued MI on walking, fatigue and QoL in pwMS was generated, and it was expressed as a valid deductive argument (Popper 1992). The research hypotheses were subjected to rigorous empirical tests (Blaikie 2010). If the null hypotheses were rejected, the theories were corroborated and supported, so not proven to be true (Popper 1963).
4.5.3 Axiology

Axiology refers to the role of values within the research process (Lincoln, Lynham & Guba 2011). Within a post-positivist paradigm, the researcher needs to be as value-neutral as possible (Popper 1963). Therefore, the author took the stance of a detached observer to guarantee the study’s objectivity (Blaikie 2007, 2010). However, although the author strived to remain detached in this study, it is always possible that research is involuntarily influenced by the values of investigators (Rosenthal 1966). In this thesis and the articles published in relation to these ideas, the style of writing is neutral by use of a third-person passive voice (Greenhalgh 1995).

4.5.4 Randomised Controlled Trial

Following a quantitative methodology, an RCT including a pilot study was conducted because this is the gold standard in research. The RCT sought to measure and compare the outcomes of walking speed, distance and perception, fatigue and QoL with the physiotherapy interventions music-verbal-MI and metronome-verbal-MI, set against a control group in pwMS, described in Chapters 7-12. This RCT fulfilled any quality criteria of RCTs according to the revised recommendations of the CONSORT Statement (2001), by exception of blinding which is difficult to perform in physiotherapy interventions (Moher, Schulz & Altman 2001), and which was not possible in this study because it was conducted by the author.

4.5.5 Variables

This study was considered to have an explanatory approach; in other words, the goal was to identify cause and effect, and to understand the nature or mechanisms of the relationship between the dependent and independent variables (Blaikie 2010). Independent variables were those that would probably cause an effect such as the intervention whereas dependent variables were those that were reliant on the independent variables (Creswell 2009). Dependent variables were the results or outcomes, such as walking distance, walking speed, walking perception, fatigue and (HR)QoL.

Control or confounder variables are a specific type of independent variables because they might influence the dependent variables (Creswell 2009). In this study, they were
the demographic variables of age, gender and disease-related variables such as disability. By use of stratification, these variables were controlled. All measures were empirical, that is numerical (Field 2009). Thus, it was crucial to identify and control the variables to observe and measure to avoid bias and be able to explain causal links between the variables (Black 1999).

4.5.6 Levels of Measurement

The levels of measurement for the dependent variables are introduced as follows: the primary outcome variables (walking speed and distance) were on a ratio scale; they were continuous variables with a true zero. The secondary outcome variables (patient-rated walking, fatigue and (HR)QoL) were on an ordinal scale with a rank order of categories, and no equal intervals between ranks. The identification of the levels of measurement was required for the statistical data analysis.

4.5.7 Summary

The theoretical perspective behind this research was post-positivism. This was the ‘umbrella’ covering all the assumptions about the natural and social world, and about how to inquire into this world (Punch 2006). A cautious realist standpoint reflected the author’s ontological worldview that was consistent with a critical rationalist epistemology. By use of a quantitative methodology and hypothetico-deductive enquiry logic, an RCT was conducted. The goal of the study was to accept or refute the null-hypotheses and so to generate new knowledge about the effect of rhythmic-cued MI on walking, fatigue and QoL in pwMS. Figure 6 summarises the research methodology of this study.
Figure 6: Research Methodology of this Study (created by the author, based on ideas from Popper (1963))
Chapter 5 - Ethics

5.1 Introduction

The research proposal of this study was approved by the Faculty of Health and Social Science, School of Health Sciences, University of Brighton; the study was conducted at the MS Clinic, Clinical Department of Neurology, Medical University of Innsbruck, Austria. The national legal foundations of both countries were explored. The same laws apply in both nations, apart from the fact that only a clinician is allowed to apply for ethics approval in Austria. Therefore, the ethics application at Innsbruck Medical University was submitted by Professor Thomas Berger, head of the MS Clinic, Innsbruck and also PI of the study; the author was explicitly stated to be the researcher who conducted the study. In this chapter, ethical considerations on this study are discussed.

Ethics in research is about how a researcher is supposed to treat the participants to facilitate their health and wellbeing. Responsible conduct of research involves the four principles of ethics: non-maleficence, beneficence, justice and autonomy (Beauchamp and Childress 2009). Based on a sense of morality and her responsibility as a researcher, the integrity of this research was upheld by the author.

5.2 Ethics Process in the UK and Austria

This study was fully approved by the Faculty Research Ethics Governance Committee (FREGC) of the University of Brighton on 9 January, 2014 (reference number 13 053 (see Appendix 4). On 2 April, 2014, the study was fully approved by the Ethics Committee of the Medical University of Innsbruck, Austria (reference number AN2014-0052 334/4.14 (see Appendix 5). After that, data collection began in accordance with the research proposal and under the supervision of Dr Raija Kuisma, Dr Angela Glynn and Prof Thomas Berger. As this is a PhD project (see Appendix 2) registered with the University of Brighton, the project was annually monitored. A brief final report was submitted to the FREGC after the completion of each study.
5.3 Research Governance

International and national laws and guidelines govern responsible conduct of human research such as the Nuremberg Code (Nuremberg Military 1996), Declaration of Helsinki (Rickham 1964), CIOMS International Guidelines for Biomedical Research (Council for International Organizations of Medical Sciences 2002; Macrae 2007), Belmont Report (Department of Health, Education and Welfare; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 2014), UK Human Rights Act (Horton 2000) and Mental Capacity Act (Shickle 2006). In the current study, all research government guidelines were met. The study conduction was closely monitored by the supervisors and some of the data collection at the MS Clinic was observed by the PI, Professor Berger.

5.4 Patient and Public Involvement

According to UK (Bogg 2010) and EU legislation (European Commission 2010), user involvement is highly recommended and the National Advisory Group for patient and public involvement (PPI) in public health, health and social care research, INVOLVE, provides support for user involvement in research (Buckland et al, 2007). This study aims to benefit pwMS; hence, it was essential for the user group views and perspectives to have a crucial impact on the study design and intervention. However, it became apparent that the rigid design of an RCT would not allow any further changes (Buckland et al, 2007).

In the planning stage of this study, members of an MS support group were asked for their advice on the study. The user group was contacted several times to receive advice on the study intervention. To value the patients’ time, expertise and skills, a drug store voucher for meetings and email contact was provided. These meetings took place in a café, with drinks and snacks offered for free. Advice from the group members had an influence on the study intervention such as the decision to use music with pleasing melodies and metronome cues with different tone pitches. In addition, group members provided insight into the daytime variability of their fatigue, so the study participants were able to practice at any time of the day. Members of the user group were informed about outcomes as soon as possible, and they were invited
to a conference held by the Austrian MS Society where the author talked about MS, music and walking, and provided practical tips.

Lay people in England who were not members of the advisory group helped to translate the English version of the participant information sheet (PIS) (see Appendix 3) and the informed consent document into lay language. Members of the advisory group in Austria helped with the translation of the German version, which was used for the study. Study results were translated into lay language with the help of the advisory group and lay people. Results were disseminated to the study participants, the Austrian MS Research Society as a funder and to scientific journals for MS.

5.5 Capacity

According to the inclusion and exclusion criteria (adults with no depression or cognitive deficits), the MS population recruited for this study was regarded to have the capacity to comprehend the information given, to consider their decision and to consent or refuse their participation in the study. Participants who would have lost their capacity during the study, as assessed by clinicians at the MS Clinic, would have been withdrawn from the study; however, their data would have been used.

5.6 Valid Informed Consent

Potential participants received the recruitment flyer from the reception staff at the Outpatient MS Clinic, Innsbruck during their usual visit; they also obtained the PIS and detailed verbal information on the study by the author. Oral and written information was presented in comprehensible lay language. All information was provided in German since this is the official language in Austria. The author made herself present during outpatient clinic times to answer any queries. The potential participants had at least twenty-four hours to consider their participation. Contact details were provided on the PIS. After one week, the participants who agreed to telephone contact were called by the author asking them about their decision. As such, all individuals were allowed a free and voluntary decision. Written informed consent was obtained by the author (see Appendix 3).
5.7 Power Relationships

There was no power relationship between the participants and the author because she was not treating them as a physiotherapist, and she was not working at the MS Clinic. Reception staff at the MS-Outpatient Clinic informed potential participants about the study and handed over the recruitment flyer to them. As the author was present, she was able to provide further information. In accordance with Austrian law, the PIS included the PI’s contact data for complaints. During the testing, the participants were offered refreshments, and they were reimbursed for their travel and parking expenses.

5.8 Vulnerability

PwMS might be regarded vulnerable because of their disability or cognitive impairment. For this study, pwMS with mild to moderate disability and without cognitive impairment were recruited. This thesis claims that anybody with a progressive disease is easily exploited; thus, this research was conducted with great responsibility concerning the four ethical principles (Beauchamp and Childress 2009) and also in line with the moral duty of the author. No unrealistic hope was instilled in the participants regarding the benefits of this study, which might have been coercive.

5.9 Risk-Benefit Ratio

Foreseeable risks might have been falls, fatigue and emotional distress during testing. The risk of falls was reduced by having participants walk close to the wall without touching and the author, as a physiotherapist, safeguarding them. Physical fatigue might have occurred as a result of travel, walking tests and questionnaires, so it was considered a moderate risk. To address fatigue, participants were allowed to rest at any time. Furthermore, it has been shown that motor fatigue is reversible and thus does not worsen the patients’ health condition (Mills and Young 2008). Mental fatigue might have occurred during the intervention, but the rhythmic-cued MI practice was short. In addition, MI has been shown to improve fatigue in pwMS. This study felt it unlikely that psychological distress would be caused during the assessments. In the case of severe distress, participants would have been transferred to a clinical psychologist at the MS Clinic, Innsbruck.
Other risks that might have been relevant to this study were travel-related incidents which were considered a low risk. This study took part in the Physiotherapy Department of the Clinical Department of Neurology, Innsbruck Medical University, thus emergency equipment and procedures were in place. The risk assessment was reviewed after the first set of data collection to ensure having captured and mitigated all relevant risks attached to this study. If any unexpected injury or adverse side effects had occurred during the study, treatment would have been provided and paid for. These types of possible but unforeseen risks were covered by an insurance policy.

The benefits of this study were not easy to predict; based on a literature search, it seemed that the intervention might have a positive impact on walking, fatigue and QoL in participants. If this were to be the case, and it appeared likely, participants in the corresponding intervention group would benefit directly. It was clearly stated to participants that this benefit might be achieved, but that it might not be definite, so as not to raise unrealistic expectations, nor to show any bias. By means of stratification for age, gender, disability and randomisation, the foreseeable risks and benefits of those participating in this study were rated to be equivalent.

5.10 Inconvenience, Payment and Reimbursement to Participants

Inconvenience to participants might have been caused by the travelling, in particular the time used for travelling. Nevertheless, only two extra visits at the MS Outpatient Clinic were required. In addition, travel (€ 0.42 or £ 0.34 per km) and parking costs were reimbursed to the participants. No extra payment was given to the participants.

5.11 Confidentiality

With regard to confidentiality, all legislation and local policies were adhered to: the Data Protection Act (Redsell and Cheater 2001), Human Rights Act (Horton 2000), University of Brighton’s guidelines on handling and storage of research data (University of Brighton 2012), Austrian and Tyrolean Data Protection Acts (Bundeskanzleramt Österreich 2003; Republik Österreich 2000;) and Austrian Physiotherapists’ Core Standards and Code of Conduct (Physio Austria, Bundesverband der PhysiotherapeutInnen Österreichs 2010). Only the PI and author had and have access to the data in addition to the academic
supervisors. Clinicians working at the MS Clinic who helped with recruitment had access to the personal data of the participants as part of their clinical routine. They were bound by the Austrian Data Protection Act (Republik Österreich 2000), as above.

All personal data were anonymised by a participant ID, so it is not at all possible to trace the participants’ identity. All files and data are saved on a password protected computer and the anonymisation procedure is saved on a password-protected folder. Passwords are kept secret and secure, and they are regularly changed. Data and files are securely stored in a locked filing cabinet in a locked room. Data were transported by the researcher and were not transferred via emails or to other countries, and they were only used for the purposes for which they were collected. Participants were informed about their right to disclosure for their own data even if these data lacked clinical utility. Results of this trial were not disclosed to participants until the study’s conclusion. Anonymised data will be kept for ten years following completion of the study.

5.12 Anonymity

All personal data (names, birth dates, locations amongst others) were anonymised with a participant ID; they will remain undisclosed and will not be published after study completion. The demographic data collected included age, gender and disability because they were required for the stratification process.

5.13 Control Group – Equipoise

The study was carried out according to the principle of equipoise, a concept first described by Hill (1963). Equipoise is defined as true uncertainty about which of the interventions or control in a controlled trial is most likely to benefit the participant (Freedman 1987; Schafer 1982). The equipoise concept requires research to be conducted with a goal to resolve existing uncertainties (Mhaskar, Bercu & Djulbegovic 2013). In this research, a comparison was required between the efficacy of music- and verbally-cued MI, to metronome- and verbally-cued MI, to no treatment with the control group. From the outset, it was unclear whether any of the interventions would lead to significant improvements in walking, fatigue and QoL when compared to the control group.
Benefits and burdens of this research were as fairly distributed as possible because participants of the control group (and the possible non-effective intervention group) were proposed to immediately receive the treatment if it was proven to be effective. It was explained to those taking part in the control group that they were as important as the treatment groups because this allowed a comparison whether the intervention was effective or not. Because this latter fact might have affected recruitment, the estimated sample size was set 10% bigger than the calculated sample size to allow for 10% attrition. Participants of the intervention and control arms of the study were recruited from the same population.

5.14 Insurance

The operating company, Innsbruck Medical Hospital including the MS Clinic (Tirol Kliniken GmbH), holds an insurance policy with the Zuerich Versicherungs-Aktiengesellschaft in Vienna, Austria, which covers research that is conducted by PhD students and includes employer´s liability, professional indemnity and public and products liability. The Policy Number is 07208763-1.

5.15 Summary

This study was conducted in compliance with international and national UK and Austrian legislation. First and foremost, a proper study design and due respect to participants was essential for the ethical conduct of this research. Beauchamp and Childress´ (2009) four ethical principles were adhered to in this study.
Chapter 6 – Study Design Considerations

Recommendations from the Consolidated Standards of Reporting Trials' (CONSORT) Statement (Schulz et al, 2010) and Standard Protocol Items and Recommendations for Interventional Trials' (SPIRIT) Statement (Chan et al, 2013) were followed.

6.1 Construct Validity

By employing a pilot study, the construct validity of this study was tested and adjustments were made in two ways. Firstly, to avoid an order effect, assessments of the main study were conducted in a different order (Podsakoff et al, 2003). Secondly, as predefined, a stratified block randomisation was used for the main study to ensure a balanced allocation to groups, and thus very similar groups.

To conquer threats to construct validity (Black 1999), predefined inclusion and exclusion criteria and sampling procedures involving permuted block randomisation and stratification were used. By having taken the stance of a detached observer, interaction with participants and bias should have been kept to a minimum. However, this thesis acknowledges that the author’s behaviour could have exerted a certain influence over the study participants. Only standardised, valid and reliable instruments were used, as discussed in Chapter 3.

6.2 Internal Validity

In the pilot study, by equivalent participant selection, data collection, measurement and statistical analysis in all groups, internal validity was guaranteed. In the main study, stratification for gender, age and disability was applied to allow for an equable distribution of participants to the treatment and control groups and to avoid the influence of confounding factors. Randomisation helped to ensure balanced baseline characteristics and limited selection bias (Turlik 2009).

A threat to internal validity in this study might have been measurement effects due to participant fatigue. To counterbalance this, in the main study, the walking tests and questionnaires were administered in a random order to reduce their influence on internal validity (Black 1999). Allocation concealment was performed in the main study by an independent researcher, using a computer-generated randomisation list.
with an allocation sequence and equal numbers of As, Bs and Cs on it (see Chapter 9.8.3). The goal of allocation concealment was to prevent selection bias (Chan et al, 2013). Blinding was not possible in this study as the whole study was performed by the author and participants were aware of which group they were allocated to.

Intention-to-treat analysis was performed to provide unbiased comparisons among groups and to limit attrition effects (Hollis and Campbell 1999). It is commonly used to ensure the analysis of all participants within the groups to which they were originally randomly assigned (Turlik 2009). All participants enrolled in this study were either analysed or, in the case of withdrawal or exclusion, accounted for after study completion to avoid analysis bias and to reduce type I error (Turlik 2009); a type I error refers to the incorrect rejection of a true null-hypothesis, that is, ‘false positive’ results (Hutson and Wilding 2012).

To control the threat of history, participants in the control group were also assessed after four weeks, a time matched to the intervention period of the intervention groups. The use of a control group in this study helped to control maturation.

6.3 External Validity

This thesis recognises that the results from the pilot study are to be treated with caution and as preliminary measure because of the small sample size. For the main study, a conservative sample size calculation was carried out to ensure a high power (90%) and to avoid a type II error; a type II error refers to the failure of rejecting a false null-hypothesis, that is, ‘false negative’ results (Hutson and Wilding 2012). Patients with comorbidities that affect their walking were excluded from the study as this might have limited external validity (Dekkers et al, 2010). There was no age-limit in this study, but biological ageing processes in older participants might influence the MI and rhythm perception ability (Allali et al, 2014). Typically, older patients present with an EDSS above 4.5; hence, they were excluded from the study.

The study setting was the MS Clinic, Clinical Department of Neurology, Medical University of Innsbruck, Austria, a well-known and established neurological hospital for MS diagnosis and treatment. It seems possible that in a different setting, the adherence to the rhythmic-cued MI could have been different. The German language
was an inclusion criterion because German is the official language in Austria and so, the familiarisation procedure, questionnaires and instructions on the CDs were in German. Despite this fact, it seems probable that pwMS speaking other languages might be able to perform the MI if the CD was translated to their native languages. Ethnicity was not an exclusion criterion for this study, yet cultural differences may be a barrier to generalise the study results worldwide.

Adverse events and their reporting might also be a threat to external validity. In this study, no adverse events occurred. Studies showed that a long study period over several months also invalidates external validity for reasons of non-adherence (Rothwell 2005) and instability; such a break could be due to the disease course or relapses of MS (Black 1999). This indicates that four weeks of study duration, as in this study, might be sufficiently short to avoid discouragement in participants. CONSORT flow diagrams (see Figures 6, 10, 19 and 24) show detailed information of participants assessed for eligibility, group allocation, attrition and analysis (Tonino et al, 2009).

6.4 Statistical Conclusion Validity

Strategies to avoid threats to statistical conclusion validity in this study were as follows. (1) $\beta$ (power) of the main study was set to 90% and $\alpha$ to 5% to ensure high validity. (2) For the analysis, non-parametric tests were chosen for ordinal variables and non-normally distributed data. For continuous data, parametric tests were used. (3) Multiple comparisons between data in the 3 groups of the study were treated with a post-hoc test (Bonferroni’s correction). (4) All assessments used showed a high reliability and validity. (5) The intervention of both intervention groups was implemented equally, (6) and all measures were taken equally. (7) Rigorous inclusion and exclusion criteria were applied.

6.5 Reliability

In Chapter 3, the reliability of measures chosen for this study is described in detail. All instruments have moderate to excellent test-retest reliability, and there are moderate to strong correlations between measures of similar constructs. Inter-rater reliability
does not apply to this study because all assessments were administered by the researcher.

6.6 Objectivity

Relationships among the independent variables which are interventions A and B and controls C, and the dependent variables of walking speed, distance and perception, fatigue and HRQoL were described after representative sampling. Participant recruitment, intervention and data collection were consistently performed and transparently described for other researchers to be reproduced (Kerlinger 1986). Questionnaires were used with objective question statements, so that the wording of questions avoided any motivation to one type of answer (Black 1999). During the 6MWT, only standardised encouragement in an even tone was used as recommended by the American Thoracic Society (A. T. S. Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories 2002) whereas the T25FW being part of the MS Functional Composite (MSFC) was carried out following MSFC (Cutter et al, 1999) instructions. The use of walking aids (canes and crutches) was kept consistent for each participant, and their falls were reported. Phone calls were noted and adverse events amongst other occurrences during the study were reported. There could have been a possible influence on the participants by the author who conducted the whole study, however, a detached and as value-neutral as possible stance was adopted by her.

6.7 Clinical Trial’s Registration Number

The study was registered under the reference number: CCT-NAPN-24406, DOI 10.1186/ISRCTN67054113 (Seebacher et al, 2014).
Chapter 7 – Pilot Study 1 Methods

7.1 Introduction

In Chapters 7-9, Pilot Study 1 is outlined, followed by a description of Main Study 1 in Chapters 10-12.

The pilot study was a three-group, parallel, randomised controlled, single-centre trial. The study involved 30 randomly allocated participants in groups of 10. It was used to compare MI with music and verbal cueing, to MI with metronome cues and verbal cueing, against a control group receiving normal treatment or no treatment if it was not required. This means controls did not have any intervention apart from their routine and weekly phone calls as did all other participants. Participants in the intervention groups also received their normal medical or no treatment. The pilot study was conducted to provide information for the subsequent larger main study. Therefore, the sample size was based on the specific objectives of the study, rather than on the estimated effects of the interventions. However, both the primary and secondary outcomes were statistically analysed. The pilot study was also used to calculate the sample size for the main study and to investigate a potential difference between the two types of rhythmic auditory cues: music and metronome, both of which were accompanied by verbal cues, applied to stimulate MI.

Both studies used the same procedure as follows: all participant information, consent procedures and data collection took place at the MS Clinic at the Clinical Department of Neurology, Innsbruck Medical University in Austria, which has approximately 2,500 patients with MS under their care. It took place in the physiotherapy department of the above clinic where the floors were marked for the walking tests. The head of the MS Clinic was the PI, as described in Chapter 5.2. As a PhD student, the whole study was performed by the author.
7.2 Participants

7.2.1 Participant Selection

The recruitment process used unselected consecutive sampling and restricted randomisation from the MS Clinic, Innsbruck and was conducted over the period from 9 April to 16 June, 2014. A CONSORT flow diagram is shown in Figure 7.

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**Figure 7**: CONSORT Flow Diagram of Pilot Study 1.
The inclusion criteria consisted in pwMS according to revised McDonald’s criteria (Polman et al, 2011), as diagnosed by the Innsbruck MS Clinic using the ICD-10 (World Health Organization 2011). They all had a mild to moderate disability (according to the EDSS 1.5 to 4.5) (Kurtzke 1983), were aged eighteen years or over, included all MS phenotypes, any ethnicity and were German speaking.

The exclusion criteria involved: concomitant diseases affecting the rhythmic-cued MI and walking (such as orthopaedic symptoms or untreated hearing loss), a relapse of MS within the last three months, new drug or physiotherapy treatment known to affect walking within the last two months, known pregnancy, any overt cognitive deficits or depression, which had been diagnosed and documented by the MS Clinic of Innsbruck. Moreover, a relapse during the intervention period would have led to the exclusion from the study.

**Rationale for Inclusion and Exclusion Criteria:**

Inclusion and exclusion criteria were chosen to eliminate confounding factors and for the sample to be representative of the general MS population. Studies showed that pwMS have a compromised MI ability, particularly at higher levels of disability (Heremans et al, 2012a) and if they are cognitively impaired (Heremans et al, 2012a; Tabrizi et al, 2013a) or depressed (Tabrizi et al, 2014). There was also a discrepancy between actual and imagined movements in pwMS with minimal (EDSS <1.5) (Nogueira et al, 2013), mild (EDSS <3.5) (Tabrizi et al, 2013a) and moderate (EDSS <5) disability (Tacchino et al, 2013). Impairment in working memory crucially contributes to MI ability impairment (Schott 2012; Sung 2008), and pwMS are claimed to have a subtle reduction in working memory even in early stages of the disease (EDSS 1.0-3.5) (Mainero et al, 2004); with disability accumulation, working memory impairment becomes increasingly severe (Dineen et al, 2009; Huijbregts et al, 2006; Rogers and Panegyres 2007) even if there are no established cut-off points due to the variable nature of MS (Hoffmann, Tittgemeyer & von Cramon 2007). Cognitive impairment in pwMS correlates with disability progression (Lynch, Parmenter & Denney 2005; Patti et al, 2009). As such, persons with lower levels of disability (EDSS ≤4.5) and no depression or cognitive impairment were included in this study.
An EDSS of 1.5 refers to a patient with minimal signs on more than one out of 8 functional CNS systems, with functional systems including, among others, the pyramidal, cerebellar and brain stem systems (Kurtzke 1983). It has been found that people with an EDSS as low as ≥1.5 have walking impairment (Johansson et al, 2007; Kalron, Achiron & Dvir 2011; Martin et al, 2006; Nogueira et al, 2013; Phan-Ba et al, 2012; Sosnoff, Sandroff & Motl 2012). In these studies, balance, walking speed and walking endurance, step length and other gait parameters were evaluated, and they were found to be impaired. Therefore, people with minimal disability and an EDSS of ≥1.5 were included in the present study. PwMS and an EDSS of 4.5 are typically able to work full time with minimal help, but have a relatively severe disability, and they are unable to walk more than 300 metres without aid or rest (Kurtzke 1983), so that they may benefit from walking rehabilitation. People with severe MS were excluded from this study because they have a reduced capacity to practise MI (Heremans et al, 2012a), and they are unable to walk.

Only adults were investigated because motor learning works differently in the immature brain, which would make it inappropriate to include children. As there is no difference in the MS phenotype regarding walking impairment, all phenotypes were included. German is the official language in Austria, so validated questionnaires in German were used, which were standardised for Germany since they were not available for Austria. MI instructions were also in German.

Orthopaedic symptoms in the lower extremities compromise walking ability. Participants with a relapse of MS as an acute syndrome with specific treatment implications need to recover before recruitment. New drug or physiotherapy treatment affecting walking would have influenced the walking test results, and so study participation was possible after two months at the earliest. Pregnancy is a specific situation, and it can benefit the health status of women with MS probably for immunological reasons (Masera et al, 2015).

7.2.2 Sample Size

This was a pilot trial to provide information for the subsequent larger main study. The study involved 30 pwMS and was used to compare participants in three equally-sized groups, described above. The sample size was based on the specific objectives of
the study such as practicality, feasibility, acceptability, adverse events and preliminary results of the primary outcomes, rather than on the estimated effects of the interventions (Arnold et al, 2009). Pilot data were included in the analysis of the main study as no changes of the methods were required (Thabane et al, 2010). Results from the pilot primary outcomes were used to recalculate the main study sample size.

7.2.3 Recruitment

Recruitment used unselected consecutive sampling from the MS Clinic, Innsbruck and was conducted over the time period from 9 April to 16 June, 2014. Recruitment flyers advertised the study at the MS Clinic showing the author’s and the MS-Outpatient Clinic’s contact details. Eligible participants were informed by reception staff about the study during their regular visits and asked whether they agreed to receive a phone call from the author one week later. Further information was provided by the author, and potential participants were invited to take part in the study. They were handed participant information sheets and consent forms to enter the study. All participants were informed orally and in writing and were given at least seven days to consider their participation in the study (see Chapter 5 and Appendix 3).

7.2.4 Randomisation

Restricted randomisation was used whereby participants were allocated randomly. They were instructed to draw a sealed, opaque envelope from a black bag with 30 numbered envelopes, with the letters ‘A’, ‘B’ and ‘C’, which were consistent with the three study groups. Randomisation was restricted insofar as only 30 envelopes were in the bag. This procedure ensured that all participants had an equal chance of being in either group, with the exception of the last few participants when only a few envelopes remained in the bag. No stratification for age, gender and disability was performed because of the small sample size.

7.2.5 Allocation Concealment and Blinding

Blinding was not possible as participant recruitment, data collection, instructions, statistical analysis and writing were performed by the author. Participants realised which group they were assigned to. Within that randomisation procedure, concealment of allocation became redundant; it was not possible to have any
influence on the group allocation. Participants were instructed not to discuss allocation or intervention content with other participants and not to forward the study CDs to anybody.

7.3 Data Collection

All data were collected by the author who aimed at an objective measurement. Demographic data, such as age and sex were collected, in addition to the EDSS as a measure of disability. These data were used to see whether the group allocation was balanced. Adverse events were to be recorded at any time, such as when participants contacted the PI, which never occurred, or the author and during the weekly phone calls and at the measures. By use of an excel file, any events (relapses, withdrawals or adverse events) and participant feedback were recorded. For the data collection pre- and post-intervention, validated walking tests and patient-rated questionnaires on walking, fatigue and (HR)QoL were used, as described in Chapter 3. All assessments were taken at the same times of day because it was shown that there is a within-day variability for fatigue (Feys et al, 2012) and walking (Feys et al, 2013; Feys et al, 2014). To ensure comparability and to apply an equal procedure in all pilot study participants, the same test order was used.

7.3.1 Primary Outcomes

Primary outcomes were a change in walking speed, as measured by the T25FW (Kaufman, Moyer & Norton 2000) and a change in walking distance, as measured by the 6MWT (Goldman, Marrie & Cohen 2008). Analysis of the primary outcomes was used to re-calculate and confirm or amend the proposed sample size.

7.3.2 Secondary Outcomes

Secondary outcomes of this study were a change in walking perception, fatigue and (HR) QoL, as assessed by the MSWS-12 (Hobart et al, 2003), MFIS (Fisk et al, 1994), MSIS-29 (Hobart et al, 2001), SF-36 (Bullinger 1995) and EQ-5D-3L (EuroQuol 2013). All questionnaires were in German. Please find a clinical research file including data collection sheets in English in Appendix 8.
7.4 Intervention

The intervention of this study consisted of rhythmic-cued MI. In group A, MI was rhythmically cued by instrumental (karaoke) music at a regular beat. In group B, regular metronome cues were used with MI. In both intervention groups, rhythmic verbal cues accentuated the cueing, such as when using “step-step” or “toe-off”. For reasons of clarity, in this thesis, group A will be referred to as the ‘music-verbal-MI group’ and group B as ‘metronome-verbal-MI group’. In addition, the control group C will be referred to as ‘control group’.

After the randomisation and prior to the intervention, study participants were individually familiarised with the rhythmic-cued MI, depending on the group they were allocated to. Familiarisation with MI has been suggested in previous studies (Schuster et al, 2011; Wondrusch and Schuster-Amft 2013). These authors described the PETTLEP approach to MI in neurorehabilitation, involving the “Physical, Environmental, Task, Timing, Learning, Emotional, and Perspective” components of MI (Holmes and Collins 2001). The PETTLEP checklist is based on neuroscientific findings and was developed by Holmes and Collins (2001) for performance improvement in athletes. The PETTLEP elements concern 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 are related to the MI task, and the MI perspective. The PETTLEP ideas were applied to the context of the present study to enhance the effectiveness of the intervention. As this was a rhythmic-cued MI investigation, the cueing was used to provide an external temporal structure for the imagined walking, and designed to support the timing component.

Firstly, the participants were informed in lay language and after that theoretically about the concept of MI and its application in sports and neurorehabilitation. The new approach of rhythmic-cued MI was introduced. Examples of RAS were described (that is the music and metronome cues with gait training), plus their use in neurorehabilitation. Principles of neuroplasticity were explained with regard to the topics above. Secondly, participants also learned about the two perspectives (internal, first-person and external, third-person) and the modes of MI (kinaesthetic and visual).
Participants had the opportunity to try them out for themselves and become aware of their preferred mode or perspective. The researcher placed emphasis on internal, kinaesthetic MI, which was adopted for this study. During the training, participants were asked for MI content characteristics such as the mode and perspective they were using, for the environment or for movement aspects they were imagining. Moreover, the duration of the actual and imagined walking performance was compared to control the mental process (Wondrusch and Schuster-Amft 2013). Participants were asked to walk a six-metre distance along the marked hallway while the time was measured. After that, they were asked to imagine themselves walking the same six-metre distance and indicate when they had reached their mental finishing point. The time was measured and reported back to them. If participants wished, they could repeat the latter 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 breathe 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 music-verbal-MI group, external timing was provided: “imagine yourself walking in time with the music and verbal cues”. In the metronome-verbal-MI group, external timing was provided: “imagine yourself walking in time with the metronome and verbal cues”. In both intervention 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.

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.

These MI instructions with music or metronome cues were on a CD prepared for this study by the researcher, 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 six times a week and once a day for seventeen minutes over four 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 (Thaut 2005) and to facilitate adherence, so that four mixes, designed in the same way, were on one CD (see Chapter 2.14). 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
(Catalan et al, 2011; Jackson et al, 2001; Schuster et al, 2011). The frequency of six times per week was chosen according to evidence (Peiris et al, 2013) and a Cochrane review (Rietberg et al, 2005). A systematic literature review on best practice of MI recommended a training period for more than two weeks to be able to distinguish true differences between groups (Schuster et al, 2011). The actual practice frequency was noted in a diary but could not be directly assessed. Weekly participant reports on their practice frequency were recorded.

Participants in the control group received their normal or no treatment, as did all participants, for the same period of time, and their phone calls, which means that controls had phone calls in addition to their normal treatment. Controls were asked about their condition and well-being, the same as all other participants.

An detailed intervention script is presented in Appendix 9, Table A2, and was based on the Template for Intervention Description and Replication (TIDieR template) (Hoffmann et al, 2014).

7.4.1 Motor Imagery plus Music and Verbal Cueing

Cueing of the MI in the music-verbal-MI group 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 (Thaut 2005; Thaut and Rice 2014): 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. Music cueing was enhanced by rhythmic verbal cues of the researcher (Rice and Johnson 2013; Schulz et al, 2006). 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”) (Edwards 2011). 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. A similar approach was also used by Rice and Johnson (2013).
Moderately syncopated music with a pronounced beat and pleasing melody and harmony was selected, following recent studies showing that listening to moderately syncopated music enhances SMS (Karageorghis and Priest 2012; Witek et al, 2014). Suitable rhythmical sequences at 80-120 BPM were cut together and mixed with instructions on MI of walking, and which were provided on the CD. Various music tempos were chosen because of inter-individual differences in walking tempo, and people with mild MS are expected to walk faster than people with moderate MS (see Chapter 2.9). According to the Austrian State Authorized Society of Authors, Composers and Music Publishers (AKM) (Parnreiter-Mathys 2013), no copyright permission was required as the music was used for research purposes only.

7.4.2 Motor Imagery plus Metronome Cues and Verbal Cueing

In the metronome-verbal-MI group, cueing of the MI was provided by regular metronome cues in different tone pitches and verbal cueing while applying exactly the same procedure described above. Thereby, the tempo of the metronome cues was matched with the tempo of the music beat.

7.4.3 Phone Calls

Participants in all groups received weekly phone calls from the author. Calls were implemented to provide support with the MI, record any participant feedback, adverse events or health problems such as relapses from MS, which would have led to exclusion from the study. Another reason was to remind participants to do the MI and of their second assessment at the MS Clinic. Questions that were asked during the phone calls are shown in Appendix 10.

7.5 Data Analysis

7.5.1 Statistical Analysis

The statistical analysis of this study was based on the research question (Chapter 1.3) and null-hypotheses (Chapter 1.7). All statistics were performed using IBM SPSS software, release 21.0, Armonk, New York, and GraphPad Prism 6, San Diego, California. Descriptive statistics were reported for the demographic data, primary and secondary outcomes: the mean values ±SD were reported for continuous outcomes.
(walking speed and walking distance). Medians (min, max) were reported for ordinal data (participant compliance, walking perception, fatigue and (HR)QoL), and counts (number or participants) for nominal data (gender, 2 age groups (under 40 years and 40 years and over), 2 EDSS groups (EDSS 1.5-3.0 and EDSS 3.5-4.5)).

The CONSORT Statement (2010), the CONSORT Explanation and Elaboration and numerous articles have emphasised that testing for baseline differences between groups in RCTs is not appropriate (De Boer et al, 2015; Knol, Groenwold & Grobbee 2012; Moher et al, 2010a, 2010b; Schulz et al, 2010; Senn 1994). They argued that in consideration of an accurately performed randomisation procedure, any baseline differences between the study groups occurred due to chance. This is because when participants were randomly allocated to groups, it is already known that the groups were selected at random from the same population. Further, significant baseline differences do not influence or threaten the validity of the study results. However, particularly in small studies, randomisation can produce unbalanced groups. To limit selection bias due to systematic differences in baseline characteristics, it is, hence, essential to assess potential imbalance using relevant descriptive statistics, based on clinical judgement (Corbett, Higgins & Woolacott 2014; Roberts and Torgerson 1999). Therefore, in this thesis, baseline data were reported descriptively and without p-values.

Statistical significance was defined as two-tailed p-values ≤0.05. T25FW and 6MWT data were tested for normal distribution using the Shapiro Wilk test, Q-Q-Plots and histograms that showed approximately normally distributed data. T25FW and 6MWT data were tested for Sphericity (Mauchly’s test) and homogeneity of variance (Levene’s test). The within-subject factor was time (pre- and post-intervention) and the between-subject factor was groups (music-verbal-MI, metronome-verbal MI and control groups). In order to test the effect of the intervention on walking speed and walking distance (dependent variables), a 2-Way Mixed Design Analysis of Variance (ANOVA) was applied. Assumptions for this test are shown in Table 4 and were met. If the analysis revealed statistical significance, post-hoc Bonferroni adjustment was performed to determine the differences in pairwise comparison (Field 2009). Bonferroni was chosen as it is the most conservative post-hoc test particularly for small samples. A Chi-Square test was applied to evaluate the number of participants
with and without a clinically significant improvement in walking speed and walking distance across groups.

<table>
<thead>
<tr>
<th>Assumption No.</th>
<th>Assumption Content</th>
<th>Met in this Study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dependent variables at the continuous level</td>
<td>Yes: T25FW: seconds, 6MWT: metres</td>
</tr>
<tr>
<td>2</td>
<td>Within-subject factor should consist of at least two categorical related groups</td>
<td>Yes: time: pre- and post-intervention</td>
</tr>
<tr>
<td>3</td>
<td>Between-subjects factor independent variable should each consist of at least two categorical independent groups</td>
<td>Yes: 3 independent groups (music-verbal-MI, metronome-verbal-MI and control groups)</td>
</tr>
<tr>
<td>4</td>
<td>No significant outliers in any group of the within-subject factor or between-subject factor</td>
<td>Yes: a check for outliers using ‘studentised residuals’ showed no significant outliers</td>
</tr>
<tr>
<td>5</td>
<td>Approximately normally distributed data in terms of the dependent variable</td>
<td>Yes: approximately normal according to Q-Q-Plots and normality tests</td>
</tr>
<tr>
<td>6</td>
<td>Homogeneity of variances of the paired differences (post-minus pre-intervention T25FW, 6MWT data) of all groups were equal, for each combination of the groups of the two factors: 1) within-subject factor, 2) between-subject factor</td>
<td>Yes: 1) as the within-subject factor had only 2 cells, then Mauchly’s W=1, so no significance test for Sphericity was needed. Yes: 2) Levene’s test for homogeneity of variance of the between-factor was non-significant.</td>
</tr>
</tbody>
</table>

**Table 4:** How 2-Way Mixed Design (Factorial) ANOVA Assumptions were Met in this Study (Field 2009; Lund and Lund 2013).
Walking perception, fatigue and (HR)QoL were dependent variables on an ordinal scale; thus, parametric test assumptions were violated. As there is no nonparametric equivalent to the 2-Way Mixed Design ANOVA, a different strategy was chosen. To calculate the difference in individual changes between groups, a Kruskal Wallis test was applied. Nonetheless, the Kruskal Wallis does not show the differences between pre- and post-intervention and the time X group interaction. As such, a ratio from post-intervention (PI) and baseline (BL) data of secondary outcome values was tried (PI/BL values). The problem was that all subscales included zero-values; therefore, a ratio calculation was impossible. To overcome this problem, the differences between post- and pre-intervention values were calculated (PI-BL values), and new variables were computed from all walking perception, fatigue and (HR)QoL subscales. Based on these new variables, a Kruskal Wallis test with a post-hoc Bonferroni correction for multiple comparisons was performed. The assumptions for a Kruskal Wallis test were met, which require the dependent variable to be on ordinal or continuous scale, and the independent variable to consist of two or more categorical and independent groups.

The sample size of the main study was recalculated using PS Power and Sample Size Calculation version 3.1.2, 2014 (Dupont and Plummer 1990, 1998). A statistical analysis was performed by the researcher with statistical advice from the University of Brighton in addition to the author’s participation in the University of Brighton’s quantitative research and statistics module, and with help from statistics’ textbooks. As justified earlier, data from the pilot study were used for the main study. Intention-to-treat analyses were used, as described in Chapter 7.5.3 (Turlik 2009).

7.5.2 Missing Data

There are several types of missing data, which are concisely introduced to state how they were dealt with in this study, as suggested by relevant literature (Enders 2010; Little and Rubin 2002). Missing data can be completely at random (MCAR) in the case when participants overlook answering a random question in a questionnaire. With these data, the probability that an observation is missing is not related to the value of the observation or other variables in the analysis. With data MCAR, meaningful and unbiased results can still be produced.
Data can be considered missing at random (MAR), if they meet the requirement that their absence does not depend on the value of observation after controlling for another variable. For example, participants would refuse to answer the question on the urgency of toilet use in the MSIS-29 because they felt ashamed, and not because this question was related to the intervention. With MAR data, meaningful and unbiased parameter estimates can continue to be generated.

If data are classified as missing not at random (MNAR), this information would produce biased study results as the probability of a missing value depends on the variable that is missing. To show an example, if some of the participants have mental problems, there will be a higher probability that they leave out questions about their mental health. These missing data would have a decisive impact on the dependent variables. A model is required to produce unbiased results. As discussed below, the most conservative approach was chosen to solve any occurring problems with MNAR in the main study.

During data collection in the pilot study, every clinical research file was checked for completeness. If questions were unanswered, participants were asked to complete them, which was a procedure appreciated by participants. Files were checked by the author for missing answers also in the main study. Nevertheless, should there have been any missing data they would have been addressed in various ways:

a) User-defined “missings” (data MCAR and MAR) were predefined in SPSS before analysis (“-9”, “-99”, “-999”).

b) For data MNAR, missing values would have been replaced with the sample mean or mode with subsequent analysis as if all data were complete. Disadvantages of the method would have been that: firstly, variability would have been reduced; and secondly, covariance and correlation estimates in the data were weakened as the relationship between variables was ignored. These disadvantages would have been reduced when both the mean and mode were tried.

c) The “exclude cases pairwise” option in SPSS, which is a list-wise deletion of data, was selected if there was no post-intervention data. This means that the whole case was removed from the analysis.
d) An intention-to-treat analysis was performed for all participants referred to in the next paragraph.
e) Missing data were reported in the writing.

### 7.5.3 Intention-to-Treat Analysis

A recent systematic review (Alshurafa et al, 2012), showed that there is no consensus on intention-to-treat analysis even between trial methodology experts and authorities such as the CONSORT expert group (Moher, Schulz & Altman 2001), the Cochrane Collaboration (Elkins and Moseley 2015) and the American Statistical Association Group (Fisher et al, 1990). Alshurafa and co-workers summarised three relevant definitions from guidelines and the research literature; Table 5 shows how these were met in the current study.

<table>
<thead>
<tr>
<th>Intention-to-treat approach</th>
<th>Requirements</th>
<th>Met in this study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete follow-up</td>
<td>100% post-intervention data is absolutely necessary</td>
<td>Yes: post-intervention data were complete; attrition was 0%.</td>
</tr>
<tr>
<td>Specific strategy for missing outcome data</td>
<td>Missing outcome data must be imputed according to the state-of-the-art methods and whether they are explicitly described</td>
<td>Yes: there were no missing data. See Chapter 7.5.2 for pre-defined methods to address missing data.</td>
</tr>
<tr>
<td>Different approach to intention-to-treat analysis and missing outcome data</td>
<td>Intention-to-treat analysis is performed by an analysis of the data as randomised, regardless of the missing outcome data approach</td>
<td>Yes: the data were analysed as randomised.</td>
</tr>
</tbody>
</table>

**Table 5:** How Established Definitions of Intention-to-Treat Analysis were Met in this Study (Alshurafa et al, 2012).
Chapter 8 – Pilot Study 1 Results

8.1 Recruitment Rates and Feasibility

The feasibility of the main study was assessed on recruitment rates. According to the research proposal and ethics approval, the maximum time for the pilot and main study was twenty-two months, given the additional four months for data analysis and interpretation. The sample size for the pilot study was n=30 and for the subsequent main study n=112-150. From this, there followed a minimum recruitment rate of seven participants per month. Three participants per week could be recruited into the pilot study so that a larger study was regarded as feasible.

8.2 Baseline Data

Demographic data, such as age and gender, were collected in addition to the EDSS (Kurtzke 1983). Twenty-two females and eight males were included in the study, representing a female-to-male ratio of 2.75:1 corresponding to previously reported data from the UK with 2.4:1 (Mackenzie et al, 2014) and Austria with 2.7:1 (Trojano et al, 2012). For the music-verbal-MI group, only females were assigned whereas for the control group, as many females as men were allocated, which reflected an imbalance in gender between groups. For the metronome-verbal-MI group, seven females and three males were allocated, which corresponded to female-to-male ratios introduced above. Apart from gender, no other imbalance in groups was seen in the study population. The baseline data are shown in Table 6.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=10</th>
<th>Metronome-verbal-MI group N=10</th>
<th>Control group N=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F:M)</td>
<td>10:0</td>
<td>7:3</td>
<td>5:5</td>
</tr>
<tr>
<td>Age (years)¹</td>
<td>47.32±12.48</td>
<td>41.81±9.75</td>
<td>46.15±8.89</td>
</tr>
<tr>
<td>Age groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 40</td>
<td>N=3</td>
<td>N=5</td>
<td>N=3</td>
</tr>
<tr>
<td>40 and over</td>
<td>N=7</td>
<td>N=5</td>
<td>N=7</td>
</tr>
<tr>
<td>EDSS²</td>
<td>3 (1.5, 4.5)</td>
<td>2.5 (1.5, 4.5)</td>
<td>2.5 (1.5, 4.0)</td>
</tr>
<tr>
<td>Disability groups</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS 1.5-3.0</td>
<td>N=6</td>
<td>N=7</td>
<td>N=8</td>
</tr>
<tr>
<td>EDSS 3.5-4.5</td>
<td>N=4</td>
<td>N=3</td>
<td>N=2</td>
</tr>
<tr>
<td>T25FW¹ (s)</td>
<td>6.1±2.1</td>
<td>5.4±1.2</td>
<td>5.2±1.2</td>
</tr>
<tr>
<td>6MWT¹ (m)</td>
<td>453.1±123.1</td>
<td>428.2±105.4</td>
<td>484.7±119.1</td>
</tr>
<tr>
<td>MSWS-12²</td>
<td>55.2 (10.4, 97.9)</td>
<td>51.0 (16.7, 68.7)</td>
<td>45.8 (0.0, 64.6)</td>
</tr>
<tr>
<td>SF36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw change²</td>
<td>3.0 (1.0, 5.0)</td>
<td>3.0 (2.0, 4.0)</td>
<td>3.0 (1.0, 4.0)</td>
</tr>
<tr>
<td>Phys funct²</td>
<td>50.0 (15.0, 100.0)</td>
<td>62.5 (30.0, 90.0)</td>
<td>60.0 (10.0, 100.0)</td>
</tr>
<tr>
<td>Phys role funct²</td>
<td>37.5 (0.0, 100.0)</td>
<td>25.0 (0.0, 100.0)</td>
<td>25.0 (0.0, 100.0)</td>
</tr>
<tr>
<td>Bodily pain²</td>
<td>62.0 (20.0, 100.0)</td>
<td>82.0 (41.0, 100.0)</td>
<td>71.0 (22.0, 100.0)</td>
</tr>
<tr>
<td>General health percept²</td>
<td>56.0 (42.0, 77.0)</td>
<td>72.0 (47.0, 82.0)</td>
<td>72.0 (25.0, 97.0)</td>
</tr>
<tr>
<td>Vitality²</td>
<td>40.0 (15.0, 75.0)</td>
<td>47.5 (35.0, 75.0)</td>
<td>37.5 (30.0, 100.0)</td>
</tr>
<tr>
<td>Social role funct²</td>
<td>62.5 (37.5, 87.5)</td>
<td>93.7 (50.0, 100.0)</td>
<td>87.5 (50.0, 100.0)</td>
</tr>
<tr>
<td>Emotional role funct²</td>
<td>0.0 (0.0, 100.0)</td>
<td>83.3 (0.0, 100.0)</td>
<td>50.0 (0.0, 100.0)</td>
</tr>
</tbody>
</table>

Table 6: Participants’ Baseline Characteristics in the Pilot Study 1.
<table>
<thead>
<tr>
<th></th>
<th>Mean ± standard deviation</th>
<th>Median (Min, Max)</th>
<th>Median (Min, Max)</th>
<th>Median (Min, Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mental health</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phys sum</td>
<td>64.0 (24, 8)</td>
<td>76.0 (56.0, 92.0)</td>
<td>76.0 (40.0, 100.0)</td>
<td></td>
</tr>
<tr>
<td>Mental sum</td>
<td>41.4 (26.4, 63.3)</td>
<td>39.9 (28.1, 56.0)</td>
<td>42.8 (24.0, 57.4)</td>
<td></td>
</tr>
<tr>
<td><strong>EQ-5D-3L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index value</td>
<td>41.8 (22.7, 53.8)</td>
<td>51.1 (41.8, 64.0)</td>
<td>52.0 (35.3, 63.9)</td>
<td></td>
</tr>
<tr>
<td>VAS score</td>
<td>41.4 (26.4, 63.3)</td>
<td>39.9 (28.1, 56.0)</td>
<td>42.8 (24.0, 57.4)</td>
<td></td>
</tr>
<tr>
<td><strong>MSIS-29</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phys sub</td>
<td>24.1 (1.0, 31.0)</td>
<td>17.5 (8.0, 27.0)</td>
<td>18.0 (0.0, 25.0)</td>
<td></td>
</tr>
<tr>
<td>Psych sub</td>
<td>25.0 (2.8, 55.6)</td>
<td>13.9 (5.6, 63.9)</td>
<td>20.8 (0.0, 52.8)</td>
<td></td>
</tr>
<tr>
<td><strong>MFIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phys sub</td>
<td>19.5 (1.0, 31.0)</td>
<td>17.5 (8.0, 27.0)</td>
<td>18.0 (0.0, 25.0)</td>
<td></td>
</tr>
<tr>
<td>Cognitive sub</td>
<td>14.5 (2.0, 30.0)</td>
<td>9.0 (0.0, 24.0)</td>
<td>14.0 (0.0, 21.0)</td>
<td></td>
</tr>
<tr>
<td>Psychosocial sub</td>
<td>4.5 (0.0, 6.0)</td>
<td>3.0 (0.0, 4.0)</td>
<td>3.5 (0.0, 6.0)</td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>35.0 (3.0, 67.0)</td>
<td>32.0 (17.0, 50.0)</td>
<td>33.5 (0.0, 48.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6** (Continued): Participants’ Baseline Characteristics Pilot Study 1.

Abbreviations: F:M = female:male ratio; N = number of participants; T25FW = Timed 25-Foot Walk; s = seconds; 6MWT = 6-Minute Walk Test; EQ5D3L = EQ-5D-3L: Index = Index value; VAS = Visual Analogue Scale; MSIS-29 = MS Impact Scale-29: physical and psychological subscales; MFIS = Modified Fatigue Impact Scale; m = metres; SF-36 = Short Form-36 Health Survey: phys (role) funct = physical (role) functioning; funct = functioning; phys = physical; sum = sumscale; sub = subscale; general health percept = general health perceptions.

1 Mean ± standard deviation; 2 median (min, max). Colour coding: yellow = walking outcomes; blue = (HR)QoL outcomes; green = fatigue outcomes. **Red coloured questionnaires/tests: lower numbers indicate better performance; blue coloured questionnaires/tests: higher numbers indicate more positive health status.**
8.3 Safety, Acceptability and Adherence to the Programme

No safety-related events occurred during the assessments. Participants could use walking sticks if needed and rest at any time during instructions and assessments. The home-based intervention could be practised while seated and was reported by the participants to be safe and convenient. Thus, the author had to rely on reported adherence which was a median of five (out of a range of four to six) times per week. Ten participants were in the control group and not required to practise.

Phone calls showed that one participant had initial difficulties with the kinaesthetic MI, but these problems were solved with practice. Two participants reported concentration deficits, which also improved with practice. One participant in the music-verbal-MI group reported that her ability to perform MI decreased with increasing musical complexity. No other participants reported problems, and a majority of the participants in the music-verbal-MI group and some in the metronome-verbal-MI group reported the intervention as pleasurable. To summarise, the intervention was regarded as acceptable despite some initial barriers, which were worthy of further investigation in the main study.

8.4 Adverse Events, Missing Data and Attrition

No adverse events were reported in this study. There were no missing data, an attrition rate of zero and no relapses of MS.

8.5 Primary Outcomes

Descriptive data of the primary outcomes in all groups, pre- and post-intervention are shown in Table A3 (see Appendix 11). As can be seen, in both intervention groups, the mean time to walk decreased, that is, the walking speed increased, and the mean walking distance increased when compared to the control group.

Regarding hypothesis 1, rhythmic-cued MI improved walking speed, as assessed by the T25FW when compared to controls. The overall interaction between the groups at baseline and post-intervention was statistically significant, with a large partial eta squared effect size $\eta^2=0.43$ (Pierce 2004): $F(2,27)=10.254$, $p<0.001$. Participants in the music-verbal-MI ($p=0.007$) and metronome-verbal-MI ($p=0.007$) groups walked
significantly faster than those in the control group. Neither music nor metronome cued MI was superior to the other (p=1.0). This means that rhythmic-cued MI improved walking speed when compared to the controls. The improvement seen in the music-verbal-MI group was from 6.1±2.1 seconds at baseline to 5.2±2.1 seconds at post-intervention. In the metronome-verbal-MI group, participants walked 5.4±1.2 seconds at baseline and 4.5±1.1 seconds at post-intervention when compared to controls who walked 5.2±1.2 seconds at baseline and 5.5±1.4 seconds at post-intervention. Three participants in both the music-verbal-MI and metronome-verbal-MI groups, but no participant in the control group, showed a clinically meaningful improvement of ≥20%, as shown in Table A4 (see Appendix 11).

Referring to hypothesis 2, rhythmic-cued MI improved walking distance as measured by the 6MWT when compared to controls. The overall interaction between the groups at baseline and post-intervention was statistically significant with a large effect size: F(2,27)=18.295, p<0.001, η²=0.57. Participants in the music-verbal-MI (p<0.001) and metronome-verbal-MI (p<0.001) groups walked a greater distance when compared to the control group. In other words, rhythmic-cued MI improved walking distance when compared to the controls. The improvement seen in the music-verbal-MI group was from 453.1±123.1 metres at baseline to 521.1±129.1 metres at post-intervention. In the metronome-verbal-MI group, participants walked 428.2±105.4 metres at baseline and 521.1±93.6 metres at post-intervention when compared to the control group who walked 484.7±119.1 metres at baseline and 475.3±126.4 metres at post-intervention. Neither music- nor metronome-cued MI was superior to the other (p=0.57). Two participants in the music-verbal-MI group and 6 participants in the metronome-verbal-MI group, but no participant in the control group had a clinically meaningful improvement of ≥20%, with a significant difference between the metronome-verbal-MI and control groups (p=0.033), as shown in Table A4 (see Appendix 11).

Individual changes in the time to walk, related to walking speed, and walking distance for all participants in the intervention and control groups are presented in Figures 8, A and B.
**Figure 8, A and B**: Effect of Intervention on the Time to Walk (A) and Walking Distance (B) (Pilot Study 1).

Figures legend: individual participants are shown as symbols (circles = baseline, squares = post-intervention), means are indicated by bars (grey = baseline, white = post-intervention). Square brackets on top of the figures indicate significant group X time interactions; *significant at the 0.05 level; **significant at the 0.01 level; ***significant at the 0.001 level.

**8.6 Secondary Outcomes**

Descriptive information of all secondary outcomes was used to show individual data changes, as presented in Figures 9, A-R.
Figure 9, A-R: Descriptive Data of Secondary Outcomes (Pilot Study 1).

Figure legend: individual participants are shown as symbols (circles = baseline, squares = post-intervention); medians are indicated by bars (light grey = baseline, ORIGINAL IN COLOUR
dark grey = post-intervention). Music = music-verbal group; metronome = metronome-verbal group; control = control group. Abbreviations: SF36 = Short Form-36 Health Survey; MFIS = Modified Fatigue Impact Scale; MSIS-29 = MS Impact Scale-29.

A statistically significant difference was observed in SF-36 social role functioning in the music-verbal-MI group when compared to the control group (H=11.700, 2 df, p=0.005). There was also a significant difference in SF-36 mental health scores in the music-verbal-MI group compared to the control group (H=11.700, 2 df, p=0.008) and in the metronome-verbal-MI group when compared to the control group (H=9.450, 2 df, p=0.047). Finally, there was a significant difference in SF-36 mental sumscale scores in the music-verbal-MI group compared to the control group (H=10.200, 2 df, p=0.029). The MFIS physical subscale showed a trend for improvement (p=0.068), evidenced by p-values between 0.05 to 0.10 (Bangalore and Messerli 2006).

As only a few HRQoL measures (SF-36 social role functioning, mental health and mental sum scale) were statistically significant; one cannot speak of clinically significant changes in HRQoL. There were no significant changes in walking perception, fatigue and QoL. Results from the analysis of secondary data are shown in Table A5 (see Appendix 11).

A graphical display of statistically significant secondary outcome data is shown in Figures 10, A-C.
Figure 10, A-C: Health-Related Quality of Life: Social Role Functioning (A); Mental Health (B); Mental Sumscale (C) (Pilot Study 1).

Figures legend: square brackets indicate significant group X time interactions; *significant at the 0.05 level; **significant at the 0.01 level.
Chapter 9 – Discussion of Pilot Study 1 Findings

9.1 Introduction

Methods to use in the main study were piloted in this study to provide a justification for their use or change in the main study. In the following discussion, the pilot study results will be interpreted, and any issues that arose during participant recruitment, data collection, intervention and analysis will be discussed. Implications for the main study resulting from the pilot study will be outlined.

9.2 Trial Feasibility: Recruitment Rates, Attrition, Missing Data

Three participants per week could be recruited to the study. The reasons for this rapid recruitment might be, first and foremost, the well-known site of the MS Clinic Innsbruck, which is one of the three largest research and treatment centres in Austria. Secondly, the home-based study setting might be another reason as participants only had to travel twice to the MS Clinic. Further, no foreseeable risks were associated with the study. Finally, the study had clear-cut, but not too strict eligibility criteria, which could have affected recruitment (Khan, Preskorn & Baker 2005). Therefore, it was expected that it would be possible to recruit up to 150 participants in the main study.

In physiotherapy studies, attrition rates varied greatly from 4% (Romberg, Virtanen & Ruuttiainen 2005) to 51% (Schmidt and Wonneberger 2014). In this study, all participants completed the study which might be associated with the nature of the intervention and the weekly phone calls. However, a 0% attrition rate is not expected for the larger main study. There were no missing data since the questionnaires were immediately checked for completeness by the author, and the participants were asked to fully complete them. This procedure was continue to be used in the main study.
9.3 Intervention and Assessment Safety, Acceptability and Adherence

The intervention of this study was home-based. This thesis acknowledges that this setting might have had an impact on adherence in two respects. Firstly, participants were responsible for complying with the practice frequency of six times a week for four weeks. The author had to rely on participant adherence reports; however, it would not be practical to supervise participants on a six-times-a-week basis. Further, the setting seemed to have been beneficial particularly for more disabled participants because they were not required to travel for the intervention. The cued MI practice was performed in a sitting position, which contributed to convenience of participants and their safety. During the assessments, no falls or other safety-related events occurred, probably since participants were safeguarded by the researcher during the walking tests and allowed to rest at any time.

Participants in the intervention groups appreciated the telephone support on the cued MI practice. Any problems with kinaesthetic imagery seemed to have been solved. Participants in the music-verbal-MI group reported the intervention to be motivating or even pleasurable. Some participants reported to have had problems with concentration on the MI, which substantially improved after a few days of practice. These participants stated that the author’s rhythmic verbal cueing helped them to concentrate on the tasks. Participants in the metronome-verbal-MI group reported that the clear metronome beat helped them with MI and also with their actual walking. This facilitation effect seemed to have been enhanced by the verbal cueing so that participants in both intervention groups reported to have virtually heard the cueing and the words in their head during actual walking after having heard them on the CD.

Some participants in the metronome-verbal-MI group reported a slight boredom with the practice in contrast to participants in the music-verbal-MI group. This is suggested to be related to the monotony of the metronome cues. Unfortunately, there were too few participants in the pilot study to draw any meaningful conclusions regarding the preparation of new CDs for the main study. Therefore, the same CDs were used for the main study. All participants appreciated the reminder about participating in the study and the post-intervention assessment appointments.
9.4 Effect of Rhythmic-cued Motor Imagery on the Primary Outcomes

In terms of the first and second hypotheses, the analysis of this study showed a significant effect of both interventions on walking. The speed measures were taken manually with a stopwatch, which may have led to random measurement errors of hundredths or tenth of a second although this measurement was recommended in the MSFC instructions. The larger sample size in the main study is expected to minimise the impact of the random measurement error (Stommel and Wills 2004).

From a patient viewpoint, an improvement in walking speed is only useful if it reaches clinical significance because only then can the intervention benefit the participants in their daily living. Based on clinical judgement, a 20% improvement was suggested to enhance patients' participation in society, and so would constitute a goal in physiotherapy interventions. These suggestions were in line with relevant studies showing that a ≥20% change in walking speed exceeds the day-to-day differences in walking performance and the variability of the measurements, and represents a relevant change for the patients (Hobart et al, 2013; Schwid et al, 2002). Indeed, three participants in the intervention groups showed such a clinically significant improvement in walking speed.

Rhythmic-cued MI also significantly improved walking distance, as assessed by the 6MWT, in both intervention groups when compared to the control group. Based on clinical judgement, an improvement in walking distance of around 20% was suggested large enough to enable patients to maintain their independence and ability to work, and also to increase their range of activities. These suggestions were in agreement with that reported in a large placebo-controlled double-blind RCT whose authors considered a ≥20% improvement clinically meaningful; their judgement was based on clinical expertise, but it was not part of their study results (Applebee et al, 2015). In the current study, 2 participants in the music-verbal-MI group and 6 participants in the metronome-verbal-MI group reached a clinically significant improvement in walking distance. In contrast to the current pilot study, Baert et al. (2014) reported a change of 10% (21.6 metres) in the 6MWT measures to be sufficiently large for a clinically significant improvement. However, their study
investigated individuals with an EDSS of 6.5 and below whereas the current study included participants with an EDSS of 1.5 to 4.5, which could explain the discrepancy in results. The performance of both walking tests was performed smoothly within an optimal setting as the hallway was rarely frequented. This means that no changes to the walking tests were required in the main study.

Results obtained in this study suggested that rhythmic-cued MI improved walking speed and walking distance. The researcher’s strategy to facilitate MI was to add external rhythmic auditory cues to the MI to possibly maintain the temporal patterns of imagined walking. This had improved the MI ability (Heremans et al, 2009; Heremans et al, 2012b) and walking (Kim et al, 2011) in other studies. Apart from music and metronome cues, rhythmic verbal cueing, in accordance with the cueing tempo, was used to accentuate the temporal structure of the rhythmic cueing. A similar approach had also been proposed by the recent literature on the use of RAS with gait training in people with neurological diseases including MS (Thaut and Rice 2014).

It is possible that verbal cues helped to enhance the MI capability, particularly the timing aspect, but the words, although few and simple, may have distracted some participants from the MI. The verbal cueing could also have confounded the metronome and music cueing; however, the overall package of rhythmic-cued MI was tested in this study. Additionally, it could be suggested that people with mild MS would have less perception and attention dysfunction than patients with moderate MS. The two possible results of this are that: the music and metronome cueing alone provided a sufficiently precise cueing in those participants with mild MS. Therefore, some participants with mild MS might have had their attention diverted by the verbal cues. In contrast, for people with moderate MS, the verbal cueing could have provided an additional anchor for their attention and auditory perception and a constant reminder of the MI.

As far as we know, participants in this study were able to perform MI. These results seemed to be in contrast to previous studies demonstrating a lower capacity to practise MI in pwMS (Heremans et al, 2012a; Tabrizi et al, 2013a; Tacchino et al, 2013). However, these authors linked impaired MI in this population particularly to cognitive dysfunction (Heremans et al, 2012a; Tacchino et al, 2013) and depression
Therefore, pwMS with cognitive impairment and/or depression were excluded from the current study.

To the author´s knowledge, no comparable studies have investigated the effect of rhythmic-cued MI on walking in pwMS, but three studies explored the effect of rhythmic-auditory cueing for walking rehabilitation. Baram and Miller (2007) used an auditory feedback device with metronome cues during walking which led to non-significant improvements in gait speed and stride length only in fourteen pwMS when compared to eleven healthy controls. Conklyn et al. (2010) used cued gait training in their home-based study, with a music tempo that was 10% above the participant´s spontaneous cadence. Gait parameters did not change, only double support time decreased in this small study (n=10). Shahraki et al. (2017) conducted their study after the present pilot study, and it used gait training with metronome cues which were 10% faster than the participants’ comfortable tempo, versus non-cued gait training (n=18). They found improved gait parameters and gait speed. Only the study conducted by Heremans et al. (2012c) evaluated the effects of external cueing on the MI ability in pwMS, showing that external auditory and visual cues improved the participants’ MI. Based on their results, the current intervention was designed.

Kim et al. (2011) compared the effect of visual and kinaesthetic locomotion imagery training with and without metronome cues on walking performance in people with stroke. Similar to the current study, the authors used a detailed introduction to MI and CDs containing the instructions and metronome cues. A major difference between the studies was the length of the intervention, which were ten to twelve minutes over four days in Kim´s study compared to seventeen minutes over twenty-four days in the current study. They found that the kinaesthetic MI training with metronome cues most effectively improved walking performance in participants when compared to visual MI without auditory cues. To summarise, the evidence of RAS and MI in people with neurological disorders and MS was meagre, but the findings were interesting in relation to the approach in this pilot study.
9.5 Effect of Rhythmic-Cued Motor Imagery on the Secondary Outcomes

Rhythmic-cued MI significantly improved some HRQoL parameters, such as social role functioning and mental health, as measured by the SF-36, and which refers to hypothesis 5 of this study. There is a consensus in the literature to regard SF-36 improvements of at least 5 points as a clinically meaningful improvement (Heesen and Cohen 2014; Kappos et al, 2014; Rudick et al, 2007). As only social role functioning and mental health significantly improved, it would not be appropriate to speak of clinically significant changes in HRQoL. Changes in walking perception (hypothesis 3) and fatigue (hypothesis 4) were statistically non-significant. It is likely that the sample size was too small to detect true differences between groups. Accordingly, the sample size of the main study was at least four times greater than that of the pilot study and was based on a sample size calculation.

The completion of the questionnaires was carried out effectively by the participants. There was no need to rest for the majority of participants; however, there was sufficient time and space for a rest and to have refreshments. Participants reported no problems with the type and number of questionnaires, so that all the questionnaires were able to be used for the main study as well.

No comparable studies have been conducted so far which examined the effect of rhythmic-cued MI on walking perception, fatigue and (HR)QoL in pwMS. MI alone was found to improve fatigue (Catalan et al, 2011) and balance (Fell 2000) in pwMS. Catalan et al. had implemented a MI programme two times a week over five weeks, with initial movement execution and a physiotherapist´s guidance. In other words, the procedure of their study included the selection of individual movement elements alongside MI. The MI content of the current study related to walking in its entirety, but the study also put an emphasis on particular aspects of the movement, such as the step length. A case study treated a single participant with six weeks MI and demonstrated some improvement in balance measures; nonetheless, with only one participant in the study, these results could not be generalised (Fell 2000).

Bovendt´Eerdt et al. (2010) conducted a feasibility study on an integrated MI programme with neurorehabilitation in people with neurological diseases including...
MS. Only one person with MS was in the study, and the adherence of the participants and therapists was low despite a standardised MI introduction programme. More importantly, both study groups participated in a neurorehabilitation programme, with MI added in the experimental group. No significant differences between groups were seen probably because of the low adherence by both therapists and participants. In contrast, the familiarisation with the MI and the phone calls in the current study might have supported the participants in their understanding of MI.

One might suggest that monotonous metronome cues in addition to MI might have a positive impact on walking, but not on psychological aspects. Surprisingly, results from this pilot study showed a significant effect on the SF-36 mental health subscale, but that could also have been related to the verbal cues. Participant reports supported these conjectures. It could be suggested that the verbal cues also reduced the monotony as there were different verbal cues. Nonetheless, only nine different verbal cues were used on the four CDs in accordance with recommendations on verbal cueing (Edwards 2011). As expected, significant improvements in mental health, but also social role functioning were observed in the music-verbal-MI group, and more participants reported to have enjoyed the music-based MI practice. Music with pleasing melodies and harmony was used, which potentially had a positive impact on social role functioning and mental health since music is known to improve mood. These findings were in line with a review on music therapy in neurorehabilitation, showing that pleasurable music was effective in improving motor learning (Altenmüller and Schlaug 2013). Therefore, in the main study, the same music and metronome cues were used in which the metronome tempo was matched with the music tempo. Verbal cueing was also used because it seemed to enhance the rhythmic cueing of the MI.

9.6 Limitations and Strengths of the Study

There were several limitations to this study. Firstly, the study was underpowered because of the small sample size despite the fact that it found statistically significant differences. Thus, the results were to be considered preliminary and could not be generalised to a larger population of pwMS. However, a subsequent well-powered main study was conducted after the pilot study.
Secondly, there was an imbalance between groups with respect to gender. Nevertheless, the effect of the intervention on walking speed and walking distance remained statistically significant even after adjustment for gender, age and disability (T25FW, \( p=0.002 \) and 6MWT, \( p<0.001 \)). To ensure a balanced group allocation, stratified block randomisation was performed in the main study. As explained in more detail in Chapter 9.8.2, there were eight strata in this study, and the minimum block size for a three-group study is three. Accordingly, a simple randomisation procedure was chosen for this pilot study because it would have been impossible to fill the blocks.

Thirdly, the lack of blinding was another limitation and is a challenge in physiotherapy trials. Blinding of the participants would not have been possible as they would have realised their group allocation. Restricted randomisation made allocation concealment redundant as the author could not influence participant allocation to groups. While using a script, all instructions, support and measures were carried out as consistently as feasible. It is recognised that, without intending to, the author might have exerted an influence through her knowledge of group allocation.

Finally, during the intervention of this study, it was not possible to control for kinaesthetic MI despite repeated instructions given verbally and on the CDs. Several studies used patient-rated questionnaires, such as the Kinaesthetic and Visual Imagery Questionnaire to assess the MI ability in their participants (Heremans et al, 2012a; Tabrizi et al, 2014). The current study could have also used this questionnaire, but two walking tests and five questionnaires were to be completed by the participants; thus, adding a further questionnaire might have induced exhaustion in the participants in particular since many of them had MS related fatigue. Many MI approaches were described in the literature (Schuster et al, 2011); therefore, it was important to explicitly introduce participants into the MI theory and strategy applied (Braun et al, 2011). A strength of this study was that a MI familiarisation was carried out as suggested by Wondrusch and Schuster-Amft (2013) using the PETTLEP approach (Holmes and Collins 2001).

Further strengths of this study are described as follows. Prior to the beginning of the study, an MS advisory group had been consulted for advice to clarify any questions,
including their MI experience, their music preference, but also on the question of how much time they would spend practising. Comments from the advisory group members were very valuable to the researcher, so music with pleasing melodies was chosen, and the MI was practised in a sitting position, as recommended by this group.

Close monitoring by weekly phone calls provided support with the MI for the study participants and allowed recording of any problems, such as a relapse due to MS. The phone calls and interventions were regarded as highly acceptable by participants and were continued to be used in the main study.

This study was conducted as a single-centre study, having been an advantage, compared to multicentre studies because the study was implemented in the same way for all participants. For this reason, it was not necessary to train physiotherapists in the study protocol. Finally, only the outcomes that are reliable and valid in the MS population were used in this study (Potter et al, 2014). The application of these measures facilitated comparisons with other studies and the possibility of a meta-analysis at a later point in time. However, currently, there are no other studies which have investigated the effect of rhythmic-cued MI on walking in pwMS.

### 9.7 Confounding Factors

In this study, several strategies were applied to minimise confounding. Firstly, *a priori* inclusion and exclusion criteria were chosen to reduce variability of the study population (McDonagh et al, 2013). Secondly, stratified block randomisation was used in the main study by inclusion of the pilot study’s assignment to groups in order to avoid group differences. Thirdly, a Two-Way Mixed Design ANOVA was used to analyse the primary outcomes in addition to post-hoc tests, as appropriate. The confounding factors of this study were age, gender and disability. In the pilot study, there was a group imbalance with respect to gender. Therefore, a second pilot study analysis included the confounding factors, but the results were similar.

### 9.8 Implications for the Main Study 1

Based on the pilot study results, important consequences for conducting the main study are discussed as follows.
9.8.1 Sample Size

Based on the above results from the primary outcomes, the sample size for the main study was recalculated using PS Vanderbilt Power and Sample Size Calculator\(^3\). The estimated \textit{a priori} sample size according to the study protocol was 112-150 participants, depending on attrition and the pilot results.

In this pilot study, the change in means in the T25FW within each group was approximately normally distributed with a $\sigma=SD=15$. According to a conservative estimation and given the small sample size of the pilot study, the true difference in the intervention and control means ($\delta$) was expected to be 11.5%. Hence, when assuming a power of 90% ($\beta=0.90$; type II error probability), 43 participants were required to study in both intervention groups and 43 controls to be able to reject the null hypothesis, which stated that the population means of the experimental and control groups were equal. The type I error probability ($\alpha$) associated with this test of this null hypothesis was 0.0025 (0.05 with Bonferroni’s adjustment as 3 means were to be compared). This significance level of 0.05 and the corrected value of 0.0025, respectively, were expressed at a confidence interval of 95%, which means the author could be confident that based on the study data, 95% of the follow-up means reflected a true change in population means (Field 2009). Given an anticipated attrition of 10%, 141 participants (47 per group) were needed to study in the main study. Following recommendations on the sample size recalculation for main studies and to optimise the sample size, both primary outcomes were considered for the calculation (Lancaster, Dodd & Williamson 2004).

A conservative sample size estimation of the 6MWT resulted in a sample size of 39 participants per group ($\alpha=0.0025$, a true difference in population means $\delta=14.5$, SD=18, power=90%). By addition of 10% attrition to 117 participants, a group size of 43 resulted. In order to produce valid and generalisable results, the larger number of 141 participants was aimed at. Should it have been possible to recruit more participants, up to 150 participants would have been included, according to the ethics approvals and if the resources allowed for that. Pilot data were included in the

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analysis of the main study (Thabane et al, 2010). An alternative sample size
calculation approach yielding the same results was described in the scientific article
published in Pilot and Feasibility Studies (Seebacher et al, 2015b) (see Appendix 19).

9.8.2 Stratified Block Randomisation

As can be seen from Table 6 showing baseline characteristics, participant allocation
was unbalanced in terms of gender. In addition, more women have MS, and it is
known that age has an impact on the brain’s functioning (Compston et al, 2006). To
ensure a balanced allocation to groups, a stratified randomisation in permuted fixed
blocks of three, with a computer random number generator, was computed, as
planned in the study protocol, using Sealed Envelope software⁴. The small block size
was chosen as there were eight different strata, which might have made it difficult to
equally fill blocks of six (stratum 1: female, under 40, low EDSS; stratum 2: female,
under 40, higher EDSS; stratum 3: female, 40 and over, low EDSS; stratum 4: female,
40 and over, higher EDSS; stratum 5: male, under 40, low EDSS; stratum 6: male,
under 40, higher EDSS; stratum 7: male, 40 and over, low EDSS; stratum 8: male, 40
and over, higher EDSS). Blocks included equal numbers of As (music-verbal-MI), Bs
(metronome-verbal-MI) and Cs (controls) (Lachin, Matts & Wei 1988; Matts and
Lachin 1988). Other variables within blocks were gender (female/male), disability
(EDSS 1.5-3.0/3.5-4.5) and age (18-40/over 40), as described above. During
recruitment, participants were allocated to these blocks until the number of 3
participants per block was reached, and then they were randomly assigned to the
intervention or control groups. Participants of the pilot study were taken into account.
The stratification guaranteed that the intervention and control groups were similar in
age, gender and their EDSS.

9.8.3 Allocation Concealment

Allocation concealment was performed in the main study by an independent
researcher using a computer-generated randomisation list with a random sequence
and equal numbers of As, Bs and Cs on it. He produced sequentially numbered,
opaque, sealed envelopes for the author to request and open by participants at their
enrolment; however, after that, the group allocation became known to the author who

also instructed and assessed the participants. The goal of allocation concealment was to prevent selection bias (Chan et al, 2013).

9.8.4 Assessment Order

It is possible that during the baseline and post-intervention testing, the assessment order might have had an influence on certain results. An influence might have incurred insofar as the walking tests were administered before the MFIS. Particularly, the 6MWT might have caused a certain degree of fatigue in participants, which might have led them to different responses in the fatigue rating questionnaire (McBurney and White 2010). Whilst completing the questionnaires, questions that were previously responded to, whether within the same or a previous questionnaire, might have had an influence on the participants’ reactions to later questions (Podsakoff et al, 2003). However, all tests were administered in the same order at baseline and follow-up so that the influence may have been similar. To avoid an order effect, a random test order for the walking tests and questionnaires was applied in the main study (Podsakoff et al, 2003). The T25FW was always administered before the 6MWT because the 6MWT could have induced fatigue. The MFIS was administered not immediately after the 6MWT, for reasons of fatigue.

9.9 Dissemination of Findings

Results of this pilot study were disseminated to the participants together with the main study results, the pilot study data having been included in the main analysis. The pilot results were presented at the 12th Annual Meeting of the Austrian Society for Neurology in March, 2015 (Seebacher et al, 2015b). For this presentation, a poster prize was awarded to the author. A scientific article was published by the open access Pilot and Feasibility Studies journal on 11 July, 2015 (Seebacher et al, 2015d) (see Appendix 19). It was recognised by the author and clearly stated in the article that all intellectual property belongs to the University of Brighton.
9.10 Conclusions

Data from the pilot study showed that rhythmic-cued MI improved walking and to some extent HRQoL in pwMS and that the methods and a larger study were feasible. The interventions included (a) a thorough familiarisation process with MI; (b) MI enhancement by rhythmic-auditory cues; (c) weekly support with the MI practice; and (d) intensive practice over a longer time period of four weeks. This pilot study showed that a sample size of 141 participants and stratified block randomisation were required for the study to produce reliable and generalisable results.
Chapter 10 – Main Study Methods

In Chapters 10 to 12, the main study is described. For the main study, an additional 112 participants in three groups were enrolled. Data from the pilot study were incorporated in the main study since no changes to the methods used in the pilot study were required (Morris, Vesk & McCarthy 2013; Thabane et al, 2010; Tickle-Degnen 2013). The exceptions were, firstly, the stratified randomisation procedure applied in the main study although the pilot study participant allocation was taken into account; a further exception is the allocation concealment performed in the main study, but due to the restricted randomisation in the pilot study, the researcher could not exert any influence on participant allocation to the different groups. Finally, the main study assessment order was changed to random, as described in detail in Chapter 9.8.4, but the same tests were used and participants were allowed to rest at any time during both the pilot and main study.

10.1 Participants

10.1.1 Participant Selection

Another 112 participants were enrolled onto the study, resulting in a total study population of 142 participants. The same inclusion and exclusion criteria were applied as in the pilot study.

10.1.2 Sample Size

The sample size calculation for the main study was described in detail in Chapter 9.8.1.

10.1.3 Recruitment

Recruitment used unselected consecutive sampling and stratified block randomisation from the MS Clinic, Innsbruck and was conducted between the dates of 14 July, 2014 and 16 February, 2015. The recruitment procedure was the same as for the pilot study. A CONSORT Flow Diagram is shown in Figure10.
**Figure 11:** CONSORT Flow Diagram of Main Study 1.

### 10.1.4 Randomisation

To ensure a balanced allocation to groups, a stratified randomisation in permuted fixed blocks of three with a computer random number generator was computed, as
planned in the study protocol using Sealed Envelope software\(^5\), as described in detail in Chapter 9.8.2.

**10.1.5 Allocation Concealment and Blinding**

Allocation concealment was performed, as fully explained in Chapter 9.8.3.

**10.1.6 Assessment Order**

A random order for the walking tests and questionnaires was used, as outlined in Chapter 9.8.4.

**10.2 Data Collection**

Data collection was identical to the one described in the pilot study. All questionnaires were checked by the author for completeness, and the participants were asked to complete them if replies were missing.

**10.2.1 Primary Outcomes**

As in the pilot study, a change in walking speed and walking distance were the primary outcomes of the study, measured by the same walking tests.

**10.2.2 Secondary Outcomes**

The secondary outcomes were not changed following the pilot study and so remained as a change in walking perception, fatigue and (HR)QoL.

**10.3 Intervention**

In the music-verbal-MI and metronome-verbal-MI groups, the intervention was performed in the same way as the pilot study. All participants, including those in the control group, were called once a week to note adverse events and ask about any health problems; in the intervention groups, support was provided with the rhythmic-cued MI.

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10.4 Data Analysis

10.4.1 Statistical Analysis

The research question and hypotheses were described in detail in the pilot study. Statistical analysis was performed as in the pilot study. All statistical analysis was performed using IBM SPSS software, release 22.0 (IBM Corporation, Armonk, New York, USA) and GraphPad Prism 6 (GraphPad, San Diego, California, USA).

The 6MWT data were normally distributed and met the requirements for the Two-Way Mixed Design ANOVA. The T25FW data were not normally distributed, and there were significant outliers in the data. Standardised, studentised and non-standardised residuals of the T25FW (Field 2009) also showed a skewed distribution with a positive skew. Therefore, different data transformations were tried to correct for skewed data distribution and outliers. Log and square root transformation did not sufficiently change the distribution, but reciprocal transformation did (Field 2009). The skewness and kurtosis values were close to zero after the transformation, the histograms showed a bell-shaped curve and the Q-Q Plots showed observed values along the diagonal line. The Kolmogorov Smirnov was non-significant (see Appendix 12). Therefore, the reciprocally transformed T25FW data were used for the Mixed Design ANOVA analysis. Original T25FW data were used for the descriptive statistics because the data had been changed by the transformation (1/value), so it would not have been possible to detect the actual values in walking speed and to calculate the changes thereof. For example, if a participant needed five seconds for the T25FW, the transformed value would be 1/5=0.2 seconds. The reciprocally transformed T25FW data met all other ANOVA assumptions.

ANOVA effect size measures were calculated as partial eta squared values ($\eta^2$)(Field 2009). Testing for clinically significant improvement was performed if the overall group X time interaction was significant. In such cases, new variables were computed, based on the differences between post-intervention and baseline measures. A Chi-Square test was applied to the new variables to see how many participants in the groups reached a clinically significant improvement. If the overall $p$-value was significant, groups were compared using the Fisher’s Exact test, with a
Bonferroni correction as a post-hoc test. Intention-to-treat analysis was performed, as described in Chapter 7.5.3.

Statistical tests for the secondary outcomes were introduced in Chapter 7.5.1. If the overall Kruskal Wallis results were significant, post-hoc comparisons between the music-verbal-MI and control groups, the metronome-verbal-MI and control groups and the music-verbal-MI and metronome-verbal-MI groups were made using Dunn’s multiple comparisons test.

Participant acceptability and potential adverse events during or after the rhythmic-cued MI were recorded narratively using excel files.
Chapter 11 – Main Study Results

11.1 Safety, Acceptability and Adherence to the Programme

There was one safety-related event during the assessments, with one participant having fallen during the T25FW. According to the MSFC instructions, as the participant was not injured and felt able to repeat the test, she was allowed to rest and then she walked the 25 feet two times without falling. The falling and test repetition were noted on the data collection file and reported to the University of Brighton’s Faculty Research and Governance Ethics Committee (FREGC).

Participants were permitted to use walking sticks if desired and to rest at any time during instructions and assessments. Eight participants used unilateral or bilateral walking sticks during the pre- and post-intervention assessments. The home-based intervention could be practised while seated and was reported by the participants to be safe and convenient. In view of the setting, the author had to rely on participants’ accounts of their adherence. They reported to have practised a median of 5 (within a min-max of 4 to 6) times per week.

Eighteen participants in both the pilot and main studies reported initial problems with the kinaesthetic MI. Tips were provided by the author, such as how to consciously feel their feet touching the ground during the imagined walking or to feel their legs during the MI. These 18 participants reported that their kinaesthetic imagery improved with training; for 14 participants, this happened after one week, and for the other 4 participants, within the second week. Additionally, 7 participants reported concentration problems, which improved during practice. One participant in the metronome-verbal-MI group considered the intervention boring, but was able to adapt and kept the practice frequency of six times a week. Four participants reported that the intervention was tiring at some point during the practice, and 3 of them showed improved fatigue scores post-intervention whereas 1 participant was more fatigued. One participant reported to have problems with more complex music, but that the verbal cueing helped to a certain degree to overcome these problems. Five participants reported that they regarded the tempo variations in the music or metronome cues difficult. More specifically, it was the slow or fast tempo or the
change in tempo that was more or less difficult for these different people. All these 5 participants considered the verbal cueing supportive. Altogether, 36 out of 94 participants reported some initial problems during the interventions, which improved during practice.

Within the last two weeks of practice, 29 participants reported that they perceived an improvement in their actual walking, stairs climbing and balance, such as when standing while cooking. Twenty-three participants reported the intervention to be motivating (n=9; 7 in the music-verbal-MI group and 2 in the metronome-verbal-MI group), pleasurable (n=13; 12 in the music-verbal-MI group and 1 in the metronome-verbal-MI group) or relaxing (n=1; in the metronome-verbal-MI group). All other participants reported that they regarded the intervention as more than acceptable, and that they did not have any problems.

11.2 Baseline Data

The same baseline data were collected as in the pilot study. During recruitment, a total of 142 participants were enrolled, of whom 131 completed the study. The baseline data of these 131 participants are shown in Table 7. At baseline, 107 females and 24 males were randomised to the three groups, meaning that the female-to-male ratio was 4.45:1, and 81.7% of the study population were female. Compared to the pilot study female-to-male ratio of 2.75:1, the main study females were overrepresented. The mean age of participants was overall 44.35±11.6 years. Eight participants used walking aids (that is walking sticks or crutches: unilateral or bilateral) during the walking tests.
<table>
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<tr>
<td>EDSS 3.5-4.5</td>
<td>N=13</td>
<td>N=12</td>
<td>N=12</td>
</tr>
<tr>
<td>Walking aid use during testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/unilateral/bilateral aid</td>
<td>N=40/3/1</td>
<td>N=41/0/3</td>
<td>N=42/0/1</td>
</tr>
<tr>
<td>T25FW (s)</td>
<td>6.0±2.2</td>
<td>5.8±3.0</td>
<td>5.2±1.6</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>451.1±135.1</td>
<td>462.8±121.1</td>
<td>487.5±122.6</td>
</tr>
<tr>
<td>MSWS-12</td>
<td>47.9 (0.0, 97.9)</td>
<td>34.4 (0.0, 100.0)</td>
<td>41.7 (0.0, 89.6)</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw change</td>
<td>3.0 (1.0, 5.0)</td>
<td>3.0 (1.0, 4.0)</td>
<td>3.0 (1.0, 5.0)</td>
</tr>
<tr>
<td>Phys funct</td>
<td>55.0 (0.0, 100.0)</td>
<td>67.5 (0.0, 100.0)</td>
<td>60.0 (5.0, 100.0)</td>
</tr>
<tr>
<td>Phys role funct</td>
<td>50.0 (0.0, 100.0)</td>
<td>50.0 (0.0, 100.0)</td>
<td>50.0 (0.0, 100.0)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>82.0 (20.0, 100.0)</td>
<td>100.0 (0.0, 100.0)</td>
<td>80.0 (22.0, 100.0)</td>
</tr>
<tr>
<td>General health perc</td>
<td>58.5 (20.0, 100.0)</td>
<td>71.0 (32.0, 97.0)</td>
<td>62.0 (25.0, 97.0)</td>
</tr>
<tr>
<td>Vitality</td>
<td>45.0 (10.0, 75.0)</td>
<td>55.0 (0.0, 95.0)</td>
<td>50.0 (25.0, 100.0)</td>
</tr>
<tr>
<td>Social role funct</td>
<td>62.5 (25.0, 100.0)</td>
<td>93.7 (37.5, 100.0)</td>
<td>87.5 (37.5, 100)</td>
</tr>
</tbody>
</table>

Table 7: Participants’ Baseline Characteristics in the Main Study 1.
Table 7 (Continued): Participants’ Baseline Characteristics in the Main Study 1.

Abbreviations: EDSS = Expanded Disability Status Scale; T25FW = Timed 25-Foot Walk; 6MWT = 6-Minute Walk Test; SF-36 = Short Form-36 Health Survey; VAS = Visual Analogue Scale; MSIS-29 = MS Impact Scale-29; MFIS = Modified Fatigue Impact Scale; s = seconds; m = metres; phys = physical subscale; psych = psychological; sub = subscale; funct = functioning; sum = sumscale; emot = emotional; perc = perceptions.

1Mean ±standard deviation; 2median (min, max). Colour coding: yellow = walking outcomes; blue = (HR)QoL outcomes; green = fatigue outcomes.

### 11.3 Adverse Events, Missing Data and Attrition

No adverse events were reported in this study and there were no missing data. Participants in the main study who withdrew their participation (such as for non-adherence to the intervention) or were excluded from the study (due to an MS relapse or non-adherence) were reported and their whole case was removed from the analysis. Attrition was 7.75 %, and the numbers are shown in Figure 11. In Figure 12,
the number of excluded participants and the reasons for their drop-out from the study are shown.

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Music-verbal-MI group A</th>
<th>Metronome-verbal-MI group B</th>
<th>Control group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n = 142</td>
<td>n = 48</td>
<td>n = 46</td>
<td>n = 48</td>
</tr>
<tr>
<td>Attrition</td>
<td>n = 4</td>
<td>n = 2</td>
<td>n = 5</td>
</tr>
<tr>
<td>No motivation: n = 2</td>
<td>No motivation: n = 1</td>
<td>Could not be reached: n = 2</td>
<td></td>
</tr>
<tr>
<td>Analysis</td>
<td>Total n = 131</td>
<td>n = 44</td>
<td>n = 44</td>
</tr>
</tbody>
</table>

Figure 12: Attrition in the Main Study 1.

11.4 Bias

The purpose of the main study was to generate results from the study population which can be generalised to the MS population, or rather the target population at large (Newcombe 1999). It is recognised that the results can be generalised primarily to the Austrian MS population since the participants were recruited mainly from people living in Austria although German-speaking people from other European countries, such as Hungary, Croatia, Italy, and Germany, were also included. The Cochrane handbook for systematic reviews of interventions (The Cochrane Collaboration 2011) lists at least five key systematic biases which can likely change the results, and so threaten the validity of a study. These biases are selection, performance, detection, attrition and reporting bias. In the following paragraphs and Table 8, it is shown how these biases were addressed in the current study.
A) To encounter selection bias, it was ensured that the groups were as similar as possible in every respect. Participants of the pilot study were randomly allocated to groups by drawing sealed and opaque envelopes with As, Bs and Cs. As the groups were unbalanced in terms of gender, stratified block randomisation with a computer-generated random sequence was performed in the main study, as described in Chapter 9.8.2. In addition, allocation concealment was implemented, as introduced in Chapter 9.8.3.

B) In this study, to minimise performance bias, blinding would have been required, but this was not possible. Despite that limitation, all participants received phone calls to ensure the treatment was as equal as possible. Further, validated tests and questionnaires were used to increase the internal validity of the study.

C) To overcome detection bias, blinding of examiners is recommended, which was impossible in this study, as discussed above.

D) Attrition bias refers to systematic differences between groups in exclusions and withdrawals from a study. There were no withdrawals or exclusions in the pilot study. Five participants withdrew from the main study, and 6 participants were excluded because of a relapse from MS. Subsequently, 44 participants remained in the music-verbal-MI group, 44 participants in the metronome-verbal-MI group and 43 participants in the control group.

E) Reporting (or publication) bias refers to systematic differences between reported and unreported findings. The non-significant results of this study were also shown in this document and, more importantly, reported in published articles (Seebacher et al, 2015d, 2017).
<table>
<thead>
<tr>
<th>Type of Bias</th>
<th>Description</th>
<th>Strategies to Bias Reduction</th>
<th>Met?</th>
<th>Reasons if not met</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection bias</td>
<td>Systematic differences in baseline characteristics between study groups</td>
<td>Stratified block randomisation (random allocation sequence)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allocation concealment</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Performance bias</td>
<td>Systematic differences in treatment between groups, apart from the treatment</td>
<td>Blinding of participants and assessors</td>
<td>No</td>
<td>Only one researcher</td>
</tr>
<tr>
<td></td>
<td>being assessed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection bias</td>
<td>Systematic differences between groups in how the outcomes are measured</td>
<td>Blinding of assessors</td>
<td>No</td>
<td>Only one researcher</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attrition bias</td>
<td>Systematic differences between groups in withdrawals and exclusions from a</td>
<td>Very similar group sizes in analysis</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>study</td>
<td>No missing data</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Reporting bias</td>
<td>Systematic differences between reported (statistically significant) and</td>
<td>All relevant results were reported</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>unreported (non-significant) findings</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8: Biases and Strategies to Control these within this Study (The Cochrane Collaboration 2011; Viera and Bangdiwala 2007).
11.5 Primary Outcomes

Descriptive data of the primary outcomes (T25FW; 6MWT) in all groups, and pre- and post-intervention, are shown in Table 9. As can be seen, the mean walking speed and walking distance increased in both intervention groups, but not in the control group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=44</th>
<th>Metronome-verbal-MI group N=44</th>
<th>Control group N=43</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>T25FW (s)</td>
<td>6.0±2.2</td>
<td>5.1±2.1</td>
<td>5.8±3.0</td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>451.1±135.1</td>
<td>514.5±132.1</td>
<td>462.8±121.1</td>
</tr>
</tbody>
</table>

Table 9: Descriptive Data of Primary Outcomes for Each Study Group (Main Study 1).

Abbreviations: Pre = pre-intervention/baseline; Post = post-intervention; T25FW = Timed 25-Foot Walk; s = seconds; 6MWT = 6-Minute Walk Test; m = metres;

1Mean ±standard deviation. Red coloured tests: lower numbers indicate better performance; blue coloured tests: higher numbers indicate better performance.

Between-group analysis showed that rhythmic-cued MI improved walking speed and walking distance when compared to the control group. Individual changes in the time to walk and walking distance for participants in the intervention and control groups are shown in Figures 13, A-F.
Figure 13, A-F: Effect of Intervention on the Time to Walk (A, C & E) and Walking Distance (B, D & F) (Main Study 2).

ORIGINAL IN COLOUR
Figure legend: A-B: individual participants are shown as symbols (circles = baseline, squares = post-intervention); the means are indicated by bars (grey = baseline, white = post-intervention). C-D: differences between baseline and post-intervention measures are shown as points. E-F: the ratio between baseline and post-intervention measures is shown as points. C-F: the means are indicated by bars. The improvement direction is shown by green arrows, and a red dotted line indicates the clinically significant improvement benchmark of ≥20%. Small square brackets on top of the figures A and B show significant within-group comparisons between baseline and post-intervention; large square brackets (C-F) indicate significant group X time interactions; *significant at the 0.05 level; **significant at the 0.01 level; ***significant at the 0.001 level.

With regard to hypothesis 1, rhythmic-cued MI improved walking speed, as measured by the T25FW, when compared to controls (see Table 10). The overall interaction between the groups at baseline and post-intervention was statistically significant, T25FWreciprocal: F(2,128)=78.992, p<0.0001, with a large effect size of η²=0.55. This is because η² effect sizes above 0.26 are regarded as large (Cohen 1988; Miles and Shevlin 2001). Post-hoc analysis using Bonferroni’s correction indicated that the effect of both music-verbal-MI (p<0.0001) and metronome-verbal-MI (p<0.0001) was statistically significant, and there was no significant difference in the change of walking speed between the two intervention groups (p=0.53). Therefore, the null-hypothesis was rejected. This means that a rhythmic-cued MI improved walking speed when compared to the controls.

Six participants in the music-verbal-MI group and 8 participants in the metronome-verbal-MI group, but no participants in the control group, showed a clinically significant improvement of ≥20% in walking speed.

In relation to hypothesis 2, rhythmic-cued MI improved walking distance (endurance), as measured by the 6MWT, when compared to the controls (see Table 10). The overall interaction between the groups at baseline and follow-up was statistically significant, F(2,128)=84.777, p=3.57*10⁻²⁴ (<0.0001), with a large effect size of η²=0.57. Bonferroni correction for multiple comparisons was applied as a post-hoc test; the results indicated that the effect of music-verbal-MI (p<0.0001) and
metronome-verbal-MI (p<0.0001) was significant, and there was no interaction between the two intervention groups (p=0.52). Thus, the null-hypothesis was rejected. In other words, rhythmic-cued MI improved walking distance when compared to the controls.

Nine participants in the music-verbal-MI group and 15 participants in the metronome-verbal-MI group, but no participants in the control group, showed a clinically significant improvement ≥20%, with a significant interaction between the music-verbal-MI and control groups (p=0.006) and between the metronome-verbal-MI and control groups (p<0.001). In summary, walking distance increased in both intervention groups, and more participants in the metronome-verbal-MI group showed a clinically significant improvement in walking distance. Effects of the interventions on the primary outcomes and clinically significant improvement are shown in Table 10.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group; N=44</th>
<th>Metronome-verbal-MI group; N=44</th>
<th>Control group; N=43</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T25FW (seconds)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.8±0.35 &lt;0.001</td>
<td>-0.8±0.37 &lt;0.001</td>
<td>0.1±0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clin. sig. improvement (≥20%)</td>
<td>N=6/44 (13.6%) 0.078</td>
<td>N=8/44 (18.2%) 0.018</td>
<td>N=0/43 (0%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6MWT (metres)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>63.4±29.68 &lt;0.001</td>
<td>68.2±38.21 &lt;0.001</td>
<td>-15.3±32.09 &lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clin. sig. improvement (≥20%)</td>
<td>N=9/44 (20.5%) 0.006</td>
<td>N=15/44 (34.1%) &lt;0.001</td>
<td>N=0/43 (0%) &lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 10**: Effect on Interventions on Primary Outcomes and Clinically Significant Improvement (Main Study 1).
Abbreviations: T25FW = Timed 25-Foot Walk; 6MWT = 6-Minute Walk Test; N = number of participants; clin. sig. = clinically significant.

1 Mean ± standard deviation; 2 if overall p-value significant, post-hoc comparisons were performed between the music-verbal-MI and control groups, and the metronome-verbal-MI and control groups and between the intervention groups, with Bonferroni correction for 3 comparisons; 3 number of participants (ratio); 4 if overall p-value significant, analysed with Fisher’s Exact test and corrected for multiple comparisons. Significant changes are highlighted in bright yellow and borderline significant changes in dark yellow. Red coloured tests: lower numbers indicate better performance; blue coloured tests: higher numbers indicate better performance.

11.6 Secondary Outcomes

Participants’ walking perception improved in the intervention groups when compared to the control group, indicated by a reduction in the MSWS-12. Physical and cognitive fatigue improved in the music-verbal-MI and metronome-verbal-MI groups when compared to the control group, as shown by lower values on the MFIS. HRQoL, as assessed by the SF-36, improved both on physical and mental subscales only in the intervention groups in which larger numbers on the SF-36 indicated improvement. HRQoL, as assessed by the EQ-5D-3L VAS, improved after the intervention compared to the controls, and the EQ-5D-3L Index did not improve. Higher numbers on the VAS represent better health status. MS-associated QoL, as measured by the MSIS-29, improved in the intervention groups when compared to the control group, indicated by decreased (improved) physical and psychological subscales in the music-verbal-MI and metronome-verbal-MI groups, and increased (worsened) psychological subscales in the control group. Descriptive information of all secondary outcomes (baseline and post-intervention data) is presented in Table 11.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=44</th>
<th>Metronome-verbal-MI group N=44</th>
<th>Control group N=43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline MSWS-12^</td>
<td>47.9 (0.0, 97.9)</td>
<td>34.4 (0.0, 100.0)</td>
<td>41.7 (0.0, 89.6)</td>
</tr>
<tr>
<td>Post-intervention^</td>
<td>31.2 (0.0, 83.3)</td>
<td>21.9 (0.0, 79.2)</td>
<td>41.7 (0.0, 97.9)</td>
</tr>
<tr>
<td><strong>MFIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline phys sub^</td>
<td>18.0 (1.0, 31.0)</td>
<td>14.0 (0.0, 31.0)</td>
<td>18.0 (0.0, 25.0)</td>
</tr>
<tr>
<td>Post-intervention^</td>
<td>12.0 (0.0, 26.0)</td>
<td>10.0 (0.0, 24.0)</td>
<td>17.0 (0.0, 30.0)</td>
</tr>
<tr>
<td>Baseline cogn sub^</td>
<td>14.0 (1.0, 35.0)</td>
<td>9.0 (0.0, 27.0)</td>
<td>15.0 (0.0, 30.0)</td>
</tr>
<tr>
<td>Post-intervention^</td>
<td>7.0 (0.0, 30.0)</td>
<td>4.0 (0.0, 27.0)</td>
<td>13.0 (0.0, 32.0)</td>
</tr>
<tr>
<td>Baseline psychosoc sub^</td>
<td>3.0 (0.0, 8.0)</td>
<td>2.0 (0.0, 7.0)</td>
<td>3.0 (0.0, 8.0)</td>
</tr>
<tr>
<td>Post-intervention^</td>
<td>2.0 (0.0, 6.0)</td>
<td>1.0 (0.0, 5.0)</td>
<td>2.0 (0.0, 8.0)</td>
</tr>
<tr>
<td>Baseline total score^</td>
<td>35.0 (3.0, 69.0)</td>
<td>26.0 (0.0, 59.0)</td>
<td>32.0 (0.0, 57.0)</td>
</tr>
<tr>
<td>Post-intervention^</td>
<td>24.0 (0.0, 60.0)</td>
<td>17.0 (0.0, 50.0)</td>
<td>33.0 (0.0, 67.0)</td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline raw change^</td>
<td>3.0 (1.0, 5.0)</td>
<td>3.0 (1.0, 4.0)</td>
<td>3.0 (1.0, 5.0)</td>
</tr>
<tr>
<td>Post-intervention^</td>
<td>3.0 (1.0, 4.0)</td>
<td>3.0 (1.0, 5.0)</td>
<td>3.0 (1.0, 5.0)</td>
</tr>
<tr>
<td>Baseline phys funct^</td>
<td>55.0 (0.0, 100.0)</td>
<td>67.5 (0.0, 100.0)</td>
<td>60.0 (5.0, 100.0)</td>
</tr>
<tr>
<td>Post-intervention^</td>
<td>67.5 (10.0, 100.0)</td>
<td>75.0 (10.0, 100.0)</td>
<td>55.0 (5.0, 100.0)</td>
</tr>
<tr>
<td>Baseline phys role funct^</td>
<td>50.0 (0.0, 100.0)</td>
<td>50.0 (0.0, 100.0)</td>
<td>50.0 (0.0, 100.0)</td>
</tr>
<tr>
<td>Post-intervention</td>
<td>100.0 (0.0, 100.0)</td>
<td>100.0 (0.0, 100.0)</td>
<td>50.0 (0.0, 100.0)</td>
</tr>
<tr>
<td>Baseline bodily pain^</td>
<td>82.0 (20.0, 100.0)</td>
<td>100.0 (0.0, 100.0)</td>
<td>80.0 (22.0, 100.0)</td>
</tr>
<tr>
<td>Post-intervention^</td>
<td>92.0 (22.0, 100.0)</td>
<td>100.0 (10.0, 100.0)</td>
<td>62 (31.0, 100.0)</td>
</tr>
<tr>
<td>Baseline general health perc^</td>
<td>58.5 (20.0, 100.0)</td>
<td>71.0 (32.0, 97.0)</td>
<td>62.0 (25.0, 97.0)</td>
</tr>
<tr>
<td>Post-intervention^</td>
<td>72.0 (25.0, 92.0)</td>
<td>72.0 (37.0, 97.0)</td>
<td>52.0 (15.0, 100.0)</td>
</tr>
</tbody>
</table>

Table 11: Descriptive Data of Secondary Outcomes for Each Study Group (Main Study 1).
|                      | Baseline vitality<sup>1</sup> | Post-intervention<sup>1</sup> | Baseline social role funct<sup>1</sup> | Post-intervention<sup>1</sup> | Baseline emot role funct<sup>1</sup> | Post-intervention<sup>1</sup> | Baseline mental health<sup>1</sup> | Post-intervention<sup>1</sup> | Baseline phys sum<sup>1</sup> | Post-intervention<sup>1</sup> | Baseline mental sum<sup>1</sup> | Post-intervention<sup>1</sup> | EQ-5D-3L | Baseline index value<sup>1</sup> | Post-intervention<sup>1</sup> | Baseline VAS score<sup>1</sup> | Post-intervention<sup>1</sup> | MSIS-29 | Baseline phys sub<sup>1</sup> | Post-intervention<sup>1</sup> | Baseline psych sub<sup>1</sup> | Post-intervention<sup>1</sup> |
|----------------------|-------------------------------|-------------------------------|----------------------------------------|-------------------------------|--------------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|--------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
|                      | 45.0 (10.0, 75.0)             | 55.0 (0.0, 95.0)              | 62.5 (25.0, 100.0)                    | 93.7 (37.5, 100.0)            | 66.7 (0.0, 100.0)                    | 100.0 (0.0, 100.0)           | 66.0 (24.0, 92.0)              | 80.0 (32.0, 96.0)              | 41.1 (19.1, 63.3)             | 48.4 (23.5, 63.1)             | 46.1 (21.5, 62.4)              | 53.9 (25.2, 64.3)              | 0.9 (0.3, 1.0)                  | 0.9 (0.5, 1.0)                  | 66.0 (10.0, 100.0)            | 80.0 (40.0, 100.0)            | 27.5 (2.5, 53.7)              | 15.0 (0.0, 63.7)              | 20.8 (0.0, 55.6)              | 12.5 (0.0, 61.1)              |
|                      | 50.0 (25.0, 100.0)            | 55.0 (15.0, 90.0)             | 93.7 (37.5, 100.0)                    | 87.5 (25.0, 100.0)            | 100.0 (0.0, 100.0)                   | 66.7 (0.0, 100.0)            | 80.0 (32.0, 100.0)            | 80.0 (32.0, 100.0)            | 42.1 (24.0, 59.6)             | 36.7 (24.8, 58.1)             | 49.4 (21.8, 62.9)              | 49.0 (23.4, 62.7)              | 0.9 (0.1, 1.0)                  | 0.9 (0.2, 1.0)                  | 70.0 (20.0, 100.0)            | 72.0 (30.0, 97.0)             | 21.2 (1.2, 81.2)              | 15.6 (0.0, 63.7)              | 13.9 (0.0, 63.9)              | 5.6 (0.0, 63.9)              |
|                      | 50.0 (25.0, 100.0)            | 55.0 (20.0, 95.0)             | 93.7 (37.5, 100.0)                    | 87.5 (25.0, 100.0)            | 100.0 (0.0, 100.0)                   | 66.7 (0.0, 100.0)            | 80.0 (32.0, 100.0)            | 80.0 (32.0, 100.0)            | 42.1 (24.0, 59.6)             | 36.7 (24.8, 58.1)             | 49.4 (21.8, 62.9)              | 49.0 (23.4, 62.7)              | 0.9 (0.1, 1.0)                  | 0.9 (0.3, 1.0)                  | 75.0 (30.0, 95.0)            | 72.0 (30.0, 97.0)             | 26.2 (0.0, 52.5)              | 25.0 (0.0, 75.0)              | 13.9 (0.0, 61.1)              | 19.4 (0.0, 63.9)              |
|                      |                              |                              | 55.0 (20.0, 95.0)                     | 87.5 (25.0, 100.0)            | 100.0 (0.0, 100.0)                   | 66.7 (0.0, 100.0)            | 80.0 (32.0, 100.0)            | 80.0 (32.0, 100.0)            | 42.1 (24.0, 59.6)             | 36.7 (24.8, 58.1)             | 49.4 (21.8, 62.9)              | 49.0 (23.4, 62.7)              | 0.9 (0.1, 1.0)                  | 0.9 (0.3, 1.0)                  | 75.0 (30.0, 95.0)            | 72.0 (30.0, 97.0)             | 26.2 (0.0, 52.5)              | 25.0 (0.0, 75.0)              | 13.9 (0.0, 61.1)              | 19.4 (0.0, 63.9)              |

**Table 11 (Continued):** Descriptive Data of Secondary Outcomes for Each Study Group (Main Study 1).

Abbreviations: Phys = physical; funct = functioning; cogn = cognitive; psychosoc = psychosocial; perc = perceptions; emot = emotional; sub = subscale; sum = sumscale; psych = psychological; VAS = Visual Analogue Scale.

**ORIGINAL IN COLOUR**
Median (min, max). **Red coloured questionnaires: lower numbers indicate better performance; blue coloured questionnaires: higher numbers indicate better performance.** Yellow = walking outcomes; blue = (HR)QoL outcomes; green = fatigue outcomes.

The between-group analysis showed a significant difference in walking perception, as assessed by the MSWS-12, in the music-verbal-MI group (p=0.002) and the metronome-verbal-MI group (p<0.001) when compared to the control group. The Kruskal Wallis H-Statistics is shown in Appendix 12 and Table A6. Participants in both intervention groups reached a clinically significant improvement in walking perception (music-verbal-MI and metronome-verbal-MI groups, p=0.033) when compared to the controls (see Chapter 3 for a definition).

Physical fatigue significantly improved in the music-verbal-MI (p<0.001) and metronome-verbal-MI groups (p=0.007) when compared to the control group. Cognitive fatigue improved only in the music-verbal-MI group (p=0.001), but not in the metronome-verbal-MI and control groups. There was no significant improvement in psychosocial fatigue, as measured by the MFIS psychosocial subscale (p=0.056).

Total fatigue significantly improved (p<0.001) in the music-verbal-MI (p<0.001) and metronome-verbal-MI groups (p=0.039) when compared to the control group. Fatigue was also measured by the SF-36 vitality subscale, which significantly improved in the music-verbal-MI (p=0.011) and metronome-verbal-MI groups (p=0.032) in comparison to the control group. Clinically significant improvements in physical fatigue were observed only in the music-verbal-MI group (p=0.021).

HRQoL as assessed by the SF-36 significantly improved in the intervention groups when compared to the control group. Bodily pain improved only in the music-verbal-MI group (p=0.014), but not in the metronome-verbal-MI and control groups. The same was true for general health perceptions (p=0.003). Physical functioning and role functioning as measured by the physical functioning subscales and sumscale improved in both intervention groups when compared to the control group. The improvement on the SF-36 physical sumscale in the music-verbal-MI group (p=0.001) was similar to that in the metronome-verbal-MI group (p=0.004) when compared to the control group. Social role functioning significantly improved only in the music-
verbal-MI group (p<0.001). Emotional role functioning improved in both the music-verbal-MI (p=0.047) and metronome-verbal-MI groups (p=0.021) when compared to the control group. Further, there was a significant improvement in mental health in the music-verbal-MI (p<0.001) and metronome-verbal-MI groups (p=0.002) in contrast to the control group. This improvement was also reflected by the SF-36 mental sumscale, with an improvement in the music-verbal-MI (p<0.001) and metronome-verbal-MI groups (p=0.022) in comparison to the control group. Based on the literature, clinically significant improvement in HRQoL using the SF-36 was only evaluated for the physical and mental sumscales. Clinically significant improvements in physical HRQoL were observed in both the music-verbal-MI (p=0.006) and metronome-verbal-MI groups (p=0.006) when compared to the control group whereas in mental HRQoL such clinically significant improvements were seen only in the music-verbal-MI group (p=0.003).

No improvements in HRQoL, as assessed by the EQ-5D-3L Index value, were observed. In contrast, participants’ perception of their health status, as measured by the EQ-5D-3L VAS, significantly improved in both the music-verbal-MI (p<0.001) and metronome-verbal-MI groups (p=0.029) when compared to the control group. The VAS is similar to the SF-36 general health perceptions subscale, which improved only in the music-verbal-MI group. Clinically significant improvements in health status perception (VAS) were seen only in the music-verbal-MI group (p=0.003).

Two aspects of MS-related QoL, physical and psychological QoL, were assessed by the MSIS-29. Physical QoL significantly improved in the music-verbal-MI (p<0.001) and metronome-verbal-MI groups (p<0.001) when compared to the control group. Similarly, psychological QoL also significantly improved after the interventions in the music-verbal-MI (p<0.001) and metronome-verbal-MI groups (p=0.014) in contrast to the control group. Clinically significant improvements in physical (p=0.042) and psychological (p=0.003) QoL were observed only in the music-verbal-MI group when compared to the metronome-verbal-MI and control groups. The effects of rhythm-cued MI on all secondary outcomes and the exact numbers of participants who reached a clinically significant improvement are presented in Table 12.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=44</th>
<th>Metronome-verbal-MI group; N=44</th>
<th>Control group N=43</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MSWS-12</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline$^1$</td>
<td>-6.2 (-52.1, 8.3)</td>
<td>-9.4 (-52.1, 8.3)</td>
<td>0.0 (-39.6, 29.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted p-value$^2$</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clin sig change ≤ -15 points$^3$</td>
<td>N=13/44 (29.5%)</td>
<td>N=13/44 (29.5%)</td>
<td>N=3/43 (7%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Adjusted p-value$^4$</td>
<td>0.033</td>
<td>0.033</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MFIS physical subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline$^1$</td>
<td>-3.5 (-18.0, 5.0)</td>
<td>-4.0 (-16.0, 8.0)</td>
<td>0.0 (-10.0, 19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted p-value$^2$</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clin sig change ≤ -8.9 points$^3$</td>
<td>N=12/44 (27.3%)</td>
<td>N=9/44 (20.5%)</td>
<td>N=2/43 (4.7%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Adjusted p-value$^4$</td>
<td>0.021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MFIS cognitive subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline$^1$</td>
<td>-5.0 (-26.0, 11.0)</td>
<td>-2.0 (-14.0, 6.0)</td>
<td>0.0 (-14.0, 17.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted p-value$^2$</td>
<td>0.001</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clin sig change ≤ -8 points$^3$</td>
<td>N=12/44 (27.3%)</td>
<td>N=6/44 (13.6%)</td>
<td>N=4/43 (9.3%)</td>
<td>0.064</td>
</tr>
<tr>
<td><strong>MFIS psychosocial subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline$^1$</td>
<td>-1.0 (-5.0, 3.0)</td>
<td>0.0 (-5.0, 3.0)</td>
<td>0.0 (-4.0, 4.0)</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>MFIS total score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline$^1$</td>
<td>-9.5 (-36.0, 11.0)</td>
<td>-6.0 (-31.0, 8.0)</td>
<td>0.0 (-28.0, 37.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted p-value$^2$</td>
<td>0.001</td>
<td>0.039</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 12: Effect of Interventions on Secondary Outcomes and Clinically Significant Improvement (Main Study 1).
<table>
<thead>
<tr>
<th>Clin sig change ≤ -16.2 points³</th>
<th>N=11/44 (25%)</th>
<th>N=6/44 (13.6%)</th>
<th>N=3/43 (7%)</th>
<th>0.061</th>
</tr>
</thead>
</table>

SF-36 raw change

<table>
<thead>
<tr>
<th>Change from baseline¹</th>
<th>Adjusted p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 (-4.0, 1.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>0.0 (-2.0, 2.0)</td>
<td>0.0 -1.0, 2.0</td>
</tr>
<tr>
<td>0.0 -1.0, 2.0</td>
<td>0.004</td>
</tr>
</tbody>
</table>

SF-36 physical functioning

<table>
<thead>
<tr>
<th>Change from baseline¹</th>
<th>Adjusted p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0 (-25.0, 70.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>7.5 (-80.0, 35.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>0.0 (-35.0, 30.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SF-36 physical role functioning

<table>
<thead>
<tr>
<th>Change from baseline¹</th>
<th>Adjusted p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.0 (-75.0, 100.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.0 (-25.0, 100.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.0 (-100.0, 100.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SF-36 bodily pain

<table>
<thead>
<tr>
<th>Change from baseline¹</th>
<th>Adjusted p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 (-28.0, 43.0)</td>
<td>0.014</td>
</tr>
<tr>
<td>0.0 (-20.0, 62.0)</td>
<td>0.017</td>
</tr>
<tr>
<td>0.0 (-69.0, 33.0)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

SF-36 general health perceptions

<table>
<thead>
<tr>
<th>Change from baseline¹</th>
<th>Adjusted p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0 (-20.0, 60.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>1.5 (-23.0, 38.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>0.0 (-45.0, 20.0)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

SF-36 vitality

<table>
<thead>
<tr>
<th>Change from baseline¹</th>
<th>Adjusted p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.0 (-30.0, 45.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>5.0 (-25.0, 35.0)</td>
<td>0.032</td>
</tr>
<tr>
<td>0.0 (-55.0, 25.0)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

SF-36 social role functioning

<table>
<thead>
<tr>
<th>Change from baseline¹</th>
<th>Adjusted p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.5 (-25.0, 50.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.0 (-12.5, 50.0)</td>
<td>0.075</td>
</tr>
<tr>
<td>0.0 (-37.5, 50.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 12 (Continued): Effect of Interventions on Secondary Outcomes and Clinically Significant Improvement (Main Study 1).

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<table>
<thead>
<tr>
<th>SF-36 emotional role functioning</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change from baseline</strong>(^1)</td>
<td><strong>Adjusted p-value</strong>(^2)</td>
</tr>
<tr>
<td>0.0 (-66.7, 100.0)</td>
<td>0.021</td>
</tr>
<tr>
<td>0.0 (-100.0, 100.0)</td>
<td>0.047</td>
</tr>
<tr>
<td>0.0 (-66.7, 100.0)</td>
<td>0.012</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>SF-36 mental health</th>
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</thead>
<tbody>
<tr>
<td><strong>Change from baseline</strong>(^1)</td>
<td><strong>Adjusted p-value</strong>(^2)</td>
</tr>
<tr>
<td>8.0 (-24.0, 48.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4.0 (-16.0, 28.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>-4.0 (-20.0, 20.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SF-36 physical sumscale</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change from baseline</strong>(^1)</td>
<td><strong>Adjusted p-value</strong>(^2)</td>
</tr>
<tr>
<td>2.6 (-9.5, 25.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>2.3 (-14.5, 16.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>-2.2 (-24.5, 11.2)</td>
<td>&lt;0.001</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Clin sig change ≥ 5 points(^3)</th>
<th><strong>Adjusted p-value</strong>(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=17/44 (38.6%)</td>
<td>0.006</td>
</tr>
<tr>
<td>N=17/44 (38.6%)</td>
<td>0.006</td>
</tr>
<tr>
<td>N=4/43 (9.3%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SF-36 mental sumscale</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change from baseline</strong>(^1)</td>
<td><strong>Adjusted p-value</strong>(^2)</td>
</tr>
<tr>
<td>3.9 (-15.1, 31.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2.0 (-14, 28.1)</td>
<td>0.022</td>
</tr>
<tr>
<td>-0.3 (-14.9, 14.2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clin sig change ≥ 5 points(^3)</th>
<th><strong>Adjusted p-value</strong>(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=21/44 (47.7%)</td>
<td>0.003</td>
</tr>
<tr>
<td>N=15/44 (34.1%)</td>
<td>0.004</td>
</tr>
<tr>
<td>N=6/43 (14%)</td>
<td>0.003</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>EQ-5D-3L Index value</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Change from baseline</strong>(^1)</td>
<td><strong>Adjusted p-value</strong>(^2)</td>
</tr>
<tr>
<td>0.0 (-0.4, 0.5)</td>
<td>0.370</td>
</tr>
<tr>
<td>0.0 (0.5, 0.2)</td>
<td>0.0 (-0.6, 0.6)</td>
</tr>
<tr>
<td>0.0 (-0.6, 0.6)</td>
<td>0.370</td>
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<table>
<thead>
<tr>
<th>EQ-5D-3L VAS score</th>
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<tbody>
<tr>
<td><strong>Change from baseline</strong>(^1)</td>
<td><strong>Adjusted p-value</strong>(^2)</td>
</tr>
<tr>
<td>8.5 (-10.0, 33.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5.0 (-10.0, 75.0)</td>
<td>0.029</td>
</tr>
<tr>
<td>0.0 (-15.0, 35.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 12** (Continued): Effect of Interventions on Secondary Outcomes and Clinically Significant Improvement (Main Study 1).
<table>
<thead>
<tr>
<th>Change from baseline(^1)</th>
<th>Adjusted p-value(^2)</th>
<th>Clin sig change (\geq 5.5) units(^3)</th>
<th>Adjusted p-value(^4)</th>
<th>N=24/44 (54.5%)</th>
<th>N=15/44 (34.1%)</th>
<th>N=8/43 (18.6%)</th>
<th>0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSIS-29 physical subscale</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline(^1)</td>
<td>Adjusted p-value(^2)</td>
<td>Clin sig change (\leq -7.5) points(^3)</td>
<td>Adjusted p-value(^4)</td>
<td>N=22/44 (50%)</td>
<td>N=19/44 (43.2%)</td>
<td>N=10/43 (23.3%)</td>
<td>0.030</td>
</tr>
<tr>
<td>MSIS-29 psychological subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline(^1)</td>
<td>Adjusted p-value(^2)</td>
<td>Clin sig change (\leq -5.56) points(^3)</td>
<td>Adjusted p-value(^4)</td>
<td>N=25/44 (56.8%)</td>
<td>N=16/44 (36.4%)</td>
<td>N=9/43 (20.9%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Table 12** (Continued): Effect of Interventions on Secondary Outcomes and Clinically Significant Improvement (Main Study 1).

Abbreviations: Clin sig change = clinically significant change, that is, improvement. Colour coding: yellow = walking outcomes; blue = (HR)QoL outcomes; green = fatigue outcomes; significant changes are highlighted in bright yellow and borderline significant changes in dark yellow. **Red coloured questionnaires: lower numbers indicate better performance; blue coloured questionnaires: higher numbers indicate better performance.**

\(^1\)Median (min, max); \(^2\)if overall p-value significant, post-hoc pairwise comparisons were performed between all groups, with Bonferroni correction for 3 comparisons; \(^3\)number of participants (ratio); \(^4\)if overall p-value significant, analysed with Fisher’s Exact test and corrected for multiple comparisons.
Effects of the intervention on secondary outcomes are shown in Figures 14-19. All figures show the differences between baseline and post-intervention measures for individual participants. Medians are indicated by grey bars, and the improvement direction is shown by green arrows. Red dotted lines represent clinically significant improvement benchmarks. Square brackets on top of the figures indicate significant group X time interactions; *significant at the 0.05 level; **significant at the 0.01 level; ***significant at the 0.001 level. No figure legends are provided for reasons of redundancy.

Figure 14: Effect of Intervention on Walking Perception (Main Study 1).
Figure 15, A-D: Effect of Intervention on Physical (A), Cognitive (B), Psychosocial (C) and Total Fatigue (D) (Main Study 1).
Figure 16, A–F: Effect of Intervention on Physical and Mental Health-Related Quality of Life (SF-36) (Main Study 1).
Figure 17, A–E: Effect of Intervention on Vitality and Mental Health-Related Quality of Life (SF-36) (Main Study 1).
Figure 18, A and B: Effect of Intervention on Health-Related Quality of Life (EQ-5D-3L) (Main Study 1)

Figure 19, A and B: Effect of Intervention on Physical and Psychological Quality of Life (Main Study 1).
Chapter 12 – Discussion of the Main Study 1 Findings

12.1 Introduction

The methods used in this study had been tested in the pilot study. Apart from the randomisation and allocation concealment, which typically differ between pilot and larger studies, no changes were required. Therefore, the pilot data were used in the main study, a procedure recommended in the literature and used in other studies (Arain et al, 2010; Leon, Davis & Kraemer 2011; Thabane et al, 2010).

12.2 Power of the Study

For the sample size calculation of this main study, small expected effect sizes (Cohen 1988, 1992) had been used. The analysis from this study showed, however, large effect sizes of the improvements in walking speed ($\eta^2=0.55$) and walking distance ($\eta^2=0.57$). Partial eta squared effect sizes of 0.5 and 0.6 mean that 50-60% of the effect on the dependent variables walking speed and distance, including the error variance are attributable to the intervention (Coe 2002; Cohen 1988). Based on the pilot study findings, a formal and very conservative sample size recalculation was performed prior to the start of the main study. This sample size estimation was used to ensure an adequate $\beta$ power, with $\beta$ being the probability of a type II error ($\beta=0.10$), that is the probability to detect a true change in the population mean and median (Suresh and Chandrashekara 2012). The possibility of a false positive, that is a type I ($\alpha$) error, was reduced by choosing a two-tailed $\alpha$ of 0.05. The power of this study was increased by a large sample size of 142 participants (Button et al, 2013) and by using the most appropriate statistical tests (Erceg-Hurn and Mirosevich 2008).

12.3 Interpretation of Results

In terms of the first and second hypotheses, the analysis of this study showed a significant effect of rhythmic-cued MI on walking. Both music-verbal-MI and metronome-verbal-MI (clinically) significantly improved walking speed (hypothesis 1) and walking distance (hypothesis 2) in the intervention groups when compared to the control group. These results confirmed the pilot study results. Reasons for these effects might be that music is known to induce an ergogenic effect during walking or
running, which improves the endurance while both music and metronome cues have been shown to enhance SMS and increase the walking tempo (Bood et al, 2013; Franek, van Noorden & Rezny 2014; Leman et al, 2013).

For hypotheses 3 to 5, both interventions significantly improved walking perception (hypothesis 3), fatigue (hypothesis 4) and (HR)QoL (hypothesis 5). Interestingly, the effect of the interventions on physical fatigue was significant whereas cognitive fatigue improved only in the music-verbal-MI group and psychosocial fatigue did not improve at all. The fact that cognitive fatigue only improved in the music-verbal-MI group seems surprising since metronome cues are simple and precise cues, which was suggested to be easier. Complex music might well have increased fatigue in participants who were able to remain concentrated. Probably, the verbal cueing provided additional temporal structure to the music beat, which might have compensated for the musical complexity. Alternatively, the motivating and moderately syncopated music might have enhanced attention and SMS. Lower psychometric properties had been attributed to the psychosocial MFIS scale in contrast to the other fatigue subscales and the total MFIS scale; therefore, these authors recommended using the MFIS in clinical trials, but that the psychosocial subscale should be interpreted with caution (Kos et al, 2005). Based on the literature (Karageorghis and Priest 2012; Priest 2003), it seems probable that music-cued MI positively influenced psychosocial fatigue, but this could not be confirmed in the current study.

After the intervention, social role functioning significantly improved only in the music-verbal-MI group. Similarly, bodily pain and general health perceptions only improved in the music-verbal-MI group. In addition, clinically meaningful improvements in mental health, physical fatigue, health status perception and MS-related physical and psychological QoL were only seen in the music-verbal-MI group. In consideration of the literature (Priest 2003), music effects on mood, motivation, arousal and perceived effort are suggested to be responsible for the discrepancy in effects between music-verbal-MI and metronome-verbal-MI (Karageorghis and Jones 2014). This would mean that the music-verbal-MI may have benefitted participants in two respects: the music beat and melody enhanced mood, motivation and energy, and the verbal cueing made the music rhythm clearer and more precise. However, these aspects were not investigated in this main study.
HRQoL, as assessed by the EQ-5D-3L VAS, improved after the intervention compared to the controls, with a clinically significant improvement in health status perception only in the music-verbal-MI group. In contrast, the EQ-5D-3L Index did not improve. A reason for that might be that health-index data are generated by profile-weighting, which is a common approach for economic evaluation. Initially, the ability to perform an economic evaluation was the reason for using the EQ-5D-3L in this study, but it was abandoned because both interventions were low-cost. Both physical and psychological QoL, as measured by the MSIS-29, improved in the music-verbal-MI and metronome-verbal-MI groups. It might be that the MS-specific instrument, MSIS-29, was able to capture relevant changes for pwMS, opposed to the generic instruments, SF-36 and EQ-5D-3L. Clinically meaningful improvements in physical and psychological QoL were seen in the music-verbal-MI group, but not in the other groups, which might have been related to known effects of music on emotional functioning (Karageorghis and Terry 2009; Karageorghis et al, 2010). To summarise, music-cued MI with verbal cueing improved social role functioning, bodily pain, health status perceptions and cognitive fatigue significantly more than metronome-cued MI with verbal cueing. Reasons behind this discrepancy might have been the music effects on psychological functioning.

12.4 Limitations and Strengths of the Study

Critical reflections on this study revealed substantial weaknesses which are discussed as follows. This study was a three-group randomised controlled trial, with the aim of comparing the effects of two interventions against each other and against a control group. Based on this procedure, blinding was not possible as the author was informed about participant group allocation, and the participants realised whether they were in an intervention or control group. This was a clear limitation to this study since participants might have been biased by this knowledge and the researcher could have influenced participants unintentionally.

Furthermore, the walking improvements might have been caused mainly by motivation and not by rhythmic-cued MI. Motivation might have been greater in the intervention groups because of emotional reasons as the participants were aware that they were receiving an intervention. This is in contrast to participants in the control
group who knew that they did not receive an intervention, except weekly phone calls and their usual treatment. By contrast, one might argue that in such a case, motivational factors would have been greater in the music-verbal-MI group than in the metronome-verbal-MI group, with its rather monotonous cues, due to well-known effects from music. Thus, if motivational factors had induced the improvements, walking performance would have been significantly superior in the music-based group. Nevertheless, music-verbal-MI and metronome-verbal-MI were similarly effective on walking performance. On the contrary, clinically significant improvements in walking speed were observed only in the metronome-verbal-MI group. Nonetheless, motivational aspects could have contributed to the walking improvements in both groups because participants knew that they were in an intervention group. This problem could have been solved by use of a third intervention or placebo group.

In the planning stage of this study, measurement of music-related motivation pre- and post-intervention was considered, using the Brunel Music Rating Inventory-2 (Karageorghis et al, 2006). However, this plan was withdrawn because it would not have been feasible to assess music-related motivation in the metronome-cued MI and control groups, and a group comparison would not have been possible.

Verbal cueing was used in this study to emphasise the temporal patterns of the music and enhance attention towards the MI. Verbal cueing in the metronome-based group was also used to enhance attention towards the MI and for the interventions to be comparable. Interestingly, participants in the metronome-verbal-MI group reported that they enjoyed the verbal cues because they provided some diversification to the monotonous cueing, and they helped them to adhere to the programme. Participant acceptability of the interventions was an essential aspect of this and any other study because people would not adhere to a treatment they did not appreciate. Although the verbal cueing seemed to have increased the acceptability of the metronome-cued MI, the music-based intervention seemed to have been far preferable to the participants. Participants in the music-verbal-MI group reported that they found the intervention acceptable or even pleasurable, probably due to effects of the music. Some participants in this group reported that the verbal cueing helped them to overcome timing problems during the MI. However, these reports could not be
considered sufficient evidence to support the benefit of verbal cueing during the music-cued MI. Further, it was impossible to draw valid conclusions on the relationship between any of the cueing types and the walking improvements because two combined interventions were tested in this study.

Participants in this study seemed to have been able to perform MI. Previous studies had shown a lower capacity to practise MI in pwMS (Heremans et al, 2012a; Tabrizi et al, 2013a; Tacchino et al, 2013). These authors linked impaired MI ability in this population particularly to cognitive dysfunction (Heremans et al, 2012a; Tacchino et al, 2013) and depression (Tabrizi et al, 2014). Therefore, persons with cognitive impairment and/or depression were excluded from the current study. Despite these measures, this study failed to provide evidence demonstrating the MI ability in this population, such as by using an MI ability questionnaire or a mental chronometry measure. Hence, there was an information gap in terms of the participants’ ability to perform kinaesthetic MI (Malouin et al, 2007) and to maintain the temporal organisation in their imagined movements (Collet et al, 2011; Guillot and Collet 2005a). Participants could have used visual imagery or no MI at all. Should they have used visual imagery, potentially visual imagery might be more useful in the MS population. If participants were able to practice MI, it would have been important to know whether their ability improved with training. If they did not use any MI, an intervention mainly based on MI would have been useless. Initially, it had been proposed by the author to use fMRI scanning to measure the activations in MI related brain areas. A neuro-radiologist from Innsbruck Medical University had offered his commitment to the study. However, it was not possible for the supervisors as physiotherapists to supervise such a neuro-radiological study, and they expressed concerns about study-related risks.

SMS between the rhythmic auditory cues and walking were hypothesised to occur in this study. Rhythmic auditory cueing of the MI may have provided a temporal framework, leading to activation of the auditory-motor circuit and rhythmic entrainment. These notions were based on previous findings demonstrating that rhythmic auditory cues synchronise the motor response in such a way that people unconsciously adapt their movement, such as walking, to the tempo of an external rhythm (Roerdink et al, 2011; Tecchio et al, 2000). Indeed, participants in the main
study improved their walking performance, but it was not possible to evaluate whether any synchronisation with the cues occurred. In a study by Styns et al. (2007) healthy people with different degrees of music training walked on an athletic track and were accompanied by music or metronome beats. Some people were not able to synchronise their step frequency, but increased their walking tempo when the music or metronome tempo was fast. This phenomenon was also seen in people with Huntington´s disease who increased their gait speed with metronome cues although they did not synchronise their gait with the external cues. This observed phenomenon was even stronger with the music cueing (Thaut et al, 1999). Theoretically, in participants of the current study, the improvement in walking speed could have been associated only with a tempo modulation with the rhythmic cueing, but not with an accurate synchronisation between the cadence and rhythmic auditory cues. However, people with Huntington’s disease frequently have cognitive deficits, which may impair their timing mechanisms and synchronisation ability, particularly with complex music rhythms whereas pwMS who had impaired cognition were excluded from the current study.

To the author’s knowledge, thus far no studies have investigated gait synchronisation with rhythmic cues in pwMS. Two studies explored the effects of RAS on walking in pwMS, having shown improvement in certain gait parameters and walking speed (Baram and Miller 2007; Conklyn et al, 2010). Unfortunately, none of these studies tested for SMS, and both studies were very small and of questionable methodological quality. In people with other neurological disorders, synchronisation with metronome cues or music was mainly measured during finger tapping, but also the evidence was meagre. Some of these studies found that severe motor timing deficits in people with Parkinson´s disease improved after training (Benoit et al, 2014), as did their tapping variability (O’Boyle, Freeman & Cody 1996). Further studies found that people who had suffered from a stroke were able to synchronise their steps to metronome cues, in particular when both footfalls were cued (Roerdink et al, 2009). Other people with stroke were also able to correct for metronome phase shifts during treadmill walking although they were somewhat slower when using their hemiparetic limbs (Pelton et al, 2010). Only one study was found showing effects of music cueing on spatiotemporal gait variability in people with stroke (Thaut et al, 1993). Therefore, based on the literature and main study results, it could be hypothesised that pwMS synchronised
their imagined gait with rhythmic auditory cues, and that rhythmic entrainment contributed to their walking improvements, the latter probably being an underlying mechanism. To be able to validate these mechanisms, a further study was needed.

12.5 Future Work: Study 2

A second study was required to address any weaknesses and open questions remaining from the main study. Study 2 was used to validate the mechanism of rhythmic cueing and MI interventions on walking, fatigue and QoL in pwMS. Furthermore, the effect of different MI interventions on walking, fatigue and QoL needed to be assessed to explain some of the main study results. QoL, but not HRQoL, was measured, as the MS-specific instrument, MSIS-29, was more sensitive and able to capture changes which are relevant to pwMS. To address the concern that solely motivational factors might have caused the improvements in walking in this study, it was considered more useful to compare the effects of rhythmic-cued MI with non-cued MI, instead of employing a non-treatment control group.

Music-verbal-MI was superior to metronome-verbal-MI in terms of significantly improving social role functioning, bodily pain, health status perceptions and cognitive fatigue. In addition, a clinically meaningful improvement in mental health, physical fatigue, health status perception and physical and psychological QoL was only seen in the music-verbal-MI group. In the light of these results and due to ethical reasons, it was regarded as useful to build on the music-verbal-MI intervention in Study 2. It may not have been acceptable to use metronome-cued MI without verbal cueing for a comparison because listening to metronome cues for seventeen minutes, six days per week over four weeks might have been unduly burdensome in a home-based MI study. These suggestions were supported by participant reports on the level of their acceptability of the interventions.

Insufficient evidence on the contribution of the various rhythmic cueing elements to the improvements in walking, fatigue and QoL was produced by Study 1. Therefore, it was regarded as necessary to investigate the effect of music cueing and verbal cueing on MI ability in a further study. A comparison between non-cued MI and music-cued MI, and against music-verbal-MI, would enable an examination of whether the verbal cueing or the music helped to improve cognitive fatigue. If that
were the case for both, it would be a justification to maintain the verbally-cued music cueing of the MI to treat walking and fatigue in pwMS.

As it was not clear whether participants in the main study were able to practise kinaesthetic MI, further investigations were needed to explore the MI ability in this population. For this purpose, an MI questionnaire appropriate for pwMS and a mental chronometry test were planned for use to assess MI capacity in the participants and their use of kinaesthetic MI. A mental chronometry test either compares the duration of MI compared with that of actual movement execution, or the number of imagined movements within different time periods. Normally, both durations are expected to be similar (Decety, Jeannerod & Prablanc 1989) and the number of movements increases with longer time periods (Malouin et al, 2008b), as described in detail in Chapter 2.8.4.

For Study 2, the question arose about whether MI ability testing would be useful solely at the baseline. This is because a treatment mainly based on MI would only be reasonable if participants had adequate ability to imagine movements from the onset; in addition, only if the Study 2 results indicate an adequate MI ability in participants, it could have been used and induced any changes in Study 1. A single uncontrolled study was found that investigated the effects of MI training on fatigue, QoL and walking in pwMS, showing improvement in fatigue and QoL but not walking after ten sessions of MI training within five weeks, and the MI ability was not assessed (Catalan et al, 2011). Studies in people with neurological disorders other than MS demonstrated that MI ability can be improved by practice. For example, in people with stroke, MI ability and gait performance significantly improved after a fifteen-minute MI training program, three times a week for six weeks (Dunsky et al, 2008). Two other studies in the stroke population demonstrated significantly improved walking and kinaesthetic MI ability after daily MI practice over six weeks (Oostra et al, 2015), and significantly improved arm movements after six sessions of MI practice (Grabherr et al, 2015). Thus, for the present study, MI ability testing post intervention was also considered important as it would show potential MI training effects.

To be able to address the question of whether SMS occurred during rhythmic-cued MI, measurements were planned for gait synchronisation with rhythmically
accentuated music during real gait in Study 2. Due to the nature of the intervention in this study, functional imagery techniques would have been required to measure changes in the activation of neural circuits, which are known to be responsible for SMS. Unfortunately, neither the technique, nor the knowledge was available for the author. Alternatively, a measurement of SMS during actual walking after the intervention was considered to assess whether there was a potential transfer from the (cued) MI to actual walking. Nevertheless, there was a problem in that, according to RAS intervention recommendations (Thaut 2005), during the rhythmic-cued MI, music and metronome cues at different tempi were used and continued to be used in the new study; therefore, it would have been impossible to measure the actual step synchronisation with the cue frequency. Otherwise, it would not have been possible to account for individual gait differences and differences in gait speed between people with mild and moderate MS. Hence, it would have been impossible to know the cueing tempo at which gait synchronisation may have occurred. In terms of another approach, measuring SMS during actual walking with music or metronome cueing was considered, but it seemed possible that the mental character of MI might be compromised as actual walking and MI are different from each other. Nevertheless, the practical implementation of the synchronisation measurements required overt gait performance, and so it would have been unavoidable to violate the purely mental character of MI (Johnson 2011).

Therefore, based on the above stated justification, assessments of the synchronisation of participant gait with music at a regular metre pre- and post-intervention was chosen for Study 2. Having used this approach, it could be evaluated if and to what extent their gait synchronised with the music beat, and whether they synchronised to a greater degree after music-cued MI, with or without verbal cueing, when compared to non-cued MI.

12.4 Conclusions

Results from the main study show that rhythmic-cued MI improved walking, fatigue and (HR)QoL in pwMS when compared to no treatment. However, despite these interesting findings, it was not possible to identify the mechanisms underlying the improvement from this study design. The different elements of the interventions, the
MI and three cueing types could not be distinguished, in terms of their influence on the outcomes. As there was a non-treatment control group instead of a placebo group, the improvements could have been produced by motivational factors. Thus, the interventions needed to be compared to a third intervention group consisting of non-cued MI to address the concern that motivational factors were responsible for the improvements in walking, fatigue and QoL. It was also shown that some QoL parameters and cognitive fatigue only improved in the music-verbal-MI group, which, apart from ethical concerns, was the reason for using only music and verbal cueing in the new study.

It was still unclear after Study 1 whether the music or verbal cueing of the MI or the MI alone was the factor that improved walking, fatigue and QoL. Therefore music-cued MI with and without verbal cueing needed to be compared against each other and against non-cued MI, regarding their effects on walking, fatigue and QoL. Additionally, it was necessary to assess the MI capacity in a study population similar to that of the main study since it was unknown whether the participants actually practiced kinaesthetic MI. Moreover, to be able to link the MI in walking to the SMS of rhythmic entrainment, it was necessary to examine whether gait synchronisation with music cues occurred in participants, and whether the synchronisation would change after the interventions. To resolve all these outstanding issues, Study 2 was required.

### 12.7 Dissemination of Findings

The results of this study were disseminated to the participants. The main results were presented at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in October, 2015 (Seebacher et al, 2015c) and the 13th Annual Conference of the Austrian Society for Neurology in March, 2016 (Seebacher et al, 2016a). An article in lay language was published in the patient magazine of the Austrian MS Society (Seebacher 2016). A scientific article was published by the Multiple Sclerosis Journal (Seebacher et al, 2017) (see Appendix 19). It was recognised by the author and clearly stated in the article that all intellectual property belongs to the University of Brighton.
Chapter 13 - Introduction to Study 2

13.1 Introduction

Study 2 was used to validate the results from Study 1 and to explore the mechanisms of rhythmic cueing and MI interventions on walking, fatigue and QoL in pwMS. Following the results from Study 1, the current intervention is built on the music- and verbally-cued MI intervention, so that three intervention groups were used: (1) music- and verbally-cued MI, (2) music-cued MI and (3) non-cued MI, that is, MI alone.

The research question, aims, objectives and null-hypotheses of Study 1 and Study 2 were described in Chapter 1.3 to 1.7.

13.2 Funding

The material costs of the study were funded by the Austrian MS Research Society; all other costs were borne by the author.

13.3 Ethics Approval and Governance

Study 2 was approved by the Tier 2 College Research Ethics Committee (CREC) of the University of Brighton on 17 December, 2015 (see Appendix 14) and the Ethics Committee of the Medical University of Innsbruck on 26 February, 2016 (reference number: AN2014-0052 334/4.14 358/5.13 (3743a); see Appendix 15). All participants provided written informed consent and were reimbursed for travel expenses only. For the potential publication of photos from their video recordings, with their faces made unrecognisable, participants received a separate consent form, which they could sign or refuse to sign (see Appendix 13). All ethical principles outlined in Chapter 5 were adhered to in this study.

13.4 Clinical Trials’ Registration Number

Study 2 was prospectively registered under the reference number: ISRCTN92351899, on 10 December, 2015 at the ISRCTN Registry (Seebacher et al, 2015a). After completion, the record was updated.
13.5 Intellectual Property and Conflicts of Interest

This information was provided in Chapter 1.9.

13.6 Project Team

Study 2 employed the same research team as Study 1 (see Chapter 1.10 and Appendix 6).

13.7 Study Design

Study 2 was a three-group parallel randomised single-centre trial including a reliability study and a pilot study conducted at the MS-Clinic Innsbruck, Austria. This study sought to explore the primary outcomes: walking speed and walking distance, also the secondary outcomes: fatigue, QoL, MI ability and SMS, and of the physiotherapy interventions: (1) music- and verbally-cued MI, (2) music-cued MI and (3) MI alone in pwMS. For reasons of clarity, henceforth the music- and verbally-cued MI group is referred to as the ‘music-verbal-MI group’, the music-cued MI group as the ‘music-MI group’ and the MI alone group as the ‘non-cued-MI group’.

Chapter 14 describes the Pilot Study 2 methods and results for the primary outcomes, walking speed and walking distance, including the secondary outcomes of fatigue and QoL. The chapter focuses on how the pilot study informed the main study. Chapter 15 presents the Main Study 2 methods and results for the primary outcomes, walking speed and walking distance, and the secondary outcomes of fatigue and QoL. Chapter 16 provides the measurements of the secondary outcomes in view of the MI ability used in the Pilot and Main Study 2; it also presents the related statistics and results. Chapter 17 details the secondary outcomes of SMS used in Study 2 and a reliability study carried out to test the gait analysis system including implications for Study 2. Chapter 18 describes the SMS measurement and results in the Pilot and Main Study 2. Chapter 19 presents an in-depth discussion of Study 2. Chapter 20 provides an overall discussion on the findings from studies 1 and 2 and presents the original contribution to knowledge and recommendations for future work.
**Chapter 14 – Pilot Study 2: Walking, Fatigue and Quality of Life**

**14.1 Aims**

The aims of the pilot study were to assess the feasibility of the main study and to test the methods. The further aims of this study were to obtain preliminary information on the changes of walking speed, walking distance, fatigue, QoL and MI ability. The additional aims of this study were to collect preliminary data on the MI capability at baseline and on the changes of MI ability and SMS (Chapters 16 and 18). The study was also used to assess the reliability of the gait analysis instruments, as described in Chapter 17.

**14.2 Methods**

**14.2.1 Participants**

Study 2 was used to validate the results from Study 1 and to investigate the mechanisms of the rhythmic-cued MI intervention; therefore, identical inclusion and exclusion criteria to Study 1 were employed in this second pilot study (see Chapter 7.2.1). The participants were selected following the same procedure as Study 1. A CONSORT flow diagram is shown in Figure 20.
Figure 20: CONSORT Extension to Pilot and Feasibility Studies (Eldridge et al, 2016)
Flow Diagram of the Pilot Study 2.
14.2.2 Sample Size

The goal of this pilot study was to assess the feasibility of the subsequent fully-powered main study. The study compared 15 pwMS in three equally-sized groups, described above. The results from the pilot study’s primary outcome of walking distance were used to recalculate the main study’s sample size (Lancaster, Dodd & Williamson 2004).

14.2.3 Recruitment

Recruitment was conducted over the period from 3 March to 14 April, 2016, using exactly the same procedure as in Study 1, described in Chapter 7.2.3.

14.2.4 Randomisation

Precisely the same approach was employed for the pilot study as it was for Study 1 (see Chapter 7.2.4), except that the total number of participants was 15. Moreover, the numbered envelopes had the figures 1, 2 and 3 on them.

14.2.5 Allocation Concealment and Blinding

Blinding was not possible since the total study conduct, including the statistical analysis and writing, were performed by the author. Participants became aware which group they were allocated to; in contrast to Study 1, there were only intervention groups in this study. Participants were instructed not to discuss allocation or intervention content with other participants and not to forward the study CDs to anybody.

14.2.6 Data Collection

The data collection was performed in exactly the same way as Study 1, outlined in Chapter 7.3. The assessment order was random, as described in Chapter 9.8.4. For the data collection pre- and post-intervention, validated walking tests and patient-rated questionnaires on walking, fatigue and QoL were used (see Chapter 3).
14.2.7 Primary Outcomes: Walking Speed and Walking Distance

As in Study 1, the primary outcomes were walking speed, as measured by the T25FW (Kaufman, Moyer & Norton 2000), and walking distance, as assessed by the 6MWT (Goldman, Marrie & Cohen 2008). An analysis of the primary outcome of walking distance was used to re-calculate and confirm or amend the proposed sample size. This was because according to clinical judgement and research findings, a 20% improvement in walking distance is relevant for the patients in their daily lives (Applebee et al, 2015; Learmonth et al, 2013).

14.2.8 Secondary Outcomes: Fatigue and Quality of Life

The secondary outcomes of this study were fatigue and QoL, as assessed by the MFIS (Fisk et al, 1994) and MSIS-29 (Hobart et al, 2001). Preliminary information on the change in fatigue and QoL was collected in this study. All questionnaires were in German. A clinical research file, including data collection sheets in English, is attached in Appendix 16.

14.2.9 Feasibility

This study evaluated the feasibility of conducting a full-scale RCT. The criteria for feasibility success were: a) a target recruitment rate of 5.7% out of 174 eligible patients (that is, 10 participants per month), b) a target retention rate of 80% and c) a target minimum adherence rate of 67% (that is, 4 practice sessions per week out of a maximum of 6).

The research looked out for falls, excessive fatigue, psychological distress or other safety-related occurrences. Participants were asked to report any adverse events, during and after the interventions. Severe adverse events would have led to early study termination. During the weekly phone calls, participants were asked for their feedback on the study procedures. MI practice was noted by participants in a diary; adherence was evaluated as the (rhythmic-cued) MI practice frequency, which ranged from 0 to 6 times per week. Acceptability of the interventions referred to kinaesthetic MI, melodies, beat tempo and the verbal cueing.
14.2.10 Administration Time of Outcome Measures

The administration time and procedure of the walking, fatigue and QoL measures were introduced in Chapter 3.

14.2.11 Clinical Significance

Minimal clinically significant changes in the walking, fatigue and QoL outcomes and rationales for their choice were discussed in Chapter 3.

14.2.12 Intervention

The interventions in this study consisted of rhythmic-cued MI and non-cued MI. The intervention in the music-verbal-MI group 1 was very similar to that of the music-verbal-MI group in Study 1, described in Chapter 7.4; following participant feedback from Study 1, with suggestions about using musical pieces with a faster beat, appropriate music pieces were selected. In the music-MI group 2, exactly the same music but no verbal cueing was used with the MI. In the non-cued-MI group 3, the same MI tasks were performed as in the other groups while no cueing was used.

As in Study 1, prior to the intervention, study participants were familiarised with the rhythmic-cued and non-cued MI using the PETTLEP approach (Holmes and Collins 2001), outlined in Chapter 7.4. In the music-verbal-MI group, external timing was provided: “imagine yourself walking in time with the music and verbal cueing”. In the music-MI group, the instructions were similar: “imagine yourself walking in time with the music”. In the non-cued MI group, timing was internal and depended on the tempo and intensity of the walking tasks.

After the instructions, participants received the CD or a music download link consistent with their group allocation. To be able to validate the rhythmic-cued MI interventions and investigate the mechanisms of the improvements observed in Study 1, the duration of both the study and the practice were equal to that in Study 1. This means that participants were asked to practice kinaesthetic MI six times a week and once a day for seventeen minutes over four weeks, in a sitting position, with eyes closed. Four audio mixes, designed in the same way and one for each week, were on one CD to enhance attention towards the MI and to facilitate adherence (see Chapter
2.14). As in Study 1 and as described in Chapter 7.4.3, participants in all groups received weekly phone calls from the author. A detailed intervention script based on the Template for Intervention Description and Replication (TIDieR template) (Hoffmann et al, 2014) is presented in Appendix 9, Table A2. The intervention is shown in Figure 21.

**Figure 21:** Interventions for the Pilot Study 2 (created by the author)
14.3 Data Analysis

14.3.1 Statistical Analysis

The statistical analysis of this study was based on the research question and hypotheses of the study described above. All statistics were performed, as detailed in Chapter 7.5.1 using IBM SPSS software, release 23.0 (IBM Corporation, Armonk, New York, USA) and GraphPad Prism 6 (GraphPad, San Diego, California, USA). The recruitment rate (%) was determined by dividing the number of participants who consented by the number of patients eligible, multiplied by 100. The retention rate was estimated: \((N\ text{who\ completed\ the\ study}/N\ text{total\ sample}) \times 100\), where \(N\) is the number of participants. The adherence rate was reported as the percentage of the scheduled (cued) MI practice (6x/week), actually performed by the participants over the 4 week study period (Osterberg and Blaschke 2005). The eligibility and consent rates were calculated with 95% confidence intervals (CIs), according to the Wilson ‘score’ method cited by Newcombe (1998); when the proportion was not close to 0 or 1, a Poisson approximation, as described by Brown, Cai & DasGupta (2001), was used.

Owing to the small sample size, no significance testing was performed in this study for any of the outcomes. Participants’ baseline characteristics were presented without p-values (see Chapter 7.5.1). Descriptive statistics were reported for all outcomes. Normality tests were applied for continuous outcomes (see Appendix 17). The small sample (n=15) could have contributed to the failure of detecting a non-normal data distribution. Therefore, medians (25th-75th percentiles) were reported for ordinal and also continuous data: fatigue and QoL (both: 5 categories); walking speed and walking distance. The median (minimum, maximum), that is, (min, max), was reported for the EDSS, age and compliance (7 categories: 0-6 times per week). Raw count (frequency and percentage) was reported for nominal data (recruitment rate, retention rate, missing data, falls and adverse events). Acceptability of the intervention was reported narratively and recorded in excel files.

The sample size for the Main Study 2 was based on the between-group differences (percentage improvement) in walking distance, as assessed by the 6MWT. Relevant evidence recommended longer walking tests as superior outcome measures over short walking tests because they also assess endurance, fatigue and
cardiorespiratory fitness, all of which are relevant for peoples’ daily life activities (Feys et al, 2014; Goldman, Motl & Rudick 2010). In addition, in pwMS with low disability levels, the 6MWT has been shown to be more responsive to change than the T25FW (Hobart et al, 2003; Paltamaa et al, 2008). Therefore, the changes in 6MWT results seemed to best reflect the changes in walking performance in the study population.

The sample size was estimated through the HyLown Consulting LLC Power and Sample Size Calculator⁶ (HyLown 2013) using the following formula (Chow, Shao & Wang 2008)

\[ N = p_0 (1 - p_0) \left( \frac{Z_{1-\alpha} + Z_{1-\beta} \sqrt{p(1-p)/(p_0(1-p_0))}}{p-p_0} \right)^2 \]

where \( N \) is the sample size, \( p_0 \) is the comparison value, \( \alpha \) is the type I error rate which was set at 5%. \( Z \) is the critical value of the normal distribution at \( \alpha/2 \) (a confidence level of 95% was used, so \( \alpha=0.05 \) and \( Z=1.96 \)). \( \beta \) is the Type II error rate, which was set at 0.2 and is consistent with an 80% power (\( \text{power}=1-\beta \)).

### 14.3.2 Missing Data

The missing data were dealt with, as described in detail in Chapter 7.5.2.

### 14.3.3 Intention-to-Treat Analysis

An intention-to-treat analysis was performed, as described in Chapter 7.5.3.

### 14.4 Results

#### 14.4.1 Feasibility

a) 174 out of 339 people with MS were eligible for the study, corresponding to an eligibility rate of 51.3% (95% CI 46.0, 56.6%). Of these 174 participants, 15 consented to the study within one month, which is a recruitment rate of 8.6% (95% CI 5.2, 13.8%). This recruitment rate exceeded the target recruitment rate of 5.7%.

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b) All 15 participants completed the study and there were no missing data, both corresponding to a 100% retention rate (95% CI 76.4, 100%). This retention rate surpassed the target retention rate of 80%.

c) With reference to a maximum practice frequency of 6 times per week, participants reported to have practised median 5 (range 4, 6) times per week. This adherence rate of 83% (95% CI 0.42, 0.99) was greater than the target adherence rate of 67%.

These recruitment, retention and adherence rates indicated the success of the feasibility criteria.

No safety-related events such as falls occurred in this study. Participants were allowed to rest at any time during the instructions and assessments. The intervention could be practised at home and in a sitting position; participants reported voluntarily that this was safe and convenient. No adverse events related to this home-based study were reported. Phone calls were considered supportive by participants. One participant in the non-cued-MI group reported minor concentration problems during the MI which resolved with practice. Overall, participants in the non-cued-MI group appeared to be satisfied with the interventions. All participants in the music-verbal-MI and music-MI groups reported that they liked the music styles, melodies, and tempo changes of the music pieces. To summarise, the interventions were found to be acceptable or even pleasurable.

14.4.2 Baseline Data

The median (min, max) age of the total study population was 50.2 (42.1 to 58.3) years. The median (min, max) EDSS was 3.0 (1.5, 4.5). Participants in the non-cued-MI group were younger and walked faster and a longer distance. In the non-cued-MI group, one participant used two walking sticks during all walking tests. Participants in the music-verbal-MI group were more disabled, showed higher fatigue values and lower QoL. The female-to-male ratio was 6.5:1, as only two males participated in this study. In Table 13, participants' baseline characteristics are presented.
## Table 13: Participants’ Baseline Characteristics in Walking, Fatigue and Quality of Life (Pilot Study 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=5</th>
<th>Music-MI group N=5</th>
<th>Non-cued-MI group N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F:M)</td>
<td>N=4:1</td>
<td>N=5:0</td>
<td>N=4:1</td>
</tr>
<tr>
<td>Age (years)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>52.0 (41.0, 69.0)</td>
<td>54.0 (34.0, 72.0)</td>
<td>37.0 (27.0, 74.0)</td>
</tr>
<tr>
<td>EDSS&lt;sup&gt;1&lt;/sup&gt;</td>
<td>4.5 (2.0, 4.5)</td>
<td>2.5 (2.5, 4.5)</td>
<td>2.5 (1.5, 4.5)</td>
</tr>
</tbody>
</table>

### Walking aid use during testing within groups

<table>
<thead>
<tr>
<th>No/unilateral/</th>
<th>N=5/0/0</th>
<th>N=5/0/0</th>
<th>N=4/0/1</th>
</tr>
</thead>
<tbody>
<tr>
<td>bilateral aid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T25FW&lt;sup&gt;2&lt;/sup&gt; (seconds)</td>
<td>5.6 (5.2, 6.2)</td>
<td>7.0 (5.3, 7.0)</td>
<td>4.9 (4.6, 5.4)</td>
</tr>
<tr>
<td>6MWT&lt;sup&gt;2&lt;/sup&gt; (metres)</td>
<td>367.5 (348.0, 435.2)</td>
<td>380.6 (337.2, 392.0)</td>
<td>460.5 (442.9, 476.8)</td>
</tr>
</tbody>
</table>

### MFIS

| Physical sub<sup>2</sup> | 21.0 (2.0, 25.0)         | 12.0 (10.5, 25.0) | 16.0 (9.0, 21.0)      |
| Cognitive sub<sup>2</sup> | 17.0 (11.5, 22.5)        | 3.0 (0.0, 16.5)   | 11.0 (11.0, 14.0)     |
| Psychosocial sub<sup>2</sup> | 2.0 (1.0, 4.0)         | 2.0 (0.0, 5.0)    | 3.0 (1.5, 5.0)        |
| Total score<sup>2</sup>   | 40.0 (17.5, 51.0)        | 28.0 (13.0, 39.0) | 30.0 (23.5, 38.0)     |
| Total score ≥38           | N=3                      | N=2               | N=1                   |

### MSIS-29

| Physical sub<sup>2</sup> | 45.0 (17.5, 49.4)        | 20.0 (17.5, 39.4) | 16.2 (10.6, 35.6)     |
| Psychological sub<sup>2</sup> | 27.8 (18. 33.3)         | 11.1 (17.5, 39.4) | 11.1 (8.3, 25.0)      |

Abbreviations: F:M = females:males; N = Number of participants; EDSS = Expanded Disability Status Scale; T25FW = Timed 25-Foot Walk; 6MWT = 6-Minute Walk Test; MFIS = Modified Fatigue Impact Scale; MSIS-29 = MS Impact Scale-29; sub = subscale.

<sup>1</sup>Median (min, max); <sup>2</sup>median (25th-75th percentiles). Colour coding: yellow = walking outcomes; green = fatigue outcomes; blue = QoL outcomes. **Red coloured**
questionnaires/tests: lower numbers indicate better performance; blue coloured questionnaires/tests: higher numbers indicate better performance.

14.4.3 Primary Outcomes: Walking Speed and Walking Distance

Walking speed (T25FW) refers to hypothesis 1 and walking distance (6MWT) to hypothesis 2 of this study. Post-intervention, for all intervention groups, the median time to walk decreased, that is, walking speed increased, and the median walking distance increased. The largest median improvement in walking distance was observed in the music-verbal-MI group, with 85.5 (25th-75th percentiles 59.4, 97.1) metres, or 23%, compared to 65.1 (25th-75th percentiles 39.5, 74.8) metres (9.8%) and 33.6 (25th-75th percentiles 11.6, 77.7) metres, or 3.5%, in the music-MI and non-cued-MI groups. Descriptive data for changes in the time to walk and walking distance between baseline and post-intervention in all participants are presented in Figure 22 and Table A7 (see Appendix 17).

**Figure 22**: Walking Performance Pre- and Post-Intervention (Pilot Study 2).

Figure legend: medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and (min-max) by the whiskers.
14.4.4 Secondary Outcomes: Fatigue and Quality of Life

Fatigue (MFIS) refers to hypothesis 3 and QoL (MFIS-29) to hypothesis 4 of this study. Pre-intervention, 6 out of 15 participants had fatigue, indicated by at least 38 points on the MFIS (Flachenecker et al, 2002), with only 2 participants out of this total in the music-verbal-MI group. Post-intervention, improvement in fatigue was seen in all groups. Physical QoL improved in all groups whereas psychological QoL improved only after the music- and non-cued MI. In Table A8 (see Appendix 17), descriptive information for the fatigue and QoL data is provided. Descriptive information for all secondary outcomes at baseline and post-intervention within groups is presented graphically in Figures 23 and 24.

Figure 23: Fatigue Pre- and Post-Intervention (Pilot Study 2).

Figure legend: the red line represents the cut-off point for fatigue, as defined at ≥38 points on the MFIS. Figures 23 and 24: medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and (min-max) by the whiskers.

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14.5 Implications for the Main Study 2

This study explored the feasibility of a larger main study and piloted the methods to use to be able to justify their use or change in the main study. In this section, consequences for the main study resulting from the pilot study will be described.

14.5.1 Feasibility

The observed recruitment and retention rates and adherence rate exceeded the pre-specified target rates so that a larger study appeared feasible. Participants in all groups appreciated the telephone support on the cued or non-cued MI practice, which could have facilitated adherence. It is recognised that even with careful monitoring via phone-calls, participants could have stated their adherence rates slightly incorrectly.

No adverse events were reported by participants in this study. No falls or other safety-related events occurred. There were no missing data because the questionnaires were immediately checked for completeness by the author, and participants were asked to fully complete them. This procedure worked flawlessly; therefore, it will continue to be used in the main study.

Continuous support and intensive practice seemed to have dissolved any problems with kinaesthetic imagery. All 10 participants in the music-cued MI groups reported that they were fond of the music styles and viewed the intervention as acceptable, if
not pleasurable, which was the case in 8 out of 10 participants. Based on the high acceptability of the music types and tempo, a decision was made to use the same music in the main study. All 5 participants in the non-cued MI group were satisfied with the intervention, and two of them regarded the intervention as pleasurable since they appreciated the focus on their imagined movements without any distraction. Therefore, the same non-cued MI intervention was used in the main study.

14.5.2 Randomisation and Allocation Concealment

Recruitment in this study involved restricted randomisation since the participants drew sealed envelopes from a black bag, but with no stratification for relevant predictive factors, in view of the small sample size. Random variations in the small sample may have contributed to the imbalances in groups, with respect to population characteristics, such as gender and age, disability, fatigue and walking performance. During the planning stage of the study, identical to Study 1, the randomisation procedure for the main study was devised. Randomisation was to be stratified on the three relevant predictive factors for a change in walking in pwMS, which are age, gender and disability. For the main study, the study protocol clearly stated the predefined allocation procedure, as already described for Study 1 (see Chapter 9.8).

14.5.3 Primary Outcomes: Walking Performance and Main Study 2 Sample Size

Both walking tests (T25FW and 6MWT) were performed smoothly during the Pilot Study 2 so that no changes to the walking tests were required in the Main Study 2. Rhythmic-cued and non-cued MI improved walking distance, with greater changes seen after cued MI, of median 85.5 (25th-75th percentiles 59.4, 97.1) metres in the music-verbal-MI group, 65.1 (25th-75th percentiles 39.5, 74.8) metres in the music-MI group and 33.6 (25th-75th percentiles 11.6, 77.7) metres in the non-cued-MI group.

On basis of the improvement in walking distance observed in Study 1, according to the study protocol, the estimated a priori sample size for the Study 2 including the Pilot Study 2 was 75 participants. The sample size for the Main Study 2 was recalculated using the LLC Power and Sample Size Calculator7 (HyLown 2013). Based on the differences in walking distance between the groups as above and

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according to a conservative estimation and given the small sample size of the pilot study, the true difference in the three intervention means ($\delta$) was expected to be 20%. Hence, when assuming a power of 80% ($\beta=0.20$; type II error probability), 18 participants in each intervention group were required to be able to reject the null hypothesis, which stated that the population means of the three intervention groups were equal. The type I error probability ($\alpha$) associated with this test of this null hypothesis was 0.05. This significance level of 0.05 was expressed at a confidence interval of 95%, which means the author could be confident that based on the study data, 95% of the follow-up means reflected a true change in population means (Field 2009). Given an anticipated attrition of 10%, 60 participants (20 per group) were needed to study in the main study. This result confirmed the estimated a priori sample size calculation.

14.5.4 Secondary Outcomes: Fatigue and Quality of Life

The fatigue and QoL questionnaires were completed effectively by the participants. There was no need to rest for the majority of participants; however, there was sufficient time and space for a rest and to have refreshments. Participants reported no problems with the type and number of questionnaires, which meant that all questionnaires were able to be used for the main study as well.

14.6 Limitations of the Study

The small sample size is a limitation of this study because there was an imbalance between groups at baseline. Due to the random allocation, this was expected and did not influence the results, which were descriptive and did not include efficacy testing.

As in Study 1, the lack of blinding is certainly a limitation of this study. For practical reasons, blinding was not possible since there was no other researcher, physiotherapist or student available to assist with the assessments.
Chapter 15 – Main Study 2: Effects of Cued and Non-Cued Motor Imagery on Walking, Fatigue and Quality of Life

15.1 Methods

In this chapter, Main Study 2 will be described, only with regard to the walking, fatigue and QoL data. Data from the main and pilot studies were analysed separately although no changes to the methods and assessments were required. Triggered by the reviewers’ and editors’ feedback during the publication of the Study 1 data, guidelines and relevant literature on pilot studies were revisited (Kistin and Silverstein 2015; Lancaster, Dodd & Williamson 2004; Leon, Davis & Kraemer 2011). Following their recommendations, the pre-determined stratified randomisation was designed without the pilot data. This approach was supported by the CONSORT 2010 statement extension to randomised pilot and feasibility trials, which had not been available for Study 1 (Eldridge et al, 2016).

15.1.1 Participants

Another 60 participants were enrolled onto the study. The same inclusion and exclusion criteria were applied as in the previous studies.

15.1.2 Sample Size

The sample size calculation for the main study was described in detail in Chapter 14.5.3.

15.1.3 Recruitment

Recruitment was conducted over the period from 28 April to 16 August, 2016. The recruitment procedure was the same as for Pilot Study 2. A CONSORT Flow Diagram is shown in Figure 25.
15.1.4 Randomisation

Randomisation was implemented in an identical manner to Study 1, as described in Chapter 9.8.2.

15.1.5 Allocation Concealment and Blinding

Allocation concealment was performed, as explained in detail in Chapter 9.8.3.
Blinding of the researcher was not possible as described in Chapters 7.2.5, 10.1.5 and 14.2.5.

15.1.6 Data Collection

Data collection was identical to that of Pilot Study 2.

15.1.7 Assessment Order

A random order for the walking tests and questionnaires was used, outlined in Chapter 9.8.4.

15.1.8 Primary Outcomes: Walking Speed and Walking Distance

As in the pilot study, a change in walking speed and walking distance were the primary outcomes of the study, measured by the same walking tests.

15.1.9 Secondary Outcomes: Fatigue and Quality of Life

The secondary outcomes were not changed following the pilot study and so remained as a change in fatigue and QoL.

15.2 Intervention

The intervention was performed exactly in the same way as the pilot study.

15.3 Data Analysis

15.3.1 Statistical Analysis

The statistical analysis for this study was based on the research hypotheses, described in detail for Pilot Study 2. All statistics was performed using IBM SPSS software, release 24.0, Armonk, New York, and GraphPad Prism 6, San Diego, California. Statistics used for this study were outlined in Chapters 7.5, 10.4 and 14.3. The Kruskal Wallis H-Statistics for all secondary outcomes is shown in Appendix 18 (Table A11). Based on the same justification provided in Chapter 7.5.1, participants’ baseline characteristics are presented using relevant descriptive statistics and without p-values.
Continuous data were tested for normality, showing that the T25FW data were not normally distributed, but right skewed, and there were significant outliers in the data; hence, they were transformed. A reciprocal transformation using $1/\text{values}_{\text{T25FW}}$ changed the distribution to normal (for details, see Appendix 18). Original T25FW data were used for the descriptive statistics because the data had been changed by the transformation ($1/\text{value}$), so that it would not have been possible to detect the actual values in walking speed and to calculate the changes thereof.

To test for differences in walking speed (time to walk) and walking distance between baseline and post-intervention measures, on split file (for group) T25FW$_\text{reciprocal}$ and 6MWT data, a paired T-test was performed, followed by a Bonferroni correction for multiple comparisons. Similarly, on split file MFIS and MSIS-29 data, Wilcoxon Signed Ranks tests were performed, followed by a Bonferroni correction. These tests were used to evaluate whether one or more of the three interventions had an effect on walking performance, fatigue and QoL.

15.4 Results

15.4.1 Safety, Acceptability and Adherence to the Programme

There were no safety-related events during the assessments or intervention. Participants were allowed to use walking sticks if desired and to rest at any time during instructions and assessments. Six participants used unilateral or bilateral walking sticks during the pre- and post-intervention assessments. The home-based intervention was reported by the participants to be safe and convenient. Participants reported to have practised a median of five (within a min-max of four to six) times per week.

There were 5 participants in the cued MI groups who regarded the music to be rather fast, but after some practice, their adaptation of the imagined walking to the music beat improved; in contrast, 2 participants felt that the music was too slow, and they had no difficulties with cued MI; another 4 participants considered the imagined walking to the beat considerably easier when the music was faster. Seven participants in the music-verbal-MI group appreciated the verbal cueing and felt that it helped them to maintain the rhythm. Another participant initially regarded the verbal
cueing as irritating, but became accustomed to it. Nine participants in the music-verbal-MI (n=6) and music-MI groups (n=3), reported that they perceived a pleasant feeling in their lower limbs and could walk more easily after the training. Seventeen participants (n=9 in the music-verbal-MI group; n=6 in the music-MI group and n=2 in the non-cued-MI group) considered the tasks and the music pleasurable and motivating. One participant appreciated the extra time for herself. Another participant, also in the music-MI group, was surprised that the cued MI seemed to enhance her mood and obviously had an effect on her walking and postural control. Seven participants (n=1 in the music-verbal-MI group; n=2 in the music-MI group and n=4 in the non-cued-MI group) reported initial problems with the kinaesthetic MI. Tips were provided by the author, such as how to consciously feel their feet touching the ground during the imagined walking or to feel their legs during the MI. These 7 participants reported that their kinaesthetic imagery improved with training; for 5 of them, this occurred after one week while, for the other 2, it happened by the second week.

In the non-cued-MI group, 1 participant had sore muscles after the MI although he confirmed that he was not activating his muscles. Initially, another 2 participants in the music-MI group regarded it difficult to perform MI without moving, and they learned how to imagine walking while relaxing their muscles. Eight participants (n=2 in the music-verbal-MI group; n=2 in the music-MI group and n=4 in the non-cued-MI group) were tired immediately after the intervention, but those in both cued MI groups realised that their walking improved after the practice. In the music-MI group, 2 participants reported that they were less fatigued immediately after the intervention. Eight participants (n=1 in the music-MI group and n=7 in the non-cued-MI group) reported concentration problems, which improved in the music-MI group, but not in the non-cued-MI group. Another participant in the non-cued-MI group regarded the MI to be relaxing and pleasurable. Two participants in the cued MI groups explicitly mentioned that the cued MI to the beat of a march, one of the music pieces on the CDs, was particularly easy and pleasant.

Altogether, 28 out of 59 participants reported some initial problems during the interventions, but that the majority improved on account of the practice; unfortunately, the concentration problems in the non-cued-MI group did not disappear. Twenty-nine participants considered the interventions pleasurable and/or immediately beneficial.
for their walking, fatigue, mood and body perception. All other participants reported that they regarded the intervention as more than acceptable, and that they did not have any problems. Crucially, nearly half of the participants in all groups reported to have been encouraged to walk or to dance after the intervention.

15.4.2 Baseline Data

Forty-seven females and 12 males were included in the study, representing a female-to-male ratio of 3.9:1. Thirteen males were allocated of whom 1 had a relapse; therefore, the analysis was based on the 59 participants who completed the study. The mean age of the total study population was 44.4 (95% CI 41.7, 47.0) years. The median (min, max) EDSS was 2.5 (1.5, 4.5). Walking speed (T25FW) refers to the first research hypothesis and walking distance (6MWT) to the second. Fatigue (MFIS) refers to the third hypothesis and QoL (MSIS-29) to the fourth. In Table 14, participants' baseline characteristics are presented.
### Table 14: Participants´ Baseline Characteristics in Walking, Fatigue and Quality of Life (Main Study 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued-MI group N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F:M)</td>
<td>N=15:4</td>
<td>N=16:4</td>
<td>N=16:4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.3 (39.8, 50.8)</td>
<td>44.5 (40.5, 48.5)</td>
<td>43.3 (38.3, 48.3)</td>
</tr>
<tr>
<td><strong>Age groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>N=6</td>
<td>N=7</td>
<td>N=8</td>
</tr>
<tr>
<td>≥40 years</td>
<td>N=13</td>
<td>N=13</td>
<td>N=12</td>
</tr>
<tr>
<td><strong>EDSS</strong></td>
<td>3.0 (1.5, 4.5)</td>
<td>2.5 (1.5, 4.5)</td>
<td>2.5 (1.5, 4.5)</td>
</tr>
<tr>
<td><strong>Disability groups</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDSS 1.5-3.0</td>
<td>N=11</td>
<td>N=12</td>
<td>N=13</td>
</tr>
<tr>
<td>EDSS 3.5-4.5</td>
<td>N=8</td>
<td>N=8</td>
<td>N=7</td>
</tr>
<tr>
<td><strong>Walking aid use during testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No/unilateral/ bilateral aid</td>
<td>N=16/2/1</td>
<td>N=19/0/1</td>
<td>N=18/0/2</td>
</tr>
<tr>
<td>T25FW (seconds)</td>
<td>6.1 (5.2, 7.0)</td>
<td>6.1 (4.9, 7.3)</td>
<td>5.6 (4.7, 6.4)</td>
</tr>
<tr>
<td>6MWT (metres)</td>
<td>457.3 (394.3, 520.3)</td>
<td>461.7 (395.5, 528.0)</td>
<td>461.7 (395.5, 528.0)</td>
</tr>
<tr>
<td><strong>MFIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical sub</td>
<td>19.0 (6.0, 34.0)</td>
<td>16.0 (0.0, 30.0)</td>
<td>17.0 (0.0, 29.0)</td>
</tr>
<tr>
<td>Cognitive sub</td>
<td>18.0 (1.0, 36.0)</td>
<td>10.0 (0.0, 34.0)</td>
<td>15.0 (1.0, 23.0)</td>
</tr>
<tr>
<td>Psychosocial sub</td>
<td>4.0 (0.0, 8.0)</td>
<td>3.0 (0.0, 5.0)</td>
<td>3.0 (0.0, 7.0)</td>
</tr>
<tr>
<td>Total score</td>
<td>43.0 (11.0, 72.0)</td>
<td>28.5 (2.0, 69.0)</td>
<td>33.0 (2.0, 54.0)</td>
</tr>
<tr>
<td>Total score ≥38</td>
<td>N=8</td>
<td>N=12</td>
<td>N=12</td>
</tr>
<tr>
<td><strong>MSIS-29</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical sub</td>
<td>47.5 (12.5, 76.2)</td>
<td>25 (6.2, 56.2)</td>
<td>21.9 (3.7, 63.7)</td>
</tr>
<tr>
<td>Psychological sub</td>
<td>33.3 (2.8, 66.7)</td>
<td>19.4 (0.0, 47.2)</td>
<td>13.9 (0.0, 66.7)</td>
</tr>
</tbody>
</table>
Abbreviations: F:M = females:males; N = number of participants; EDSS = Expanded Disability Status Scale; T25FW = Timed 25-Foot Walk; 6MWT = 6-Minute Walk Test; MFIS = Modified Fatigue Impact Scale; MSIS-29 = MS Impact Scale-29; sub = subscale.

\(^1\)Mean (95% CI); \(^2\)median (min, max). Colour coding: yellow = walking outcomes; green = fatigue outcomes, blue = QoL outcomes. Red coloured questionnaires/tests: lower numbers indicate better performance; blue coloured questionnaires/tests: higher numbers indicate better performance.

15.4.3 Adverse Events, Missing Data and Attrition

No adverse events were reported. As in the other studies, questionnaires were checked for completeness to ensure that there were no missing data. A single participant in the music-verbal-MI group was excluded from the study due to an MS relapse, which was reported, and his whole case was removed from the analysis. Therefore, attrition was 1.7%, and the numbers are shown in Figure 25.

15.4.4 Bias

In Chapter 11.4, it was explained in detail how the threats of systematic biases were treated in Study 1. The same applied for Study 2, with the exception that attrition was lower. Subsequently, 19 participants remained in the music-verbal-MI group, and 20 participants in both the music-MI and non-cued-MI groups.

15.4.5 Primary Outcomes: Walking Speed and Walking Distance

Descriptive data of the primary outcomes (T25FW; 6MWT) in all groups and pre- and post-intervention are shown in Table 15. As can be seen, the mean walking speed and walking distance increased in all intervention groups; both rhythmic-cued and non-cued MI improved walking performance from baseline to post-intervention assessments.
Table 15: Differences in Walking Performance between Baseline and Post-Intervention for Each Study Group (Main Study 2).

Abbreviations: Pre = pre-intervention/baseline; Post = post-intervention; T25FW = Timed 25-Foot Walk; 6MWT = 6-Minute Walk Test.

1Mean (95% CI); p-values are corrected for multiple comparisons; significant p-values are highlighted in bright yellow. **Red coloured tests: lower numbers indicate better performance; blue coloured tests: higher numbers indicate better performance.**

The results showed that rhythmic-cued MI improved walking speed and walking distance when compared to non-cued MI. Changes in the time to walk (related to walking speed) and walking distance for participants in the intervention groups are shown in Figure 26, A-B.
**Figure 26, A-B**: Effect of Intervention on the Time to Walk and Walking Distance (Main Study 2).

Figure legend: small square brackets above the figure indicate significant within-group comparisons between baseline and post-intervention; large square brackets 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.

With regard to hypothesis 1, music- and verbally-cued MI improved walking speed, that is, reduced the time to walk, when compared to music-cued MI and non-cued MI (see Table 16). The overall interaction between the groups at baseline and post-intervention was statistically significant, T25FW-reciprocal: $F(2,56)=4.65$, $p=0.013$, with a medium effect size of $\eta^2=0.143$ (Cohen 1988; Miles and Shevlin 2001). The effect of music- and verbally-cued MI in comparison to non-cued MI ($p=0.024$) was significantly greater. In addition, there was no significant difference in the change of walking speed between the two cued MI groups ($p=0.999$) and between the music-cued MI and the non-cued MI groups ($p=0.138$). Therefore, the first null hypothesis was rejected. This means that music- and verbally-cued MI improved walking speed, as measured by the T25FW, when compared to music-cued MI and MI alone. Four participants in the music-verbal-MI group and 3 participants in the music-MI group, but no participant in the non-cued-MI group, showed a clinically significant
improvement of $\geq 20\%$ in walking speed (a reduction in the time to walk) while the group interaction was not significant.

In view of hypothesis two, music-verbal-MI improved walking distance when compared to music-MI and non-cued-MI. The overall interaction between the groups at baseline and follow-up was statistically significant, $F(2,56)=3.53, p=0.036$, with a medium effect size of $\eta^2=0.112$. The effect of music-verbal-MI was significant in comparison to non-cued-MI ($p=0.001$). There was no significant difference in the change of walking speed between the music-verbal-MI and music-MI groups ($p=0.816$) and between the music-MI and the non-cued-MI groups ($p=0.582$). As a result, the second null hypothesis was rejected. In other words, music-verbal-MI improved walking distance, as measured by the 6MWT, when compared to music-MI and non-cued-MI. Five participants in the music-verbal-MI group, 2 participants in the music-MI group and 1 participant in the non-cued-MI group showed a clinically meaningful improvement of $\geq 20\%$ in walking distance, and the group interaction was not significant.

In summary, music-verbal-MI was superior to music-MI and non-cued-MI in improving walking speed and walking distance. In Table 16, the effect of the intervention on walking performance is shown.
**Table 16:** Effect of Interventions on Primary Outcomes and Clinically Significant Improvement (Main Study 2).

Abbreviations: T25FW = Timed 25-Foot Walk; 6MWT = 6-Minute Walk Test; N = number of participants; clin sig= clinically significant change, i.e. improvement.  

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal MI group N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued MI group N=20</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T25FW (seconds)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post-intervention</strong></td>
<td>5.3 (4.5, 6.1)</td>
<td>5.2 (4.4, 6.0)</td>
<td>5.3 (4.4, 6.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td>-0.8 (-1.0, -0.6)</td>
<td>-0.9 (-1.4, -0.4)</td>
<td>-0.3 (-0.5, -0.06)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Adjusted p-value</strong></td>
<td>0.024</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clin sig change ≥20%</strong></td>
<td>N=4 (21.1%)</td>
<td>N=3 (15%)</td>
<td>N=0 (0%)</td>
<td>0.110</td>
</tr>
<tr>
<td><strong>6MWT (metres)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Post-intervention</strong></td>
<td>510.3 (450.5, 570.2)</td>
<td>499.1 (433.8, 564.3)</td>
<td>491.7 (424.0, 559.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td>53.0 (38.2, 67.7)</td>
<td>37.3 (12.4, 62.3)</td>
<td>19.1 (4.8, 33.5)</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Adjusted p-value</strong></td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clin sig change ≥20%</strong></td>
<td>N=5/20 (26.3%)</td>
<td>N=2/20 (10%)</td>
<td>N=1/20 (5%)</td>
<td>0.128</td>
</tr>
</tbody>
</table>

15.4.6 Secondary Outcomes: Fatigue and Quality of Life

Physical and total fatigue significantly improved after the intervention in all groups, but the changes in the non-cued-MI group were not significant. Cognitive fatigue significantly improved after cued MI, and there was a borderline improvement...
following non-cued MI. Psychosocial fatigue significantly improved in all groups. Physical QoL improved in both cued MI groups. Psychological QoL improved only in the music-verbal-MI group. Descriptive data of the secondary outcomes (MFIS, MSIS-29) in all groups, and pre- and post-intervention are shown in Table 17.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group; N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued-MI group; N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MFIS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline phys sub¹</td>
<td>19.0 (6.0, 34.0)</td>
<td>16.0 (0.0, 30.0)</td>
<td>17.0 (0.0, 29.0)</td>
</tr>
<tr>
<td>Post-intervention¹</td>
<td>13.0 (0.0, 28.0)</td>
<td>9.5 (0.0, 17.0)</td>
<td>12.0 (1.0, 27.0)</td>
</tr>
<tr>
<td>P-value²</td>
<td>0.003</td>
<td>0.009</td>
<td>0.321</td>
</tr>
<tr>
<td>Baseline cogn sub¹</td>
<td>18.0 (1.0, 36.0)</td>
<td>10.0 (0.0, 34.0)</td>
<td>15.0 (1.0, 23.0)</td>
</tr>
<tr>
<td>Post-intervention¹</td>
<td>14.0 (0.0, 25.0)</td>
<td>5.5 (0.0, 26.0)</td>
<td>10.0 (0.0, 22.0)</td>
</tr>
<tr>
<td>P-value²</td>
<td>0.003</td>
<td>0.003</td>
<td>0.069</td>
</tr>
<tr>
<td>Baseline psychos sub¹</td>
<td>4.0 (0.0, 8.0)</td>
<td>3.0 (0.0, 5.0)</td>
<td>3.0 (0.0, 7.0)</td>
</tr>
<tr>
<td>Post-intervention¹</td>
<td>2.0 (0.0, 5.0)</td>
<td>1.0 (0.0, 5.0)</td>
<td>2.0 (0.0, 5.0)</td>
</tr>
<tr>
<td>P-value²</td>
<td>&lt;0.001</td>
<td>0.003</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline total score¹</td>
<td>43.0 (11.0, 72.0)</td>
<td>28.5 (2.0, 69.0)</td>
<td>33.0 (2.0, 54.0)</td>
</tr>
<tr>
<td>Post-intervention¹</td>
<td>27.0 (1.0, 55.0)</td>
<td>19.5 (0.0, 45.0)</td>
<td>23.5 (2.0, 52.0)</td>
</tr>
<tr>
<td>P-value²</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.165</td>
</tr>
<tr>
<td>Post total score ≥38</td>
<td>N=6</td>
<td>N=2</td>
<td>N=3</td>
</tr>
</tbody>
</table>

| **MSIS-29**          |                             |                     |                         |
| Baseline phys sub¹   | 47.5 (12.5, 76.2)            | 25 (6.2, 56.2)      | 21.9 (3.7, 63.7)         |
| Post-intervention¹   | 25 (5.6, 61.2)              | 21.2 (2.5, 37.5)    | 16.2 (2.5, 51.2)         |
| P-value²             | <0.001                      | 0.003               | 0.096                   |
| Baseline psych sub¹  | 33.3 (2.8, 66.7)            | 19.4 (0.4, 47.2)    | 13.9 (0.0, 66.7)         |
| Post-intervention¹   | 25 (2.8, 50)                | 11.1 (0.0, 36.1)    | 8.3 (0.0, 52.8)          |
| P-value²             | 0.030                       | 0.090               | 0.330                   |

Table 17: Differences in Fatigue and Quality of Life between Baseline and Post-intervention for Each Study Group (Main Study 2).
Abbreviations: N = number of participants; MFIS = Modified Fatigue Impact Scale; MSIS-29 = MS Impact Scale-29; phys = physical; cogn = cognitive; psychos = psychosocial; sub = subscale; psych = psychological; post = post-intervention.  
\(^1\)Median (min, max); \(^2\)p-values are corrected for multiple comparisons; significant p-values are highlighted in bright yellow and borderline significant changes in dark yellow; red coloured questionnaires: lower numbers indicate better performance. Colour coding: green = fatigue outcomes; blue = QoL outcomes.

Effects of the intervention on fatigue and QoL are shown in Figures 27 and 28. If the same type of graph was used, figure legends are shown only once, for reasons of redundancy.

Figure 27, A-D: Effect of Intervention on Physical, Cognitive, Psychosocial and Total Fatigue (Main Study 2).

Figure legend for Figures 27 and 28: medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and min-max by the
whiskers. Small square brackets on top of the figures show significant within-group comparisons between baseline and post-intervention; large square brackets indicate significant group X time interactions; the dashed red line in Figure 27 D indicates the cut-off score for fatigue at 38 points on the total MFIS. *Significant at the 0.05 level; **significant at the 0.01 level; ***significant at the 0.001 level.

**Figure 28, A-B:** Effect of Intervention on Physical and Psychological Quality of Life (Main Study 2).

Between baseline and post-intervention, significant improvements in physical, cognitive and total fatigue were observed only in the music-verbal-MI and the music-MI groups. Group X time interaction analysis showed a significant difference in psychosocial fatigue only in the music-verbal-MI group (p=0.041) versus the non-cued-MI group; hence, the third null-hypothesis was rejected.

In this study, 22 (music-verbal-MI group, n=7; music-MI group, n=9 and non-cued-MI group, n=6) and 19 (music-verbal-MI group, n=6; music-MI group, n=7 and non-cued-MI group, n=6) out of the 59 participants reached a clinically significant improvement in physical and total fatigue. Fourteen (music-verbal-MI group, n=4; music-MI group, n=6 and non-cued-MI group, n=4) and 11 (music-verbal-MI group, n=4; music-MI group, n=3 and non-cued-MI group, n=4) participants showed a clinically significant improvement in cognitive and psychosocial fatigue, and there was no significant difference between groups.

After the intervention, there was an overall improvement in physical QoL (p=0.007). A group comparison showed that only the music-verbal-MI group contributed to this
improvement (p=0.005). Therefore, the fourth null-hypothesis was rejected. Thirty-two (music-verbal-MI group, n=15; music-MI group, n=10 and non-cued-MI group, n=7) out of 59 participants reached a clinically significant improvement in physical QoL of which significantly more participants were in the music-verbal-MI group (p=0.030). Twenty-nine (music-verbal-MI group, n=12; music-MI group, n=9 and non-cued-MI group, n=8) participants showed a clinically significant improvement in psychological QoL, and there was no significant difference between groups. Detailed information about the intervention effects on fatigue and QoL is provided in Table 18.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group</th>
<th>Music-MI group</th>
<th>Non-cued-MI group</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=19</td>
<td>N=20</td>
<td>N=20</td>
<td></td>
</tr>
<tr>
<td>MFIS physical subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post^1</td>
<td>13.0 (0.0, 28.0)</td>
<td>9.5 (0.0, 17.0)</td>
<td>12.0 (1.0, 27.0)</td>
<td></td>
</tr>
<tr>
<td>Change from BL^1</td>
<td>-6.0 (-19.0, 4.0)</td>
<td>-7.5 (-24.0, 13.0)</td>
<td>-1.0 (-19.0, 12.0)</td>
<td>0.296</td>
</tr>
<tr>
<td>Clin sig ch ≤ -8.9 pts^2</td>
<td>N=7</td>
<td>N=9</td>
<td>N=6</td>
<td>0.617</td>
</tr>
<tr>
<td></td>
<td>(36.8%)</td>
<td>(45%)</td>
<td>(30%)</td>
<td></td>
</tr>
<tr>
<td>MFIS cognitive subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post^1</td>
<td>14.0 (0.0, 25.0)</td>
<td>5.5 (0.0, 26.0)</td>
<td>10.0 (0.0, 22.0)</td>
<td></td>
</tr>
<tr>
<td>Change from BL^1</td>
<td>-5.0 (-11.0, 5.0)</td>
<td>-4.0 (-15.0, 3.0)</td>
<td>-2.5 (-16.0, 7.0)</td>
<td>0.483</td>
</tr>
<tr>
<td>Clin sig ch ≤ 8 pts^2</td>
<td>N=4</td>
<td>N=6</td>
<td>N=4</td>
<td>0.718</td>
</tr>
<tr>
<td></td>
<td>(21%)</td>
<td>(30%)</td>
<td>(20%)</td>
<td></td>
</tr>
<tr>
<td>MFIS psychosocial subscale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post^1</td>
<td>2.0 (0.0, 5.0)</td>
<td>1.0 (0.0, 5.0)</td>
<td>2.0 (0.0, 5.0)</td>
<td></td>
</tr>
<tr>
<td>Change from BL^1</td>
<td>-2.0 (-6.0, 2.0)</td>
<td>0.0 (-4.0, 0.0)</td>
<td>0.0 (-5.0, 2.0)</td>
<td>0.027</td>
</tr>
<tr>
<td>p-value^3_adj</td>
<td>0.041</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clin sig ch ≤ -2.3 pts^2</td>
<td>N=4</td>
<td>N=3</td>
<td>N=4</td>
<td>0.873</td>
</tr>
<tr>
<td></td>
<td>(21.1%)</td>
<td>(15%)</td>
<td>(20%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 18: Effect of Intervention on Fatigue and Quality of Life, and Clinically Significant Improvement (Main Study 2).
### MFIS total score

<table>
<thead>
<tr>
<th></th>
<th>Post(^1)</th>
<th>Change from BL(^1)</th>
<th>Clin sig ch ≤-16.2 pts(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (min, max)</td>
<td>Median (min, max)</td>
<td>Number (Ratio)</td>
</tr>
<tr>
<td></td>
<td>27.0 (1.0, 55.0)</td>
<td>-12.0 (-31.0, 5.0)</td>
<td>N=6 (31.6%)</td>
</tr>
<tr>
<td></td>
<td>19.5 (0.0, 45.0)</td>
<td>-10.0 (-37.0, 7.0)</td>
<td>N=7 (35%)</td>
</tr>
<tr>
<td></td>
<td>23.5 (2.0, 52.0)</td>
<td>-4.0 (-40.0, 11.0)</td>
<td>N=6 (30%)</td>
</tr>
<tr>
<td></td>
<td>19.5 (0.0, 45.0)</td>
<td>-10.0 (-37.0, 7.0)</td>
<td>0.197</td>
</tr>
<tr>
<td></td>
<td>23.5 (2.0, 52.0)</td>
<td>-4.0 (-40.0, 11.0)</td>
<td>0.942</td>
</tr>
</tbody>
</table>

### MSIS-29 physical subscore

<table>
<thead>
<tr>
<th></th>
<th>Post(^1)</th>
<th>Change from BL(^1)</th>
<th>Clin sig ch ≤-7.5 pts(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (min, max)</td>
<td>Median (min, max)</td>
<td>Number (Ratio)</td>
</tr>
<tr>
<td></td>
<td>25.0 (5.0, 61.2)</td>
<td>-15.0 (-38.7, -1.2)</td>
<td>N=15 (78.9%)</td>
</tr>
<tr>
<td></td>
<td>21.2 (2.5, 37.5)</td>
<td>-7.5 (-28.7, 8.7)</td>
<td>N=10 (50%)</td>
</tr>
<tr>
<td></td>
<td>16.2 (2.5, 51.2)</td>
<td>-3.1 (-41.2, 8.7)</td>
<td>N=7 (35%)</td>
</tr>
<tr>
<td></td>
<td>19.5 (0.0, 45.0)</td>
<td>-10.0 (-37.0, 7.0)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>23.5 (2.0, 52.0)</td>
<td>-4.0 (-40.0, 11.0)</td>
<td>0.020</td>
</tr>
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</table>

### MSIS-29 psychological subscore

<table>
<thead>
<tr>
<th></th>
<th>Post(^1)</th>
<th>Change from BL(^1)</th>
<th>Clin sig ch ≤-5.56 pts(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (min, max)</td>
<td>Median (min, max)</td>
<td>Number (Ratio)</td>
</tr>
<tr>
<td></td>
<td>25.0 (5.0, 61.2)</td>
<td>-11.1 (-50.0, 16.7)</td>
<td>N=12 (63.2%)</td>
</tr>
<tr>
<td></td>
<td>11.1 (0.0, 36.1)</td>
<td>-2.3 (-19.4, 13.9)</td>
<td>N=9 (45%)</td>
</tr>
<tr>
<td></td>
<td>8.3 (0.0, 52.8)</td>
<td>-1.4 (-38.9, 19.4)</td>
<td>N=8 (40%)</td>
</tr>
<tr>
<td></td>
<td>23.5 (2.0, 52.0)</td>
<td>-4.0 (-40.0, 11.0)</td>
<td>0.233</td>
</tr>
<tr>
<td></td>
<td>23.5 (2.0, 52.0)</td>
<td>-4.0 (-40.0, 11.0)</td>
<td>0.317</td>
</tr>
</tbody>
</table>

Table 18 (Continued): Effect of Intervention on Fatigue and Quality of Life, and Clinically Significant Improvement (Main Study 2).

Abbreviations: BL = baseline; post = post-intervention; clin sig ch = clinically significant change, that is, improvement; pts = points; N = number of participants; MFIS = Modified Fatigue Impact Scale; MSIS-29 = Multiple Sclerosis Impact Scale-29. \(^1\)Median (min, max); \(^2\)number, ratio; \(^3\)p-values\(_{adj}\) refer to the comparisons between the music-verbal-MI and non-cued-MI groups and they are corrected for multiple comparisons. Significant differences are highlighted in bright yellow. Red coloured questionnaires: lower numbers indicate better performance. Colour coding: green = fatigue outcomes; blue = QoL outcomes.

ORIGINAL IN COLOUR
Chapter 16 – Study 2: Motor Imagery Ability

Study 2 also explored MI to see whether this could have been a mechanism which contributed to the improvements in Study 1. Accordingly, while using the same participants, the study assessed the MI capability at baseline and investigated the effects of music-cued MI with and without verbal cueing and of non-cued MI on MI ability as a secondary outcome. This chapter firstly explains the methods used, starting with the MI ability measurement in the present study; it also shows how Pilot Study 2 informed Main Study 2. Finally, it presents the Main Study 2 results.

16.1 Methods

Evidence from the key literature suggested the necessity to comprehensively assess MI ability using two different approaches. This is because, some people may have problems generating vivid images and intense sensations and/or to subjectively describe their imagined movements while others may have difficulty with the temporal organisation of their MI (Guillot and Collet 2010; Malouin et al, 2008a; Williams et al, 2015). In other words, both questionnaire type and mental chronometry (that is, temporal congruence) tests are required to assess the MI capability.

16.1.1 Kinaesthetic and Visual Imagery Questionnaire-10

Jeannerod described self-report questionnaires as being suitable measures of the MI ability (Jeannerod 1994, 1997), which were used by various studies (De Vries et al, 2013; Gregg, Hall & Butler 2010; Malouin, Richards & Durand 2012; Oostra et al, 2012; Schuster et al, 2012c). For the current study, an MI ability questionnaire appropriate for pwMS was chosen: the Kinaesthetic and Visual Imagery Questionnaire (KVIQ) (Malouin et al, 2007). The KVIQ was developed for people with physical disabilities as it measures MI vividness and does not require self-assessment. In addition, the movements used are not as complex as in other MI ability questionnaires (Malouin et al, 2007), such as the Movement and Imagery Questionnaire (MIQ) (Hall and Pongrac 1983) and the Vividness of MI Questionnaire (VMIQ) (Isaac, Marks & Russell 1986). The KVIQ is available in a long version, the KVIQ-20, and a short version, the KVIQ-10 (Malouin et al, 2007). The KVIQ-20 requires up to 45 minutes administration time (Malouin et al, 2007) whereas half the
time is needed for the KVIQ-10 (Schuster, et al, 2012c). Taking fatigue in pwMS into account, the KVIQ-10 was regarded as suitable.

The KVIQ has been used for studies in healthy people (Saimpont et al, 2015; Wondrusch and Schuster-Amft 2013), people with stroke (Deutsch, Maidan & Dickstein 2012; Kumar, Chakrapani & Kedambadi 2016), Parkinson’s disease (Heremans et al, 2012b; Peterson, Pickett & Earhart 2012) and MS (Heremans et al, 2012a; Heremans et al, 2012c). Moderate to excellent validity and reliability of both KVIQ versions were found in these populations, as shown in Table 19. The KVIQ-10 was translated into German and validated in a German-speaking population, and so the German KVIQ-G-10 (Schuster et al, 2012c) was chosen for Study 2.

**Table 19: Psychometric Properties of the Kinaesthetic and Visual Imagery Questionnaire.**

<table>
<thead>
<tr>
<th>Initial KVIQ development in people with stroke (Malouin et al, 2007)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychometric properties</strong></td>
</tr>
<tr>
<td>Test retest-variability¹</td>
</tr>
<tr>
<td>Test-retest reliability²</td>
</tr>
<tr>
<td>Affected vs unaffected and dominant vs non-dominant limbs¹</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Internal consistency³</td>
</tr>
<tr>
<td>Factorial analysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study in pwMS, using the KVIQ-20 (Tabrizi et al, 2013b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test-retest reliability²</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Concurrent validity⁴</strong></td>
</tr>
<tr>
<td><strong>Internal Consistency³</strong></td>
</tr>
<tr>
<td><strong>Factorial analysis</strong></td>
</tr>
</tbody>
</table>
KVIQ-20 and KVIQ-10 validation of the German version (KIVQ-G) in people with MS, stroke and Parkinson’s disease (Schuster, et al, 2012c)

<table>
<thead>
<tr>
<th></th>
<th>KVIQ-20</th>
<th>KVIQ-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test-retest reliability$^2$</td>
<td>(V) ICC=0.77 (0.65–0.85)</td>
<td>(V) ICC=0.77 (0.66–0.85)</td>
</tr>
<tr>
<td></td>
<td>(K) ICC=0.83 (0.74–0.89)</td>
<td>(K) ICC=0.85 (0.77–0.90)</td>
</tr>
<tr>
<td>Internal consistency$^3$</td>
<td>(V) 0.94 (0.92–0.96)</td>
<td>(V) 0.88 (0.83–0.92)</td>
</tr>
<tr>
<td></td>
<td>(K) 0.96 (0.94–0.97)</td>
<td>(K) 0.92 (0.88–0.94)</td>
</tr>
<tr>
<td>Concurrent validity$^4$</td>
<td>$\rho=0.36$ ($p=0.13$)</td>
<td></td>
</tr>
<tr>
<td>Standard Error of</td>
<td>(V) 2.2 points</td>
<td>(V) 1.56 points</td>
</tr>
<tr>
<td>Measurement (SEM)</td>
<td>(K) 2.4 points</td>
<td>(K) 1.73 points</td>
</tr>
<tr>
<td>Minimal detectable</td>
<td>(V) 6.2 points</td>
<td>(V) 4.3 points</td>
</tr>
<tr>
<td>change (MDC)</td>
<td>(K) 6.7 points</td>
<td>(K) 4.8 points</td>
</tr>
<tr>
<td>Factor analysis</td>
<td>2 factors (V and K)</td>
<td>correlated with $r=0.36$. Both explained 69.7% of total variance.</td>
</tr>
</tbody>
</table>

Table 19 (Continued): Psychometric Properties of the Kinaesthetic and Visual Imagery Questionnaire.

Table legend: abbreviations: ICC = Intraclass Correlation Coefficient; V = visual subscale; K = kinaesthetic subscale; MIQ-R = Movement Imagery Questionnaire (Hall, Pongrac & Buckholz 1985).

$^1$Min–max ICC; $^2$ICC (95% confidence interval, lower bound or lower and upper bounds); $^3$Cronbach’s $\alpha$ (95% confidence interval); $^4$Spearman’s $\rho$.

The KVIQ-G-10 was used after the MI familiarisation at baseline, but in a random order with all the other assessments. The KVIQ-(G)-10 includes 10 items (5 movements in each of the visual and kinaesthetic subscales: 2 for the upper limbs, 1 for the upper body and 2 for the lower limbs) (Malouin et al, 2007; Schuster et al, 2012c). According to the questionnaire instructions, some of the 5 movements were repeated on the other side of the body (see Table 20). Each test item involved the following steps: a) the participant was asked to assume the start position demonstrated by the researcher; b) the researcher demonstrated the movement, and then the participant was asked to physically execute the movement only once; c) the
participant was then asked to return to the starting position and to imagine performing the same movement, which they had just executed; d) the researcher asked the participant to rate their imagery using the operational definition of each category on a five-point Likert scale; this meant the clarity of their visual image (1 = “no image”, 2 = “blurred image”, 3 = “moderately clear image”, 4 = “clear image”, 5 = “image as clear as seeing”) or the intensity of their sensations (1 = “no sensation”, 2 = “mildly intense”, 3 = “moderately intense”, 4 = “intense”, 5 = “as intense as executing the action”) associated with the imagined movement. The numbered scale was recorded by the author of this study and only used for the computation of the data (Malouin et al, 2007). For scoring, the values of the 5 items for the visual and kinaesthetic subscales and the total score were summed up. The maximum total score is 50 where greater numbers indicate a higher MI ability. For the KVIQ-10, no clear cut-off score was defined to indicate moderate/high MI ability although one study used a cut-off score of >2.5 points out of 5 in healthy people (Holper and Wolf 2010). Another study defined a cut-off score of 3 points out of 5 on both subscales, to indicate moderate/high MI ability in healthy people (Saimpont et al, 2015). Therefore, a cut-off score of 3 points was used in the current study. Table 20 presents the movements used for the KVIQ-(G)-10.

<table>
<thead>
<tr>
<th>Movements</th>
<th>KVIQ-G-10 visual</th>
<th>KVIQ-G-10 kinaesthetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lift the arm completely</td>
<td>3 Vnd</td>
<td>3 Knd</td>
</tr>
<tr>
<td>Touch the fingertips with the thumb</td>
<td>5 Vd</td>
<td>5 Kd</td>
</tr>
<tr>
<td>*Repeat #3 and #5 on the other side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bend the body forwards</td>
<td>6 V</td>
<td>6 K</td>
</tr>
<tr>
<td>Move the leg to the side</td>
<td>8 Vd</td>
<td>8 Kd</td>
</tr>
<tr>
<td>Tap the foot</td>
<td>9 Vnd</td>
<td>9 Knd</td>
</tr>
<tr>
<td>*Repeat #8 and #9 on the other side</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 20: Movements for the KVIQ-(G)-10 for the Visual and Kinaesthetic Subscales (Malouin et al, 2007; Schuster et al, 2012c).
*Indicates a movement description change in the German version compared to the original version by Malouin et al. (2007). V = visual; K = kinaesthetic; nd = non-dominant side; d = dominant side.

16.1.2 Time-Dependent Motor Imagery Screening Test

With regard to the mental chronometry assessment, a test based on movements of the lower extremities seemed reasonable since walking was the primary outcome in Studies 1 and 2. Bakker et al. (2007) developed a mental chronometry test which involved healthy individuals using MI to walk along a walkway presented on a computer screen and to move a disc along the same walkway. Additionally, participants actually had to walk along the very same walkway. This test was not exposed to psychometric testing, and the present participants were already required to perform three different walking tests and a short walking task during the familiarisation with MI so, another walking test could have overburdened them; therefore, the test was not selected for the current study.

There is a close relationship between stepping and walking, so the Time-Dependent Motor Imagery screening test (TDMI) (Malouin et al, 2008a) appeared appropriate. In this test, the number of imagined stepping movements imagined over three time periods is recorded (Malouin et al, 2008b). The TDMI test has been used in people with stroke, traumatic brain injury, late blindness, amputation and immobilisation (Kumar, Chakrapani & Kedambadi 2016; Malouin et al, 2009; Malouin, Richards & Durand 2012; Oostra et al, 2012; Oostra et al, 2015). In pwMS, so far, only mental chronometry tests of the upper limbs have been used (Heremans et al, 2012a; Heremans et al, 2012c; Tacchino et al, 2013). The psychometric properties of the TDMI were assessed in people with stroke (Malouin et al, 2008b). Good to excellent reliability was found, as evidenced by low standard errors of measurement (SEM) of 1-3 movements, increasing with duration, and excellent ICCs (0.88-0.93). Therefore, the TDMI screening test was considered a reliable instrument for use in the current study although its psychometric properties were not tested in pwMS.

Administration of the TDMI required recording the number of imagined stepping movements over three time periods (15, 25, and 45 seconds) (Malouin et al, 2008b). While seated on a chair, participants were asked to imagine repeatedly placing one
foot forward onto a board and then back again. The board (41 x 26 x 2 centimetres) was laid about 5 centimetres in front of the feet. Before the testing, the movement was once demonstrated by the researcher. Thereafter, to ensure that participants were able to fully understand the procedure and perform the task, they physically and mentally practised a few times. Participants were allowed to rest for 30 seconds between the training and testing periods. During formal testing, they were asked to close their eyes and to verbally indicate each time they imagined touching the target with their foot; these numbers were counted by the researcher. To encourage kinaesthetic MI from a first-person perspective, participants were asked to feel themselves moving their lower limb. For each TDMI assessment, the test developers recommended taking five different measures and to choose the order of the 15, 25 and 45 seconds measurement time periods, and the left or right body sides. For example, if the first test duration was 25 seconds on the right side, it was followed by 15 seconds on the left side and so on, so that the participants were unaware of the time durations.

For the analysis of the TDMI, there was an evaluation as to whether the number of imagined movements significantly increased with the time duration, and also whether this increase was similar between the two sides; it was expected that they would be at least moderately, if not highly correlated, if the participants had an adequate MI capability (Malouin et al, 2008b).

16.1.3 Data Collection

In the Pilot and Main Study 2, the MI ability was assessed by the KVIQ-G-10 and TDMI, both in German. A clinical research file including data collection sheets in English is attached in Appendix 16.

16.1.4 Administration Time of Motor Imagery Ability Measures

The administration time of the KVIQ-(G)-10 is 20 to 25 minutes (Malouin et al, 2007; Schuster et al, 2012c) and of the TDMI is 4 to 8 minutes (Malouin et al, 2008b).
16.1.5 Clinical Significance

An improvement in MI ability (KVIQ-G-10) was considered clinically relevant if it was $\geq 4.3$ points on the visual subscale and $\geq 4.8$ points on the kinaesthetic subscale (Schuster et al, 2012c). This study has been the only one to present data on the MDCs in people with stroke (n=51), Parkinson’s disease (n=8), left parietal lobe damage (n=7) and MS (n=7). Nonetheless, the MDC represents the smallest real change in scores which are higher than the measurement error whereas the minimal clinically important difference (MCID), or (minimal) clinically significant change, indicates a moderate functional change that is relevant for the patient (De Vet et al, 2006). As such, MCIDs would presumably be higher than MDCs. The administration procedure of the TDMI made significance testing and evaluation of clinically significant changes redundant.

16.1.6 Statistical Analysis

The statistical analysis of the MI ability outcomes was based on hypothesis five. For the pilot study, only descriptive statistics were used. Based on the small sample size, medians (25th-75th percentiles) were reported for ordinal data (KVIQ-G-10: 5 categories) and continuous data (TDMI). The median MI 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. Scatterplots showed a linear relationship in the TDMI data, which was also normally distributed (see Appendix 17); but with a small number of observations, tests of normality are likely to be underpowered to detect non-normality (Ghasemi and Zahediasl 2012; Lilliefors 1967). Thus, bivariate Spearman’s correlation coefficients (25th-75th percentiles) were used to correlate the numbers of imagined stepping movements over 15, 25 and 45 seconds.

For the main study, 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 time duration; and c) the numbers of imagined stepping movements and durations are
moderately to strongly correlated and the correlations are significant. Differences between baseline and post-intervention correlations were not calculated.

The TDMI Main Study data were linearly related, but not normally distributed and included outliers; outlier removal did not change the distribution (see Appendix 18). The main study KVIQ-G-10 and TDMI data are shown as a median (min, max) and were analysed as described previously for ordinal scale data (see Chapters 7.5, 10.4, 14.3 and 15.3). The Kruskal Wallis H-Statistics is shown in Table A11 in Appendix 18.

For the main study, to test whether there was a significant difference between the numbers of imagined movements with the left or right lower extremities within the same time periods, the Wilcoxon Signed Rank test was applied. The same test was used to examine the differences between baseline and post-intervention MI ability (KVIQ-G-10), and both were followed by a Bonferroni correction, as appropriate. To evaluate whether the number of imagined movements significantly increased with the duration, Friedman’s ANOVA was performed. The MDC was evaluated using the Chi-Square test; if the overall p-value was significant, it was analysed with Fisher’s Exact test and corrected for multiple comparisons.

16.2 Pilot Study Results

16.2.1 Baseline Data

At baseline, participants seemed to have been able to practice MI, as indicated by median KVIQ-G-10 vividness scores of 4.0 (25th-75th percentiles 3.2, 4.6) out of 5.0, although slightly lower kinaesthetic subscale values were observed in the music-verbal-MI group, with a 25th percentile of 2.7. Additionally, there was an overall strong positive correlation (Evans 1996) of the median ρ=0.78 (25th-75th percentiles 0.77, 0.84) for the numbers of imagined stepping movements over 15, 25 and 45 seconds for both lower limbs. In the music-verbal-MI and non-cued-MI groups, a strong correlation was observed whereas the correlation in the music-MI group was moderate. In Table 21, participants’ pilot baseline characteristics in MI ability are presented.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=5</th>
<th>Music-MI group N=5</th>
<th>Non-cued-MI group N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KVIQ-G-10</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual sub$^1$</td>
<td>21.0 (17.5, 23.5)</td>
<td>20.0 (17.5, 24.5)</td>
<td>21.0 (17.5, 24.0)</td>
</tr>
<tr>
<td>Median visual score$^1$</td>
<td>4.2 (3.5, 4.7)</td>
<td>4.0 (3.5, 4.9)</td>
<td>4.2 (3.5, 4.8)</td>
</tr>
<tr>
<td>Kinaesthetic sub$^1$</td>
<td>15.0 (13.5, 18.5)</td>
<td>24.0 (15.5, 24.5)</td>
<td>23.0 (18.0, 23.5)</td>
</tr>
<tr>
<td>Median kin score$^1$</td>
<td>3.0 (2.7, 3.7)</td>
<td>4.8 (3.1, 4.9)</td>
<td>4.6 (3.6, 4.7)</td>
</tr>
<tr>
<td>Total scale$^1$</td>
<td>40.0 (31.0, 40.0)</td>
<td>43.0 (33.5, 49.0)</td>
<td>44.0 (36.0, 47.0)</td>
</tr>
<tr>
<td>Median total score$^1$</td>
<td>4.0 (3.1, 4.0)</td>
<td>4.3 (3.3, 4.9)</td>
<td>4.4 (3.6, 4.7)</td>
</tr>
</tbody>
</table>

| **TDMI** |                           |                    |                       |
| 25 seconds right$^1$ | 15.0 (12.0, 22.0) | 14.0 (12.0, 16.0) | 16.0 (11.5, 23.0) |
| 15 seconds left$^1$ | 10.0 (9.0, 11.5) | 9.0 (7.5, 11.0) | 13.0 (6.5, 14.5) |
| 45 seconds right$^1$ | 27.0 (19.5, 36.0) | 23.0 (19.0, 31.0) | 33.0 (20.0, 38.5) |
| 15 seconds left-2$^1$ | 10.0 (8.5, 12.0) | 8.0 (8.0, 9.5) | 12.0 (7.5, 13.0) |
| 25 seconds left$^1$ | 16.0 (14.5, 19.5) | 16.0 (14.5, 18.0) | 20.0 (12.0, 21.0) |
| Spearman’s ρ correlations$^{1,2}$ | 0.72 (0.47, 0.82) | 0.59 (0.46, 0.72) | 0.87 (0.80, 0.97) |

**Table 21:** Participants’ Motor Imagery Ability at Baseline (Pilot Study 2).

Abbreviations: KVIQ-G-10 = Kinaesthetic and Visual Imagery Questionnaire, German short version; sub = subscale; kin = kinaesthetic; TDMI = Time-Dependent Motor Imagery screening test.

$^1$Median (25th-75th percentiles); $^2$Spearman’s correlations (25th-75th percentiles) were significant at the ≤0.01 level (two-tailed; all pairwise correlations); blue-coloured questionnaire: higher numbers indicate better performance.
16.2.2 Post-Intervention Data

Post-intervention, as compared to baseline, participants showed higher MI abilities. This was indicated by an overall total KVIQ-G-10 score with a median vividness score of 4.0 (25th-75th percentiles of 4.1 to 4.8) and strongly correlated TDMI measures with a median of $\rho=0.89$ (25th-75th percentiles of 0.84 to 0.91). In all groups, strong correlations were observed. In Table A9 (see Appendix 17), descriptive information for the MI ability data is provided. The pilot MI ability outcomes are represented graphically in Figures 29 and 30.

**Figure 29:** Motor Imagery Ability (KVIQ-G-10) Pre- and Post-Intervention (Pilot Study 2).

Figure legend: abbreviations: KVIQ-G-10 = Kinaesthetic and Visual Imagery Questionnaire-10:

Figures 29 and 30: medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and min-max by the whiskers.
16.3 Implications for the Main Study 2

The findings from the pilot study showed that, firstly, the data collection could be performed without effort. Following the MI familiarisation, participants understood well what was asked of them during the KVIQ-G-10 and TDMI assessments. They reported no problems with the KVIQ-G-10 performance and appreciated that the TDMI screening test could be performed in a sitting position, so both tests were continued to be used in the main study.

Participants in the music-verbal-MI group had lower baseline kinaesthetic MI scores than all other participants. The discrepancy in results could be associated with their higher disability and fatigue. Apart from a single 25th percentile of 2.7 in the music-verbal-MI group, all median KVIQ-G-10 subscores were >3 points, which indicated moderate/high MI ability. Post-intervention, the greatest improvement in the kinaesthetic MI ability was observed in the music-verbal-MI group, so that this group’s scores were comparable to those from the other groups. In agreement with Heremans et al. (2012b), who found that external cueing significantly improved the MI quality in
pwMS, the music and verbal cueing could have enhanced their kinaesthetic MI capability.

16.4 Main Study Results

16.4.1 Baseline Data

At baseline, all 59 participants were found to be able to perform MI, as assessed by median KVIQ-G-10 scores of 3.7, ranging from 2.9 to 5.0 out of 5.0. Adequate MI ability was also demonstrated by the TDMI screening test. The median (min, max) Spearman’s ρ was 0.91 (0.88, 0.95). Table 22 presents participants’ baseline MI ability.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued-MI group N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>KVIQ-G-10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual sub†</td>
<td>18.0 (14.0, 25.0)</td>
<td>18.0 (13.0, 25.0)</td>
<td>20.0 (14.0, 25.0)</td>
</tr>
<tr>
<td>Median visual score†</td>
<td>3.6 (2.8, 5.0)</td>
<td>3.6 (2.6, 5.0)</td>
<td>4.0 (2.8, 5.0)</td>
</tr>
<tr>
<td>Kinaesthetic sub†</td>
<td>19.0 (13.0, 25.0)</td>
<td>20.0 (12.0, 25.0)</td>
<td>18.0 (13.0, 25.0)</td>
</tr>
<tr>
<td>Median kin score†</td>
<td>3.8 (2.6, 5.0)</td>
<td>4.0 (2.4, 5.0)</td>
<td>3.6 (2.6, 5.0)</td>
</tr>
<tr>
<td>Total score†</td>
<td>37.0 (31.0, 49.0)</td>
<td>38.0 (29.0, 50.0)</td>
<td>35.0 (29.0, 50.0)</td>
</tr>
<tr>
<td>Median total score†</td>
<td>3.7 (3.1, 4.9)</td>
<td>3.8 (2.9, 5.0)</td>
<td>3.5 (2.9, 5.0)</td>
</tr>
</tbody>
</table>

TDMI

<table>
<thead>
<tr>
<th></th>
<th>Music-verbal-MI group N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued-MI group N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 seconds right†</td>
<td>14.0 (9.0, 25.0)</td>
<td>15.0 (9.0, 23.0)</td>
<td>14.0 (9.0, 22.0)</td>
</tr>
<tr>
<td>15 seconds left†</td>
<td>9.0 (6.0, 18.0)</td>
<td>10.0 (6.0, 16.0)</td>
<td>8.0 (5.0, 14.0)</td>
</tr>
<tr>
<td>45 seconds right†</td>
<td>27.0 (18.0, 41.0)</td>
<td>28.0 (18.0, 41.0)</td>
<td>25.0 (15.0, 39.0)</td>
</tr>
<tr>
<td>15 seconds left-2†</td>
<td>10.0 (6.0, 17.0)</td>
<td>10.0 (7.0, 15.0)</td>
<td>9.0 (5.0, 14.0)</td>
</tr>
<tr>
<td>25 seconds left†</td>
<td>16.0 (9.0, 26.0)</td>
<td>16.0 (9.0, 23.0)</td>
<td>14.0 (8.0, 21.0)</td>
</tr>
<tr>
<td>Spearman’s ρ†,2</td>
<td>0.94 (0.87, 0.98)</td>
<td>0.86 (0.76, 0.92)</td>
<td>0.90 (0.85, 0.87)</td>
</tr>
</tbody>
</table>

Table 22: Participants’ Motor Imagery Ability at Baseline (Main Study 2).
Abbreviations: KVIQ-G-10 = Kinaesthetic and Visual Imagery Questionnaire-10, German short version; kin = kinaesthetic; sub = subscale; TDMI = Time-Dependent Motor Imagery screening test.

¹Median (min, max); ²all pairwise correlations; significant at 0.01 (two-tailed); blue-coloured questionnaire: higher numbers indicate better performance.

16.4.2 Effects of Cued and Non-Cued Motor Imagery on Motor Imagery Ability

MI ability relates to the fifth hypothesis. Post-intervention, overall, participants improved their MI ability, as evidenced by the median KVIQ-G-10 values of 4.1 (ranging from 2.9 to 5.0) out of 5.0. In all groups, the medians were higher than the cut-off value of 3 points for moderate/high visual and kinaesthetic MI ability; the minimum values were between 2.6 and 3.5 points. The clarity of the images, which means the visual MI ability, did not improve in any group, however, it was borderline in the music-verbal-MI group. The intensity of the sensations, that is the kinaesthetic MI ability, significantly improved after music-MI and non-cued MI, but not after music-verbal-MI. The total MI ability significantly improved in both cued MI groups and borderline in the non-cued MI group.

The improved MI ability after the intervention was also shown by the TDMI screening test (see Chapter 16.1.6 for a definition). The numbers of imagined stepping movements and durations were strongly correlated, as indicated by a median (min, max) Spearman’s ρ of 0.91 (0.88, 0.95), which were all significant. To summarise, post-intervention, participants in all groups improved their MI ability. The results are shown in Table 23.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued-MI group N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>KVIQ-G-10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual sub\textsuperscript{1} at BL</td>
<td>18.0 (14.0, 25.0)</td>
<td>18.0 (13.0, 25.0)</td>
<td>20.0 (14.0, 25.0)</td>
</tr>
<tr>
<td>Post-intervention (PI)\textsuperscript{1}</td>
<td>19.0 (15.0, 25.0)</td>
<td>20.0 (14.0, 25.0)</td>
<td>22.0 (13.0, 25.0)</td>
</tr>
<tr>
<td>Mean PI visual score\textsuperscript{1}</td>
<td>3.8 (3.0, 5.0)</td>
<td>4.0 (2.8, 5.0)</td>
<td>4.4 (2.6, 5.0)</td>
</tr>
<tr>
<td>P-value\textsuperscript{2}</td>
<td>0.072</td>
<td>0.129</td>
<td>0.420</td>
</tr>
<tr>
<td>Kin sub\textsuperscript{1} at BL</td>
<td>19.0 (13.0, 25.0)</td>
<td>20.0 (12.0, 25.0)</td>
<td>18.0 (13.0, 25.0)</td>
</tr>
<tr>
<td>Post-intervention\textsuperscript{1}</td>
<td>21.0 (13.0, 25.0)</td>
<td>21.0 (14.0, 25.0)</td>
<td>21.0 (16.0, 25.0)</td>
</tr>
<tr>
<td>Mean PI kin score\textsuperscript{1}</td>
<td>4.2 (2.6, 5.0)</td>
<td>4.2 (2.8, 5.0)</td>
<td>4.2 (3.2, 5.0)</td>
</tr>
<tr>
<td>P-value\textsuperscript{2}</td>
<td>0.102</td>
<td>0.015</td>
<td>0.021</td>
</tr>
<tr>
<td>Total score\textsuperscript{1} at BL</td>
<td>37.0 (31.0, 49.0)</td>
<td>38.0 (29.0, 50.0)</td>
<td>35.0 (29.0, 50.0)</td>
</tr>
<tr>
<td>Post-intervention\textsuperscript{1}</td>
<td>40.0 (32.0, 50.0)</td>
<td>41.0 (35.0, 50.0)</td>
<td>42.0 (29.0, 50.0)</td>
</tr>
<tr>
<td>Mean PI total score\textsuperscript{1}</td>
<td>4.0 (3.2, 5.0)</td>
<td>4.1 (3.5, 5.0)</td>
<td>4.2 (2.9, 5.0)</td>
</tr>
<tr>
<td>P-value\textsuperscript{2}</td>
<td>0.045</td>
<td>0.024</td>
<td>0.069</td>
</tr>
<tr>
<td>TDMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 seconds right\textsuperscript{1} at BL</td>
<td>14.0 (9.0, 25.0)</td>
<td>15.0 (9.0, 23.0)</td>
<td>14.0 (9.0, 22.0)</td>
</tr>
<tr>
<td>Post-intervention\textsuperscript{1}</td>
<td>16.0 (12.0, 30.0)</td>
<td>19.0 (12.0, 26.0)</td>
<td>19.0 (11.0, 25.0)</td>
</tr>
<tr>
<td>15 seconds left\textsuperscript{1} at BL</td>
<td>9.0 (6.0, 18.0)</td>
<td>10.0 (6.0, 16.0)</td>
<td>8.0 (5.0, 14.0)</td>
</tr>
<tr>
<td>Post-intervention\textsuperscript{1}</td>
<td>11.0 (8.0, 19.0)</td>
<td>12.0 (8.0, 18.0)</td>
<td>12.0 (7.0, 16.0)</td>
</tr>
<tr>
<td>45 seconds right\textsuperscript{1} at BL</td>
<td>27.0 (18.0, 41.0)</td>
<td>28.0 (18.0, 41.0)</td>
<td>25.0 (15.0, 39.0)</td>
</tr>
<tr>
<td>Post-intervention\textsuperscript{1}</td>
<td>30.0 (21.0, 54.0)</td>
<td>33.0 (24.0, 54.0)</td>
<td>32.0 (20.0, 48.0)</td>
</tr>
<tr>
<td>15 seconds left\textsuperscript{1} at BL</td>
<td>10.0 (6.0, 17.0)</td>
<td>10.0 (7.0, 15.0)</td>
<td>9.0 (5.0, 14.0)</td>
</tr>
<tr>
<td>Post-intervention\textsuperscript{2}</td>
<td>11.0 (7.0, 17.0)</td>
<td>12.0 (8.0, 20.0)</td>
<td>11.0 (6.0, 16.0)</td>
</tr>
<tr>
<td>25 seconds left\textsuperscript{1} at BL</td>
<td>16.0 (9.0, 26.0)</td>
<td>16.0 (9.0, 23.0)</td>
<td>14.0 (8.0, 21.0)</td>
</tr>
<tr>
<td>Post-intervention\textsuperscript{1}</td>
<td>17.0 (12.0, 29.0)</td>
<td>18.0 (13.0, 26.0)</td>
<td>18 (11.0, 25.0)</td>
</tr>
<tr>
<td>Spearman’s $p$\textsuperscript{1,3} at BL</td>
<td>0.94 (0.87, 0.98)</td>
<td>0.86 (0.76, 0.92)</td>
<td>0.90 (0.85, 0.87)</td>
</tr>
<tr>
<td>Post-intervention\textsuperscript{1,3}</td>
<td>0.95 (0.91, 0.98)</td>
<td>0.90 (0.85, 0.96)</td>
<td>0.91 (0.78, 0.96)</td>
</tr>
</tbody>
</table>

Table 23: Differences in Motor Imagery Ability between Baseline and Post-intervention for Each Study Group (Main Study 2).
Abbreviations: BL = baseline; PI = post-intervention; N = number of participants; KVIQ-G-10 = Kinaesthetic and Visual Imagery Questionnaire-10, German short version; sub = subscale; kin. = kinaesthetic; TDIM = Time-dependent Motor Imagery screening test.

1Median (min, max); 2p-values were corrected for multiple comparisons; significant p-values are highlighted in bright yellow and borderline significant changes in dark yellow; 310 pairwise correlations; all correlations were significant at ≤0.01 (two-tailed); blue-coloured questionnaire: higher numbers indicate better performance.

MI ability at baseline and post-intervention and effects of the intervention on MI ability for all study groups are shown in Figures 31 and 32.

Figure 31, A-C: Effect of Intervention on Visual, Kinaesthetic and Total Motor Imagery Ability (Main Study 2).
Figure legend: medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and min-max by the whiskers. Square brackets on top of the figures show significant within-group comparisons between baseline and post-intervention. *Significant at the 0.05 level.

**Figure 32, A-C:** Motor Imagery Ability, as Assessed by Mental Chronometry, at Baseline and Post-intervention (Main Study 2).

Figure legend: A-B = bar charts represent medians and error bars indicate their min-max. C = grey circles and black squares show medians, and error bars indicate their min-max.

A comparison between groups and time found no interaction for the MI capability, as assessed by the KVIQ-G-10. An improvement in visual and kinaesthetic MI ability above the MDC was seen in all groups in overall 9 (music-verbal-MI group, n=3; music-MI group, n=5 and non-cued-MI group, n=1) and 8 (music-verbal-MI group, n=2; music-MI group, n=3 and non-cued-MI group, n=3) out of 59 participants, respectively. The analysis of the TDMI data found high mental chronometry in all
groups (as shown in Table 22). Therefore, the fifth null-hypothesis was not rejected. The intervention effects on the MI ability are shown in Table 24.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued-MI group N=20</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KVIQ-G-10 visual subscale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from BL¹</td>
<td>1.0 (-2.0, 9.0)</td>
<td>1.5 (-4.0, 8.0)</td>
<td>1.5 (-4.0, 10.0)</td>
<td>0.923</td>
</tr>
<tr>
<td>Post-intervention¹</td>
<td>19.0 (15.0, 25.0)</td>
<td>20.0 (14.0, 25.0)</td>
<td>22.0 (13.0, 25.0)</td>
<td></td>
</tr>
<tr>
<td>Visual sub¹</td>
<td>3.8 (3.0, 5.0)</td>
<td>4.0 (2.8, 5.0)</td>
<td>4.4 (2.6, 5.0)</td>
<td></td>
</tr>
<tr>
<td>Change ≥4.3 points²</td>
<td>N=3 (15.8%)</td>
<td>N=5 (25%)</td>
<td>N=1 (5%)</td>
<td>0.212</td>
</tr>
</tbody>
</table>

| **KVIQ-G-10 kinaesthetic subscale** |                            |                     |                        |                 |
| Change from BL¹     | 1.0 (-2.0, 6.0)            | 2.0 (-4.0, 7.0)     | 2.0 (-3.0, 6.0)        | 0.336           |
| Post-intervention¹  | 21.0 (13.0, 25.0)          | 21.0 (14.0, 25.0)   | 21.0 (16.0, 25.0)      |                 |
| Kinaesthetic sub¹   | 4.2 (2.6, 5.0)             | 4.2 (2.8, 5.0)      | 4.2 (3.2, 5.0)         |                 |
| Change ≥4.8 points² | N=2 (5.3%)                 | N=3 (15%)           | N=3 (15%)              | 0.558           |

| **KVIQ-G-10 total score** |                            |                     |                        |                 |
| Change from BL¹     | 1.0 (-2.0, 12)             | 2.5 (-5.0, 13.0)    | 3.0 (-6.0, 16.0)       | 0.745           |
| Post-intervention¹  | 40.0 (32.0, 50.0)          | 41.0 (35.0, 50.0)   | 42.0 (29.0, 50.0)      |                 |
| **Total score¹**    | 4.0 (3.2, 5.0)             | 4.1 (3.5, 5.0)      | 4.2 (2.0, 5.0)         |                 |

**Table 24:** Effect of Intervention on Visual, Kinaesthetic and Total Motor Imagery Ability (Main Study 2).

Abbreviations: KVIQ-G-10 = Kinaesthetic and Visual Imagery Questionnaire-10, German short version; N = number of participants; BL = baseline; sub = subscale; ¹Median (min, max); ²number (ratio); blue-coloured questionnaire: higher numbers indicate better performance.
Chapter 17 – Reliability Study of the Gait Analysis System

The sixth objective of Study 2 was to investigate whether there is a difference between the effects of MI with music and verbal cueing, MI with music, and MI on SMS in pwMS. In other words, the synchronisation of the participants’ gait with the beat of instrumental and regular music was assessed. This reliability study tested gait analysis instruments during cued gait in pwMS and was part of Pilot Study 2. It was conducted in the same setting and on the same participants, as described in Chapter 14.

This chapter, firstly, presents the background to SMS-related gait parameters and gait analysis approaches; it, secondly, introduces the purpose of the current study. It further justifies and describes the optical system used to assess SMS in this study. Fourthly, this chapter outlines preparatory work that was performed to enhance the validity and reliability of the gait analysis system. Following to this, it explains how the data were collected and analysed. Finally, this chapter presents the results from the reliability analysis and the usability of the instruments for Study 2.

17.1 Background

SMS is the synchronisation of movement and, in this case, gait with the beat of instrumental music in regular metre (Thaut 2005). The degree of SMS is represented by the variability in gait and the adaption of footfalls with external cueing (Roerdink et al, 2011). Both the spatiotemporal gait parameters and gait variability reflect the motor control in gait (Hausdorff 2005). In this study, the ‘initial contact’ moment of the gait cycle was considered the most relevant to access spatiotemporal step length and step time data. In healthy individuals and people with mild MS presenting relatively preserved motor control, the initial contact would be the heel strike whereas moderately disabled people frequently have weak foot dorsiflexion or spasticity; this may lead to a mid-foot or forefoot strike during the initial contact phase of gait (Shumway-Cook and Woollacott 2012).

Gait variability measures across repeated walking trials are used to determine reliability (Brach et al, 2008). In healthy adults, stride-to-stride fluctuations are relatively small and the variability in step time or step length (as evidenced by the
Coefficient of Variation) is minimal, amounting to a small percentage (Hausdorff et al, 1997; Terrier and Schutz 2003). In contrast, persons with MS and even minimal disability showed greater step time variability (Sosnoff et al, 2011) and step length variability when they were compared with controls (Flegel, Knox & Nickel 2012). In general, gait variability appeared to be significantly larger in pwMS as in healthy individuals (Crenshaw et al, 2006). Surprisingly, there was no difference in gait variability between 284 patients with mild and moderate MS over a short distance of 4.9 metres (Preiningerova et al, 2015); the study’s results contradicted an earlier investigation showing significant differences in the variability of step time and step length between 88 pwMS and healthy controls (Socie et al, 2013a). Socie and colleagues (2012) observed a strong correlation between step time or step length variability and disability levels, as represented by the EDSS. This means patients with more severe disability showed greater gait variability. A small study found similar results during treadmill walking, with greater stride length variability in persons with moderate MS when compared to those with mild disability (Kaipust et al, 2012). The discrepancy in findings seems unclear as, according to the author’s clinical judgement, it seems logical that there would be a difference in gait variability parameters between pwMS at different disability levels. A recent large study shed some light on the puzzle by showing that the gait variability was mainly influenced by the functional system involved (Kalron 2016). When the corticospinal tract of the CNS was affected, significantly greater gait variability was observed than when the sensory system was affected. Depending on the functional system involved, higher values in gait variability are likely to be related to ‘cautious gait’ and falls (Hausdorff 2005), and linked to spasticity, muscle weakness, ataxia, fatigue, balance, coordination and timing dysfunction (Moon et al, 2016; Socie and Sosnoff 2013).

There are various methods to measure gait in people, such as observational gait analysis (Eastlack et al, 1991). Observational gait analysis is based on subjective clinical gait observation and can be used with or without videotaping. The subjectivity of ratings may be the reason for its low to moderate reliability (Brunnekreef et al, 2005). Striving for high scientific quality in Study 2, miscellaneous quantitative gait analysis approaches were considered, in terms of their reliability, validity and practicality:
• Optical systems which allow for a three-dimensional (3D) gait analysis appear to be the gold standard in research (Paul et al, 2016; Ugbolue et al, 2013). These 3D systems are employed in a gait laboratory and consist of at least two cameras, but typically as much as 8 to 12 cameras. Reflective markers are placed on the participant’s joints and other predefined body locations. To allow for optimum quality of video footages, infrared lighting is required. Unfortunately, in the MS-Clinic, Innsbruck, or the surrounding area, no gait laboratory was available for the author.

• Apart from 3D motion analysis systems, accelerometers are widely used instruments for human gait analysis (Huisinga et al, 2013; Motl et al, 2010). No accelerometers were available for the author, and the research budget did not allow purchasing multiple devices for the participants who simultaneously participated in the study.

• Another well-established technological means for assessing gait would be pressure sensing electronic walkways, such as the GAITrite system (Givon, Zeilig & Achiron 2009). These systems were found to be exorbitantly expensive, so reasonably priced and practicable alternatives were sought.

• Eventually, software supported two-dimensional (2D) motion analysis seemed to be a viable approach (Baker 2013). The advantage of video-based 2D gait analysis over observational analysis is its potential to objectively measure relevant gait parameters. Another benefit of 2D analysis even over 3D analysis is that it uses natural light. Thanks to significantly improved camera and software technology, 2D gait analysis regained significance for research.

Recent work evaluated the validity and reliability of 2D systems for the analysis of motion. A 2015 study examined the intra- and inter-rater reliability of a 2D high-speed video-based system at 300 frames per second during treadmill running; the examiners were required to identify the various foot-strike patterns at initial contact (Damsted, Larsen & Nielsen 2015). Excellent intra-rater reliability was found, as evidenced by weighted Kappa coefficients of 0.83–0.88, and moderate inter-rater agreement, shown by Kappa coefficients of 0.50–0.63 (Cohen 1968). Another study compared the reliability of a ten-high-speed camera 3D system against a single
camera 2D system (the frame rate is not mentioned) during treadmill running in healthy people; the authors measured frontal plane pelvis drop and displacement of thigh and shank and found excellent reliability of the 2D system (ICCs >0.96). Moderate concurrent validity was shown for lower limb displacement by Pearson correlation coefficients around 0.6, p<0.01 (Maykut et al, 2015). Recent research assessed the validity and reliability of a 2D motion analysis instrument while comparing a ten camera 3D against a simple 2D motion analysis system (Paul et al, 2016). With the 3D system, video data at 150 Hertz (Hz) were captured, as opposed to 30 Hz with the 2D system. Excellent agreement between the two systems was found during testing of postural control (ICCs 0.96–0.99, 95% CIs 0.92–0.99), apart from excellent test-retest reliability (ICCs 0.89–1.0, 95% CIs 0.76–1.0) and inter-rater reliability (ICCs 0.77–1.0, 95% CIs 0.61–1.0) of 2D system obtained outcomes. Based on this evidence, to assess SMS in this PhD project, a 2D gait analysis system was chosen for use.

17.2 Purpose of the Study

The purpose of this study was to: a) try out the gait analysis system, and b) examine its reliability.

17.3 Preparatory Work

A range of preparatory work was undertaken to obtain as precise and reliable results from this study as possible, described in this section. The evaluation of SMS required knowledge of spatiotemporal gait parameters, such as step time and step length, and the music beat frequency.

During over ground walking, 2 to 3 strides, which means 3 to 4 metres, are required to achieve a constant gait speed (Plotnik et al, 2015) and reliable gait analysis (Baker 2013). During cued walking, if the music beat corresponds to people’s preferred cadence, approximately four steps are needed for adjustment; if the music beat is faster or slower, more steps are required to achieve synchronisation (Roerdink et al, 2011). Owing to space constraints in the aforementioned physiotherapy department, it was necessary to make optimum use of the field of view. Thus, the preparatory work included the following:
In advance of the study, the video recording was tested by the researcher together with her husband. Different rooms were tested. Different camera set-ups were examined, and relevant distances were measured to determine the most suitable video-recording location. Eventually, a long corridor, with two side corridors leading off from the main one, was chosen for the SMS measurement. Thus, sufficient space was available for acceleration and deceleration. The central 4.5 metres of the hallway could be recorded and, around three full strides from a healthy tall male could be captured without moving the camera. The space was considered sufficient as usually persons with MS take shorter strides (Preiningerova et al, 2015; Socie et al, 2013a).

A pure frontal plane view of the participant was used because base width would not have provided useful information on SMS (Baker 2013). Therefore, the camera was set up perpendicular to the frontal plane. However, it has been shown that an accurate view of the plane in question is possible only in the centre of the field of view (Kirtley 2006). The further from the centre the person is, the more it seems that he or she walks at a slight angle to the camera, a phenomenon referred to as parallax error (Tian, Kyte & Messer 2002). Parallax error increases with the person’s distance from the centre of view, but decreases when the camera is placed further away from the participant (Kirtley 2006). That is why the camera was mounted as far as possible (5 metres) from the participant. To ensure bright illumination, maintaining the field of view to a small number of strides has been recommended (Baker 2013); this was adhered to in the current study on account of the space constraints. Parallax error was reduced further by placing the camera at a height of 1.3 metres on a high-quality tripod, enabling a precise adjustment of the inclining angle of the tripod head. This thesis also acknowledges that parallax is a constant, systematic error in the data across all data sets, so the data can be reliable despite its presence. There is also the repercussion of a similar likelihood of finding differences between groups or trials, with or without parallax. The main difference that parallax may have exerted was over the validity of the actual numbers recorded although this is only applied to the step length data, and not to any of the time data.
The video-footage was analysed using CCC Utilius Fairplay-5 Software⁸. Utilius fairplay-5 was chosen for this study because of its function and tools, which are comparable to other established motion analysis software packages. As opposed to other software, it allowed a recording of both video and audio. In addition, the field of view could be calibrated to minimise the parallax error, discussed above. The exact field of view was unobtrusively marked on the floor and could be aligned with the motion analysis software calibration grid. Prior to this study, the accuracy of the motion analysis software calibration grid had been explored, by using a 7x1 metres large grid mat shown in Figure 33. The mat was specifically produced for this purpose, with 20x20 centimetres large grid fields, which covered the marked walkway precisely. Analysis of the video footage showed perfect congruence between the grid fields of the grid mat and the video calibration grid.

![Figure 33: Grid Mat Used to Test the Motion Analysis Software Calibration Grid.](image)

Prior to the study, the measurement set-up was tested on 13 healthy team colleagues. Different rooms and camera angles were tested. Once the set-up was established, test-retest and intra-rater reliability and internal consistency analysis were performed. The results from the physiotherapy team colleagues were comparable to that reported by the literature: step time and step length variability between 1.5% and 3.4% were found (Kaipust et al, 2012; Shimada et al, 2006), and ICCs above 0.9 indicated excellent test-retest reliability. Cronbach’s $\alpha$ above 0.95 indicated excellent internal consistency, and measurement errors between 1.8 and 5 millimetres or 0.002 seconds indicated that the variations in observed scores to be expected were rather low.

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17.4 Methods

17.4.1 Data Collection

As this reliability study was part of Pilot Study 2, the same gait analysis approach was used in Study 2 if the reliability of the gait analysis instruments was at least moderate. For the gait data collection, participants were asked to walk in time with instrumental (karaoke) music. They were allowed to wear shoes or walk barefoot and the type of footwear or its absence was to be kept consistent during all trials. The selection of the music tempo and beat was based on the researcher’s eleven years of musical training (see Appendix 6) and existing evidence (see Chapter 2):

A) For gait cueing in people with neurological disorders, music pieces were used on 2/4 or 4/4 metre, and a tempo range between 40 and 120 BPM (Thaut 2005; Wittwer, Webster & Hill 2013b). B) Synchronisation of gait with rhythmic cues was achieved best at cueing rates near the preferred cadence (Roerdink et al, 2011; Thaut 2005).

Music beat frequencies at 75 BPM and 110 BPM were selected for the assessments. The slow and fast trials were chosen in view of the different levels in walking abilities; for example, persons with moderate MS might not be able to synchronise their steps with a music tempo of 110 BPM. By contrast, people with mild MS might be more easily able to synchronise their steps with the faster beat since it would be nearer to their natural cadence. Importantly, so far, not a single study was found that investigated the SMS during cued gait in pwMS. For this reliability study, only the 110 BPM trials were used since the measurement principles were identical.

Music was played with an Apple i-phone and X-Mi-X-Mini-II Capsule-Loudspeakers and the hallway was quiet and free of obstacles. While the participants walked four-to-six times back and forth on the marked walkway, the number of repetitions being dependent on their approximate step length, it was possible to capture 25 to 35 steps. The videos were taken with a Panasonic HC-WX979 4K camcorder with a large lens and frame rate of 50 fields per second. This means that the increments of measurement were 0.02 seconds. To ensure good quality, prior to the study, several video cameras had been tested by the author. The camera was mounted on a 1.3 metre high Haehnel 9994180 Triad-40-Lite Tripod at 5 metres from the participant.
(Baker 2013). The camera position was marked on the floor to ensure exactly the same recording distances and comparability of the video clips. Excellent image exposure was achieved owing to the 4K camcorder technology and bright lighting. The video-footages were analysed using CCC Utilius Fairplay-5 Software⁹. Reliability analysis involved the repeated measurement (5 times) of step lengths and step times on the video footages. In Figure 34, the location is presented where the gait measurement took place.

![Marked Walkway for Gait (and Sensorimotor Synchronisation) Measurement.](image)

**Figure 34:** Marked Walkway for Gait (and Sensorimotor Synchronisation) Measurement.

### 17.4.2 Administration Time of Gait (Sensorimotor Synchronisation) Measures

The gait (SMS) measurement required participants to walk a 13-metre distance 4 to 6 times, that is 52 to 78 metres. The administration time for the SMS measures was estimated at 5 to 10 minutes, with reference to T25FW.

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17.4.3 Statistical Analysis

Assuming normality, the within-subjects gait variability is evaluated by the Coefficient of Variation (CV), using the equation CV(%)=((SD/Mean)*100); lower variability reflects more stable gait (Atkinson and Nevill 1998; Hausdorff 2005). Normality tests and plots showed that the step time data were not normally distributed and there were significant outliers. Owing to this and the small sample size (see Chapter 7.5 and Appendix 17), for the singular measures of the total sample, as robust analogues to the SD and CV, the Median Absolute Deviation (MAD) (Leys et al, 2013; Pham-Gia and Hung 2001; Srinivasan and Mathiassen 2012) and the Coefficient of Mean Deviation about the Median (CV MAD) were used (Habib 2012; Sharma 2007). The MAD was calculated analogously to the SD, MAD=median(|x_i−median(x)|), where the median(X) is the median of the sample. X_i are the absolute differences, which means without minus-values, between the sample values and their median values; the MAD is the median of these absolute differences (Habib 2012). The CV MAD was calculated using the formula CV MAD(%)=(Median MAD/Median)*100 (Sharma 2007).

To assess relative (test-retest) reliability, Intra-Class Correlation Coefficients (ICCs) were calculated; internal consistency was assessed using Cronbach’s α (Atkinson and Nevill 1998; Bartlett and Frost 2008; Morrow and Jackson 1993). The ICC and Cronbach’s α were calculated with their 95% CI, using a Two-Way Mixed Model based on absolute agreement, with a conservative single measure analysis (Field 2009). Point estimates of the ICC were rated as excellent (0.9–1), good (0.75–0.9), moderate (0.4–0.74) and poor (0–0.39) (Fleiss 1986). Cronbach’s α was rated as unacceptable (<0.7), acceptable (0.7–0.79) and excellent (>0.8) (Bland and Altman 1997). As a measure of absolute reliability, the Standard Error of measurement (SEM) was evaluated, quantifying the dispersion (SD) of the measurement errors in repeated measures (Hopkins 2000). The SEM is the root mean square average of the SDs of the measures for the same person and was calculated using the formula: SEM= √(V1+V2+V3+…+V15/15) where V is the variance i.e. SD*SD (Baker 2016). The 95% CI of the SEM was calculated using the equation SEM±(1.96*SEM) (Atkinson and Nevill 1998).
The MDC, or smallest real change (SRC), represents the smallest amount of change, which is beyond the measurement error and thus is a ‘genuine’ change and clinically relevant (Donoghue et al, 2009). The MDC was determined and presented with a 95% CI (Altman 1991; Bland and Altman 1986) using the equation: $1.96 \times \sqrt{2} \times \text{SEM}$ where 1.96 is the Z-score representing 95% if the area is under the normal curve; the 95% CI was calculated as above, and the results were quantified in seconds (step time) or metres (step length) (Bland and Altman 1986; Rietberg, Van Wegen & Kwakkel 2010; Van Kampen et al, 2013).

### 17.5 Results

Excellent test-retest reliability between measures was found, as evidenced by ICCs around 0.98 for step length and of 0.88 for step time. Correspondingly, excellent internal consistency was observed, as represented by Cronbach alphas above 0.96. The mean measurement error for the step time measures was 6 millimetres, and the mean measurement error for the step time measures was 0.007 seconds. The SEM for repeated measures was greater than the SEM for a single measure, with an SEM difference for step length of 0.00057 metres (95% CI -0.00055, 0.0017 metres) and for step time of 0.00069 seconds (95% CI -0.00066, 0.0020 seconds). Accordingly, the MDC for step length was 18 millimetres and for step time 0.02 seconds. This means that the ‘true’ change in step length and step time, which exceeded the measurement error, was between 18 to 53 millimetres and 0.02 to 0.05 seconds, respectively. The reliability of the gait measurement system is presented in Table 25.
Table 25: Reliability of the Gait Analysis System used in Study 2.

<table>
<thead>
<tr>
<th>SINGULAR MEASURE OF TOTAL SAMPLE, N=15</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Step length variability&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CV MAD 2.24% (1.94, 2.67%); Min, max 1.33, 5.26%</td>
</tr>
<tr>
<td>Step time variability&lt;sup&gt;2&lt;/sup&gt;</td>
<td>CV MAD 3.45% (1.79, 3.70%); Min, max 0, 4.17%</td>
</tr>
<tr>
<td>SEM step length&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.0058 (-0.0056, 0.0173) metres</td>
</tr>
<tr>
<td>SEM step time&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.0059 (-0.0056, 0.0174) seconds</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REPEATED MEASURES OF TOTAL SAMPLE (5 repetitions)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ICC step length&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.978 (0.973, 0.982)</td>
</tr>
<tr>
<td>ICC step time&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.880 (0.855, 0.902)</td>
</tr>
<tr>
<td>Cronbach’s alpha step length&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.995 (0.994, 0.996)</td>
</tr>
<tr>
<td>Cronbach’s alpha step time&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.973 (0.967, 0.979)</td>
</tr>
<tr>
<td>SEM step length&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.0064 (-0.0062, 0.019) metres</td>
</tr>
<tr>
<td>SEM step time&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.0066 (-0.0063, 0.019) seconds</td>
</tr>
<tr>
<td>MDC step length&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.018 (-0.017, 0.053) metres</td>
</tr>
<tr>
<td>MDC step time&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.018 (-0.017, 0.054) seconds</td>
</tr>
</tbody>
</table>

Abbreviations: CV MAD = Coefficient of Mean Deviation about the Median (%); SEM = standard error of measurement (in metres and seconds); ICC = intraclass-correlation coefficient; MDC = minimal detectable change.

<sup>1</sup>(95% CI); <sup>2</sup>Median (25th-75th percentiles).

17.6 Implications for Study 2

The results from this reliability study showed that the median step length variability was 2.24% (1.94, 2.67%, with a maximum of 5.26%) and the median step time variability 3.45% (1.79, 3.70%, and a maximum of 4.17%). In comparison to this, a recent review found a mean step length variability, represented by the CV, of 4.29%
(95% CI 2.45, 6.13%) and a mean step time variability of 4.18% (95% CI 2.22, 6.14%) in pwMS (Moon et al, 2016). The differences in variability could be explained by the disability level which was 1.5-4.5 in the current investigation and up to 6.5 in the studies presented in the review.

The analysis further showed that the gait analysis system was a reliable instrument, as evidenced by excellent ICCs above 0.85. In addition, measurement errors that were detected with reference to the step time data (a mean SEM of 0.0059 (95% CI -0.0056, 0.017) seconds) were smaller than errors which were related to step length data (SEM 0.0058 (-0.0056, 0.017) metres). Accordingly, the MDC for the step time measures was 0.018 (-0.017, 0.054) seconds and 0.018 (-0.017, 0.053) metres for the step length measures. Comparable research showed similar or slightly higher measurement errors for step time (SEM 0.001–0.009 seconds) and step length (SEM 0.03–0.07 metres) measures while using a 2D video-based gait analysis in healthy people (Padulo et al, 2013). In agreement with this, a further study, which investigated the SEM and MDC using an electronic walkway, found measurement errors for step time of 0.007 seconds in younger individuals and of 0.015 seconds in older people; the SEM for step length was 0.006 metres and 0.017 metres in the same population. The same study found a MDC of 0.019 seconds and 0.042 seconds for step time and of 0.016 metres and 0.047 metres for step length for younger and older people, respectively (Almarwani et al, 2016). Consistent with this, another study found measurement errors of 0.024–0.064 seconds for step time and of 0.001-0.015 metres for step length, obtained from a 2D gait analysis system compared to a 3D system (Paul et al, 2016). The present results suggested that the music-cueing impacted on the participants’ gait as this was the only study which used music-cueing, but this could not be substantiated. Overall, the findings from the reliability study showed that the gait analysis system could be used with confidence to measure gait synchronisation with music beat in Study 2.
Chapter 18 - Study 2: Sensorimotor Synchronisation

The sixth objective of Study 2 was to investigate whether there is a difference between the effects of MI with music and verbal cueing, MI with music-cueing, and MI on SMS in pwMS. In this study, SMS was investigated within the same setting and on the same participants as in the pilot and main studies. This chapter explains the synchronisation parameters which were secondary outcomes in Study 2. The pilot study was used to test the methods; thus, based on the pilot study performance, this chapter also outlines the implications for the main study. Finally, the chapter presents the main study results on the effect of differently cued and non-cued MI on SMS.

18.1 Methods

18.1.1 Sensorimotor Synchronisation parameters

1. SMS can be determined using either the music tempo at BPM or the music inter-onset interval (IOI), that is the interval between two consecutive beats (Tsang 2006). The music tempo at BPM can easily be compared to the cadence, which is the step frequency (calculated from the step time) (Repp 2003; Repp and Su 2013); this has been referred to as stepwise synchronisation (Roerdink et al, 2011).

2. The music IOI can be compared to the step time (Bank, Roerdink & Peper 2011; Wittwer, Webster & Hill 2013a) and has been referred to as absolute accuracy (Benoit et al, 2014).

3. Another parameter to reflect the stability of SMS is the gait variability (Elliott, Wing & Welchman 2010); it is defined as the fluctuations in gait parameters (step time and step length) from one stride to the next where lower variability reflects more stable gait (Hausdorff 2005). Assessment of SMS requires knowledge of the step length and step time.

18.1.2 Data Collection

SMS was measured exactly as described in Chapter 17. Participants were asked to walk in time with the music played at 110 BPM (=545 milliseconds IOI) and 75 BPM (=800 milliseconds IOI). Therefore, it was not relevant whether their initial contact moments were temporally congruent with the stressed beats (on-beat), or whether
they occurred slightly earlier or later (off-beat) (Repp 2007). Instead, the relationship between the music frequency and the participants’ cadence or step time was assessed. SMS (step time and step length variability, stepwise synchronisation and absolute accuracy) were assessed at baseline and post-intervention.

18.1.3 Statistical Analysis

The calculation of the SMS parameters used was described in Chapters 17.4.3. Only descriptive statistics were used in the pilot study outlined in Chapter 14.3.1. For both the pilot and main studies, normality tests showed that the step time data were not normally distributed and included significant outliers (see Appendices 16 and 17). Thus, robust parameters were estimated: medians were presented and the CV MAD was used as a measure of gait variability, and non-parametric statistics were performed.

The music Inter-onset Interval (IOI, in milliseconds, ms) was calculated according to the equation: $\text{IOI}=(E_{1\text{onset}}-E_{2\text{onset}})$, whereby $E_1=$event 1 (first beat), $E_2=$event 2 (second beat) (Dixon 2001). In reference to a music beat of 75 and 110 BPM, a conversion from BPM to IOI was performed using the equation:

$\text{IOI}_{\text{ms}}=(60/\text{IOI}_{\text{BPM}})*1000$ (Honing 2013a). This means that a music tempo of 75 BPM stands for an IOI of 800 ms, that is 75 BPM=$(60/75)*1000=0.8 \text{ sec}*1000=800 \text{ ms IOI}$. Likewise, a music tempo of 110 BPM stands for an IOI of 545 ms.

Cadence, or rather step frequency, was determined from the median right and left step times: cadence (steps/minute)=$60/\text{median step time}_{\text{right+left}}$ (Baker 2013; Tanawongsuwan and Bobick 2002). Stepwise synchronisation was determined by calculating the ratio of the music beat frequency (110 BPM or 75 BPM) over the median cadence and was expressed as a percentage of the music beat frequency (Roerdink et al, 2011). Absolute accuracy was obtained by calculating the ratio between the beats and the steps, referring to the ratio of the IOI (545 ms or 800 ms) over the median step time, which was expressed as a percentage of the IOI (Benoit et al, 2014; Giovannelli et al, 2014).

For repeated measurements (baseline; post-intervention) of all variables in the main study, Wilcoxon Signed Rank test with split file (for group) was used, followed by
Bonferroni corrections as appropriate. Group X time interactions were evaluated, as explained for ordinal scale data in Study 1. Differences between mild and moderate disability groups (at baseline; post-intervention) were analysed post hoc using the Mann Whitney-U test.

18.2 Pilot Study Results

18.2.1 Baseline Data

Data collection ran smoothly. The SMS pilot baseline data are presented in Table 26.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=5</th>
<th>Music-MI group N=5</th>
<th>Non-cued-MI group N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast music trial, 110 BPM = 545 milliseconds IOI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step length var¹</td>
<td>2.2 (1.5, 2.7)</td>
<td>2.0 (2.0, 3.8)</td>
<td>2.3 (1.9, 3.6)</td>
</tr>
<tr>
<td>Step time var¹</td>
<td>1.8 (0.9, 3.6)</td>
<td>3.6 (2.5, 3.8)</td>
<td>3.6 (1.9, 3.9)</td>
</tr>
<tr>
<td>Stepwise synchronisation¹</td>
<td>1.01 (0.95, 1.04)</td>
<td>1.03 (0.95, 1.09)</td>
<td>1.03 (0.93, 1.05)</td>
</tr>
<tr>
<td>Absolute accuracy¹</td>
<td>0.99 (0.95, 1.05)</td>
<td>0.98 (0.92, 1.05)</td>
<td>0.97 (0.95, 1.07)</td>
</tr>
<tr>
<td>Slow music trial, 75 BPM = 800 milliseconds IOI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step length var¹</td>
<td>2.4 (1.6, 3.0)</td>
<td>2.0 (1.8, 2.8)</td>
<td>2.7 (2.5, 3.0)</td>
</tr>
<tr>
<td>Step time var¹</td>
<td>3.4 (2.0, 3.8)</td>
<td>3.2 (1.8, 3.7)</td>
<td>2.5 (0.6, 3.1)</td>
</tr>
<tr>
<td>Stepwise synchronisation¹</td>
<td>0.95 (0.76, 1.00)</td>
<td>0.96 (0.75, 1.00)</td>
<td>0.92 (0.80, 1.00)</td>
</tr>
<tr>
<td>Absolute accuracy¹</td>
<td>1.05 (1.00, 1.31)</td>
<td>1.04 (0.97, 1.33)</td>
<td>1.08 (1.00, 1.27)</td>
</tr>
</tbody>
</table>

Table 26: Participants´ Baseline Characteristics in Sensorimotor Synchronisation (Pilot Study 2).

Abbreviations: IOI: Inter-Onset Interval; BPM = Beats per Minute; var = variability (Coefficient of Mean Deviation about the Median (%)).
¹Median (25th-75th percentiles).
18.2.2 Post-Intervention Data

The data collection and analysis ran smoothly. Preliminary and descriptive pilot study data on SMS at baseline and post-intervention are presented graphically in Figures 35 to 39. Post-intervention SMS data are shown in Table A10 (see Appendix 17).

![Step Length Variability Pre- and Post-Intervention (Pilot Study 2)](image)

**Figure 35, A-B:** Step Length Variability Pre- and Post-Intervention (Pilot Study 2).

**Figure legend for Figures 35 and 37:** Abbreviation: BPM = beats per minute. Bar graphs indicate medians, and error bars show the 25th-75th percentiles.

![Step Time Variability Pre- and Post-Intervention (Pilot Study 2)](image)

**Figure 36, A-B:** Step Time Variability Pre- and Post-Intervention (Pilot Study 2).
**Figure 37, A-B**: Cadence and Music Beat Frequency Pre- and Post-Intervention (Pilot Study 2).

Figure legend: the dashed red lines indicate the optimum cadence synchronisation with the music beat frequency.

**Figure 38**: Stepwise Synchronisation Pre- and Post-Intervention (Pilot Study 2).

Figure legend for Figures 38 and 39: medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and min-max by the whiskers. Dashed red lines show the optimum synchronisation ratio at 1.0.
Figure 39: Absolute Accuracy Pre- and Post-Intervention (Pilot Study 2).

18.3 Implications for the Main Study 2

The reliability study had already confirmed the usability and feasibility of the SMS measurement. This pilot study was used to further explore the methods including the most robust and reasonable data analysis. Both the reliability and pilot studies performance and results showed that the methods and analysis could confidently be continued to be used in the main study.

18.4 Main Study Results

18.4.1 Baseline Data

At baseline, gait variability and gait synchronisation with the music beat were similar in all groups. In Table 27, participant baseline SMS data are shown.
### Table 27: Participants’ Baseline Characteristics in Sensorimotor Synchronisation (Main Study 2).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued-MI group N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast music trial, 110 BPM = 545 milliseconds IOI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step length var&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.22 (0.85, 6.33)</td>
<td>3.03 (1.20, 5.66)</td>
<td>2.14 (1.28, 6.52)</td>
</tr>
<tr>
<td>Step time var&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.92 (0.00, 6.60)</td>
<td>3.45 (0.00, 8.77)</td>
<td>1.83 (0.00, 8.77)</td>
</tr>
<tr>
<td>Stepwise synchronisation&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.03 (0.90, 1.94)</td>
<td>1.02 (0.81, 1.28)</td>
<td>1.04 (0.93, 1.37)</td>
</tr>
<tr>
<td>Absolute accuracy&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.97 (0.51, 1.11)</td>
<td>0.98 (0.78, 1.24)</td>
<td>0.96 (0.73, 1.07)</td>
</tr>
<tr>
<td><strong>Slow music trial, 75 BPM = 800 milliseconds IOI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step length var&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.61 (0.96, 5.22)</td>
<td>2.80 (1.59, 7.77)</td>
<td>2.04 (1.27, 7.87)</td>
</tr>
<tr>
<td>Step time var&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.70 (0.00, 5.00)</td>
<td>3.39 (1.37, 9.33)</td>
<td>2.50 (0.00, 17.24)</td>
</tr>
<tr>
<td>Stepwise synchronisation&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.90 (0.72, 1.98)</td>
<td>0.92 (0.65, 1.02)</td>
<td>0.91 (0.75, 1.02)</td>
</tr>
<tr>
<td>Absolute accuracy&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1.11 (0.50, 1.38)</td>
<td>1.09 (0.98, 1.54)</td>
<td>1.10 (0.98, 1.33)</td>
</tr>
</tbody>
</table>

Abbreviations: BPM = Beats per Minute; IOI = Inter-Onset Interval; var = variability (Coefficient of Mean Deviation about the Median (%)).

<sup>1</sup>Median (min, max).

### 18.4.2 Effects of Cued and Non-Cued Motor Imagery on Sensorimotor Synchronisation

Firstly, the main study analysis compared SMS at baseline with SMS post-intervention and separately for all groups. During the fast 110 BPM trials, after music-cued MI, the step length variability, as measured by the CV MAD, significantly improved (p=0.045). There was a trend for an improvement in the music-verbal-MI group (p=0.060), but not the non-cued-MI group. Step time variability did not change in any of the cued MI groups and even worsened in the non-cued-MI group (p=0.030).
There was a trend for an improvement in stepwise synchronisation in the music-verbal-MI group (p=0.057).

During the slow trials with music at 75 BPM, following music-cued MI with (p=0.003) and without (p<0.001) verbal cueing, step length variability significantly improved, but this was not the case after non-cued MI. Step time variability significantly improved only in the music-MI group (p=0.018). There was a trend for an improvement in stepwise synchronisation in both cued MI groups (both: p=0.066) and a significant worsening in the non-cued-MI group (p=0.036). Absolute accuracy significantly improved in the music-MI group (p=0.042), and there was a trend in the music-verbal-MI group (p=0.051) and a significant worsening in the non-cued-MI group (p=0.027).

To summarise, the study results showed that cued MI was significantly superior to non-cued MI to improve SMS in participants. Descriptive information on the SMS outcomes for all study groups is provided in Table 28.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued-MI group N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast music trial, 110 BPM = 545 milliseconds IOI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step length var$^1$ at BL</td>
<td>2.22 (0.85, 6.33)</td>
<td>3.03 (1.20, 5.66)</td>
<td>2.14 (1.28, 6.52)</td>
</tr>
<tr>
<td>Post-intervention$^1$</td>
<td>1.82 (0.70, 5.06)</td>
<td>1.56 (0.70, 6.32)</td>
<td>1.80 (0.59, 6.52)</td>
</tr>
<tr>
<td>P-value$^2$</td>
<td>0.060</td>
<td>0.045</td>
<td>0.861</td>
</tr>
<tr>
<td>Step time var$^1$ at BL</td>
<td>1.92 (0.00, 6.60)</td>
<td>3.45 (0.00, 8.77)</td>
<td>1.83 (0.00, 8.77)</td>
</tr>
<tr>
<td>Post-intervention$^1$</td>
<td>1.85 (0.00, 6.67)</td>
<td>1.96 (0.00, 6.76)</td>
<td>2.67 (0.00, 10.34)</td>
</tr>
<tr>
<td>P-value$^2$</td>
<td>0.351</td>
<td>0.426</td>
<td>0.036 worsening</td>
</tr>
<tr>
<td>Stepwise sync$^1$ at BL</td>
<td>1.03 (0.90, 1.94)</td>
<td>1.02 (0.81, 1.28)</td>
<td>1.04 (0.93, 1.37)</td>
</tr>
<tr>
<td>Post-intervention$^1$</td>
<td>0.99 (0.97, 1.37)</td>
<td>0.99 (0.92, 1.36)</td>
<td>1.04 (0.95, 1.37)</td>
</tr>
<tr>
<td>P-value$^2$</td>
<td>0.057</td>
<td>0.948</td>
<td>0.948</td>
</tr>
<tr>
<td>Abs accuracy$^1$ at BL</td>
<td>0.97 (0.51, 1.11)</td>
<td>0.98 (0.78, 1.24)</td>
<td>0.96 (0.73, 1.07)</td>
</tr>
<tr>
<td>Post-intervention$^1$</td>
<td>1.01 (0.73, 1.03)</td>
<td>1.01 (0.74, 1.09)</td>
<td>0.96 (0.28, 1.05)</td>
</tr>
<tr>
<td>P-value$^2$</td>
<td>0.114</td>
<td>1.000</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Slow music trial, 75 BPM = 800 milliseconds IOI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step length var$^1$ at BL</td>
<td>2.61 (0.96, 5.22)</td>
<td>2.80 (1.59, 7.77)</td>
<td>2.04 (1.27, 7.87)</td>
</tr>
<tr>
<td>Post-intervention$^1$</td>
<td>1.72 (0.78, 3.74)</td>
<td>1.93 (0.00, 4.17)</td>
<td>1.94 (1.54, 4.95)</td>
</tr>
<tr>
<td>P-value$^2$</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>1.000</td>
</tr>
<tr>
<td>Step time var$^1$ at BL</td>
<td>2.70 (0.00, 5.00)</td>
<td>3.39 (1.37, 9.33)</td>
<td>2.50 (0.00, 17.24)</td>
</tr>
<tr>
<td>Post-intervention$^1$</td>
<td>2.50 (0.00, 4.29)</td>
<td>2.50 (0.00, 8.11)</td>
<td>2.76 (0.00, 18.97)</td>
</tr>
<tr>
<td>P-value$^2$</td>
<td>0.828</td>
<td>0.018</td>
<td>0.579</td>
</tr>
<tr>
<td>Stepwise sync$^1$ at BL</td>
<td>0.90 (0.72, 1.98)</td>
<td>0.92 (0.65, 1.02)</td>
<td>0.91 (0.75, 1.02)</td>
</tr>
<tr>
<td>Post-intervention$^1$</td>
<td>1.00 (0.77, 1.22)</td>
<td>0.95 (0.69, 1.01)</td>
<td>0.88 (0.72, 1.01)</td>
</tr>
<tr>
<td>P-value$^2$</td>
<td>0.066</td>
<td>0.066</td>
<td>0.036 worsening</td>
</tr>
<tr>
<td>Abs accuracy$^1$ at BL</td>
<td>1.11 (0.50, 1.38)</td>
<td>1.09 (0.98, 1.54)</td>
<td>1.10 (0.98, 1.33)</td>
</tr>
<tr>
<td>Post-intervention$^1$</td>
<td>1.00 (0.82, 1.29)</td>
<td>1.05 (0.99, 1.45)</td>
<td>1.13 (0.99, 1.38)</td>
</tr>
<tr>
<td>P-value$^2$</td>
<td>0.051</td>
<td>0.042</td>
<td>0.027 worsening</td>
</tr>
</tbody>
</table>

Table 28: Differences in Sensorimotor Synchronisation between Baseline and Post-intervention for Each Study Group (Main Study 2).

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Abbreviations: Abs = absolute; BL = baseline; BPM = beats per minute; N = number of participants; IOI = Inter-Onset Interval; sync = synchronisation; var = variability (Coefficient of Mean Deviation about the Median (%)).

1 Median (min, max); 2 p-values corrected for multiple comparisons if appropriate; significant p-values are highlighted in bright yellow and borderline significant changes are highlighted in dark yellow.

Secondly, the analysis evaluated the differences in SMS between baseline and post-intervention and between groups. During the 110 BPM trials post-intervention, there was a significant improvement in the step time variability (p=0.008), after music-cued MI with (p=0.031) and without verbal cueing (p=0.015) when compared to non-cued-MI, mainly due to a worsening in the non-cued MI group. In contrast, the step length variability was not different between groups and between baseline and post-intervention measures (p=0.462). From baseline to post-intervention, neither stepwise synchronisation nor absolute accuracy was significantly different between groups.

During the 75 BPM trials, there was a significant improvement in step length variability in both cued MI groups with (p=0.030) and without verbal cueing (p=0.006) when compared to the non-cued-MI group. Contrastingly, step time variability improved only in the music-MI group (p=0.008) versus the other groups. Stepwise synchronisation significantly improved after music-verbal-MI (p=0.001) and music-MI (p=0.008) when compared to non-cued-MI. Absolute accuracy significantly improved from pre- to post-intervention in the music-verbal-MI (p=0.001) and music-MI (p=0.008) groups when compared to the non-cued-MI group.

To summarise, SMS significantly improved after both types of cued MI, with greater improvement observed in the music-MI group in contrast to the non-cued-MI group. Therefore, the sixth null-hypothesis was rejected. Effects of the intervention on SMS are shown in Table 29.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Music-verbal-MI group N=19</th>
<th>Music-MI group N=20</th>
<th>Non-cued-MI group N=20</th>
<th>Overall p-value²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Music at 110 BPM = 545 milliseconds IOI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step length variability (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline¹</td>
<td>-0.80 (-2.13, 1.50)</td>
<td>-0.75 (-2.71, 1.46)</td>
<td>-0.06 (-3.16, 1.67)</td>
<td>0.462</td>
</tr>
<tr>
<td>Post-intervention¹</td>
<td>2.22 (0.85, 6.33)</td>
<td>3.03 (1.20, 5.66)</td>
<td>2.14 (1.28, 6.52)</td>
<td></td>
</tr>
<tr>
<td><strong>Step time variability (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline¹</td>
<td>-1.38 (-3.57, 1.88)</td>
<td>-1.82 (-6.90, 3.85)</td>
<td>1.71 (-3.33, 3.85)</td>
<td>0.008</td>
</tr>
<tr>
<td>Adjusted p-value²</td>
<td>0.031</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-intervention¹</td>
<td>1.92 (0.00, 6.60)</td>
<td>3.45 (0.00, 8.77)</td>
<td>1.83 (0.00, 8.77)</td>
<td></td>
</tr>
<tr>
<td><strong>Stepwise synchronisation (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline¹</td>
<td>-0.04 (-0.57, 0.07)</td>
<td>-0.02 (-0.11, 0.15)</td>
<td>0.00 (-0.06, 0.04)</td>
<td>0.131</td>
</tr>
<tr>
<td>Post-intervention¹</td>
<td>1.03 (0.90, 1.94)</td>
<td>1.02 (0.81, 1.28)</td>
<td>1.04 (0.93, 1.37)</td>
<td></td>
</tr>
<tr>
<td><strong>Absolute accuracy (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline¹</td>
<td>0.04 (-0.08, 0.21)</td>
<td>0.02 (-0.19, 0.10)</td>
<td>0.00 (-0.03, 0.06)</td>
<td>0.151</td>
</tr>
<tr>
<td>Post-intervention¹</td>
<td>0.97 (0.51, 1.11)</td>
<td>0.98 (0.78, 1.24)</td>
<td>0.96 (0.73, 1.07)</td>
<td></td>
</tr>
<tr>
<td><strong>Music at 75 BPM = 800 milliseconds IOI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Step length variability (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline¹</td>
<td>-0.89 (-2.36, 0.86)</td>
<td>-0.76 (-5.79, 0.25)</td>
<td>0.03 (-3.32, 1.58)</td>
<td>0.004</td>
</tr>
<tr>
<td>Adjusted p-value²</td>
<td>0.030</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 29: Effect of Intervention on Sensorimotor Synchronisation (Main Study 2).
<table>
<thead>
<tr>
<th></th>
<th>Median (min, max)</th>
<th>Median (min, max)</th>
<th>Median (min, max)</th>
<th>Adjusted p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step time variability (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.13 (-3.33, 3.80)</td>
<td>-1.31 (-3.66, 3.50)</td>
<td>0.07 (-4.62, 3.23)</td>
<td>0.011</td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-intervention</td>
<td>2.50 (0.00, 4.29)</td>
<td>2.50 (0.00, 8.11)</td>
<td>2.76 (0.00, 18.97)</td>
<td></td>
</tr>
<tr>
<td><strong>Stepwise synchronisation (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0.05 (-0.76, 0.26)</td>
<td>0.03 (-0.10, 0.24)</td>
<td>-0.02 (-0.08, 0.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td>0.001</td>
<td>0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-intervention</td>
<td>1.00 (0.77, 1.22)</td>
<td>0.95 (0.69, 1.01)</td>
<td>0.88 (0.72, 1.01)</td>
<td></td>
</tr>
<tr>
<td><strong>Absolute accuracy (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-0.07 (-0.37, 0.31)</td>
<td>-0.04 (-0.33, 0.11)</td>
<td>0.02 (-0.05, 0.10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted p-value</td>
<td>0.001</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-intervention</td>
<td>1.00 (0.82, 1.29)</td>
<td>1.05 (0.99, 1.45)</td>
<td>1.13 (0.99, 1.38)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 29 (Continued):** Effect of Intervention on Sensorimotor Synchronisation (Main Study 2).

Table legend: abbreviations: BPM = beats per minute; IOI = Inter-onset Interval.  
¹Median (min, max); ²if overall p-value significant, post-hoc comparisons were performed between the music-verbal-MI and non-cued-MI groups, and the music-MI and non-cued-MI groups and between the music-verbal-MI and music-MI groups, with Bonferroni correction for 3 comparisons; significant adjusted p-values are highlighted in yellow.

The effects of the intervention on SMS during the fast and slow trials are also shown graphically in Figures 40 to 46. All figures show the differences between baseline and post-intervention measures and between groups.

**ORIGINAL IN COLOUR**
**Figure 40, A-B:** Effect of Intervention on Step Length Variability (Main Study 2).

Figure legend for Figures 40 to 41 and 43 to 44: medians are shown by lines in the centre of the box-plots; the 25th-75th percentiles are indicated by the boxes and min-max by the whiskers. Small square brackets on top of the figures show significant within-group comparisons between baseline and post-intervention; medium and large square brackets indicate the groups compared; dashed red lines show the optimum synchronisation ratio at 1.0. *Significant at the 0.05 level; **significant at the 0.01 level; ***significant at the 0.001 level.

**Figure 41, A-B:** Effect of Intervention on Step Time Variability (Main Study 2).
**Figure 42:** Cadence and Music Beat Frequency Pre- and Post-intervention (Main Study 2).

Figure legend: bar charts represent medians, and error bars indicate 25th-75th percentiles; dashed red lines show the optimum cadence in relation to the music beat frequency. *Significant at the 0.05 level; **significant at the 0.01 level.

**Figure 43, A-B:** Effect of Intervention on Stepwise Synchronisation (Main Study 2).
18.4.3 Post-Hoc Analysis: Sensorimotor Synchronisation in Participants with Mild and Moderate MS

The study results suggested that all participants preferred the fast music tempo during cued gait (see Figure 42). Therefore, the data were further explored to find out whether there was a difference in SMS parameters between participants with mild and moderate disability. Baseline and post-intervention step length, step time, cadence and the synchronisation parameters were compared between participants with mild disability (EDSS 1.5-3.0; n=36) and moderate disability (EDSS 3.5-4.5; n=23). In general, all parameters improved within both groups between baseline and post-intervention. Participants with higher disability levels took significantly shorter steps and showed significantly higher step length variability (p-values<0.01) during all trials than those with lower disability (p-values<0.03). At baseline, but not post-intervention, while walking to the fast music, step times were significantly longer (p=0.004) and cadence was significantly lower (p=0.004) in the moderate disability group; both at baseline and post-intervention, fast and slow step time variability were larger in the moderate disability group (both p=0.004). In people with moderate disability scores, at baseline, gait synchronisation with a fast music beat was significantly worse than participants with mild disability (all p=0.004). There were no disability group differences in step time, cadence and SMS during the slow trials.
To summarise, when participants with higher disability levels walked to the fast music beat, they took shorter steps for which they needed more time, so their cadence was lower. In this way, during the fast trials, the difference in median step lengths between participants in the lower and higher EDSS groups was around 10 centimetres whereas during the slow trials it was only 6 centimetres. Furthermore, more impaired participants had greater step length and step time variability and were less easily able to synchronise their steps with the music beat (for more details, see Appendix 18, Table A12 and Figures A1 to 3).
Chapter 19 – Discussion of the Study 2 Findings

19.1 Introduction

This PhD project investigated the effects of differently cued MI on walking, fatigue, QoL and HRQoL in pwMS. Results from Study 1 showed that music- and metronome-cued MI with verbal cueing improved walking, fatigue and (HR)QoL in pwMS when compared to no treatment. Findings from Study 2 showed that rhythmic-cued MI was more effective in improving walking, fatigue and QoL than non-cued MI. The study also examined whether gait synchronisation with music cues occurred in participants, and whether the synchronisation changed after the interventions, to be able to link the MI in walking to the SMS of rhythmic entrainment. Additionally, Study 2 assessed the MI capacity pre- and post-intervention, in a study population similar to that of Study 1. This was relevant for Study 1 because it was unknown whether the participants actually practiced kinaesthetic MI; it is only if MI was practised that it could be a mechanism behind any improvement. Three intervention groups were compared to each other in the second study to see whether motivation could have contributed to the improvements observed. Following the pilot study (n=15), which included a reliability study to test the gait analysis instruments to be used in Study 2, fifty-nine out of sixty participants completed this main study and were fully analysed.

This chapter discusses the interpretation of the findings of this study and compares the findings with the published research findings. Objectives 1 to 6 will be discussed under each outcome measure in turn. Prior to this, a separate section is added to the reliability study as it relates less directly to the 6 objectives. The methodological considerations of the study are discussed in addition to the notion of motivation, which may have influenced the results. This chapter also describes how the results were disseminated.

19.2 Reliability Study

A 2D video-based optic gait analysis system was subjected to reliability testing. Overall, the analysis showed a step length and step time variability, which was comparable to that reported in pwMS with a similar disability level. Excellent test-retest reliability and internal consistency were found. From a clinical perspective, the
observed measurement errors for step time appeared small, with an SEM of 6.6 (-6.3, 19) milliseconds. Contrastingly, the measurement errors for step length seemed medium, with an SEM of 6.4 (-6.2, 19) millimetres. Even though a calibration grid was used for the analysis, which was congruent with the testing grid on the floor during the preparation phase of this study, perspective errors could have been responsible for the slightly greater inaccuracy of the spatial measures. Nonetheless, these findings are in agreement with recent research that demonstrated excellent validity and reliability of a 2D optical system when compared to a 3D system (Paul et al, 2016).

The MDC statistic indicated the changes that would be required to occur in order to ensure that a change was due to treatment. The mean MDC was below 0.02 seconds, with an upper 95% CI limit of 0.05 seconds, for step time. The mean MDC for step length was 18 millimetres, with an upper 95% CI limit of 53 millimetres. Despite similar or higher measurement errors and MDC values, which have been shown by comparable research (Almarwani et al, 2016; Padulo et al, 2013), the accuracy of the gait analysis instruments to measure step length appears medium (see Chapters 17.6 and 19.11). Whilst using a 2D gait analysis, knowledge of the MDC could be relevant for future studies which examine the effects of any treatment on (cued) gait.

The analysis from the reliability study showed a median step length variability of 2.24% (min, max 1.33, 5.25%) and a median step time variability of 3.45% (min-max 0, 4.17%) during music-cued gait at 110 BPM. Thus far, no studies were found that investigated the gait variability during cued gait in pwMS, but several studies explored the gait variability in non-cued gait. This study’s results are comparable to a recent review, showing a mean step length variability of 4.29% (2.45, 6.13%) and a mean step time variability of 4.18% (2.22, 6.14%), both expressed at a 95% CI, in pwMS (Moon et al, 2016). Lower gait variability was observed in people with mild MS, as represented by EDSS scores of 1.0 to 3.5 (Sosnoff, Sandroff & Motl 2012), and higher gait variability was recorded in people with moderate to severe MS with EDSS scores of up to 6.5 (Socie et al, 2013a).

Remarkably, no study has been found that shows median-based gait variability data; therefore, the aforementioned comparisons were not perfectly accurate. Owing to the
small sample size and non-normally distributed step time data, in the present study, median-based statistics were used. This approach was in line with the relevant literature, which advocates that the research data should be carefully assessed to ensure that they do not violate the assumptions of the statistical test being used; this might inflate type I and II errors and lead to erroneous results (Bonate 2000; Hoekstra, Kiers & Johnson 2012). The MAD and CV MAD were used in various studies that investigated gait in different study populations, but not in pwMS (Di Marco et al, 2016; Floría, Gómez-Landero & Harrison 2015; Tucker and Hanley 2016).

However, a majority of studies reported normally distributed gait data and the SD (Preiningerova et al, 2015; Wright et al, 2016) and CV (Moon et al, 2016; Socie et al, 2013a); if the data distributions were not normal, the SD, MAD and CV were presented (Chisholm et al, 2014), or the median (25th-75th percentiles) of the CV was calculated using the mean and SD (Moon et al, 2015) and then analysed using non-parametric tests (Hordacre et al, 2015); alternatively, the SD and CV were analysed using non-parametric tests (Tanimoto et al, 2016). In light of these inconsistencies, this reliability study aimed at using the most robust measures to represent the central tendency of the distribution and yield reliable and accurate results. It is, however, recognised that the choice of statistics may not make a relevant difference to the clinical application of these studies.

Despite these discrepancies, the similarities in gait variability to that of other studies were important because they were suggestive of measurement accuracy. Moreover, this study’s results were comparable to a recent study that found excellent reliability and validity of a 2D motion analysis system to assess postural deficits in people with and without neurological impairment; the 2D system strongly agreed with a sophisticated 3D system (Paul et al, 2016). Another study showed similar excellent agreement on the stride lengths and lower limb joint angles, between a 2D single camera and 3D six camera system (Quixadá et al, 2016).

Excellent reliability of the equipment was an indispensable requirement to be able to assess SMS in Study 2. Careful planning and a range of preparatory work in advance of the study may have helped to detect and correct for any shortcomings in the measurement set-up. During the preparation phase of the study, different rooms with different lighting were tested. The height of the camera was changed to obtain a
rectangular field of view. Marking of the walkway was changed, so as to enable the calibration of the field of view and avoid influencing the participants’ walking.

19.3 Adverse Events, Acceptability and Compliance

As in Study 1, concerning the (cued) MI intervention, no safety-related occurrences or adverse events were reported by the participants in this study. This was regarded as a relevant result and was coherent with the ethical principle of ‘non-maleficience’ (see Chapter 5) and the WHO Patient Safety Curriculum Guide (World Health Organization 2001). The acceptability and usability of a physiotherapy intervention depends essentially on its tolerability and absence of side effects.

All participants received weekly phone calls to support their (cued) MI practice and solve any upcoming problems. In both studies, the author had to rely on participants’ accounts of their adherence. They reported that they had practised a median of five (within a range of four-to-six) times per week. It is recognised that the participants could have stated their compliance rates slightly incorrectly to meet the presumed expectations of the researcher.

About half of the participants reported some initial problems during the interventions, yet the majority of these improved during practice; unfortunately, the concentration problems in the non-cued MI group did not disappear. This could have been related to low arousal levels during MI and sitting with one’s eyes closed. Fifty percent of the participants considered the interventions as pleasurable and/or immediately beneficial for their walking, fatigue, mood and body perception. The remaining participants reported no problems and regarded the intervention as highly acceptable. The cued MI interventions were reported as more than acceptable by participants, mainly because they liked the music, and it helped them to remain concentrated. Anecdotal evidence showed that nearly half of the participants in the cued MI groups felt encouraged to move after the intervention. Notably, the urge to move would be a relevant impact of this research, particularly in view of a sedentary lifestyle in many pwMS (Mayo et al, 2013).

Theoretically, the phone call support could have contributed to the improvements in this study. For example, the calls were designed to help participants in adopting a
kinaesthetic imagery perspective, relaxing their muscles and remaining concentrated during the (cued) MI. In addition, the phone calls were also used to remind participants of their practice sessions and their post-intervention assessment at the MS Clinic. Participants in the intervention groups appreciated the support of their (cued) MI practice. Hence, it is likely that the phone calls fostered adherence to the programme. Indeed, low drop-out rates suggested high acceptability and tolerability of the study intervention. These calls may also have increased their MI capacity because participants were guided by the researcher on a one-to-one basis, but this was not examined. In agreement with these speculations, a review showed that interventions using telephone communication have small-to-medium effects on participant health-related behaviour, such as treatment adherence (Webb et al, 2010). Moreover, that review demonstrated that participant access to an advisor positively influenced behaviour. During the current study, as detailed above, participants were also given the option to seek advice on the intervention, and they did actually ask for support. In relation to this, other work has found that phone calls and text messages improved the health care outcomes and processes in different populations and countries; these were mainly related to compliance, self-efficacy and appointment keeping (Krishna, Boren & Balas 2009; Smith et al, 2015). Based on this evidence and the present study results, in all likelihood, the phone calls facilitated participant MI ability and adherence; they could have impacted on the findings in all groups. Therefore, it seems reasonable to recommend supportive phone calls for home-based (cued) MI practice.

19.4 Bias

This study was a three-group parallel randomised trial to compare the effects of three interventions against each other. Low attrition occurred in this research. In the pilot study, attrition was 0%, and in the second main study, 1.7% (n=1). Based on these low attrition rates, group sizes were similar, which reduced statistical bias.

Blinding was not possible as the author conducted the whole study and was informed about participant group allocation. The participants were also aware of the intervention group they were assigned to. Thus, it is acknowledged that the researcher could unconsciously have influenced the participants during the
assessments and phone calls. It is possible that participants reported what they thought was expected of them. This is named observer-expectancy effect, expectancy bias, observer effect or the Rosenthal effect (Rosenthal 1964; Salvia and Meisel 1980). Rosenthal found that, in studies with a non-blinded outcome, assessors inadvertently influence participants in favour of a specific intervention (Rosenthal 2009). He reported that this may be particularly the case if the variables are imprecisely defined, subjective outcome measures are necessary and/or the researcher is emotionally involved. In agreement with this, certain reviews have stressed the possibility of participants overestimating the effect size of their improvements when patient-reported outcomes (Hrobjartsson et al, 2014a) and subjective outcome measures are used (Hrobjartsson et al, 2014b). A large systematic review demonstrated that an observer effect occurs particularly in studies including binary outcomes (Hrobjartsson et al, 2012), which were not used in this study.

This study used clear-cut outcome measures, and the walking speed, walking distance, SMS and mental chronometry measures were objective. It is acknowledged that walking tests are effort dependent, and their outcomes can inadvertently be influenced by motivation. The fatigue, QoL and second MI ability assessments were patient-reported subjective outcomes. This was because, otherwise, it would not have been feasible to assess fatigue and QoL. MI ability was assessed using two different (subjective and objective) measures. As for these outcomes, it is recognised that, although the researcher sought to maintain a detached observer’s stance with all participants, her behaviour might unconsciously have been influenced by her assumptions.

Similarly, in any study, a Hawthorne effect could occur, which might mask or exaggerate a true intervention effect (McCambidge, Witton & Elbourne 2014). In other words, participants’ awareness of being observed or having their walking performance assessed may have provoked beliefs about the researcher’s expectations. Arguably, similar results were found in Study 2 and in Study 1, which included a non-treatment control group. Bias and strategies to minimise them in this thesis were also addressed in Chapter 11.4.
19.5 Objectives 1 and 2: Walking Speed and Walking Distance

The analysis of this study showed that both types of cued MI and non-cued MI were effective in improving walking speed and walking distance. The current effects of non-cued MI on walking performance were more significant than those seen by Catalan et al. (2011). In their small uncontrolled study in pwMS, they found a significant improvement in fatigue and QoL, but not in walking speed, as assessed by the T25FW. Reasons for the discrepancy between the present results and their 2011 study could be related to their small sample size, in addition to the differential procedure. The Catalan et al. study included the execution of various movements alongside MI whereas the current study used pure MI of walking only. MI of walking alone involved high numbers of repetitions, which has been evidenced to boost motor performance (Butefisch et al, 1995; Waddell et al, 2014).

A group interaction analysis revealed that music- and verbally-cued MI was superior to music-cued and non-cued MI in improving walking speed and walking distance; therefore, the first and second null-hypotheses were rejected. These results, with medium effect sizes, confirmed the Study 1 results with its large effect sizes; medium effect sizes in this study could have been associated with the smaller sample size. Reasons for these differential effects on walking between cued and non-cued MI might be the walking facilitation by rhythmic auditory cues, similar to RAS during real walking (Thaut 2005; Thaut and Rice 2014). Hence, it is likely that the music beat, and the verbal cueing, which emphasised the music pulse, supported participants’ imagined walking performance.

Given the lack of existing evidence on the effects of (cued) MI on walking in pwMS, it appeared reasonable to compare the present results with RAS studies in the MS population. Baram and Miller (2007) used an auditory feedback device that produced a tic in accordance with the participants’ steps. They observed non-significant short-term effects on walking speed and stride length only in pwMS (n=14) when compared to healthy controls (n=11). Later research in healthy older and younger people found increased reaction times during cued walking as opposed to non-cued walking (Peper, Oorthuizen & Roerdink 2012). Similarly, a 2015 study in people with Parkinson’s disease versus healthy people found improved gait parameters after gait
training, with cues adjusted to the individual’s gait, only in people with Parkinson’s disease (Brodie et al, 2015). All this evidence implies that coordination and timing deficits in pwMS and Parkinson’s disease are receptive to cued gait interventions. Mechanisms underlying RAS are rhythmic entrainment, which then induces SMS (Thaut 2005). In other words, rhythmic auditory cueing appears to compensate for the impairment of the brain’s temporal mechanisms; although based on the brain areas affected, the temporal deterioration underlying Parkinson’s disease is clearly different to that in pwMS (Beudel et al, 2008; Petter et al, 2016). The results from two further RAS studies in pwMS were in line with the above. In their small (n=10) home-based and uncontrolled study, Conklyn et al. (2010) used music with embedded metronome cues and gait training in which the music beat was 10% above the participant’s natural cadence. Their results showed no change in gait parameters, only a decrease in double support time. Recent work in 18 pwMS found significant improvements in stride length, stride time, cadence and gait speed after three weeks of metronome-cued gait training versus non-cued gait training; the metronome tempo was 10% above the participants’ preferred cadence (Shahraki et al, 2017). These studies support the current findings since they showed that rhythmic cueing has an effect on walking in pwMS.

As the present study was a pure MI study with and without cueing, its results were also compared to MI studies in people with neurological diseases other than MS. A single study in fifteen people with stroke was identified to investigate the effect of cued versus non-cued MI on walking and muscle activation. Kim and co-workers observed significantly improved walking performance, mainly after kinaesthetic MI practice with metronome cueing when compared to non-cued kinaesthetic MI training or visually-cued and non-cued MI practice (Kim et al, 2011). Their findings are akin to the current ones in which cued MI was also significantly superior to non-cued MI in improving walking speed and walking distance. In contrast to the Kim et al. study, the present investigation also used verbal cueing in one of the study groups. Indeed, the music- and verbally-cued MI intervention induced greater walking improvements than the music-only and non-cued MI. There is little research looking at the effect of verbal cues on walking in the neurological population. A study in people with Parkinson’s disease used instructional verbal cues (“take long steps”) (Lehman et al, 2005). The authors reported significantly improved step lengths after two weeks of verbally-cued
gait training compared to non-cued gait training. They also found significant changes in cadence and gait speed in both intervention groups. Notably, their assessments were taken in the absence of verbal cues, which is comparable to the current study. Similar results were found by a previous study in people with Parkinson’s disease who significantly increased their step lengths and gait speed after verbally-cued gait training (Behrman, Teitelbaum & Cauraugh 1998). Consistent with the motor learning literature, this suggests that verbal cueing was able to prompt specific aspects of (imagined) walking and help participants to focus their attention on these aspects (Schmidt and Wrisberg 2008). These speculations agreed with anecdotal feedback from participants in the music- and verbally-cued MI group.

19.6 Objective 3: Fatigue

The analysis of this study showed that between pre- and post-intervention, rhythmic-cued MI significantly improved fatigue. Music-cued MI with and without verbal cueing was effective in improving all types of fatigue while non-cued MI only improved psychosocial fatigue. The observed effects of MI only on psychosocial fatigue were less substantial than those of another study, which found significant improvements in fatigue and QoL after five weeks MI practice in twenty pwMS; these were maintained at six-month follow-up (Catalan et al, 2011). Firstly, reasons for these differential results could be linked to the differences in the study design and the treatment setting, and that the Catalan et al. study was a non-controlled study. The intervention of the present study was home-based and all instructions were given on a study CD whereas the Catalan et al. (2011) study provided the MI treatment in a one-to-one setting. The individual support made it possible to tailor the MI to the participant’s needs whereas, in the current study, support was provided during weekly phone calls.

Mental fatigue refers to the impaired ability to adequately perform cognitive tasks (Abd-Elfattah, Abdelazeim & Elshennawy 2015). Research has shown that mental fatigue was elicited by MI during shooting training in athletes (Guillot et al, 2004). This was supported by a study which found increased mental fatigue levels, as assessed by electro-encephalography, after MI of different arm movements in healthy people (Pomer-Escher et al, 2014). Based on this evidence, it is a possible explanation that the lack of improvement in fatigue after MI in the present study was related to mental
fatigue. It seems improbable that an intervention would improve fatigue if it induced mental fatigue. No studies were found that investigated the effects of MI on fatigue and brain activation in pwMS, which could have provided explanations. Advanced MRI studies showed that MS related fatigue is associated with the lesion localisation rather than the global lesion load. Damage to specific brain regions, particularly prefrontal areas, the basal ganglia, thalamus and nucleus accumbens and their connections, contributes to the development of fatigue (Rocca et al, 2014). Based on this, some of the current participants could have had a lower potential to benefit from non-cued MI. It is possible that cued MI would have been more effective in eliciting arousal or improving fatigue.

As introduced above, both types of music-cued MI improved physical, cognitive, psychosocial and total fatigue. Presumably these findings are primarily related to the effects of music and secondarily to the effects of verbal cueing. Firstly, music effects on mood, motivation, arousal and perceived effort have been evidenced by various studies (Karageorghis and Jones 2014; Karageorghis and Priest 2012; Priest, Karageorghis & Sharp 2004). As described in Chapter 2.10, listening to music influences arousal and mood, which then induces changes in cognitive performance (Husain, Thompson & Schellenberg 2002), and so it would impact on MI. For MI practice to be possible, dynamic motor representations in working memory are required, and also sustained levels of attention and cognitive control (Decety 1996b). It is well established that fatigue in pwMS is associated with both changes in the CNS processing and psychological functioning; this affects mood, effort perception, motivation, temporal and performance feedback and arousal (Krumhansl 1997; Rudroff, Kindred & Ketelhut 2016). This would suggest that the music boosted arousal, attention, mood and motivation in the participants in this study. The boost could have contributed to the improvements in fatigue which remains speculative because arousal and motivation were not assessed in this study.

Secondly, the music-verbal-MI was superior in effectiveness over the other groups in the improvement of psychosocial fatigue; therefore, the third null-hypothesis was rejected. These findings implied that the verbal cueing could have been another factor which improved fatigue. There is no evidence on the effects of verbal cueing on fatigue to be compared to; nevertheless, these present results appeared to be in
contrast to those of Study 1 where significant improvements in physical and cognitive, but not psychosocial fatigue, were observed in the intervention groups. This was in comparison to the control group. The discrepancies in results may be explained by the different groups used in Studies 1 and 2, with a non-treatment control and two intervention groups in Study 1 versus three intervention groups in Study 2. Excluding psychosocial fatigue, the improvements in fatigue in both cued MI groups in the present study were significant, which may explain the absent interactions between the time and the groups. As discussed earlier, the psychosocial MFIS scale has been attributed to lower psychometric properties than the other fatigue subscales and the total MFIS scale (Kos et al, 2005) which means this subscale may not accurately reflect psychosocial fatigue.

To summarise, both studies showed that rhythmic-cued MI significantly improves fatigue. Metrononome- and verbally-cued MI led to significant improvements in physical and total fatigue whereas music-cued MI, with and without verbal cueing, induced significant improvements in all types of fatigue. Music- and verbally-cued MI was superior to all interventions in significantly improving cognitive and psychosocial fatigue. These changes in fatigue were considered relevant because fatigue is a disabling symptom in pwMS.

19.7 Objective 4: Quality of Life

The analysis from this study showed that music- and verbally-cued MI improved both physical and psychological QoL while music-cued MI improved only physical QoL, and non-cued MI had no effect on QoL. These results are in contrast to those from the aforementioned uncontrolled study by Catalan et al. (2011), which showed significant improvements in QoL after five weeks of non-cued MI practice, combined with actual movements. So far, no other studies were found to investigate the effects of MI on QoL in pwMS, but a 2015 study in people with stroke supported the Catalan et al. results. This research showed that MI related to upper extremity tasks, as an add-on to upper limb training of daily life activities, improved upper limb functioning and QoL significantly more than upper limb training alone (Rajesh 2015). The discrepancies in results between these two studies and the present study may be related to the fact that both studies used a combined intervention, consisting of
visually-cued MI and physical practice (Rajesh 2015) or executed individual movements, alongside MI, in a one-to-one setting (Catalan et al, 2011). As opposed to the current study’s approach with home-based MI practice, the individual and performance-based support and visual stimulation may have served as potent facilitators of the MI. Another study used a comparable multifaceted approach in twenty-six people with stroke (Uttam, Midha & Arumugam 2015). The authors demonstrated that six weeks of graded MI practice, consisting of left-right discrimination training, MI and mirror therapy, led to significant improvements in upper limb function and QoL when compared to conventional therapy. So far, no other studies were found to explore the effects of pure MI training in people with neurological diseases. Nonetheless, all these results indicate that MI combined with specific sensory cueing or individual feedback and guidance improves QoL more than pure MI.

What has just been stated was confirmed by further study analysis. The comparison between groups and time-points showed significant differences in physical QoL between the music-verbal-MI group and the non-cued-MI group, in favour of music-verbal-MI; thus, the fourth null-hypothesis was rejected. These improvements were even clinically significant. There were no other significant differences between groups, nor in psychological QoL. Established effects of music on psychological functioning could be responsible for the superiority of music-cued MI over non-cued MI; those were detailed in Chapter 2.10 and the above sections. Notwithstanding, this cannot explain the role of verbal cueing in improving physical QoL. It is speculated that the verbal cueing increased the amount of rhythmic cueing, by emphasising the music beat and directing the attention towards relevant movement aspects. In absence of similar studies, findings from an RAS study were convergent with that speculation. In twenty people with stroke, gait training with musical RAS on five days per week, for six weeks improved walking, balance and QoL significantly more than the same training without RAS (Cha et al, 2014). It is acknowledged that the current study cannot fully explain the findings and further research is needed.
19.8 Objective 5: Motor Imagery Ability

In this study, the MI capability was measured in participants to figure out whether it could, at least to a certain extent, explain the improvements in Study 1. At baseline, all fifty-nine participants were found to be able to perform MI, as assessed by median KVIQ-G-10 scores of 3.7 for all items, ranging from 2.9 to 5.0 out of 5.0. These scores indicated high MI vividness (Malouin et al, 2007) and were consistent with another study that observed very similar KVIQ-G-10 scores in 30 pwMS (Heremans et al, 2012a). Comparable scores with a mean of 3.7±0.73 were also observed by other authors (Tabrizi et al, 2014) who found higher mean values of 4.11±0.47 in healthy controls. Their analysis showed that depression accounted for the difference between pwMS and healthy people, as discussed below. One study found slightly slower KVIQ-G-10 scores on the kinaesthetic subscale, consistent with average MI ability in pwMS, but they only investigated seven pwMS (Schuster et al, 2012c).

Adequate MI ability was also demonstrated by the TDMI screening test. Findings from this mental chronometry test showed that the numbers of imagined stepping movements within the three time periods were strongly related. These results were suggestive of a high temporal congruence of the imagined stepping movements; it signifies a strong MI capability (Malouin et al, 2008b). These findings seem to contradict findings from previous studies in pwMS which used different mental chronometry tests, related to the upper extremities (Tabrizi et al, 2014; Tacchino et al, 2013). However, these studies linked impaired MI ability in pwMS to their cognitive dysfunction (Tacchino et al, 2013) and depression (Tabrizi et al, 2014); this is why patients with cognitive impairment and/or depression were excluded from Studies 1 and 2. It is likely that the MI familiarisation created an understanding of MI in participants and enhanced their performance during the assessments and home-based practice. This procedure was performed since the literature had found that an adequate level of prior knowledge is required for MI to be effective (Holmes and Collins 2001; Jackson et al, 2001; Olsson et al, 2008; Schuster et al, 2011).

Four weeks of cued and non-cued MI practice seemed to improve the overall ability to imagine movements. The high MI capability, at baseline and post-intervention, suggests that participants were actually undertaking MI; this further supports MI being
a reasonable explanation for the improvements in outcomes seen. Regarding the MI capability, a comparison between groups and time found no interaction, as assessed by the KVIQ-G-10. Therefore, the fifth null-hypothesis was not rejected. Nevertheless, overall, participants improved their MI ability. This was evidenced by the median KVIQ-G-10 values for all items of 4.1 (ranging from 2.9 to 5.0) out of 5.0. After all MI interventions, these scores were similar to those from healthy people, reported by Tabrizi et al. (2014). Concerning the MI perspectives, at post-intervention, differential results were observed in the three groups. The clarity of the images, which means the visual MI ability, did not improve in any group, yet it was borderline in the music-verbal-MI group. The intensity of the sensations, that is the kinaesthetic MI ability, significantly improved after music-MI and non-cued MI, but not after music-verbal-MI. The total MI ability significantly improved in both cued MI groups, and it was borderline in the non-cued MI group. These results require further consideration because kinaesthetic MI was applied in this study. It suggests that after the intervention, primarily kinaesthetic MI ability would improve. The reasons for the greater improvement in visual MI in the music-verbal-MI group are unknown, particularly as the same music was used in the music-MI group. It does not seem plausible that the verbal cueing would facilitate visual MI or ameliorate visual MI capability. It is recognised that some statistical changes observed could have occurred by chance, despite the corrections for multiple comparisons.

Nevertheless, the findings suggested that the music- and verbal-cueing drew participants’ attention to the rhythm, which could have influenced their MI. Supported by research on cognitive-motor interaction (Leisman, Moustafa & Shafir 2016) and the similarities in rhythm in language and music (Patel 2008), it could be suggested that the human brain does not perceive rhythmic-cued MI as an interaction or even contradiction of different components, but as an inseparable entity. It is acknowledged that the present study could not illuminate these complex interrelationships.

Post-intervention, a high mental chronometry was shown by the TDMI screening test. These results confirmed those shown by the KVIQ-G-10 although it was recognised that the two measures assess a slightly different construct, or characteristic, of MI (Williams et al, 2015). The present findings were in line with a 2015 study, which compared the MI ability assessment via a questionnaire similar to the KVIQ, a mental
chronometry test and a MI controllability test; the latter involved mental rotation using a finger-to-thumb opposition task (Saimpont et al, 2015). Except for minimal differences in mental rotation in favour of younger participants, regardless of the type of measurement, similar ability to imagine movements was observed. This implied that despite measuring different aspects of MI ability, all assessments yielded very similar results. All studies that examined the MI ability in pwMS used at least two different measures; their results were in agreement with each other, the cited studies and this thesis.

This study showed that (cued) MI practice improved not only walking performance, but also the MI ability in pwMS. Catalan et al., who conducted the only MI intervention study in pwMS, have not assessed MI ability in their participants; thus it was not possible to draw any comparisons with their results (Catalan et al, 2011). Several studies investigated the effect of MI training, combined with physical practice, on motor function and the MI ability in people with stroke (Oostra et al, 2015; Schuster et al, 2012a). A pilot study found that the MI ability improved after two weeks of MI training which was embedded into physiotherapy, but not after MI training performed after physiotherapy or physiotherapy alone; contrastingly, the performance of a complex motor task improved in all groups. MI ability was assessed by the KVIQ and a computer-based MI ability questionnaire (Schuster et al, 2012a). Another study showed that six weeks of MI training, as add-on therapy to standard rehabilitation, significantly improved walking and the MI ability when compared to relaxation, as assessed by a questionnaire and a mental chronometry test (Oostra et al, 2015). Although it has to be pointed out that a combination between MI and physiotherapy was used in the latter studies, which could have influenced the findings, these were consistent with those from the current study, suggesting that MI practice can enhance motor performance and MI ability. Probably, the MI practice and weekly phone call support assisted participants in their MI aptitude and augmented their home-based training. Importantly, as all participants in this study were able to imagine movements, it seemed reasonable that the participants in Study 1 indeed had practised MI; this was a similar study population to that in Study 2. Notably, MI was, thus, considered a potential mechanism underlying the improvements in walking, fatigue and (HR)QoL in Study 1.
In theory and based on relevant literature, (cued) MI practice could have improved participants' body perception, via simulated sensory input, or, more specifically, enhanced proprioception (Grush 2004). In other words, the activation of brain areas responsible for overt walking and body perception during kinaesthetic MI could have replaced the sensory feedback that would be generated by real walking (Anema and Dijkerman 2013). Repeated motor area activation and body perception, which are known to advance motor control and coordination (Schmidt and Lee 2011) may have contributed to the walking improvements in this research. Nonetheless, this remains speculation because it was not investigated in the current project.

19.9 Objective 6: Sensorimotor Synchronisation

In this study, SMS was explored during gait with fast (at 110 BPM) and slow (at 75 BPM) music. Music-cued MI with and without verbal cueing were found to be significantly more effective for SMS than MI alone. Within the fast music trials, significant improvements in gait variability were seen in the music-MI groups when compared to the non-cued MI group. Some of these differences were generated by a worsening in step time variability after non-cued MI. The deterioration in SMS in this group could have been caused by the enormous contrast between the silent MI practice and the music-cued gait analysis, which might have interfered with each other; however, this was not investigated in this study. No changes were seen in stepwise synchronisation or absolute accuracy.

In all likelihood, the rhythmic-cued walking imagery practice positively impacted on the spatiotemporal gait variability, comparable to 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 had their gait cued; cued gait training did not change the gait variability in healthy controls (Ellis et al, 2015). Another recent study has compared the effects of four weeks of cued gait training on gait parameters in people with stroke, in comparison to gait training without cueing. Significantly improved gait was observed only when RAS was used (Song and Ryu 2016). In accordance with this, a study in ten people with Parkinson’s disease observed improved step time variability during metronome-cued gait when compared to non-cued gait. The same study
reported that the cueing worsened gait variability in healthy older adults, but had no effect on variability in healthy younger adults (Brodie et al, 2015). The authors suggested that the cueing would intervene with automated gait patterns in healthy older people, which could be related to the reduced inhibition of their auditory cortex by frontal brain areas caused by ageing (Cheng, Baillet & Lin 2015). This may have affected their ability to reflexively respond to sound such as in auditory cueing (Patel 2008). In contrast, healthy younger people were observed to have faster perceptual-motor speed or shorter reaction times (Chen et al, 2009), so their gait may be more flexibly organised (Kang and Dingwell 2008). Hence, in response to cueing or other perturbations, healthy younger people are capable of maintaining their physiological gait patterns to a greater extent compared to older people. Findings from all these studies implied that cueing enhances the temporal organisation of (imagined) gait in people with motor performance deficit. Furthermore, with increasing age, the human brain seems to be more susceptible to disruptions in gait pattern. In the present study, the participants were aged between 21 and 70 years, with a mean age of 50 years. Naturally, an older age is associated with higher disability levels in pwMS. There were indeed differences in SMS between participants with lower and higher disability (age), as discussed in more detail below. This means that presumably both participants’ age and walking impairment influenced their response to the rhythmic-cued MI.

No studies have investigated gait variability during cued gait in pwMS. However, it is known that pwMS have impaired gait stability, consistent with increased stride-to-stride variability (Socie and Sosnoff 2013). Therefore, it was suggested that cueing of (imagined) walking would improve the gait steadiness also in this population, which would enhance the gait parameters. Indeed, three studies, which investigated the effects of RAS-based gait training in pwMS, were compatible with the above described research in people with Parkinson’s. One of these studies found non-significant improvements in walking speed and stride length in pwMS, but not in healthy controls (Baram and Miller 2007). Another small (n=10) home-based study noticed reduced double support time, but no other gait parameter changes in pwMS after cued versus non-cued gait training (Conklyn et al, 2010). Recent work confirmed these results while showing significant improvements in stride length and stride time, cadence and gait speed, only after cued but not non-cued gait training in pwMS.
These studies demonstrated that gait training with rhythmic-auditory cueing benefits the walking in pwMS more than gait training alone.

In the current study, based on work from Grahn and Brett (2007), alternative explanations could be provided for the SMS improvements only in the cued MI groups. Increased MI capability could have been related to auditory-motor coupling occurring even in the absence of overt movement, particularly as people were actively listening to music (Grahn and Brett 2007). In other words, reinforced auditory-motor coupling could explain the improvements in SMS in the cued MI study groups; this may have impacted the temporal organisation of their walking. Grahn and Brett also found that regular beat, in contrast to irregular beat, improves the rhythm perception and reproduction. This suggests that enhanced rhythm perception in the present participants, who were exposed to regular beat, could have facilitated their gait synchronisation with the beat.

In this study, during the slow music trials, in general, participants took shorter steps. Similar results were reported by two studies, showing that the slow beat of non-stimulating music reduced the step length (Buhmann et al, 2016), and that slow relaxing music reduced the gait tempo and step length (Leman et al, 2013). In the present study, due to its slow tempo, the 75 BPM music piece was not as stimulating and motivating as the majority of songs on the CDs and the 110 BPM piece. Even if the music beat was regular, this could have modified participants’ walking performance. It was outside the scope of this study to explore whether the mood or atmosphere which music creates impacts on walking.

Within the slow music trials, between pre- and post-intervention, step length variability significantly improved in both cued MI groups, but not after non-cued MI. In contrast, step time variability only improved in the music-MI group. Verbal cueing was used in the music-verbal-MI group to emphasise the temporal patterns of the music and to enhance attention throughout the MI whereas only music cueing was employed in the music-MI group. The participants in the music-verbal-MI group heard the verbal emphasis of the beat across all practice sessions for four weeks. It could be that in the music- and verbally-cued MI group, the lack of verbal cueing during the
assessments of SMS contributed to their slightly poorer performance when compared with the music-only-cued MI group.

In the absence of similar studies in pwMS, evidence was sought to back up these suggestions that the removal of a cue during the assessments could have contributed to the results. A study in people with Parkinson’s disease found improvements in gait speed and stride length after two weeks of home-based auditory-cued gait training, implemented twice daily. After removal of the cueing, the authors observed smaller, but still present, improvements in gait (Espay et al, 2010). In agreement with these results, it is speculated that a carry-over effect is created by any type of rhythmic-auditory cueing even after removal of the cueing (Giladi, Bloem & Hausdorff 2007). More specifically, after rhythmic-cued MI practice, it is likely that a gain in SMS positively influenced the actual walking performance and that these effects, however small, remained for a certain period. This conjecture is supported by the literature on rehabilitation-induced performance progress and related brain plasticity (Prosperini et al, 2015). Echoing the existing literature (Beer, Khan & Kesselring 2012), although this was not investigated in the current study, its results would endorse a long-term rhythmic-cued MI practice to retain the gains in performance.

A post-hoc analysis to this study demonstrated disparities in SMS between the fast and slow synchronisation trials at baseline. During all assessments, more participants were able to adjust their gait to the fast music beat. These results were plausible in participants with mild MS since evidence showed that SMS was most accurate at faster music frequencies that were close to people’s preferred gait speed (Leow, Parrott & Grahn 2014; Roerdink et al, 2011). Furthermore, a previous study observed that healthy people walked faster while synchronising to a faster beat, but, most optimally, this occurred at around 120 BPM, ranging from 106 to 130 BPM (Styns et al, 2007). The same might have been true in mildly disabled participants in the current study and was in line with pwMS’ cadence. A mean cadence of 109.1±23.3 steps/minute was observed in pwMS who scored 2.5-4.0 on the EDSS (Wajda et al, 2013). However, considerably impaired participants also showed greater improvements in SMS when the beat was faster; they simply shortened their step lengths. Using this compensation strategy, synchronising with a faster beat appeared to be more easily manageable than with a very slow frequency. More severely
disabled participants showed greater gait variability and were less able to synchronise their steps with the music beat compared to those with lower disability. Prior to the study, it was expected that participants with moderate disability who have spasticity-related lower limb stiffness and ataxic coordination deficits would adapt their cadence more easily to the slower music beat.

In spite of this, it was recognised that 75 BPM is a rather slow frequency to adjust one’s gait to. This might be based on the fact that higher levels of postural control are required for very slow (simulated) walking. For example, a study showed that kinaesthetic, but not visual, MI of lower body movements affected postural control parameters, such as postural sway (Stins et al, 2015). Underpinned by a 2011 piece of research, their findings suggested that during MI, people re-activated motor representations of their imagined movements, which would necessarily involve postural control (Grangeon, Guillot & Collet 2011). This means, that the present post-hoc findings supported those from Stins et al. (2015) and Grangeon and colleagues (2011). It would be interesting to validate these findings in a further study using music at medium beat frequencies such as 90 or 110 BPM.

Post-intervention, the differences in step length, step time and their respective variabilities, cadence and SMS between disability groups diminished or vanished. The rhythmic-cued MI intervention may have improved the participants’ ability to flexibly adjust their gait parameters, which was shown to be an important feature of physiological gait (Hove and Keller 2015; Styns et al, 2007). The current results confirmed those from RAS studies in people with stroke (Cha, Kim & Chung 2014), Parkinson’s disease (Hausdorff et al, 2007) and traumatic brain injury (Hurt et al, 1998). They observed participants’ gait adaption with different cueing tempos, as in the present study, while the degree of gait synchronisation was dependent on the participants’ disability level.

The current intervention used music tempos between 80 and 120 BPM to provide an opportunity for all participants to achieve synchronisation of their imagined steps with the external rhythmic beat. This approach was in alignment with a study that found reduced gait flexibility during RAS which employed a fixed single cueing speed in people with Parkinson’s disease and healthy controls (Hove et al, 2012). The cueing
at just one tempo might have impaired the physiological gait adaptability mentioned above (Hove and Keller 2015; Styns et al, 2007). It appeared likely that the same would apply to imagined gait, but it was not investigated in this thesis.

In both cued MI groups, participants were explicitly asked to imagine taking a step with every prominent beat. Similarly, during the SMS assessments, participants were explicitly instructed to walk in time with the music beat. In the absence of external cueing, participants in the non-cued MI group were instructed to imagine themselves walking. Results from SMS studies suggest that participants are capable of synchronising their gait with external beat only if explicitly asked to. Additionally, healthy people were found to adjust their steps to music or step cues only if they were explicitly instructed (Mendonca et al, 2014). People with Parkinson’s disease failed to synchronise their gait with a music beat since that was not explicitly stated (Brown et al, 2009). These findings suggest that the explicit synchronisation instructions contributed to the present results.

To summarise, music-cued MI with and without verbal cueing led to significantly greater improvement in SMS as opposed to non-cued MI, presumably related to enhanced auditory-motor coupling and motor learning. Therefore, the sixth null-hypothesis was rejected. These findings may help to explain the walking improvements in Study 1. The improvements in SMS only after cued MI indicated that SMS was a possible mechanism contributing to the walking improvement in this research.

19.10 Mood, Motivation, Arousal and Self-Perception

The analysis from this study showed that music-cued MI with verbal cueing produced greater improvements in walking, psychosocial fatigue and QoL than music-only-cued or non-cued MI. Both types of cued MI led to significant improvements in physical, cognitive and total fatigue and SMS whereas for all outcomes, pure MI was the least effective. Apart from the MI and rhythmic cueing, motivation could have played a role in the improvements. Beneficial effects of motivational music with pleasing melodies on psychological functioning were stressed earlier in this thesis (Karageorghis et al, 2009; Kendelhardt 2003); some of those include motivation, delayed fatigue or mood enhancement, which may have been present in the cued MI groups. Listening to
motivational or high-groove music (Leow, Parrott & Grahn 2014) activates the brain’s reward network areas and is associated with high levels of pleasure and arousal in the listener (Csikszentmihalyi 1997; Lehmann 1994). Indeed, participants reported that they regarded the intervention as pleasurable, and that they enjoyed the music. Furthermore, as a majority of participants in the cued (versus the non-cued) MI groups reported that they were able to focus on the MI, this may also have heightened their arousal. Evidence suggested that arousal and fatigue are negatively correlated so that fatigue results may be indicative of arousal (Niepel et al, 2013; Terry and Karageorghis 2006). As a consequence, higher arousal levels in the music-based groups could have boosted attention in participants and reduced their perception of fatigue during the MI (Brewer 1995). In addition, as music has been shown to enhance mood and cognition (Jensen 2000; Levitin 2007) and impact on coping, autonomy and self-regulation (Laiho 2004), it could have been a powerful motivator in this research. It is suggested that the combined effects of the MI, via enhanced body representation (discussed below) and music-induced improvement in mood and motivation, contributed to the improvements seen.

Unfortunately, it was not possible to test for motivation or mood connected to the musical experience. The proposal was to measure arousal in this study, but it would have been problematic to measure arousal at baseline because it is a core affect that shows an immediate response to a stimulus, whether it be pictures or exercise experiences (Boettger et al, 2009; Ekkekakis et al, 2000). Thus, it only would have been feasible to measure arousal post-intervention, in response to the intervention. For this purpose, the Self-Assessment Manikin (SAM) was considered for use to assess basic emotions, such as pleasure and arousal, while the music was being played (Bradley and Lang 1994; Lang 1980). The choice of the music in the current study was based on the author’s understanding of pleasant music, which was confirmed by the participants. Initially, the Brunel Music Rating Inventory-2 was planned to be used to measure the motivational qualities of the music played (Karageorghis et al, 2006). However, both instruments could only have been utilised in the music-cued MI groups, which would have made it impossible to compare the groups. A large amount of outcome measures were used in this study and it did not seem reasonable to ask the participants to complete any more, and so the idea was dismissed.
Another reason for the improved performance observed could be the motivation of the participants whilst performing the assessments. In order to be consistent with each participant, the researcher did not offer verbal encouragement or feedback to the participant during any of the assessments. Nonetheless, the current participants may have performed better at post-intervention assessments since they intended to improve on their previous performances (Hopkins 2000).

The repeated MI rehearsal of walking could have boosted self-confidence in relation to walking in participants. As in Study 1, a large proportion of participants in all groups reported that after the intervention, they felt more balanced and self-competent while standing or walking, such as during cooking or while walking in a crowd of people. This sense of increased stability could have been connected with MI-linked enhancement of the body schema, which was supported by existing evidence (Jeannerod 1995). As such, the body schema refers to the position of the body parts in relation to one another, particularly during movement and the unconscious representation of it (Coslett, Saffran & Schwoebel 2002). Jeannerod pointed out that the normally unconscious motor representation can be accessed during MI so that the process becomes conscious (Jeannerod 1995). Shenton, Schwoebel & Coslett (2004) used a mental rotation task of the hands to explore the relevance of specific feedback for the body schema. They found that kinaesthetic feedback significantly improved the mental rotation when compared to visual feedback. This is of relevance because mental rotation is known to be required for implicit MI (Oostra et al, 2012). Based on these studies, although this suggestion could not be substantiated in the current study, it seems plausible that MI enhanced access to the body schema in participants who improved their motor control.

19.11 Limitations and Strengths of the Study

Critical reflections on this study revealed some limitations and strengths, which will be discussed as follows. The lack of blinding and its possible implications were discussed in detail in Chapter 19.4.

A strength of this study was that only reliable and valid outcomes which were previously tested in pwMS (Schuster, et al, 2012c; Tabrizi et al, 2013b) and stroke
(Malouin et al, 2007; Malouin et al, 2008b) were used, if no data in pwMS were available.

A further strength of this research was the availability of reliability data from the reliability study. This means that, prior to the main study performance the gait system was already known to be reliable. In terms of the reliability study, a weakness may be related to the MDCs for the step length measurement. In some cases, a change in step length could only be considered a ‘true’ change if it was greater than 5.3 centimetres. This fact would be relevant to consider in a further study which intended to use the MDCs. Nevertheless, comparable studies found similar or greater measurement errors, as discussed in Chapters 17.6 and 19.2. The MDC in step lengths and step times were only estimated as part of the reliability analysis, but were not used for the Pilot or Main Study 2.

A limitation to this study refers to the assessment of cognitive dysfunction and depression, both of which were exclusion criteria in this study. These were examined by the PI of the study, using established clinical criteria, but they were not formally tested. It is possible that validated tests can detect changes in cognition or mood at an earlier stage than a clinical examination. It is also conceivable that an experienced neurologist and MS expert can identify any impairment at a very early stage. In the event of a lack in identification of patients with cognitive dysfunction and/or depression, they were treated as eligible, with a similar probability of participating in the two cued MI or the non-cued MI groups. The impact on this research would thus have been the same in all groups.

High acceptability of an intervention is of vital importance in any study, and even more so for long-term treatment of patients with a chronic neurological disorder. However, this RCT could not take the participants’ experiences, understanding and beliefs about the intervention into account. It would have been valuable to gain insight into these, such as with a semi- or unstructured interview.

As a result of this study, significant improvements in walking speed and walking distance were observed in all groups, with the greatest improvements after music- and verbally-cued MI. These walking improvements could have been caused mainly by motivation and not by (rhythmic-cued) MI. The third intervention group was
employed to overcome this potential limitation. Based on participant reports, it has yet to be recognised if there was still a difference in motivation between the groups, most likely induced by the music.

Both studies assessed the participants at baseline and post-intervention and no follow-up assessment was performed. It is recognised that a follow-up assessment after a few months would have provided information on the medium-term effects of rhythmic-cued MI on walking, fatigue and (HR)QoL. It was not the intention of this study to perform follow-up assessments.

19.12 Conclusions

The overall aim of this thesis was to determine the effects of differently cued and non-cued MI on walking, fatigue, QoL, MI ability and SMS in pwMS. Overall, there was a significant improvement in walking performance between pre- and post-intervention measures in all groups, consistent with other studies and probably due to a gain in motor control. The greatest effects on walking were produced by music- and verbally-cued MI. The suggested underlying mechanisms are rhythmic entrainment leading to SMS and walking improvement. This is because, overall, there were significant improvements in gait variability and SMS in the music-cued groups when compared to the non-cued MI group. In correspondence with the existing literature, rhythmic cueing seemed to have facilitated participants’ temporal organisation of gait and their gait adaptability.

The reliability of the video-based gait analysis instruments was found to be excellent and endorsed existing evidence. Along with low to moderate measurement errors in step length and step time, the MDC was acceptable. Gait variability findings in this study created new literature on music-cued gait in people with mild to moderate MS, and it supported some of the work performed during non-cued gait in pwMS.

There was a significant improvement in fatigue after music-cued MI with and without verbal cueing. By contrast, with non-cued MI, only psychosocial fatigue improved. The predominance of music- and verbally-cued MI was confirmed only for psychosocial fatigue. The lack of changes in the MI group could be explained by mental fatigue induced by the MI intervention. Consistent with the literature on music-
related effects on psychological functioning, the cueing appeared to have boosted arousal, attention, mood and motivation; these appeared to have contributed to the improvements in fatigue.

The analysis showed significant differences in physical QoL between the music-verbal-MI group and the non-cued-MI group, in favour of music-verbal-MI. These improvements were clinically significant and may have been associated with the aforementioned effects of music. So far, in absence of comparable literature, apart from potential musical effects on QoL, the findings cannot be entirely explained, so they require further research.

In this study, the MI capability was measured in participants to find out whether it could, at least to a certain extent, explain the improvements in Study 1. In agreement with other studies in pwMS, adequate to high MI ability was found, as assessed by two complementary measures. In all likelihood, the MI familiarisation enhanced participants’ MI ability. As this study measured the MI capability but was not able to assess the *cued* MI ability in participants, the results were not comparable to that from relevant work (Heremans et al, 2012c); this study has shown improved ability to imagine movements in pwMS when the movements were cued. The current study analysis found significant improvements in MI capability in all groups, but no group interaction, therefore, the fifth null-hypothesis was the only one which was accepted.

**19.13 Dissemination of Findings**

The results from the pilot and main studies were disseminated to participants in lay language via letters. The pilot results were presented at the Annual Conference of the Austrian Society for Neurology in March, 2016 (Seebacher et al, 2016a) and the 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in September, 2016 (Seebacher et al, 2016b). A scientific article is under review at the open access BMC journal ‘Archives of Physiotherapy’. The findings from the overall project were published in the Austrian MS Society’s online and print patient magazine (Seebacher 2016). A scientific article will be published in a scientific journal for MS (the Multiple Sclerosis Journal).
Chapter 20 – Overall Discussion of Findings, Contribution to Knowledge and Suggestions for Future Work

20.1 Overall Discussion of Findings

The aim of this PhD project was to investigate the effects and mechanisms of rhythmic-cued MI on walking, fatigue and QoL in pwMS. This chapter discusses the key findings of this thesis and their applicability for pwMS and their caregivers, physiotherapists and for the relevant research in the field.

20.1.1 Key Findings

This thesis presents new knowledge on the usability of rhythmic-cued MI as a physiotherapy intervention in pwMS. Prior to this study, it was unknown whether cued MI would be an effective treatment for pwMS by enhancing their walking speed and distance, fatigue and (HR)QoL. The principal message of this thesis is that cued MI improves walking, fatigue and (HR)QoL in pwMS, even without physical practice. Results from this study showed that rhythmic cueing is the core element of the intervention since MI alone proved to be less effective. In relation to the MI cueing, music- and verbal cueing are the most effective in improving walking, fatigue and (HR)QoL.

This research also showed that metronome- and verbally-cued MI improves walking speed and distance, physical fatigue and QoL. Although metronome-cueing could be monotonous for some people, it may be preferable when suitable instrumental music is difficult to access. It may also prove to be beneficial when people dislike certain types of music.

This study also examined potential mechanisms which could have contributed to the walking improvements. In this context, SMS was explored, which refers to the synchronisation of the imagined and real walking with external cueing. The analysis showed that SMS could be a mechanism underlying the walking improvements. This claim is made because synchronisation improved only in the music-cued MI groups, with and without verbal cueing. Non-cued MI had no effect on SMS.
Results from this study further showed that MI without physical practice improves walking speed and walking distance in pwMS. This adds to the current literature as, thus far, only one small uncontrolled study has contributed to this area (Catalan et al, 2011), yet no RCT was undertaken to investigate the effect of MI on walking in the MS population. Catalan et al. (2001) have shown improvements in fatigue and QoL but not walking speed after MI practice in twenty pwMS, discussed in more detail in the previous chapter. Research studies which investigated people with neurological diseases other than MS have used MI primarily as a complementary intervention tool, in combination with physical practice, rather than on its own (Malouin, Jackson & Richards 2013; Peters and Page 2015; Schuster et al, 2011). Numerous studies cited in these reviews have demonstrated the effectiveness of MI embedded into or added after physical practice. As a novel finding, this thesis shows that MI practice is also effective on its own.

Therefore, since this thesis has shown that cued MI is an effective treatment in pwMS, patients can be advised to perform cued MI in particular conditions when physical practice is not possible or other interventions may be detrimental. PwMS are known to experience frequent falls of which 11% to 42% lead to physical injuries (Gunn et al, 2013; Gunn et al, 2014; Gunn et al, 2015; Mazumder et al, 2014). Hence, should pwMS recover from a fall, cued MI could be used as a replacement for physical practice to accelerate the rehabilitation process. Additionally, the high prevalence of fatigue suggests that cued MI training is a valuable treatment in this population. Considering the improvements in physical, mental and cognitive fatigue shown by this thesis, cued MI can be employed by physiotherapists as a further treatment to select from if their patients have physical fatigue, which may impair their ability to engage in physical practice.

The analysis from this study showed that after a detailed familiarisation with MI, people with mild to moderate MS who are not suffering from depression or cognitive impairment have a high MI ability. This finding adds to the existing dataset on the MI capacity of this population (Azin et al, 2016; Heremans et al, 2012; Tabrizi et al, 2013; Tabrizi et al, 2014; Tacchino et al, 2013) and the MI ability was assessed after a familiarisation (Holmes and Collins 2001; Schuster et al, 2011; Wondrusch and Schuster-Amft 2013). Moreover, this finding is in agreement with those from the
existing literature who demonstrated high MI abilities in pwMS who have preserved
cognitive function and no signs of depression.

20.1.2 Applications of the Findings

As previously mentioned, the newly designed treatment is home-based. A home-
based cued MI practice may benefit patients, particularly considering the limited
access to healthcare for people with disabilities in many countries (Gibson and
O’Connor 2010). The CDs or the download of the audio-mix with the cued MI
instructions, verbal cueing and music or metronome cues should be disseminated for
free, such as by the National MS Societies, but via physiotherapists to ensure that
patients are undertaking the intervention effectively. The dissemination of cued MI via
physiotherapists would enable: a) the provision of relevant theoretical and practical
information for the patient; b) the application of the principles in the respective
language; and c) coaching of the patient. This is in line with a recent qualitative study
which identified unmet needs in pwMS regarding information on the benefits of
exercise, including specific recommendations and tools for participating in exercise in
the community and at home (Learmonth et al, 2016). After an introduction to the
programme by a physiotherapist, pwMS could independently practise cued MI,
addressing their unmet needs. This could easily be achieved as the intervention was
found to be safe and convenient. Based on the results from this thesis, in all
likelihood, the phone calls facilitated participant MI ability and adherence; they could
have impacted on the findings in all groups. Therefore, it seems reasonable to
recommend supportive phone calls for home-based (cued) MI practice, which could
be remotely delivered by a physiotherapist.

The home-based approach takes account not only of the needs of pwMS with
restricted mobility or higher levels of fatigue, but also people who are employed
and/or take care of children, older family members or those living in remote places.
Apart from this, pwMS who practise rhythmic-cued MI do not require the assistance of
caregivers since for the practice, only a CD player, mobile phone or laptop is needed
as the MI takes place in their heads. Moreover, any walking and fatigue
improvements achieved through the novel home-based treatment may reduce the
responsibilities of caregivers and places the patients in an active role in their own
recovery. In accordance with the UK National Institute for Health and Care Excellence (NICE) Public Health Guideline 49, it seems advisable that pwMS maintain their exercise routine after treatment programmes terminate to accomplish longer term benefits (National Institute for Health and Clinical Excellence 2014). Home-based cued MI could be one of the rehabilitation options to select from. Hence, there would also be a public value linked to such an approach; this is because, with increasing health care costs, no health care system would be able to provide a long-lasting intensive physiotherapy, on a one-to-one basis, for their clients. Therefore, alternative approaches of physiotherapy delivery for pwMS appear recommendable.

The reliability study tested the gait analysis instruments which were used in this research. The analysis demonstrated an excellent reliability of the 2D video-based gait analysis system to assess step length and step time when the setting was chosen appropriately (see Chapter 17.4.3 for a definition of excellent reliability). The MDCs for step length and step time measurement during cued gait were reported. Knowledge about the MDCs for step length and step time measures can be used for 2D (cued) gait analysis in clinical settings or research; using an inexpensive quantitative gait analysis system, this can help detect gait changes which are relevant to patients with MS. These findings add to the current literature on spatio-temporal gait measures in pwMS (see Cofre Lizama et al. (2016) for a review) and could be relevant for physiotherapists as this was the first study to use a low-priced 2D video-based gait analysis system in pwMS.

The materials required for the physiotherapy treatment used in this project are inexpensive. These include a music-download, music software and audio-CDs or just a web-based link; therefore, the intervention can be regarded as low-cost. This is an important feature because studies have found that a loss of income, due to reduced working hours or unemployment, is of great concern for pwMS; this is alongside increased expenses for their health and personal care, mobility equipment and domestic support and presents a considerable challenge (De Judicibus and McCabe 2007). Hence, pwMS are seeking reasonable treatments (Crank et al. 2017) such as cued MI. The treatment being low-cost also makes it more easily accessible for their physiotherapists.
As an important aspect, due to the novelty of the combined intervention, physiotherapists in Austria, the UK and other countries are not necessarily informed about the details of cued MI in pwMS. To overcome this potential limitation, there is a plan to publish two scientific articles: a) about the findings from Study 2 on the effects and mechanisms of cued MI on walking, fatigue and QoL in pwMS; and, more importantly, b) about the reflections on rhythmic-cued MI interventions in pwMS and the implications for physiotherapists. The latter article will provide detailed information on cued MI as a first step towards the worldwide implementation of the novel treatment (see Appendix 19). Lack of theoretical and practical knowledge about the new treatment might be a barrier for physiotherapists to use cued MI. Thus, there is a further plan to disseminate the principles of cued MI and the findings from this thesis at relevant neurorehabilitation conferences, via presentations and workshops for physiotherapists. Nonetheless, to engage pwMS and physiotherapists globally, a website may be required. Regarding a worldwide application of cued MI, it is acknowledged that potential cultural differences in people’s perception of music and their expectations towards healthcare need to be considered (see Chapter 20.1.3).

All studies within this PhD project were conducted in Austria, in a German speaking study population. Therefore, the results from this thesis are generalisable to German speaking pwMS in Austria, and most likely in Germany and Switzerland, but they could also be applicable to pwMS from other countries, who are (or become) familiar with the type of music employed for rhythmic-cued MI. The results are further generalisable to adult pwMS with mild to moderate disability, as evidenced by an EDSS between 1.5 and 4.5. Notably, the German language was chosen as an inclusion criterion because the official language in Austria is German; for further application, the materials for this intervention have to be translated into English and other languages. The findings can only be generalised to pwMS without cognitive impairment or depression, so the MI ability was unlikely to be compromised.

20.1.3 Limitations

Concerning the dissemination of rhythmic-cued MI to other countries, cultural differences in the perception of music and expectations towards healthcare need to be considered and are discussed in this section. This is because cultural ideas,
values and viewpoints impact on people’s experience in all aspects of life (Betancourt 2004, Hunt 2007). Cultural ideas and behaviour may differ between people from Western countries such as Europe, the Americas, Israel, Australia and New Zealand (Huntington 2002), and people from Asia or Africa. General health care expectations and attitudes towards medical treatment could diverge between people from various backgrounds (Betancourt 2004; Donnelly and Long 2003), such as between Western and Arabian sociocultural contexts (Adib 2004; Al-Eraky et al, 2014). Expectations of pwMS towards healthcare professionals and treatment in many cultures worldwide could be fundamentally distinct from those in Austria or the UK. Therefore, to be able to disseminate the knowledge about the use of rhythmic-cued MI to physiotherapists and pwMS worldwide, cultural competence appears to be critical (Norris and Allotey 2008).

The aforementioned discussion of culture also applies to the selection of music employed for the cueing of the MI since music is perceived differently in diverse cultural settings (Stevens 2012). Abundant research has explored similarities and differences in music perception between members of different cultural groups (Cameron, Bentley & Grahn 2015; Drake and Ben El Heni 2003; Hannon, Soley & Ullal 2012; Kalender, Trehub & Schellenberg 2013; Stevens 2012), which are relevant for the dissemination of rhythmic-cued MI worldwide. The awareness of people’s differing perception of musical elements is crucial, if music is used as part of the intervention. Related to this thesis, rhythm perception and reproduction seem to be the most relevant elements because they are essential for SMS. Research has shown that music is differently perceived in diverging cultural settings (Stevens 2012). In contrast to Western music, which mainly comprises a regular metre such as the 2/4 or 4/4 metre, in Balkan, Asian and African music, irregular metre is preferably used (Stevens 2012). Accordingly, learned rhythmic expectations vary between members of the different cultural groups (Morrison and Demorest 2009; Stevens 2012). Other work has confirmed these findings and found cultural disparities in the perception of temporal structures of the beat (Morrison and Demorest 2009). Contrastingly, Cameron, Bentley & Grahn (2015) demonstrated that there were no differences in the rhythm discrimination between East African and North American adults, and that both groups could reproduce, or rather, imitate from memory East African rhythms more accurately than North American rhythms. However, East African participants
reproduced the rhythms they were culturally familiar with significantly more accuracy than North American participants. Notably, while tapping along with the beat, both groups reproduced culturally familiar beats more accurately (Cameron, Bentley & Grahn 2015). Similar results were shown by a study which compared the SMS between French and Tunisian people using a tapping task (Drake and Ben El Heni 2003). Participants in both groups synchronised their tapping rate more precisely with music from their own culture. These findings were corroborated by other research, which was conducted on Turkish and North American individuals (Hannon, Soley & Ullal 2012; Kalender, Trehub & Schellenberg 2013). Cumulatively, this evidence suggests that music at a regular beat, which is required for rhythmic-cued MI, is more accurately perceived by individuals from a Western cultural background or Western people who have different cultural backgrounds but share both cultures.

20.2 Original Contribution to Knowledge

This thesis provides an original contribution to knowledge in the field of physiotherapy in pwMS because as a unique output, it developed a novel home-based physiotherapy treatment as an add-on to usual care. Based on the findings, this thesis provided specific recommendations for physiotherapists and research in the field.

Study 1 was able to address some of the gaps identified in the literature by performing an RCT. This study analysed the effects of a combined treatment consisting of MI and different rhythmic auditory cueing using a collection of measures of walking performance and perception, fatigue and (HR)QoL. This study provided evidence that metronome- and verbally cued MI improves walking, physical fatigue and QoL and that music- and verbally cued MI improves walking, physical, cognitive and psychosocial fatigue, QoL and HRQoL, which had not previously been investigated.

The reliability study in this thesis provided innovative evidence on the excellent test-retest reliability of an optical 2D gait analysis system used during cued gait in pwMS, including the calculation of SEM and MDC. The analysis revealed very low measurement errors for the step time measures and moderate errors for the step
length measures which were similar to or even smaller than that of comparable work. Therefore, the gait analysis system can be recommended for use. MDC in pwMS’ step length and step time during music-cued gait is now available for physiotherapists in clinical practice or research. After the reliability testing, the equipment was used to carry out the SMS data collection in Study 2.

Study 2 was the first to undertake a comprehensive investigation of the effects of non-cued and differently cued MI interventions in pwMS, with the specific goal of validating the results from Study 1 and revealing underlying mechanisms which contribute to the improvements shown in the first study. The outcomes of Study 2 are significant in that they build on the findings of Study 1 by confirming its findings. By identifying the preserved ability of imagining movements in pwMS, this finding added to the existing dataset concerning the MI ability in pwMS while familiarisation with (rhythmic-cued) MI was achieved. The results of Study 2 also showed that non-cued MI improves walking speed and walking distance.

The originality of the study is further grounded in the identification of gait synchronisation with rhythmic cueing, which was associated with improved walking. SMS was a probable mechanism underlying the improvements only in the cued MI groups versus the non-cued MI group. Therefore, this was the first study to demonstrate that rhythmic cueing during MI improved SMS during actual gait whilst adjusting to music at a fast and slow metre. The study was able to detect relationships between the cueing tempo and cadence as well as step length in people with mild compared to moderate MS. The post-hoc findings demonstrated that people with moderate MS increase their cadence and reduce their step length to be able to synchronise with a fast beat of 110 BPM. In terms of novel outcomes, the study showed that the music-cued MI treatment significantly reduced the gait differences between people with lower and higher disability.

The study provided exclusive evidence that music-cued MI with verbal cueing is superior to music-cued and non-cued MI in improving walking, fatigue and QoL in pwMS. The findings will be of value, both from a physiotherapy perspective as they can be integrated into the physiotherapy treatment in pwMS, but also to guide the
development of further research projects in this area. In this respect, this thesis was the first to provide recommendations for physiotherapists on the treatment of pwMS using music-cued MI with verbal cueing. Moreover, further information on the use of cued MI will be disseminated to physiotherapists in Western countries (in terms of worldwide dissemination, see the section Limitations above). Following this, the newly developed experimental intervention can be gradually transformed into clinical practice.

20.3 Recommendations for Future Work

Having undertaken a number of studies which explored the effectiveness of differently cued MI on walking, fatigue and QoL in pwMS, the next priority is to build on the music- and verbally-cued MI intervention to answer emerging questions.

Anecdotal evidence from Study 2 showed that nearly half of the participants in the cued MI groups were encouraged to move after the intervention. This was considered an important impact of the research as it seemed to have increased participants' physical activity levels. Future-cued MI studies could assess the physical activity in everyday lives of their participants.

This research showed that music- and metronome-cued MI with verbal cueing was effective in improving walking, fatigue and (HR)QoL in pwMS when compared to no treatment, non-cued MI or solely music-cued MI. Participant reports from both studies indicated that the verbal cueing helped their concentration on the MI task. Verbal cueing emphasised the rhythm of the cueing; therefore, it could have supported participants in maintaining the auditory rhythm. A further quantitative study could explore the role of the verbal cueing in more depth while employing a rhythmic perception and reproduction (tapping) task during music-cued MI with and without verbal cueing. Alternatively, a qualitative study could investigate participants’ experiences during cued MI with and without verbal cueing.

The assessments in both studies were at baseline and at four weeks, post-intervention. Thus, no long-term effects of cued MI were measured. Future studies could include follow-up assessments to look at longitudinal effects of cued MI.
Results from both studies found that the music-based interventions led to greater improvement in fatigue and (HR)QoL. This suggested that psychological effects of the music contributed to the improvements. However, although participants with depression were excluded from the studies, no formal testing for changes in mood, motivation or arousal was performed. Future music-cued MI studies could investigate the impact of music used for cueing on psychological function and particularly motivation in pwMS.

This research project showed that rhythmic-cued MI can be used by physiotherapists as a powerful tool to treat pwMS and impaired walking, fatigue and reduced QoL. It would be important that future work explored the effects of rhythmic-cued MI on upper limb or upper body movements in people with more advanced disease stages of MS.

All participants in Study 2 were found capable of imagining movements. Notably, two of the three intervention groups used rhythmic-cued MI, which seems likely to be a different, however similarly complex, construct to MI alone. Neither MI nor rhythmic-cued MI is directly observable. Future studies could investigate the rhythmic-cued MI ability in pwMS, such as with brain-computer interfaces or oculographic measures. Further research could also include people with cognitive impairment and/or depression who were excluded from the present work. This was because studies have shown their impairment in (non-cued) MI ability; it is possible that their results would have been different if cued MI ability was tested.

The favourable findings from this work suggest that motor learning and neural plasticity were present in those participants who benefitted from the cued MI practice. It was not possible to use functional MRI in this study to evaluate any changes in brain activations after the cued MI training. To evidence potential motor learning and neural plasticity, future fMRI studies could explore whether any changes in the auditory-motor circuit of the brain are induced by cued MI.

Finally, there were areas this quantitative study was not able to explore, including how the participants perceived the impact of the metronome, musical melodies and beats or the verbal cueing on their imagined walking, body perception and emotional states. It would be useful to learn in what ways the participants in the cued MI groups experienced the MI when the cueing was present. Was it one comprehensive
package or were there different elements to respond to? Moreover, it remains unknown how the participants in the non-cued MI group experienced the silence during the MI tasks. Did they digress and revert to their usual thought processes and emotions? What influence did the MI have on their body perception? A future qualitative study could be used to explore participant experiences during the cued and non-cued MI. The knowledge learned from the patients might help to modify and improve the intervention and to adjust its various components to the needs of diversified populations.

20.4 Conclusions

This thesis demonstrated that

- 17 minutes of non-cued MI 6 times per week for 4 weeks with weekly phone calls can be used without physical practice to effectively treat walking impairment in pwMS with mild to moderate disability and without depression or cognitive impairment.

- 17 minutes of rhythmic-cued MI 6 times per week for 4 weeks with weekly phone calls is effective on its own in improving walking, fatigue and (HR)QoL in pwMS with mild to moderate disability and without depression or cognitive impairment.

- music- and verbally-cued MI is superior to metronome- and verbally-cued MI or music-cued MI or non-cued MI in improving walking, fatigue and (HR)QoL in pwMS with mild to moderate disability and without depression or cognitive impairment.

- sensorimotor synchronisation and high MI ability after familiarisation with MI are likely to be part of the mechanisms underlying the improvements observed.

- music- and verbally-cued MI can be recommended for use particularly to accelerate the rehabilitation process following a fall-related or other injury or in mildly to moderately disabled pwMS with physical fatigue and without depression or cognitive impairment.
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