Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Is there a difference in learning sequences between a visual, melody or sound condition within an embodied environment in Persons with MS and healthy controls: a pilot study

Inneke Huion
Marit Putzeys

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

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2018
2019

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Acknowledgements

Firstly, we would like to express our gratitude to our supervisor Lousin Moumdjian. It was a difficult process with unnecessary obstacles because of the development of the platform but she always stayed calm and reassured that everything was going to be all right. Thank you for your patience.

Special thanks to Prof. dr. Peter Feys to lead us in the right direction.

We would like to acknowledge the University of Hasselt and Ghent to make this study possible and to develop the AMPEL platform.

A grateful thanks to all the participants of this study for their effort and collaboration.

Finally, we would like to thank each other for the great cooperation, as well as our family and friends for the support.

Landen, Bunsbeek, 07/05/2019 H.I., P.M.

Context

This master thesis situates in the topic of neurological rehabilitation of people with Multiple Sclerosis (PwMS). The importance of this thesis is the determination of alternative or improved rehabilitation methods in neurological populations, more precise people with Multiple Sclerosis. MS is a progressive autoimmune disease that affects the myelin of the central nervous system. Balance disorders and cognitive impairment are common symptoms of MS and can have a high impact on daily life. PwMS require a lifelong rehabilitation, therefore patient compliance is an important target factor. The main objective of this thesis is the use of embodied learning in rehabilitation. Until now, this topic is only researched in an educational context. This pilot study wants to investigate if the concept of embodied learning can be extended to neurological rehabilitation by using auditory stimuli versus visual stimuli.

The master thesis is part of a PhD study of Lousin Moumdjian named "Effect of musical biofeedback system on cognitive and motor functions in multiple sclerosis". The PhD project (2016-2020) is co-funded and conducted in the Universities of Hasselt (BOF) and Ghent. At the university of Ghent this project situates in the Institute of Psychoacoustics and Electronic Music (IPEM) led by Prof. dr. Marc Leman. The PhD project aims to investigate the application of entrainment and sonification, which are concepts in the field of systematic musicology, on motor and cognitive functions in PwMS. In this pilot study, reported in this thesis, we investigated the difference between PwMS and healthy controls in learning sequences with auditory or visual feedback, thereby fitting in the PhD project. A sonified platform was made in cooperation with an engineer especially for this PhD project, namely the AMPEL platform. This platform was also used in this master thesis.

This thesis is a duo-master thesis under supervision of promotor Prof. dr. Peter Feys and our supervisor Lousin Moumdjian at the research centre REVAL of the University of Hasselt in Diepenbeek.

The documents for the approval of the ethical committee were realized by cooperation of the two students and supervisor Lousin Moumdjian. The research question was defined together with promotor Peter Feys and our supervisor Lousin Moumdjian. Furthermore, the analysis of the data and the writing of the pilot study were done by the two students together.

Other master students did the recruitment of participants, the tests and the data collection. The research design and the methodology were established in consultation with supervisor Lousin Moumdjian and promotor Peter Feys. This thesis was possible due to a good cooperation of both students and Lousin Moumdjian.

Abstract

Background:

Positive results on motor and cognitive functions have been found in patients with neurological diseases after music-based interventions. In this context, music as a form of auditory feedback for motor learning has not yet been investigated. Particularly, there are limited studies about the theories of embodied association, which assume that a sequence can be learned more easily when spatial body movement is involved[1].

Objective:

The aim of this study is to investigate if there is a difference in learning sequences between a visual, melody or sound condition within an embodied environment in PwMS and healthy controls (HC). A sonified platform was used called AMPEL.

Participants:

In this pilot study, 17 participants were allocated, including 10 PwMS and 7 healthy controls. All healthy controls were female and in the MS group, three participants were male and seven were female. They did not differ statistically significant in baseline characteristics except for music experience (*p=0.0498*)*.

Measurements:

Descriptive measurements were made by using cognitive tests, motor tests and questionnaires. The outcome measures in this pilot study were mean interstep interval (seconds), total onset time (seconds) and fault percentage. They were measured by the AMPEL-platform. Subjective questions were asked to know more about the experience of the participants.

Results:

There was no statistically significant difference between HC and PwMS in the visual condition, melody condition and sound condition for mental fatigue, the easiness of execution, the easiness of remembering, frustration, the amount of effort used for learning the sequence or performing the sequence. However, a significant difference in pre- and post-physical fatigue was found for the visual (pre: *p= 0.0015**, post: *p= 0.0005*),* melody condition (pre: *p= 0.0005**, post: *p=0.0007*)* and sound condition (pre: *p= 0.0228**, post: *p= 0.0030**).

Group and condition didn't have statistically significant effects on all outcome measures while comparing immediate and delayed recall. In the delayed recall a significant interaction between condition and accuracy could be found *(p= 0.0460*)* for the mean interstep interval. Group didn't have any significant effects in the immediate recall and the delayed recall.

Conclusion:

Due to the small sample size of this pilot study, results must be interpreted with caution. Even though PwMS were more physically exhausted before and after each condition, they were still as capable of learning the sequences compared to HC. The visual feedback type seemed to be more mentally exhausting for PwMS although it did not affect learning. Furthermore, PwMS were equally capable of remembering the sequences compared to the HC. Lastly, there was no superiority of one condition compared to another during learning for both groups. However, further research should investigate these statements with a bigger sample size.

Introduction

Multiple sclerosis (MS) is a chronic progressive auto-immune disease which is characterized by random, multifocal demyelination in the central nervous system (Lundy-Ekman, 2013). Symptoms are highly variable because the demyelination can appear in a wide range of locations and the extent of lesions varies (Lundy-Ekman, 2013). Many people with MS (PwMS) exhibit cognitive dysfunctions which mostly manifest in slowed processing speed, executive dysfunctions, learning deficits and memory impairments[2]. However, McGowan et al. suggests that PwMS with mild disability can learn and retain a novel visuomotor mapping during a precision-based walking task[3]. This indicates that neural plasticity is preserved, because they are capable to do short-term motor learning and retention[3].

Growing evidence exists that music might directly promote neuroplasticity[4-6] through increased activation of auditory-motor, cortico-spinal, and mesolimbic dopaminergic pathways[4-6]. After music-based interventions positive results on motor and cognitive functions have been found in patients with neurological diseases[7]. Moumdjian et al. reported an improvement of motricity, fine motor dexterity, gross motor functions, verbal memory and focused attention with music-based interventions in the neurological population[7]. Moreover, instrument-based music interventions, for example piano based music-supported therapy showed improvements of the upper extremity motor functions. This kind of research did not focus on the ability to learn the musical scores (i.e. learning), but merely on the clinical motor outcome. Furthermore, Thaut et al. investigated the use of musical mnemonics during word learning in PwMS[8] and reported that verbal learning was enhanced due to the temporal structure in musical stimuli[8]. It also results in sharpening of the timing of neural dynamics in brain networks degraded by demyelination in MS[8]. Another important feature of music-based interventions is the positive effect on mood (e.g. depressive and anxiety disorders), emotional expression, communication, interpersonal skills, self-esteem, and quality of life[9].

To expand previous studies and learning, in this thesis, the concept of embodied learning is investigated. Embodied learning describes the interaction of cognitive and motor processes during learning a task in a specific environment[10]. It is the process of learning something cognitively while performing bodily movements (e.g. gestures, dancing, playing an instrument, etc.). This learning needs to happen in an embodied environment, which can be created using current technological advances. Theories of embodied association in learning assume that a sequence can be more easily learned when spatial body movement is involved (i.e. a choreography or sequence of steps that execute the sequence)[1]. Embodied associations are processes that facilitate the recall and execution of sequences due to neural connections between the motor system and the auditory system[1,11]. In this pilot study, auditory stimuli as a form of sonified feedback and visual feedback are used to investigate the concept of embodied learning. Based on the theories of embodied associations, we hypothesize that PwMS will be able to learn better when melodies are used as feedback because the auditory system will be more actively engaged than when a sound or visual feedback type is used. Also, because of the cognitive problems that accompany multiple sclerosis, we expect that healthy controls will remember the sequences more correctly than PwMS.

Until now, the effect of learning a sequence with a sonified platform in PwMS is not yet investigated. Therefore, the aim of this study is to investigate if learning sequences within an embodied environment differs between two different kinds of auditory feedback (i.e. music and sound) compared to visual feedback in PwMS and HC.

Methods

Participants

This study included 10 patients with multiple sclerosis (age 49.7 ±9.92; 7 F, 3 M; 9 RR, 1 PP, 0 SP)* who had a Timed-Up-and-Go score between 8 and 21 seconds and were able to walk/take steps without walking aid. They were age matched and compared with seven healthy controls (age 62 ±13; 7 F, 0 M). Participants who had cognitive impairment hindering the understanding and execution of the experimental procedures were excluded. Other exclusion criteria were pregnancy, hearing impairment, amusia, and colour blindness (i.e. green, red and blue colour blindness). Hearing impairment was tested by asking the participants if they heard the different notes playing during the familiarization session. Therapists and researchers used study flyers to recruit patients from MS Center Melsbroek. All participants gave informed consent, which was approved by the Local Ethical committee. The approval document from the ethical committee (document 1) and flyers can be found in the appendix (document 2 & 3).

Procedure

Design and setting

This study is an observational pilot study. The participants took part in two sessions. The test period for each participant was two weeks with a rest period of one week between the two sessions. Each session had a duration of two hours. Once participants were included, they underwent a descriptive session where an anamnesis and clinical descriptive data were collected. Participants were then familiarized with the platform. The second session was an observational session. Both were conducted in the MS center of Melsbroek. See Figure 2 in the appendix for a detailed description.

* F=female, M=male, RR=relapsing remitting, PP=primary progressive, SP=secondary progressive

Technical information

A specially designed platform, called "AMPEL": Augmented Movement Platform for Embodied Learning, was developed by a team of engineers and researchers of the University of Ghent[12]. It exists out of 21 tiles, two speakers and a laptop with the software and user interface program. The tiles can be triggered by stepping on them and give real-time auditory and visual feedback because the sensor pads are sonified. Pre-made sequences were stored on a computer which was only used for the experiment. You can find an example of these sequences in Figure 1 in the appendix. AMPEL was tested for reliability and feasibility on healthy controls.

Session 1: descriptive and familiarization session

In this session, an anamnesis and clinical descriptive data were collected being age, gender, BMI, education, music experience and type MS. Additionally, motor tests, cognitive tests and patient reported questionnaires were conducted. Administered motor tests were the Timed Up and Go Test (TUG), the 6 Minute Walking Test (6MWT), the Timed 25 Feet Walking test (T25FWT), The Four Square Step Test (FSST), the Dynamic Gait Test (DGI) and the mini BESTest[13-16]. Administered cognitive tests were the Spatial Recall Test, the Symbol Digit Modalities test and the Paced Auditory Serial Addition Test. Additionally, administered patient reported questionnaires were collected being the MS Walking Scale-12, the Falls Efficacy Scale, the Modified Fatigue Impact Scale, the Hospital Anxiety Depression Scale and the Barcelona Music Reward Questionnaire. Participants were then familiarized with AMPEL. During this session, participants were familiarized with different movement patterns in the three conditions (i.e. melody, sound and visual) on AMPEL. The feedback types during correct and incorrect steps were explained and explored. Participants had to learn sequences and reproduce them by stepping on the tiles.

Session 2: Observational (experimental) session

Three conditions were tested: two auditory ones of which a music condition and a single tones condition, and one visual condition with resting time in between. These conditions were randomized using a randomization program. The duration of each condition depended on the time needed by the participant for executing the sequence correctly three times in a row. Before and after every condition, a range of subjective questions were asked about perceived physical and mental fatigue, how easy it was to execute and remember the sequence, frustration and the effort put into learning and performing the sequence. Participants had to give a score out of 10 on these questions.

The melody condition*.* The session started by an automatic demonstration of the melodic sequence once, meaning the tiles lit up in the pattern of the sequence they had to learn, and at the same time a melody was formed by the tiles that lit up. Each tile corresponded to a tone and by playing a sequence of tones, a melody was formed. This happened with a constant rhythm (i.e. each tile of the sequence was lit for 1 second). Afterwards, the participant had to reproduce the sequence by stepping on the correct tiles and hereby form the correct melody. The sequences were always 7 steps long as a result of the pilot tests. By producing the correct sequence, the participant controlled the unravelling of the melody. If the wrong tile was stepped on, the melody was distorted. Once the participant produced the sequence correctly three times in a row, a three-minute break was given. After this break they had to reproduce the sequence again three times correctly. If it was not three times correct, the sequence was shown again and practiced until it was again three times correct. If it was correct, a distractor sequence was given which they had to practice until they could execute it two times correct. After this distractor sequence, they had to reproduce the first learned sequence again to investigate their immediate recall ability. Then, after a 15-minute break, they were asked to execute the first learned sequence again. In this way, we could also investigate the delayed recall ability of the participants. A schematic overview of this protocol can be found in Figure 2 in the appendix.

The sound condition*.* The same procedure was applied as in the music condition, but one note was used to map every tile. Therefore, a melody was not formed.

The visual condition. The same procedure was applied as the other conditions, but the feedback was only visual instead of auditory feedback.

Outcome measures

The mean interstep interval, total onset time, fault percentage and accuracy were used as outcome measures. The mean interstep interval (seconds) is defined as the mean time used to step from one tile to the other tile when performing the whole sequence. The total onset time (seconds) is the total time the tiles were on, in other words: it is the time that the participants needed to perform the sequence from the first tile until the last one. A fault percentage was calculated by dividing the number of mistakes performed by the total number of steps performed per sequence. Mistakes were identified as stepping on the tile that was not in the learned sequence or not in the correct order of the sequence. For example, if the correct sequence was '1-5-7-9' and the participant did '1-7-9-6', the participant had three mistakes out of four. A nominal accuracy outcome measure was derived from the fault percentage. Accuracy was defined as a completely correct execution or an incorrect execution of the sequence (at least one mistake). Subjective questions were asked to get an idea of the experience by the participants. For example, fatigue was asked before and after the execution of one condition on a VAS-scale of 1 until 10, with 1 not being fatigued at all and 10 being extremely fatigued.

Statistics/data analyse

The software used for the statistical analysis was JMP Pro 14. The objective of the statistics was to compare PwMS with healthy controls. All continuous variables were screened for normal distribution using the Goodness-of-Fit Test. The variances were tested for equality by the Brown-Forsythe test. If both distributions were normal and the variances equal, the pooled t-test was used to identify the p-value. If in this situation the variances were not equal, the Welch test was used. When one or both groups were not normally distributed, and variances were still equal, the non-parametrical Wilcoxon Rank Sum test was used. Categorical data were analysed by the fisher's exact test because of the small sample size. To investigate if there were differences in learning at timepoints 'immediate recall' and 'delayed recall', a mixed model ANOVA was applied with factors of condition (melody, sound and visual conditions), group (healthy controls and PwMS) and accuracy (correct, incorrect) on the outcome measures mean interstep interval, total onset time and fault percentage. To further investigate if there were differences between the recall timepoints, a mixed model ANOVA was applied with factors timepoints (immediate recall, delayed recall), condition (melody, sound and visual conditions) and group (healthy controls and PwMS) in the outcome measures mean interstep interval, total onset time and fault percentage. Outcomes of the subjective questions were analyzed as continuous variables, as described above.

Results

Participants

Twenty participants were enrolled in this pilot study whereof 13 MS patients and seven healthy controls. Two MS patients were excluded because of short-term memory problems, which were discovered with the descriptive tests. Also, one MS patient dropped out because of distress and personal reasons after completing the first session. The distress had nothing to do with the session. In the end, 17 participants were included in the analysis. A flow diagram can be found in the appendix demonstrating the process of inclusion and exclusion of the participants (Figure 3).

Baseline characteristics

All healthy controls were female. Three participants of the MS group were male and seven were female. There were no statistically significant differences between both groups for age (*p=0.0654),* BMI (*p=0.5822)* and education *(p=1).* Musical experience (*p=0.0498*)* differed significantly between both groups. For a more detailed overview of the baseline characteristics, see Table 1 in the appendix.

Motor tests

The Timed 25 Feet Walk test (*p=0.213)*, the Four Square Step test (*p=0.3198)*, the Dynamic Gait Index (*p=0.0753)* and Mini BESTest (*p=0.1183)* were not significantly different between both groups. However, the Timed Up and Go test (*p=0.0208*)* and 6 Minute Walking test (*p=0.0175*)* were statistically significant.

Cognitive tests

There was no statistically significant difference between HC and PwMS for the Spatial Recall Test (*p= 0.4709*), the Paced Auditory Serial Addition Test (raw: *p= 0.2998,* corrected: *p= 0.1015*) and the Symbol Digit Modalities Test (*p= 0.3069*).

Questionnaires

MS participants scored a mean of 34.3 on the MS Walking Scale-12 (SD±13.81). The Falls Efficacy Scale (*p=0.0531)*, the Hospital Anxiety Depression Scale (*p=0.2152)* and the Barcelona Music Reward Questionnaire (*p=0.5813)* were not statistically significant different between both groups. In contrast, The Modified Fatigue Impact Scale (*p=0.0066*)* differed statistically significant between both groups.

Experimental outcome measures

Subjective questions

A detailed table of the results of the subjective questions can be found in Table 2 in the appendix. There was no statistically significant difference between HC and PwMS in the visual condition for mental fatigue (pre: *p= 0.0843,* post: *p= 0.0819*), the easiness of execution (*p= 0.1936*), the easiness of remembering (*p= 0.9716*), frustration (*p= 0.8079*), the amount of effort (*p= 0.9471*) used for learning the sequence or performing (*p= 0.7801*) the sequence. However, a significant difference in pre- and post-physical fatigue was found (pre: *p= 0.0015*,* post: *p= 0.0005*)*.

In the melody condition, there was also no statistically significant difference between HC and PwMS for mental fatigue (pre: *p= 0.1393,* post: *p= 0.1084*), the easiness of execution (*p= 0.5538*), the easiness of remembering (*p= 0.3628*), frustration (*p= 0.767*), the amount of effort (*p= 0.9294*) used for learning the sequence or performing (*p= 0.5604*) the sequence. However, there was a statistically significant difference in pre- and post-physical fatigue in this melody condition (pre: *p= 0.0005*,* post: *p= 0.0007*).*

In the sound condition physical fatigue (pre: *p=0.0228*,* post: *p= 0.0030**) was also significantly higher for PwMS compared to HC. Furthermore, in contrast to the other conditions, post-mental fatigue (*p=0.0557)* was significantly higher for the PwMS. Easiness of execution (*p= 0.4274*), easiness of remembering (*p=0.7979*), frustration (*p= 0.8788*), effort used for learning (*p= 0.7487*) and performing (*p= 0.3014*) the sequence were not significantly different between HC and PwMS.

Between conditions and groups

Immediate recall

Accuracy (correct/incorrect sequence execution) was significant for the mean interstep interval (*p=0.0002**), total onset time (*p= 0.0001*)* and fault percentage *(p<0.0001*)*. Group and condition didn't have significant differences. There were no significant interaction effects. When performing the sequence fully correct, a shorter mean interstep interval, total onset time and a lower fault percentage could be seen in all conditions and for both groups.

Delayed recall

A significant interaction between condition and accuracy *(p= 0.0460*)* for the mean interstep interval was found. The performance of the sequence in the sound condition showed a significant difference between the correct and incorrect performance *(p= 0.0025*)*. Participants who executed the sequence incorrect in the sound condition had a longer mean interstep interval compared to participants who executed the sequence correctly in the sound condition.

The accuracy was significantly different for the mean interstep interval *(p= 0.0046*)*, total onset time *(p= 0.0041*)* and fault percentage *(p< 0.0001*)*. When performing the sequence correctly a shorter mean interstep interval, total onset time and a lower fault percentage could be seen for all participants. There was no significant difference for group and no other interaction effects could be found.

Immediate recall versus delayed recall

For a detailed overview of the data, see Table 3 in the appendix.

Total onset time

No significant differences were found in total onset time for group *(p= 0.1187)*, condition *(p= 0.9744)* or recall *(p= 0.1348).* There were no significant interaction effects between group, condition and/or recall.

Interstep interval

There were no significant differences in interstep interval mean for group *(p= 0.1073)*, condition *(p= 0.9089)* or recall *(p= 0.1296)*. There were no significant interaction effects between group, condition and/or recall.

Fault percentage

There were no significant differences in fault percentage for group *(p= 0.3131),* condition *(p= 0.8488)* or recall *(p= 0.0588).* There were no significant interaction effects between group, condition and/or recall.

Discussion

Our study was based on the theories of embodied association. Embodied associations are processes that facilitate the recall and execution of sequences due to neural connections between the motor system and the auditory system. Because this concept is not yet investigated in a rehabilitation context, the aim of this study is to investigate if learning sequences within an embodied environment differs between two different kinds of auditory feedback (i.e. music and sound) compared to visual feedback in PwMS and HC.

Our results showed some differences between the baseline characteristics of both groups. The MS group and healthy control group differed statistically significant for music experience. Four out of ten PwMS were still recently engaged in musical activities being dancing, playing an instrument, singing in a choir or being a DJ. Two other PwMS had musical experience from activities in the past (i.e. dancing and playing flute). However, it is not clear how long ago this was and how long they have been doing this. So, it is possible that this difference in musical experience between PwMS and HC could be a confounder in the results. Nevertheless, because of our small sample size one must be cautious with overall interpretations. PwMS showed a significantly longer execution time for the TUG and walked a significantly shorter distance during the 6MWT compared to the healthy controls. In community dwelling elderly, the longer it takes to execute the TUG, the higher the fall risk[17]. However, according to Dibble et al.[18] the TUG is not able to discriminate very well between, fallers and non-fallers in the MS population. Also, the other balance tests were not significantly different compared to the healthy controls, so a balance problem can be ruled out. Our finding of a shorter walking distance during the 6MWT is consistent with the findings of Goldman et al[19]. The 6MWT is well correlated to subjective measures of general and physical fatigue, physical health status and perceived walking ability[19]. So, because PwMS showed a statistically significant shorter walking distance on the 6MWT it seems that they were more easily fatigued. This can also be seen in the subjective question results discussed below. The differences on the TUG and 6MWT didn’t seem to have an influence on the total onset time, mean interstep interval and fault percentage in this small sample. There were no significant differences found between HC and PwMS on all outcome measures. These results might confirm the feasibility of the AMPEL-platform with PwMS with a lower 6MWT and a higher TUG. The modified fatigue index was also significantly different, but it didn’t seem to have an influence on the total onset time, mean interstep interval and fault percentage with PwMS. This suggests that fatigue didn’t interfere with the performance of this study protocol. However, a statistically significant difference was found for pre- and post-physical fatigue in all conditions. Additionally, in the visual condition, the PwMS were more post-mentally fatigued than the HC. It’s interesting that only after the visual condition the mental fatigue differed. So, it might be that the visual condition was more mentally exhausting for PwMS than the other conditions. Literature shows that one of the most common and disabling symptoms of PwMS is perceived fatigue[20]. Loy et al. also showed a significant relationship between perceived fatigue and fatiguability in PwMS[20]. People which report elevated fatigue seem to be also highly fatigable[20]. Perceived fatigue can be defined as subjective sensations of reduced capacity[20]. On contrary, fatiguability can be defined as a decline in objective measure of physical performance over a certain amount of time[20]. So, it seems normal that there was a significant difference in fatigue seen in the 6MWT, the modified fatigue index and the subjective questions. Our results also show that all participants found it as easy or as hard to execute and remember the sequence in all conditions. Furthermore, participants showed the same amount of frustration, effort of learning and effort of performing the sequence for every condition. With these results, one must keep in mind that the results of the subjective questions are subjective.

In the immediate recall, the PwMS and HC were equally able to learn in all conditions, because there was no significant effect for groups and conditions for the different outcome measures. Logically, when participants made a mistake they had a longer mean interstep interval, total onset time and higher fault percentage in contrast to when the sequence was correctly executed. However, in the delayed recall was a significant interaction effect between condition and accuracy for the mean interstep interval. Participants who did the sequence wrongly in the sound condition had a longer mean interstep interval compared to participants who executed the sequence correctly in the sound condition. So, it is possible that the participants hesitated more or were more confused while doing the sequence wrongly in the sound condition than in the melody and visual condition in the second time point. This might be because they had more difficulties in correcting their mistakes. In contrast, the participants didn’t make more mistakes in the sound condition than in the other conditions. In the visual and melody condition were no significant interaction effects for all outcome measures. This could suggest that the participants were equally capable of learning with both feedback types.

When the participants were asked which method they preferred, all participants mentioned the visual and melody feedback. No participants mentioned the sound feedback. Furthermore, most people explained that they used a visuo-spatially learning strategy and did not really use the tonality as a learning strategy. Additionally, most participants noticed a difference between the melody condition and sound condition. However, a bigger sample size is needed to investigate if there will be differences between melody and visual feedback. When looking at the different recall time points, the PwMS and the HC executed the sequences with the same amount of time in the delayed recall as in the immediate recall. Furthermore, no significant differences were seen for the fault percentage and mean interstep interval between the two time points for both groups in all conditions. This suggests it was not harder to remember the sequence after a longer time for both groups in all conditions.

Because of the small sample size, it is difficult to draw strong conclusions. Due to technical difficulties with the AMPEL device, only 17 participants were tested. This causes a limitation, because the results need to be interpreted with caution. The AMPEL device itself was not easy to transport from one place to the other, therefore it limits the testings to one location at a time. There was missing data in the baseline characteristics for the cognitive tests and in the delayed visual condition. The resting time of one week between the descriptive session and the observational session was not always applied by the testers due to time management problems. Because of these interruptions, it is possible that the participants had another experience during the tests and therefore the results need to be interpreted with caution. The difference in sequences learned by the participants made it harder to draw conclusions. Also, not all participants did the same number of steps on the platform. It's easier to make an analysis of the number of mistakes when the same sequence is used with a fixed number of steps. The program wasn't always right in analyzing mistakes in the sequences. Because of this, mistakes were manually corrected in the datasets. Furthermore, it would have been interesting if it was possible to extract data about the learning process itself, for example: how long it took until they were able to do the three sequences correctly, how many mistakes they made before they learned the sequence, etc. This was currently not yet possible due to technical reasons. Although there are some limitations, there are certainly also strengths about our pilot study. This pilot study was done by using a new custom-made sonified platform, that is not broadly used by other researchers. This protocol is feasible with PwMS experiencing fatigue and mild balance problems. A good description was made of the participants based on different tests, so the baseline characteristics were clearly mentioned. The inclusion criteria were broad, so that the results could be more generalized if it was a bigger sample size. The sequences were tested in advance for feasibility.

Furthermore, the way instructions were being offered must be taken into account. Sarabandi et al. showed that MS patients benefit more from implicit learning than when the task is explained or described[21]. In contrast, Tacchino et al. found difficulties in sequence-specific learning in both implicit and explicit condition, with more pronounced impairment in the implicit condition[22]. Consequently, there could be an involvement of multiple circuits in implicit and explicit sequence learning that could decay at different disease stages[22]. Common involved areas during auditory-motor learning independent of implicit or explicit learning are the premotor area, cerebellum, superior temporal gyrus, parietal area, frontal gyrus and cingulate area.

As a conclusion, the results of this pilot study must be interpreted with caution, but we can assume that even though PwMS were more physically exhausted before and after each condition, they were still as capable of learning the sequences compared to HC. PwMS were more mentally fatigued after the visual condition so we might conclude that this type of feedback is more mentally exhausting for PwMS. However, this showed no influence on the learning ability. Also, there was no difference between the two timepoints, so we might conclude that despite the cognitive problems that MS poses, the PwMS were equally capable of remembering the sequences compared to the HC. Lastly, our hypothesis that PwMS are able to learn better with melody feedback may be rejected because there was no difference in learning between all conditions for both groups. However, further research should investigate these statements with a bigger sample size.

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APPENDIX

Table 1

Results of the Descriptive Outcome Measures

Descriptive outcome measures			MS (n=10) Mean	MS (n=10) ±SD	HC (n=7) Mean	HC (n=7) ±SD	P-value (prob > |t|)
Age (years)			50	±10	62	±13	ns
Gender	Male		3 (30%)	-	0 (0%)	-	
	Female		7 (70%)	-	7 (100%)	-	ns
BMI (kg/m²)			26,7	±4,73	25,43	±3,62	ns
Education	Highschool		5 (50%)	-	4 (57%)	-	
	Bachelor		5 (50%)	-	3 (43%)	-	ns
	Master		0 (0%)	-	0 (0%)	-	
Music experience	Yes		7 (70%)	-	1 (14%)	-	0,0498*
	No		3 (30%)	-	6 (86%)	-	
Type MS	Relapsing-remitting		9 (90%)	-	-	-	
	Primary progressive		1 (10%)	-	-	-	-
	Secondary progressive		0 (0%)	-	-	-	
Questionnaires	MSWS-12		34,3	±13,81	-	-	-
	FES		31,3	±11,3	22,3	±4,77	ns
	MFIS		37,5	±16,59	12,71	±10,81	0,0066*
	HADS	Anxiety	4,8	±2,6	4	±2,2	ns
		Depression	4,3	±3,58	2,43	±1,29	ns
		Total	9,1	±5,94	6,43	±2,97	ns
	BMRQ		67,7	±6,03	64,86	±13,13	ns
Motor tests	TUG (s)		8,30	±1,14	6,91	±1,17	0,0208*
	6MWT (m)		466,64	±80,32	567,86	±71,4	0,0175*
	T25FW (s)		5,99	±0,62	5,75	±0,43	ns
	FSST (s)		9	±2,83	7,49	±2,27	ns
	DGI		21,64	±2,53	23,57	±0,73	ns
	Mini BEST		22,27	±4,22	25,57	±1,76	ns
Cognitive tests	SRT		46,88	±8,08	48,67	±10,37	ns
	PASAT	Raw	52,67	±6,41	47,2	±10,01	ns
		Corrected	54,17	±6,68	44,8	±10,31	ns
	SDMT		60,11	±19,09	51,86	±8,4	ns

Note. MSWS-12= Multiple Sclerosis Walking Scale – 12, MFIS= the Modified Fatigue Impact Scale ,FES= Falls Efficacy Scale, HADS= the Hospital Anxiety Depression Scale, BMRQ= the Barcelona Music Reward Questionnaire., TUG= Timed Up and Go Test,6MWT= the 6 Minute Walking Test, T25FWT= the Timed 25 Feet Walking test, FSST= The Four Square Step Test, DGI= the Dynamic Gait Test, Mini BEST= mini Balance Evaluation Systems Test, SRT= Spatial Recall Test, SDMT= the Symbol Digit Modalities test, PASAT= Paced Auditory Serial Addition test, ns = non-significant , *P-value <0,05

Table 2

Results of the Subjective Questions per condition

Condition	Questions	MS (n=10)		HC (n=7)		P-value (prob > |t|)
		Mean	±SD	Mean	±SD	
Visual	Pre-physical fatigue	3,56	±2,17	0,29	±0,45	0,0015*
	Post physical fatigue	3,78	±1,87	0,43	±0,49	0,0005*
	Pre-mental fatigue	4	±2,54	1,71	±1,91	ns
	Post mental fatigue	4,44	±2,83	1,71	±1,67	ns
	Easy execution	3	±1,83	1,86	±2,36	ns
	Easy remembering	5,67	±2,83	5,71	±1,83	ns
	Frustration	4,44	±2,45	4,43	±1,99	ns
	Effort learning	5,67	±2,87	5,57	±2,26	ns
	Effort performing	2,89	±1,59	2,57	±2,56	ns
Melody	Pre-physical fatigue	3,56	±2,01	0,43	±0,49	0,0005*
	Post physical fatigue	3,56	±2,11	0,57	±0,49	0,0007*
	Pre-mental fatigue	3,22	±2,35	1,57	±1,92	ns
	Post mental fatigue	3,67	±2,4	1,71	±1,67	ns
	Easy execution	2,44	±1,83	3,14	±2,47	ns
	Easy remembering	4,89	±2,42	6	±1,85	ns
	Frustration	4,11	±2,28	4,57	±1,99	ns
	Effort learning	5,22	±2,3	5,14	±1,46	ns
	Effort performing	2,33	±1,33	2,14	±2,36	ns
Sound	Pre-physical fatigue	3,44	±2,01	1	±2,28	0,0228*
	Post physical fatigue	3,44	±1,95	0,43	±0,49	0,0030*
	Pre-mental fatigue	3,56	±2,36	1,14	±1,73	ns
	Post mental fatigue	3,78	±2,48	1,43	±1,05	0,0457*
	Easy execution	2,56	±2,36	2	±2,67	ns
	Easy remembering	5,67	±2,91	5,29	±2,43	ns
	Frustration	5,67	±2,58	5,26	±1,81	ns
	Effort learning	5,78	±2,86	5,29	±2,71	ns
	Effort performing	1,89	±1,73	1,43	±2,38	ns

Note. ns = non-significant, *P-value <0,05

Table 3

Results of the Experimental Outcome Measures in the Immediate Recall and Delayed Recall per condition

Outcome measure	Recall	Condition	MS (n=10)				HC (n=7)				P-value (prob > |t|)		
			Mean	**±SD**	**Median**	**Q1 - Q3**	**Mean**	**SD**	**Median**	**Q1 - Q3**			
		Visual	1,63	±0,85	1	0,8 - 1,2	1,1	±0,27	0,94	0,67 - 1,5	ns		
	Immediate	Sound	1,36	±0,55	0,93	0,67 - 1,38	1,43	±0,98	0,93	0,73 - 1,13	ns	ns	
Interstep interval (s)		Melody	1,3	±0,66	1	0,73 - 1,73	1,17	±0,47	0,93	0,68 - 1,13	ns		ns
		Visual	1,92	±0,73	0,93	0,67 - 1,73	0,95	±0,3	0,87	0,6 - 1,42	0,0064*	0,0460*: sound x accuracy	
	Delayed	Sound	1,86	±1,34	1,07	0,68 - 1,98	1,34	±0,97	0,87	0,67 - 1,27	ns		
		Melody	1,67	±0,76	1,03	0,72 - 2,15	1,5	±1,01	0,87	0,67 - 1,42	ns		
		Visual	9,31	±4,75	7,8	5,1 - 14,28	6,61	±0,11	0,93	5,37 - 9,47	ns		
	Immediate	Sound	8,19	±3,7	6,13	5,37 - 11,88	9,08	±6,66	5,73	5 - 9,4	ns	ns	
Total onset time (s)		Melody	8,15	±8,15	6,66	5,42 - 9,53	6,45	±1,89	6,67	4,13 - 7,73	ns		ns
		Visual	11,25	±4,27	11,93	6,37 - 14,87	6,14	±2,36	5,73	4,6 - 10,2	0,0273*		
	Delayed	Sound	10,31	±7,03	8,5	5 - 22,58	7,57	±4,25	6,07	5,67 - 8,47	ns	ns	
		Melody	10,8	±4,29	11,3	5,73 - 14,35	9,16	±6,09	5,73	4,73 - 16,73	ns		
		Visual	15,71	±25,27	0	0 - 42,86	19,73	±25	0	0 - 44,65	ns		
	Immediate	Sound	24	±32,92	0	0 - 42,86	11,22	±18,65	0	0 - 37,5	ns	ns	
Faults (%)		Melody	23,85	±24,36	0	0 - 44,65	11,07	±21,7	0	0 - 44,65	ns		ns
		Visual	32,67	±30,16	0	0 - 42,15	36,73	±34,46	0	0 - 50	ns		
	Delayed	Sound	38,19	±37,59	0	0 - 42,86	15,99	±29,11	0	0 - 37,5	ns	ns	
		Melody	29,16	±25,45	0	0 - 44,65	17,26	±29,92	0	0 - 44,65	ns		

Note. ns= non-significant, *P-value <0,05

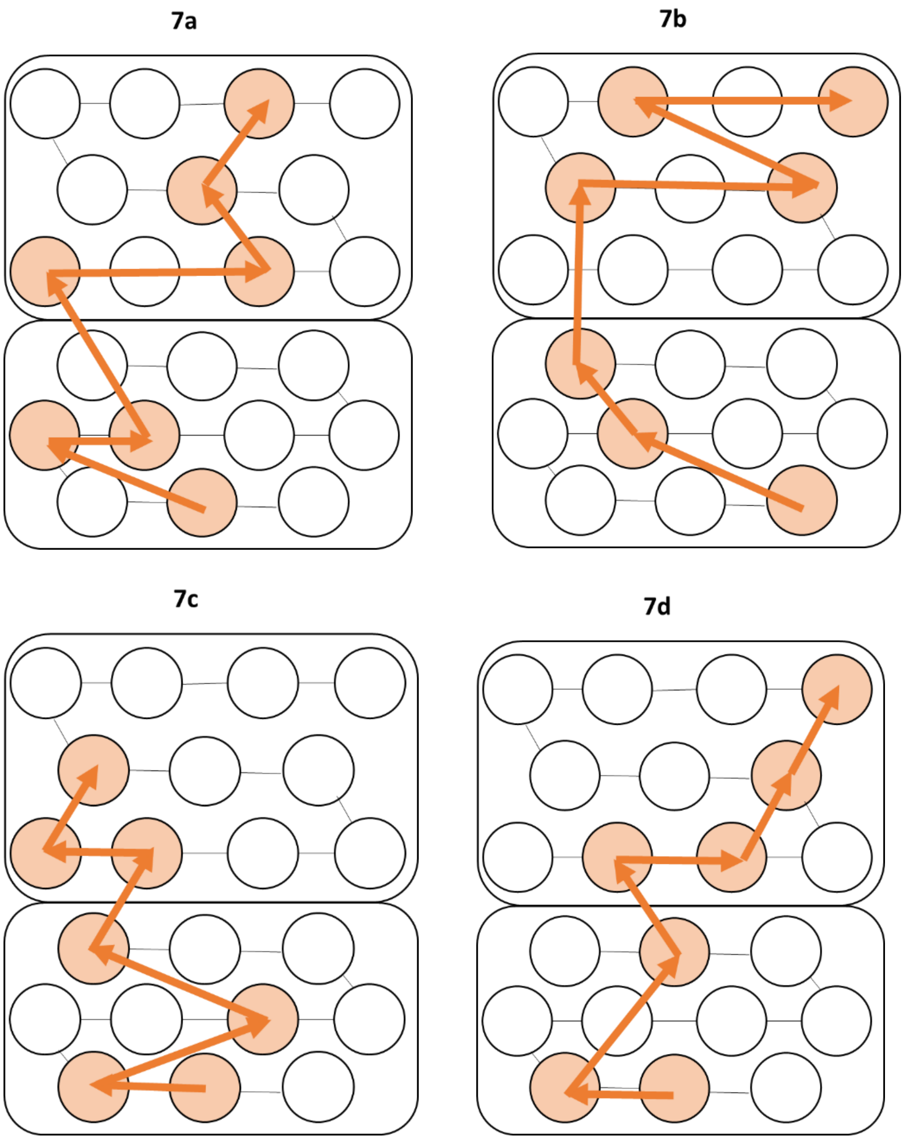

Figure 1. Example of sequences that subjects needed to walk on the AMPEL device.

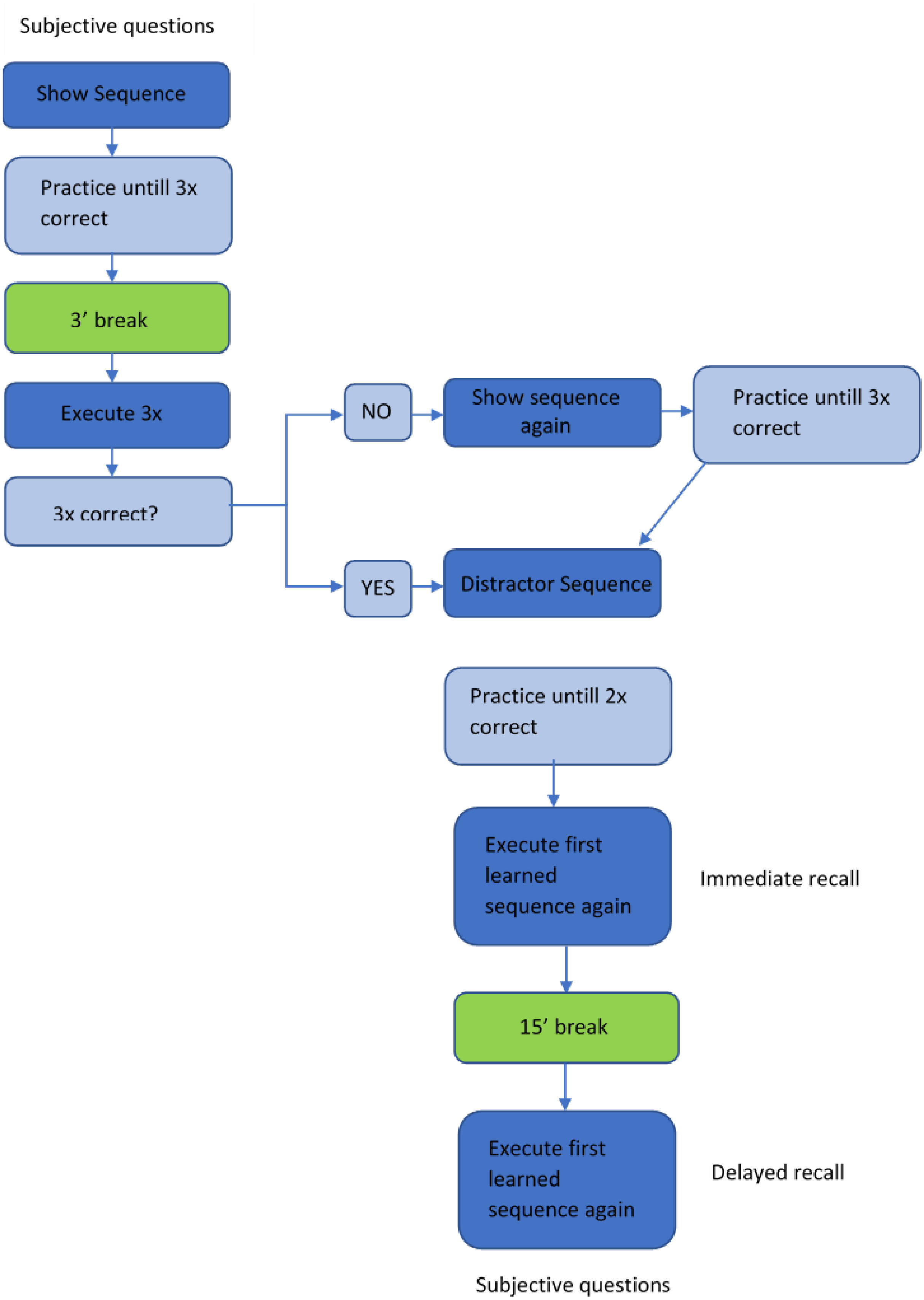

Figure 2. Experimental protocol.

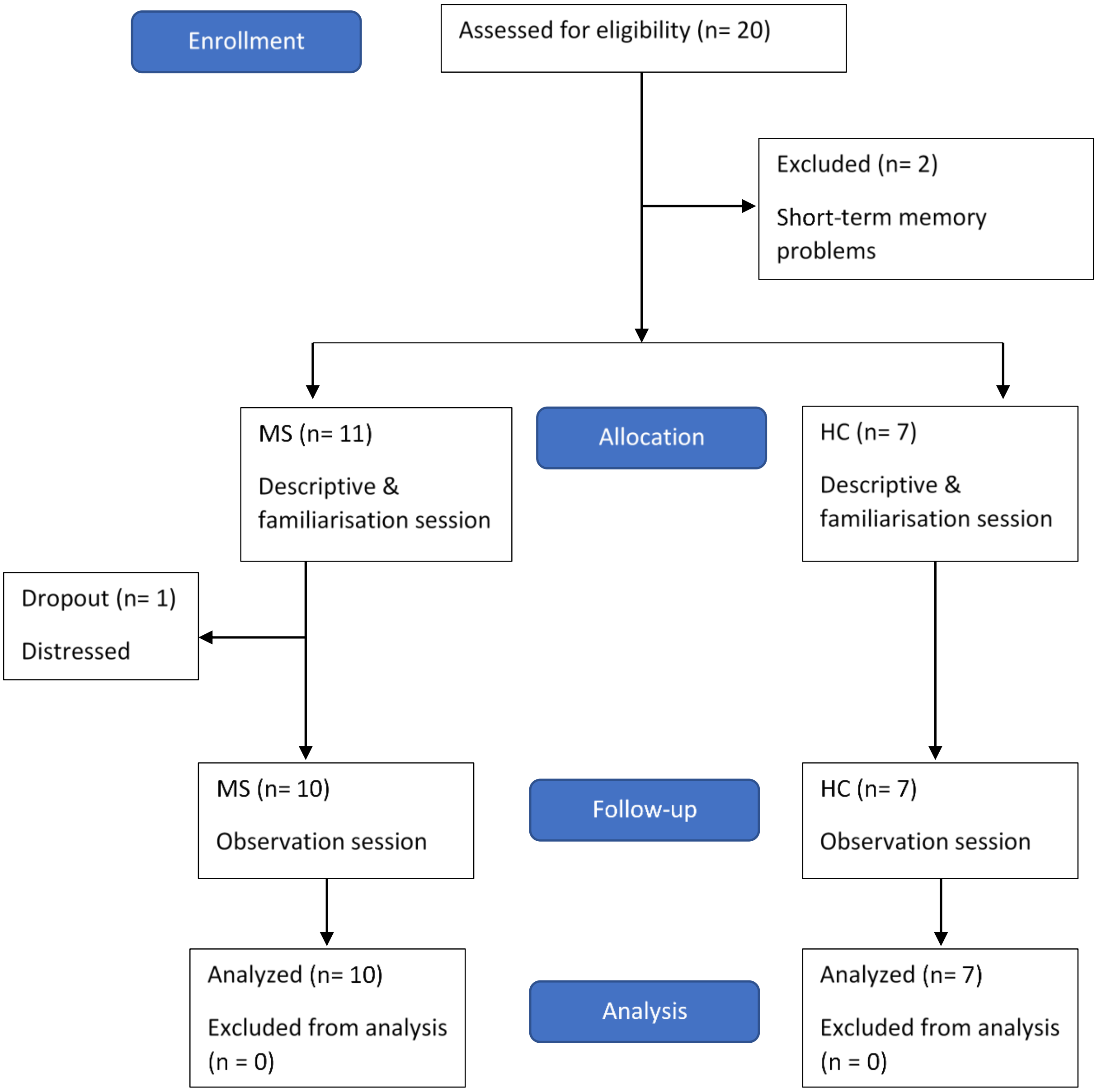

Figure 3. Flowchart of participant recruitment.

Document 1. Approval document ethical committee.

Afz: Commissie voor Medische Ethiek (UZP074)

COMMISSIE VOOR MEDISCHE ETHIEK

Voorzitter:
Prof. Dr. D. Matthys
Secretaris:
Prof. Dr. J. Decruyenaere

Universiteit Hasselt
REVAKI
Prof. dr. Peter FEYS
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UW KENMERK	**ONS KENMERK**	**DATUM**	**KOPIE**
	2018/1295	19-dec-18	Zie "CC"

BETREFT
DEFINITIEF ENIG (centraal) ADVIES voor studie met als titel:
Investigating auditory sonification (melodic and single tones) and visual real-time feedback as a tool for embodied associations, and its effects on learning and balance in persons with multiple sclerosis: an observational case-control study.

Belgisch Registratienummer: B670201837795

* Adviesaanvraagformulier (versie 1, dd. 24/09/2018) (volledig ontvangen dd. 22/10/2018)
* Begeleidende brief dd. 15/10/2018
* Verzekeringscertificaat dd. 12/10/2018
* Financiële overeenkomst
* Diverse
  - Flyer MS
  - Flyer HC
* Vragenlijsten
  - Dynamic gait balance
  - Mini Balance Evaluation Systems test
  - Neuropsychological batteries
  - Multiple Sclerosis walking scale
  - Modified fatigue impact scale
  - Activities-specific balance test
  - Hospital Anxiety and depression scale
  - Barcelona music reward questionnaire
  - Dual task questionnaire
* CV deelnemende onderzoekers
* Advies lokale EC's
  Revalidatie MS Centrum te Overpelt dd 31/10/2018
  Nationaal MS Centrum te Melsbroek dd 06/11/2018
  Universiteit Hasselt dd 22/10/2018
* Antwoord onderzoeker dd. 10/12/2018 op opmerkingen EC dd. 20/11/2018
* Protocol (aangepaste versie cfr. Brief onderzoeker dd. 10/12/2018)
* Antwoord onderzoekers ontv. 17/12/2018 op bijkomende opmerkingen EC dd. 11/12/2018
* (Patiënten)informatie- en toestemmingsformulier dd. 17/12/2018

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

BOVENVERMELDE DOCUMENTEN WERDEN DOOR HET ETHISCH COMITÉ BEOORDEELD.
ER WERD EEN DEFINITIEF ENIG (CENTRAAL) POSITIEF ADVIES GEGEVEN OVER DIT PROTOCOL OP 18/12/2018. INDIEN DE STUDIE NIET WORDT OPGESTART VOOR 18/12/2019, VERVALT HET ADVIES EN MOET HET PROJECT TERUG INGEDIEND WORDEN.
Vooraleer het onderzoek te starten dient contact te worden genomen met Bimetra Clinics (09/332 05 00).

THE ABOVE MENTIONED DOCUMENTS HAVE BEEN REVIEWED BY THE ETHICS COMMITTEE.
A DEFINITIVE SINGLE POSITIVE ADVICE WAS GIVEN FOR THIS PROTOCOL ON, 18/12/2018. IN CASE THIS STUDY IS NOT STARTED BY 18/12/2019, THIS ADVICE WILL BE NO LONGER VALID AND THE PROJECT MUST BE RESUBMITTED.
Before initiating the study, please contact Bimetra Clinics (09/332 05 00).

THIS ADVICE APPEARS IN THE PROCEEDINGS OF THE MEETING OF THE ETHICS COMMITTEE OF 18/12/2018
DIT ADVIES WORDT OPGENOMEN IN HET VERSLAG VAN DE VERGADERING VAN HET ETHISCH COMITE VAN 18/12/2018

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UW KENMERK	**ONS KENMERK**	**DATUM**	**KOPIE**
	2018/1295	19-dec-18	Zie "CC"

Vervolg blz. 2 van het adviesformulier betreffende project EC UZG 2018/1295

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

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

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

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

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

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

CC: De heer T. VERSCHOORE - UZ Gent - Bimetra Clinics
Nationaal MS Center - Ethisch Comité; Vanheylenstraat 16 1820 Melsbroek
Revalidatie & MS Centrum - Ethisch Comité; Boemerangstraat 2 3900 Overpelt
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FAGG - Research & Development; Victor Hortaplein 40, postbus 40 1060 Brussel

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Document 2. Recruitment Flyer for MS patients.

MULTIPLE SCLEROSIS ONDERZOEK

Wat

Een reeks van opeenvolgende geluiden of lichtsignalen onthouden. Vervolgens moet je deze reeks reproduceren door op tegels te stappen.

Doel

Bijdragen aan de verbetering van de behandeling van MS en symptomen die hiermee gepaard gaan.

LEEFTIJD:
18 - 70

DUUR:
2 SESSIES VAN 3U EN 2U

WAAR:
MELSBROEK OF OVERPELT OF DIEPENBEEK

WANNEER:
OKTOBER 2018 – MEI 2019

INTERESSE? CONTACTEER:

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of
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0476/63.86.15

Document 3. Recruitment flyer for healthy controls.

GEZONDE PARTICIPANTEN GEZOCHT
MS ONDERZOEK

Wat

Een reeks van opeenvolgende geluiden of lichtsignalen onthouden. Vervolgens moet je deze reeks reproduceren door op tegels te stappen.

Doel

Bijdragen aan de verbetering van de behandeling van MS en symptomen die hiermee gepaard gaan.

UHASSELT KNOWLEDGE IN ACTION — National MS center Melsbroek — Revalidatie & MS-Centrum | Overpelt — UNIVERSITEIT GENT

LEEFTIJD:
18 - 70

DUUR:
2 SESSIES VAN 3U EN 2U

WAAR:
MELSBROEK OF OVERPELT OF DIEPENBEEK

WANNEER:
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UHASSELT
KNOWLEDGE IN ACTION

INVENTARISATIEFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
10/09/2018	ethical comittee piloting device protocol flyer, recrutement	Promotor: Copromotor/Begeleider: Student(e): Student(e):
12/11/2018	ethical comittee research question	Promotor: Copromotor/Begeleider: Student(e): Student(e):
25/02/2019	Files in drive general information about what was going to happen (both students were abroad)	Promotor: Copromotor/Begeleider: Student(e): Student(e):
14/03/2019	research question methodology	Promotor: Copromotor/Begeleider: Student(e): Student(e):
27/03/2019	data processing graphs statistics methodology	Promotor: Copromotor/Begeleider: Student(e): Student(e):
23/04/2019	introduction methodology tables and statistics results	Promotor: Copromotor/Begeleider: Student(e): Student(e):
13/05/2019	statistics results	Promotor: Copromotor/Begeleider: Student(e): Student(e):
15/05/2019	statistics	Promotor: Copromotor/Begeleider: Student(e): Student(e):
16/05/2019	statistics results discussion	Promotor: Copromotor/Begeleider: Student(e): Student(e):
		Promotor: Copromotor/Begeleider: Student(e): Student(e):

In te vullen door de promotor(en) en eventuele copromotor aan het einde van MP2:

Naam Student(e): Inneke Huion and Marit Putzeys **Datum:** 28/5/2019

Titel Masterproef: Is there a difference in learning sequences between a visual, melody or sound condition within an embodied environment in persons with

1) Geef aan in hoeverre de student(e) onderstaande competenties zelfstandig uitvoerde:
   - NVT: De student(e) leverde hierin geen bijdrage, aangezien hij/zij in een reeds lopende studie meewerkte.
   - 1: De student(e) was niet zelfstandig en sterk afhankelijk van medestudent(e) of promotor en teamleden bij de uitwerking en uitvoering.
   - 2: De student(e) had veel hulp en ondersteuning nodig bij de uitwerking en uitvoering.
   - 3: De student(e) was redelijk zelfstandig bij de uitwerking en uitvoering
   - 4: De student(e) had weinig tot geringe hulp nodig bij de uitwerking en uitvoering.
   - 5: De student(e) werkte zeer zelfstandig en had slechts zeer sporadisch hulp en bijsturing nodig van de promotor of zijn team bij de uitwerking en uitvoering.

Competenties	NVT	1	2	3	4	5
Opstelling onderzoeksvraag	O	O	O	✓	O	O
Methodologische uitwerking	O	O	✓	O	O	O
Data acquisitie	O	O	✓	O	O	O
Data management	O	O	O	O	✓	O
Dataverwerking/Statistiek	O	O	O	✓	O	O
Rapportage	O	O	O	O	✓	O

2) Niet-bindend advies: Student(e) krijgt toelating/geen toelating (schrappen wat niet past) om bovenvermelde Wetenschappelijke stage/masterproef deel 2 te verdedigen in bovenvermelde periode. Deze eventuele toelating houdt geen garantie in dat de student geslaagd is voor dit opleidingsonderdeel.

   Yes, the thesis can be defended in June.

3) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) openbaar verdedigd worden.

   Yes

4) Deze wetenschappelijke stage/masterproef deel 2 mag wel/niet (schrappen wat niet past) opgenomen worden in de bibliotheek en docserver van de UHasselt.

   Yes

Datum en handtekening Student(e)	Datum en handtekening promotor(en)	Datum en handtekening Co-promotor(en)
	23/5/2019	