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Original Article

Embodied learning in multiple sclerosis using melodic, sound, and visual feedback: a potential rehabilitation approach

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Given the prevalence of motor and cognitive functions in persons with multiple sclerosis (PwMS), we proposed that the theoretical framework of embodiment could provide a rehabilitation avenue to train these functions as one functional unit. PwMS ($n = 31$) and age- and gender-matched healthy controls ($n = 30$) underwent an embodied learning protocol. This involved learning a cognitive sequence while performing it through bodily stepping movement under three feedback conditions (melody, sound, and visual). Cognitive and movement performance was assessed by a delayed recall 15 min after undergoing the embodied learning protocol. Half of participants correctly recalled the sequence in all three conditions, while 70% of healthy controls achieved correct recall within the melody condition. Balance impairment predicted the speed of executing the sequence irrespective of learning, most apparent in the melody condition. Information processing speed predicted the speed of executing the sequence in the melody and sound conditions between participants as well as over time. Those who learned performed the sequence faster in the melody condition only and overall were faster over time. We propose how embodied learning could expand the current context of rehabilitation of cognitive and motor control in PwMS.

Keywords: embodiment learning; multiple sclerosis; auditory and visual feedback; information processing speed; dynamic balance

Introduction

Multiple sclerosis (MS) is a neurological inflammatory, demyelinating, and neurodegenerative disease resulting in impairments in motor and cognitive functioning.[1] Motor impairments have a negative impact on walking[2–4] and functional mobility.[5] Symptoms include muscle weakness, dysfunctions of balance and coordination,[2] and gait abnormalities, with a prevalence of 50% for falls.[6] Cognitive impairments are also prevalent in the domains of information processing speed, working memory, sustained attention, and executive functioning in persons with MS (PwMS).[7–9] Particularly, memory disturbance and learning impairment have a prevalence of 60% and affect working and long-term memory.[10] In PwMS, learning difficulties have been shown to be with acquisition of new knowledge rather than retrieval from long-term storage.[8] This differentiation can be explained by information processing speed. Processing speed can be seen as the component that drives information in memory, contributing to impaired acquisition of new knowledge, and thus learning.[11]

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Rehabilitation remains an essential part of the overall care of these impairments in PwMS, with the aim to improve motor and cognitive functioning.[12,13] In PwMS, exercise therapy has shown to be effective for improving or maintaining motor functions, such as muscle strength[14] and physical fitness, and to some extent functional mobility.[15,16] Furthermore, approaches varying from specific balance exercises[17,18] to pilates[19] have been found effective for improving balance. In addition, with the emphasis to motor training, research has shown that visual feedback[20,21] and auditory feedback[22] are effective to improve gait in PwMS. Furthermore, studies on music-based interventions focused on walking are encouraging in PwMS.[23,24] Moreover, evidence for cognitive rehabilitation, in terms of compensative and restorative approaches, has shown promising results for PwMS directed toward cognitive functions,[25,26] including memory.[27] Although the above approaches have shown to be effective in training the individual motor and cognitive functions, these approaches tend to target these functions independently.

Multidimensional rehabilitation approaches have emerged in recent years, such as exercise therapy to improve cognitive functions.[28,29] Additionally, supported by theoretical frameworks, attention has been devoted to merging both physical and cognitive rehabilitations, for example, by applying integrated dual task (DT) training.[30] While DT training is effective,[30] it does require constant conscious cognitive attention for engagement, likely difficult in more impaired PwMS.

Despite the shift in rehabilitation mindset with these approaches, overall it remains quite common that motor and cognitive functions continue to be viewed as two independent units. In what follows, we present a rehabilitation approach in which motor and cognitive functions are considered as an integrated functional unit. We propose that this integrated approach can be embedded within the broader framework of embodiment theory,[31,32] which offers a dynamic viewpoint on human–environment interactions. In this theory, the mind is seen as a unit for complexity control, emerging from bodily functions in relation to the environment.[33,34] The learning of sequences through bodily interactions is a form of embodied learning, where the sequence learning may be facilitated through body movements. The latter adds motor-spatial information that facilitates sequence recall due to possible simulations of the actions needed to carry out the sequence. The mind can be seen as a conscious control of this process, and as an emergent self-model about this interaction.[32,35,36] Examples of embodied learning have been studied in children with[37] and without[38] learning disabilities and motor impairments, with positive effects being reported on outcomes, such as motor performance and learning.

To comply to the embodied approach, we aimed to target sequence learning (engaging information processing speed and working memory) in conjunction with dynamic movements of the body through steps that carry out the sequence (engaging balance) using multimodal feedback approaches. In line with this aim, we developed an interactive environment called: the augmented movement platform for embodied learning (AMPEL).[39] In this study, the AMPEL was used so that it provided a platform for the user to dynamically move around by stepping on its different tiles, while eliciting information by providing the user with immediate feedback as a response to each step.

We thus investigated if PwMS could learn and perform a cognitive sequence during an embodied task by dynamic stepping movements under three different feedback modalities and whether balance and information processing speed were factors that affected learning and motor performance compared to healthy controls (HCs). Learning was investigated by a delayed recall task. We hypothesized to find a superior cognitive performance in HC as compared to PwMS, given the prevalence of cognitive and motor impairments in the MS population. We also expected that PwMS would be able to learn the cognitive sequence along with the embodied task, first because of their intact sensory encoding and cognitive storage capacity,[40] and second because of the embodied and spatial context (i.e., the dynamic movement) in which sensory encoding and cognitive storage are informed by a sequence of movements and spatial orientations. The different feedback modalities included in the experimental design were visual and auditory feedback to investigate whether type of feedback effected learning or motor performance. The auditory feedback was further differentiated to simple sounds and melodic components. It was

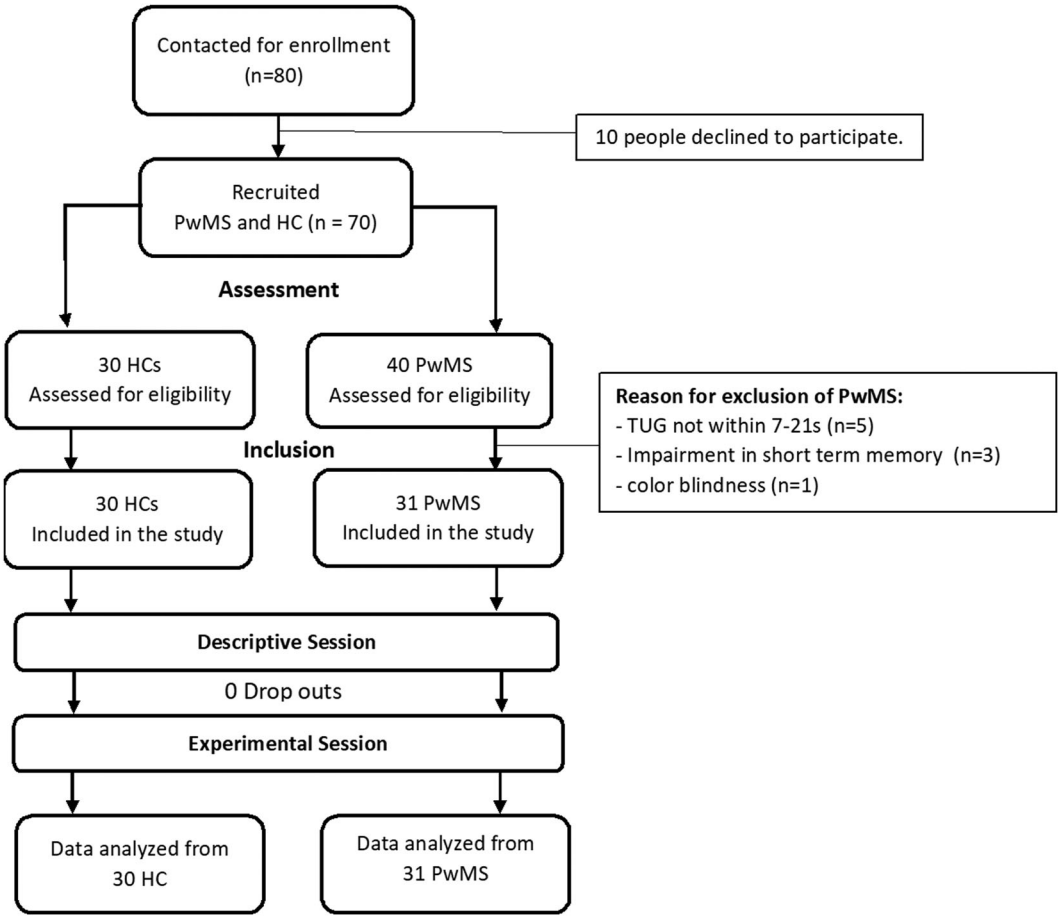

Figure 1. **An overview of the study selection process and participant flow. HC, healthy controls; PwMS, persons with multiple sclerosis**

hypothesized that melodic feedback would boost and affect learning and movements, compared to visual and simple sound feedback, as melodies are structured and could serve as an additional semantic representation to the sequence, and second, because melody required a certain speed of performance to be perceived intelligibly.

Methods

Participants

The case–control observational study was approved by the Medical Ethical Committees of Gent and Hasselt Universities (Belgium), The National MS Center Melsbroek, and Noorderhart Rehabilitation and MS Center in 2018 (B670201837795). The study was registered at clinicaltrials.gov (NCT03931278). Participants were recruited and tested in the MS centers and the REVAL research center of Hasselt University through distributing flyers in person and on social media. Participants were included if they had a score of 7–21 s on the Timed Up and Go test and excluded if presenting with: color blindness; cognitive impairment in the domain of short-term memory where the understanding and execution of the experiment was not possible, pregnancy. PwMS ($n = 31$) and HCs ($n = 30$) were included and signed the informed consent. Figure 1 provides an overview of the study selection process and participant flow.

Study design

The study included two testing sessions: a descriptive session to conduct clinical tests and to familiarize participants on the AMPEL and an experimental

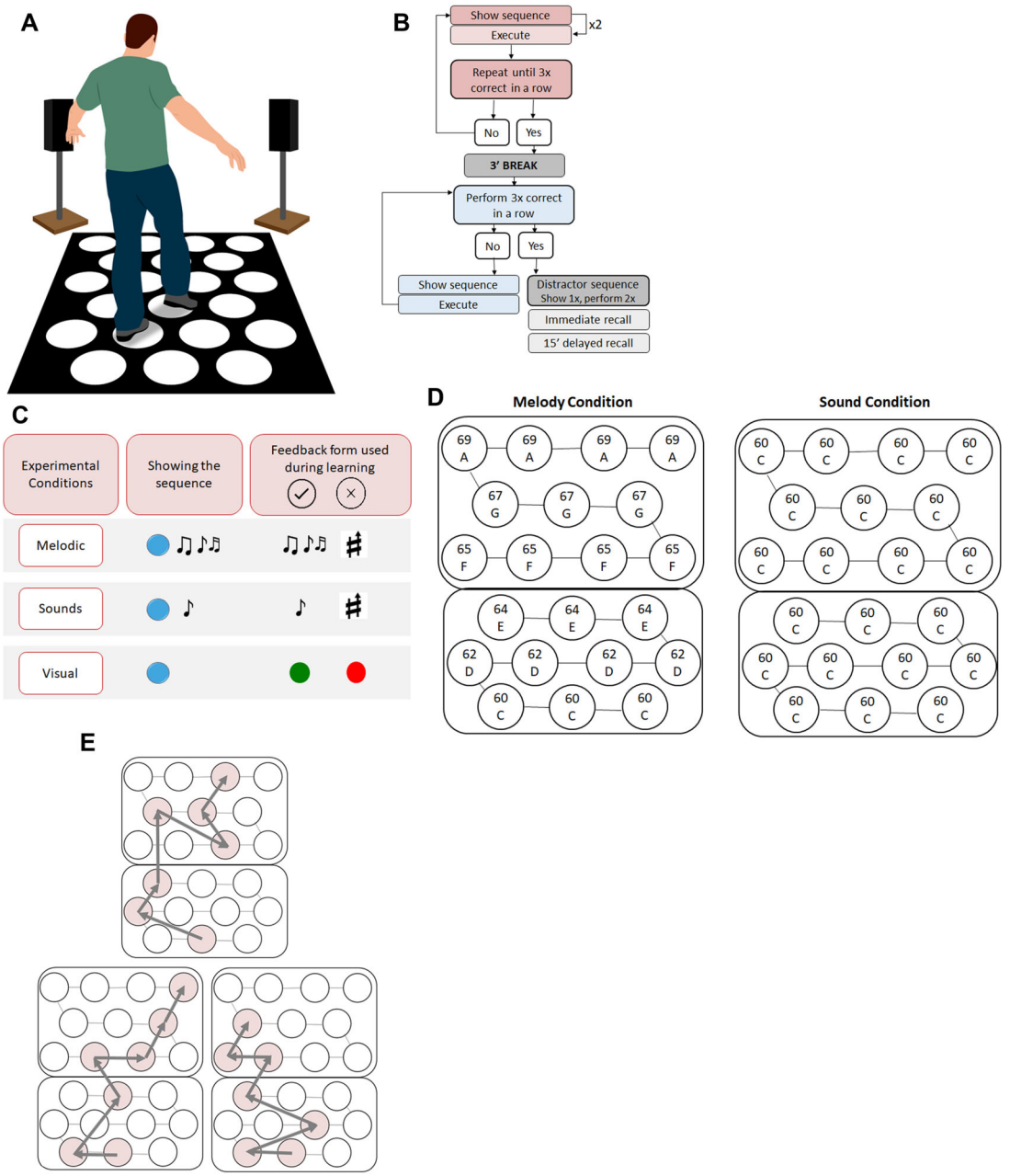

Figure 2. (A) An illustration of a participant on the AMPEL. (B) The procedure of the embodied learning protocol. (C) An illustration of how the sequences were shown and the feedback received upon stepping on the tiles per experimental condition. (D) Illustrates the mapping of tiles to notes in the melody and sound conditions. (E) Illustrates the three sequences used in the learning protocol

session. The experiment was performed on the AMPEL (Fig. 2A); a custom made platform with 20 tiles, controlled by custom made software.[39]

Session 1. The descriptive session. During this session, demographics and disease information were collected, as well as conducting the descriptive

clinical tests and familiarization with the AMPEL described below.

Motor functions. To evaluate walking abilities and balance, the following tests were performed: Timed up and Go (TUG),[41] Timed 25-Foot walk test,[42] Four Step Square Test,[43] Six Minute Walking Test,[44] Dynamic Gait Index,[45] and the Mini BEST test.[46]

Cognitive functions. Rao's brief repeatable battery was conducted:[47,48] Buschke Selective Reminding test to assess verbal learning and memory, 7/24 Spatial Recall test to assess visual learning and recall, Word-List Generation test to asses verbal fluency assessment, Paced Auditory Serial Addition Test to assess auditory information processing speed, and Symbol Digit Modality Test (SDMT) to assess information processing speed. In addition, the Stroop color test was conducted to assess executive function and inhibition.[49]

Self-reported questionnaires. Participants were asked to complete the following: the Hospital Anxiety Depression Scale (HADS),[50] the Modified Fatigue Impact Scale,[51] and the Falls Efficacy Scale.[52] PwMS additionally received the Multiple Sclerosis Walking Scale[53] to complete.

Familiarization with the AMPEL. Participants were asked to walk freely on the AMPEL to feel comfortable with taking various types of steps depending on the direction of stepping. Thereafter, participants received a standardized set of instructions in the context of using the AMPEL to perform the embodied learning protocol. These were the following: participants had to always start moving with the right leg. The next step after a correct step was always either a row close or one row further; this was to ensure safety as well as maintain a certain level of difficulty in movement. As an additional safety measure, steps with delicate balance maneuvers, such as crossing legs, were not requested.

The goal of the experimental task was explained, which was that a sequence of seven steps had to be produced correctly three times in a row. Thereafter, experimental protocol implemented to achieve this goal was demonstrated three times (once per condition); with melody, sound, and visual feedback. Table S1 (online only) shows the standardized instructions. This was conducted in order to familiarize participants with how the correct and incorrect feedback would look and sound like per condition. The following additional rules were also explained, when a step was incorrect, participants were allowed to explore until the correct step was found (details explained below). This exploration was standardized by giving the opportunity to find the correct step with a maximum of three incorrect steps. Thus, when three incorrect steps were taken before the correct step was found during the exploratory phase, participants were asked to stop and start the sequence from the beginning. Finally, a cheering sound was heard once a sequence was performed three times correctly. The order of the steps was also of importance: tiles in the sequence could not be skipped. Please note, sequences that were used to familiarize participants were different than the sequences used in the experimental protocol. The checklist used to conduct the familiarization is found in Supplementary Information File S1 (online only).

Session 2. The experimental session. Familiarization with the AMPEL was repeated once more, to ensure that participants knew how the AMPEL functioned in the context of the embodied learning protocol and the manner of which the three different experimental conditions provided feedback.

The embodied learning protocol (Fig. 2B). Per condition, participants were presented a sequence of seven tiles on the AMPEL and were asked to perform the sequence (i.e., the series of steps) on the AMPEL. After the first attempt, participants were shown the sequence once more. Participants were then asked to reach the goal of performing the sequence correctly three times in a row. In addition, participants were asked to use the feedback they received because of stepping on the tiles. Feedback was provided after each step, indicating whether the step was correct or wrong, given the sequence. Once participants were able to execute the sequence three times in a row correctly, a 3-min break was given. After this break, participants were asked to repeat the learned sequence three times in a row. Once successful, a distractor sequence was shown, and participants were then asked to attempt to perform this distractor sequence twice. The distractor attempts were immediately followed by asking participants to perform the original learned sequence once again immediately to measure immediate recall, and 15 min later to measure delayed recall. During both recall measurements, no feedback was delivered.

The experimental conditions. Three different feedback modalities were used, these were: melodic, sound, and visual. The sequence was always shown by blue lights and the corresponding visual or auditory feedback condition, as shown in Figure 2C. Accordingly, when executing the sequence, participants were able to differentiate between the correct and incorrect step because of the feedback they received when stepping on the tiles. The differences between the experimental conditions were there by determined by the delivered feedback (Fig. 2C). When executing the sequence, the participants could differentiate between a correct and incorrect step given the following mapping (Fig. 2D). (1) *Melody.* Each row of tiles on the AMPEL was mapped to a different note. Upon stepping on a tile correctly, the corresponding mapped note was heard. An incorrect tile was heard through a pitch bend of the mapped note. (2) *Sound.* All tiles on the AMPEL were mapped to one single note (C_4). Upon stepping on a tile correctly, C_4 was heard. An incorrect step was heard through a pitch bend of C_4. (3) *Visual.* A correct step was indicated by the tile lighting up in green, and an incorrect step was indicated by tile lighting up in red.

The sequences. The to-be-learned and distractor sequences were different for each experimental feedback condition, resulting in three learning (Fig. 2E) and three distractor sequences. All sequences and conditions were randomized across participants using a digital randomization program.

Outcome measures

Subjective perception measurements. Prior to starting the learning protocol, participants were asked to rate their physical and cognitive fatigue on a visual analog scale (VAS) ranging from 0 to 10 (0 = not tired at all, 10 = exhaustion). At the end of the learning protocol, they were asked to rate the following on the VAS (0 lowest and 10 highest perception): physical and cognitive fatigue; easiness of executing and remembering the sequence; effort and frustration to learn and perform the sequence.

Primary outcome measures. The cognitive and motor performances at delayed recall were defined as primary outcome measures. The *cognitive performance* was defined as the recall, reported by sequence learned or not learned using the formula below. A binomial distribution, 1 and 0, was allocated. The value of 1 signified that the sequence was recalled without any mistakes, and thus it was learned. The value of 0 signified that the sequence was either not learned and/or recalled with mistakes, or edits (e.g., additions, substitutions, or omissions).

$$(1 + (\text{number of correct tiles performed} - \text{number of steps performed})/\text{sequence length}) = 1 \rightarrow 1$$

$$(1 + (\text{number of correct tiles performed} - \text{number of steps performed})/\text{sequence length}) < 1 \rightarrow 0$$

The *motor performance* was defined as the movement performance of the steps when completing the sequence. This was quantified by inter-step-intervals (ISI) mean. ISI was defined as the duration of movement (in milliseconds) between two consecutive steps.

Statistical analysis

The descriptive data collected in session 1 were checked for normality using the Shapiro–Wilk test. To investigate between group differences, *t*-tests and Wilcoxon signed-rank tests were used for normally and non-normally distributed data, respectively. Subjective experimental data as well as objective descriptions of the number of participants who learned and did not learn the sequence across participants and groups were reported using the outcome measure *cognitive performance*. An analysis of variance was applied to determine if there were differences between conditions and groups in the subjective experimental data, as well as in the process of learning data.

To investigate the embodied performance in more detail, the response variable of motor performance was used within multi-level regression models. The response variable (coded as the $\log_2$ of ISImean) was fitted using a multi-level model based on the (within person) experimental conditions (Visual, Sound, and Melody) and the (between person) covariates TUG and SDMT, with Participants as random variable. In two derivate models, Participants were grouped as patients and HCs: Group (PwMS, HC), and in those who learned the sequence and those who did not learn the sequence: Learned (No, Yes). Lastly, the presentation of the experimental conditions in subsequent measurements is incorporated using the variable

Trial as metrical variable standing for linear time in a growth model approach.

Specifications of the model

The basic model for ISImean-Log_2 specifies that the average duration of a foot on a tile (ISImean-Log_2) of a participant is based on an average ISImean-Log_2 value over all participants, changing over trials. The error component accounts for the deviance of this model to the participant's ISImean-Log_2 values. The residual error variance is captured by $\sigma_\epsilon{}^2$:

$$Y_{ik} = \pi_i^0 + \pi_i^1 Trial_{ik} + \in_{ik},$$

$$\text{with } \in_{ik} \sim N(0, \sigma_\in^2),$$

$$\pi_i^0 = \gamma_0^0 + \zeta_1^0,$$

$$\pi_i^1 = \gamma_0^1 + \zeta_i^1.$$

The intercept $\pi_i{}^0$ is fixed by $\gamma_0{}^0$, which is the average of ISImean-Log_2 over all participants plus a (within-subject) variance $\zeta_i{}^0$ that is specific for each participant. The slope $\pi_i{}^1$ is fixed by $\gamma_0{}^1$, which is the average change per trial, plus a variance $\zeta_i{}^1$ that is specific for each participant. Taken together, the basis model with random effects and slopes is:

$$Y_{ik} = \gamma_0^0 + \gamma_0^1 Trial_{ik} + \left(\zeta_i^0 + \zeta_i^1 Trial_{ik} + \in_{ik}\right),$$

$$with \quad \in_{ik} \sim N\left(0,\ \sigma_\in^2\right) \ and$$

$$\begin{bmatrix} \zeta_i^0 \\ \zeta_i^1 \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{vmatrix} \sigma_{\zeta^0}^2 & \sigma_{\zeta^{01}}^2 \\ \sigma_{\zeta^{01}}^2 & \sigma_{\zeta^1}^2 \end{vmatrix}\right).$$

Under the same logic, Condition (termed *modality* in the model) is added to the first level because the conditions change with trial, differently for each subject. TUG, SDMT, and Learned (Yes, No) are then added covariates at level 2.

The final model

We tested several model variants using a leave-one-out cross-validation, and the best model was the one with a skew_normal link function. As Group had no effect, we excluded it from the model. Expressed in lme4 syntax, the final model is characterized as:

$$\text{ISImean-}Log_2 \sim 1 + (\text{Learned} + \text{TUG} + \text{SDMT})$$

$$*(\text{Condition} + \text{Trial}) + (1 + (\text{Learned}$$

$$+ \text{TUG} + \text{SDMT}) * \text{Trial}|\text{Participant}).$$

The operational model code can be found in Supplementary Information File S2 (online only). The above analyses were performed using R (RStudio, PBC, Boston), applying a Bayesian modeling in the Stan computational framework (http://mc-stan.org/) and assessed using the R-package brms.[54,55] The models were diagnosed with posterior-prediction checks, revealing that the distribution of the original data of Learned and ISImean was approximated by the models (the illustrating of this approximation is included in Supplementary Information File S2, online only).

Results

Participants

In total, 31 PwMS and 30 HC were included in the study (Fig. 1). There were no significant differences between groups in terms of demographics or cognitive functioning. Differences were found in terms of motor functions, fatigue, and depression in the direction of higher impairment levels in the PwMS, as shown in Table 1. Within our patient sample, seven PwMS were classified as cognitively impaired in accordance to the categorization of Fischer *et al.*[56]

Descriptive and subjective experimental measures

The number of times that participants observed the sequences and executed it during the learning protocol did not significantly differ between conditions or groups, as shown in Table 2. Significant differences between groups were present in almost all the answers rated on the VAS in all conditions as shown in detail in Table 3. No statistical differences for subjective ratings were found between conditions and groups.

Primary outcomes

Cognitive performance. Within Group, more HCs learned the sequence in the melody condition, compared to all other conditions as seen in Figure 3A.

Motor performance. *Main effects of Group (PwMS, HC).* No effect of Group was found.

Main effects of TUG and SDMT. The model revealed that TUG had 93.11% of its posterior probability mass above zero, which means that TUG was a highly significant contributor to taking longer step times (slower performance with increasing TUG). The model revealed that SDMT had 53.71% of its posterior probability mass above zero, which means

Table 1. Descriptive information of study participants

Descriptive information	PwMS ($n = 31$)	HC ($n = 30$)	t ratio	P value
Demographic				
Age (years)	46.91 ± 11.6	48.87 ± 12.83	$t(58.5) = -0.62$	Not significant
Gender (M:F)	13:19	12:18	$\chi^2(1, n=62) = 0.003$[a]	Not significant
Height (centimeters)	171.38 ± 8.43	171.27 ± 8.33	$t(59.8) = 0.05$	Not significant
Weight (kilograms)	79.31 ± 18.84	73 ± 12.33	$t(53.8) = 1.57$	Not significant
Education (years)	16.48 ± 2.28	17.53 ± 2.74	N/A	Not significant
MS specific				
Type of MS (RR:SP:PP)	24:4:3	N/A	N/A	N/A
EDSS	Range: 0.5-6.5 Median: 4 25%, 75% quartile: 3, 5	N/A	N/A	N/A
Years since diagnosis	11.81 ± 9.06	N/A	N/A	N/A
Motor function				
TUG (seconds)	8.74 ± 1.85	6.38 ± 1.16	$t(52.6) = 6.06$	<0.0001
T25FWT (meters)	5.99 ± 1.11	4.41 ± 0.91	$t(55.8) = 6.18$	<0.0001
6MWT (meters)	446.30 ± 92.75	602.93 ± 67.47	$t(54.8) = -7.56$	<0.0001
FSST (seconds)	11.23 ± 5.35	6.93 ± 1.77	$t(38.1) = 4.30$	<0.0001
MiniBEST (total number)	20.59 ± 4.96	27.07 ± 1.46	$t(36.7) = -7.07$	<0.0001
DGI (total number)	18.97 ± 4.08	23.90 ± 0.40	$t(31.6) = -6.81$	<0.0001
Cognitive function				
Buschke LTS (a.u.)	40.48 ± 14.29	45.24 ± 12.66	$t(48.4) = -1.29$	Not significant
Buschke CLTR (a.u.)	31.19 ± 15.40	36.28 ± 14.14	$t(51.0) = -1.27$	Not significant
Buschke Delayed (a.u.)	8.65 ± 2.62	9.34 ± 2.55	$t(52.0) = -0.99$	Not significant
7/24 SRT 1-5 (a.u.)	31.57 ± 4.07	30.48 ± 5.32	$t(52.5) = 0.88$	Not significant
7/24 SRT B (a.u.)	4.64 ± 1.66	5.03 ± 2.01	$t(53.7) = -0.80$	Not significant
7/24 SRT A6 (a.u.)	5.82 ± 1.74	6.13 ± 1.55	$t(53.8) = -0.72$	Not significant
7/24 SRT A7 (a.u.)	6.14 ± 1.51	6.28 ± 1.41	$t(54.4) = -0.34$	Not significant
WLG (a.u.)	33.52 ± 9.6	36.0 ± 10.01	$t(48.2) = -0.89$	Not significant
PASAT (a.u.)	44.57 ± 12.59	47.59 ± 8.45	$t(51.0) = -1.07$	Not significant
SDMT (a.u.)	57.41 ± 15.49	62.45 ± 11.63	$t(48.1) = -1.37$	Not significant
Stroop interference (seconds)	30.18 ± 15.04	24.93 ± 10.73	$t(48.7) = 1.51$	Not significant
Self-reported questionnaires				
MSWS-12 (100)	48.61 ± 25.68	N/A	N/A	N/A
FES (16–64)	32.76 ± 9.77	19.93 ± 4.03	$t(38.6) = 6.65$	<0.0001
MFIS total score (84)	42.23 ± 15.71	16.59 ± 10.56	$t(50.9) = 7.38$	<0.0001
MFIS physical part (0–36)	19.63 ± 7.09	6.41 ± 5.55	$t(54.7) = 7.99$	<0.0001
MFIS cognitive part (0–40)	18.5 ± 8.15	8.31 ± 5.29	$t(50.0) = 5.71$	<0.0001
MFIS psychological (0–8)	4.1 ± 2.32	1.86 ± 1.64	$t(52.2) = 4.28$	0.0003
HADS total (0–42)	12.83 ± 6.56	7.93 ± 5.04	$t(54.4) = 3.24$	0.0022
HADS anxiety (0–21)	6.3 ± 2.85	4.97 ± 3.03	$t(57.8) = 1.75$	Not significant
HADS depression (0–21)	6.53 ± 4.26	2.97 ± 2.62	$t(48.2) = 3.91$	0.0003

[a] Chi-square test is conducted owing to the nature of the data.

PwMS, persons with multiple sclerosis; HC, healthy controls; M, male; F, female; RR, relapsing remitting; PP, primary progressive; SP, secondary progressive; EDSS, Expanded Disability Severity Scale; TUG, Timed Up and Go; T25FW, Time 25 Foot Walk; 6MWT, 6-Minute Walk Test; FSST, Four Square Step Test; miniBEST, mini Balance Evaluation System Test; DGI, Dynamic Gait Index; a.u., arbitrary units; Buschke LTS, Long-Term Storage; CLRT, Consistent Long-Term Retrieval; 7/24 SRT, Spatial Recall Test; WLG, Word List Generation; PASAT, Paced Auditory Serial Addition Test; SDMT, Symbol Digit Modality Test; MSWS-12, Multiple Sclerosis Walking Scale-12; FES, Falls Efficacy Scale; MFIS, Modified Fatigue Impact Scale; HADS, Hospital Anxiety and Depression Scale; N/A, not applicable.

Table 2. Number of times participants observed the sequences and executed it during the learning protocol, and the results of the statistical analysis

Experimental conditions	Learning process	Persons with multiple sclerosis				Healthy controls				Between condition and group statistics	Within condition, between group
		Mean	Median	25% quartile	75% quartile	Mean	Median	25% quartile	75% quartile		
Melody	Number of shows	3.3 ± 1.4	3	2	4	2.9 ± 1.3	3	2	3		
	Number of tries	11.4 ± 5.5	10	7	15.5	8.7 ± 5.1	7	5	11		ns
Sound	Number of shows	3.4 ± 1.7	3	2	4	2.6 ± 0.9	2	2	3		
	Number of tries	11.9 ± 6.9	10	7	14	9 ± 4.9	8	6	12.5	ns	ns
Visual	Number of shows	2.8 ± 1.1	3	2	4	2.8 ± 1.1	2	2	4		
	Number of tries	10.2 ± 4.4	9	7	12	9.7 ± 5	8	6	11		ns

that SDMT was not contributing to taking longer step times.

Significant interactions were found between Learned and Conditions. Learned (Yes)∗Condition (Melody) had 99.11% of its posterior probability mass below zero, which means that having learned the sequence was a significant contributor in taking shorter step times in the melody condition (faster performance). Learned (Yes)∗Condition (Sound) had 81.54% of its posterior probability mass below zero, which means that having learned the sequence was a weak contributor in taking shorter step times in the sound condition (faster performance).

Significant interactions were found between Learned and Trial. Learned (Yes)∗Trial had 98.68% of its posterior probability mass below zero, which means that having learned the sequence was a significant contributor in taking shorter step times over time (faster performance in subsequent trials).

Significant interactions were found between Condition and TUG and SDMT. TUG∗Condition (Melody) had 78.72% of its posterior probability mass below zero, which means that TUG was a very weak contributor to taking shorter step times during the melody condition (faster performance). TUG∗Condition (Sound) had 67.89% of its posterior probability mass above zero, which means that TUG was no real contributor to taking longer step times during the sound condition (slower performance). SDMT∗Condition (Melody) had 95.54% of its posterior probability mass above zero, which means that SDMT was a significant contributor to taking longer step times during the melody condition (slower performance). SDMT∗Condition (Sound) had 99.57% of its posterior probability mass above zero, which means that SDMT was a significant contributor to taking longer step times during the sound condition (slower performance).

Significant interactions were found between Trial and TUG and SDMT. TUG∗Trial had 58.72% of its posterior probability mass below 0, which means that TUG had no overall contribution in taking shorter step times over the three consecutive trails (i.e., over time). SDMT∗Trial had 93.28% of its posterior probability mass below 0, which means that SDMT had a significant contribution in taking shorter step times over the three consecutive trials (i.e., over time). Fitted parameters can be used to generate posterior predictions. Figure 3B and C thereby clarifies how the experimental conditions are estimated by TUG and SDMT. In addition, the model summary outputs can be found in Table 4.

Discussion

In this study, we investigated embodied learning on the AMPEL with a task consisting of learning a sequence through movement in PwMS compared to HCs, using visual and auditory (melodic and sound) feedback conditions.

The descriptive results showed that half of the PwMS and HCs recalled the sequence correctly without making any mistakes at the 15-min delayed recall time-point within the sound and visual

Table 3. Mean and standard deviation values on the subjective experience questions on the visual analog scale, ranging from 0 to 10, and the results of the statistical analysis

Subjective experience (visual analog scale 0−10)			Statistics	
	PwMS ($n = 31$)	HC ($n = 30$)	Group (P value)	Conditions (P value)
Melody				
Physical fatigue (pre)	4.32 ± 2.2	1.47 ± 1.87	<0.0001	
Mental fatigue (pre)	4.29 ± 2.62	2.5 ± 2.1	0.0086	
Physical fatigue (post)	4.81 ± 2.04	1.47 ± 1.80	<0.0001	
Mental fatigue (post)	5.13 ± 2.7	2.6 ± 2.27	0.0004	
Executing sequence (ease)	3.74 ± 2.39	1.07 ± 2.05	<0.0001	
Remembering sequence (ease)	5.45 ± 2.21	4.6 ± 2.51	ns	
Learning sequence (frustration)	4.53 ± 3.24	2.87 ± 2.43	0.0319	
Learning sequence (effort)	6 ± 2.59	4.13 ± 2.21	0.0037	
Performing sequence (effort)	3.77 ± 2.69	0.87 ± 1.85	<0.0001	
Sound				
Physical fatigue (pre)	4.13 ± 2.11	1.63 ± 1.87	<0.0001	
Mental fatigue (pre)	4.39 ± 2.63	2.4 ± 2.24	0.0028	
Physical fatigue (post)	4.55 ± 2.13	1.47 ± 1.66	<0.0001	
Mental fatigue (post)	4.9 ± 2.59	2.87 ± 2.22	0.0018	Not significant between conditions
Executing sequence (ease)	3.45 ± 2.26	0.9 ± 1.86	<0.0001	
Remembering sequence (ease)	5.55 ± 2.92	4.27 ± 2.27	0.0466	
Learning sequence (frustration)	4.81 ± 3.25	3.33 ± 2.82	ns	
Learning sequence (effort)	5.84 ± 2.96	4.17 ± 2.25	0.0194	
Performing sequence (effort)	3.23 ± 2.55	0.83 ± 1.78	<0.0001	
Visual				
Physical fatigue (pre)	4.16 ± 2.15	1.5 ± 1.94	<0.0001	
Mental fatigue (pre)	4.42 ± 2.86	2.5 ± 2.27	0.0066	
Physical fatigue (post)	4.45 ± 2.05	1.53 ± 1.85	<0.0001	
Mental fatigue (post)	4.84 ± 2.81	2.8 ± 2.04	0.0026	
Executing sequence (ease)	3.26 ± 2.11	0.93 ± 1.89	<0.0001	
Remembering sequence (ease)	5.23 ± 2.53	4.33 ± 2.02	ns	
Learning sequence (frustration)	4.19 ± 2.99	3.17 ± 2.48	ns	
Learning sequence (effort)	5.16 ± 2.56	4.23 ± 2.21	ns	
Performing sequence (effort)	3.29 ± 2.12	0.87 ± 1.78	<0.0001	

condition. However, within the melody condition, a higher percentage of HC (70%) recalled the sequence correctly. Notably, the number of times participants observed and performed the sequence during the learning phase of the protocol was not significantly different across groups and conditions. The result that more HC recalled the sequence correctly in the melody condition is thus not due to differences in the number of times participants observed or performed the sequence. This is in line with our hypothesis that the melodic structure would provide extra structural information—somewhat an anchor—to guide the learner. Yet, it is important to note that this difference was only seen in the HC, and not in PwMS. Objectively, at group level, there were no significant differences of the baseline cognitive functions between the groups, yet in our study sample, we did have seven cognitive impaired PwMS classified according to the categorization of Fischer *et al.*[56] Although one could consider attributing this difference to cognitive impairment, it is noteworthy to mention that the SDMT (although a measure of a specific cognitive domain) was not a factor in learning within melody condition only. In the attempt to further explain the difference between groups within the melody condition, two further considerations are discussed. First, at baseline, our sample of PwMS was more depressed than our HC, as reported by the depression subscale of the HADS.[50] This could be of

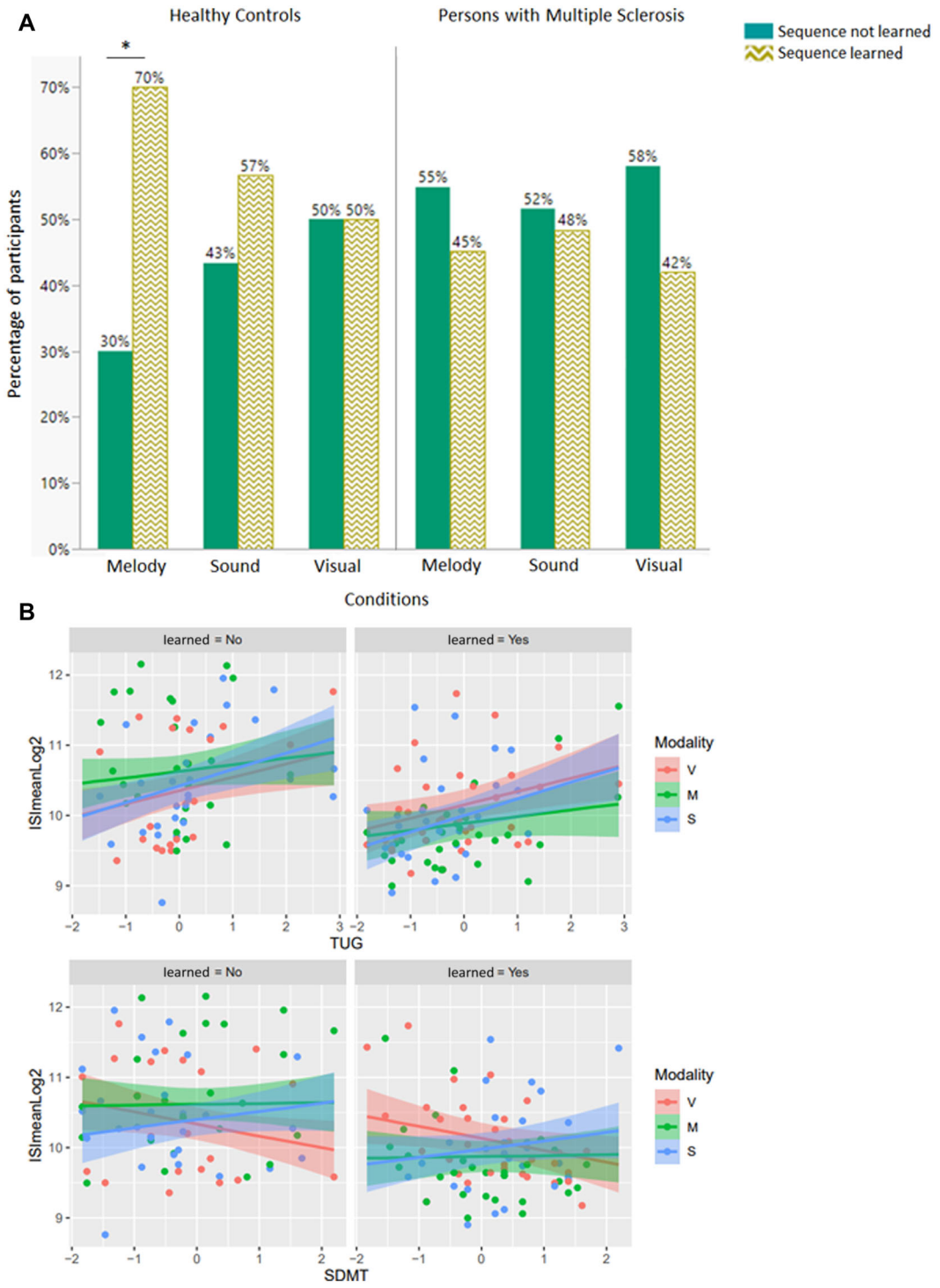

Figure 3. Experimental results. (A) The percentage of participants who learned and did not learn the per group within each condition. (B) The effect of experimental conditions on inter-step-interval mean (ISImean-Log_2) with covariates TUG and SDMT for participants who learned and did not learn the sequence, across the different conditions (V, visual, M, melody, S, sound). (C) The effects of the TUG and SDMT for participants who learned and did not learn across the three subsequent trials

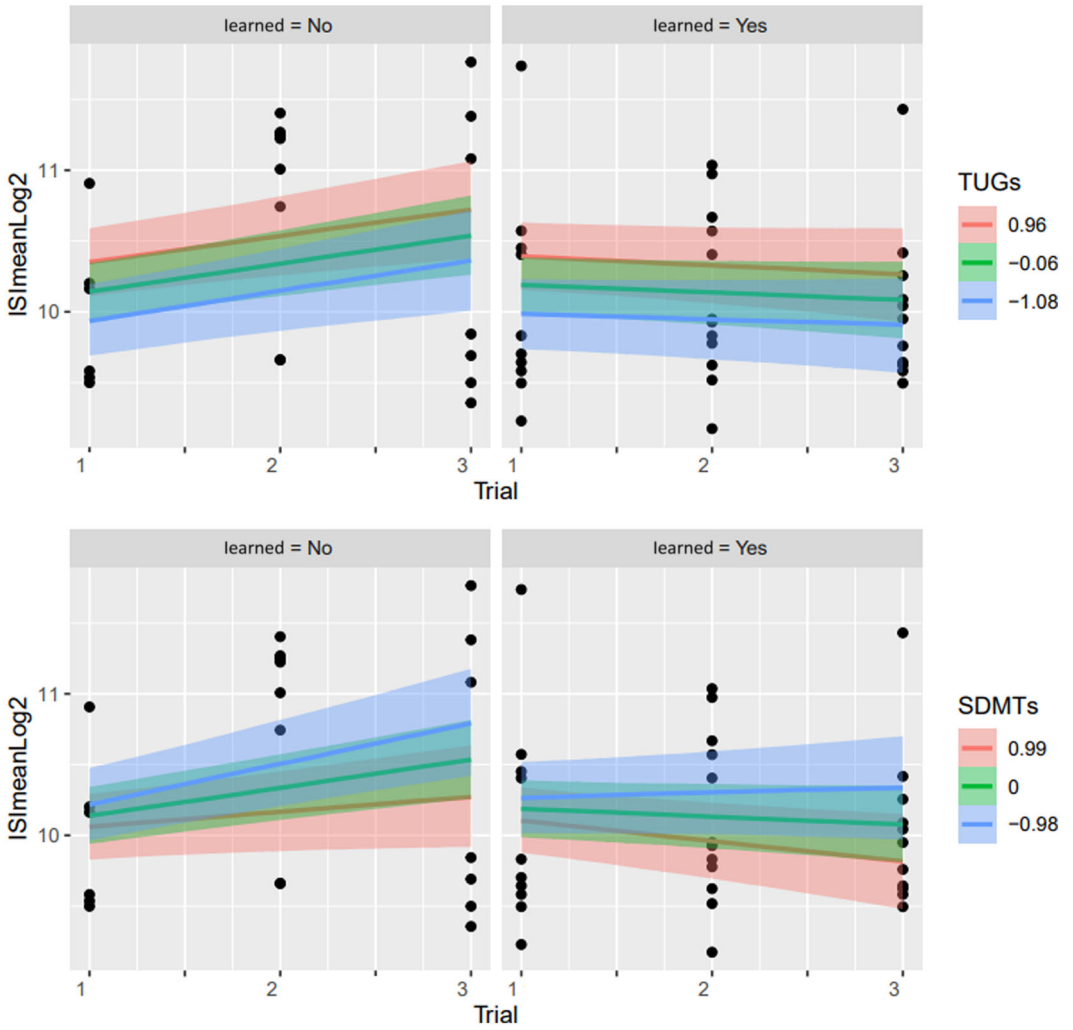

Figure 3. *Continued*

significance, given the assumption that learning could have been facilitated by the presence of melody. To elaborate, the melody—much like music—could have caused participants to have a higher emotional engagement and motivation and engage the mesolimbic dopaminergic system;[57,58] reward circuitries which have been shown to be associated to learning.[59] While expanding on the connections between reward circuitry and depression is out of the scope of this current study, exploring these connections in future dedicated paradigms is encouraged. The second consideration lies in the fact that our PwMS had motor impairments, and thus moved without a certain timing structure on the AMPEL. This could have affected their perception of the given melody. In other words, the melody was not perceived as such in this population.

When looking at the ISI mean duration and considering performance over time, participants who learned the sequence performed it with increasing speed over the three consecutive trials regardless of the condition. PwMS with higher balance impairments performed the recall slower than those with lower balance impairments, as was quantified by the TUG. This was irrespective of the ability to learn. In addition, when considering performance over time, TUG was found to be a very weak contributor

Table 4. The summary outputs of the fitted model on the response variable $\log_2$ ISI mean

Parameter	Median	89% Confidence interval	Probability direction	% in ROPE	R-hat	ESS
(Intercept)	9.96	[9.58, 10.34]	100%	0%	1	8984
Learned (Yes)	0.30	[−0.20, 0.78]	88.11%	12.63%	1	7346
TUG	0.21	[−0.08, 0.48]	93.11%	15.11%	1	7658
SDMT	0.01	[−0.27, 0.27]	53.71%	44.90%	1	7855
Condition melody	0.27	[−0.05, 0.58]	95.30%	9.47%	1	7335
Condition sound	0.06	[−0.25, 0.37]	64.48%	37.28%	1	7073
Trial	0.20	[0.03, 0.36]	99.11%	5.19%	1	7495
Learned (Yes): Condition melody	−0.53	[−0.96, −0.10]	99.21%	0	1	7452
Learned (Yes): Condition sound	−0.21	[−0.65, 0.26]	81.54%	18.46%	1	6859
Learned (Yes): Trial	−0.25	[−0.47, −0.03]	98.68%	3.87%	1	7671
TUG: Condition melody	−0.09	[−0.32, 0.13]	78.71%	40.21%	1	8650
TUG: Condition sound	0.05	[−0.15, 0.26]	67.89	50.99	1	10,489
TUG: Trials	−1.01	[−0.13, 0.11]	58.71	84.82%	1	9371
SDMT: Condition melody	0.18	[−0.03, 0.40]	95.54%	14.12%	1	9474
SDMT: Condition sound	0.29	[0.07, 0.50]	99.57%	0.72%	1	10,299
SDMT: Trial	−0.09	[−0.21, 0.03]	93.28%	39.71%	1	7777

to the sequence execution speed over the three consecutive trials regardless of the condition, indicating that balance impairment was not a predictor affecting the motor performance over time.

In addition, results showed that those who learned the sequence performed it faster to those who did not learn, and this result was significantly pronounced in the melody only. These findings could indicate that the melody condition implicitly imposed an isochronous tempo in performing and thus that participants had to move at a certain tempo for the melody to have been intelligible. In contrast to sound and visual conditions, the melody forms part of a larger feedback structure, which is both predictive and motivational, thus leading to more intelligibility, confidence, and satisfaction. In light of these results, one can propose that the melody condition could be superior to use for those PwMS with higher balance impairments given that TUG was found to be a very weak contributor in taking shorter steps only in this condition. This is an indication that balance impairment was not a predictor affecting motor performance during the melody condition. Using melodies that are very well known to the patients might help in establishing the effect.

Apart from balance, information processing speed as quantified by the SDMT was also found to be a highly significant contributor to the speed of sequence performance in the melody and sound conditions. An explanation for this result could be that the mapping used in the auditory conditions engaged information processing speed, which in turn affected step time. We did verify that the above explanation in the auditory conditions was purely affecting movement and was not influenced by whether the sequence was learned or not. When considering performance over time, the results show that the SDMT contributed significantly to increasing the speed of executing the sequence over the three consecutive trials regardless of the condition. Note that we did not have an equal distribution of high and low impairment of information processing speed in our study participants, as this was not the focus for the inclusion criteria. Future research is warranted in the context of embodied learning with the inclusion of participants with cognitive impairments.

Our embodied learning task was feasible and safe for PwMS, including those with balance impairments. Despite the observational nature of this study, we believe that our study offers ingredients suggesting possibilities for expanding the embodied framework toward a clinical training approach, with the capabilities of training the motor and cognitive systems as one functional unit.

The experimental task was designed in view of the embodiment theoretical framework, and

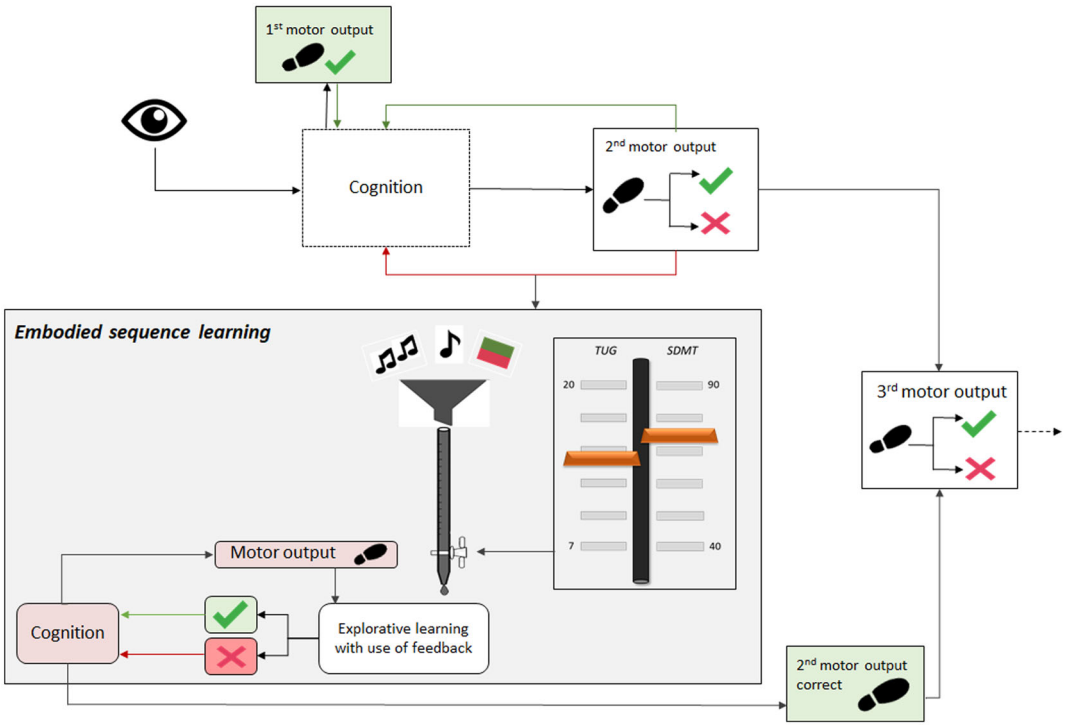

Figure 4. **A graphical illustration to explain the components of the experimental embodied learning task, and proposition to expanding the embodiment framework toward a clinical training approach, with the capabilities of training the motor and cognitive systems as one functional unit**

the performance of our participants was explained within this framework, as graphically illustrated in Figure 4. The goal of the task was to perform a series of seven steps three times correctly in a row. The task started by participants observing the sequence. We propose that once the sequence was observed, it engaged cognition. One can refer to the working memory model proposed by Baddeley[60,61] as participants attempt to commit the sequence to memory. Next, the task required to reproduce the sequence, by stepping on the tiles, thus engaging the motor system to execute the movement. Participants always performed the first step of the sequence correctly and received confirmation that the step was correct through feedback. This feedback is taken up back into cognition, while simultaneously, the motor system initiates another step to continue with the task at hand. When the second step is executed, feedback is received. The participant thus becomes aware whether the step is correct or incorrect and passes this information back into cognition. Accordingly, two possible scenarios can unfold: producing either a correct or an incorrect second step. If the second step is correct, this information becomes updated in cognition, meanwhile recalling and generating the third consecutive step. In the case of an incorrect second step, this information becomes updated in cognition and the participant now has the opportunity to use explorative learning, by finding the correct step using the feedback delivered through explorative stepping on the tiles.

Embodied learning assumes that the cognitive and motor systems must work as one functional unit to carry out the task. In other words, the feedback received upon a step must be registered and updated within cognition and processed, for a decision to be executed by the motor system, which in turn activates the receival of further information, which in turn is processed and tested once more via the motor system. One cannot exclude that motor learning is occurring as the motor system is engaged in testing the assumptions of the cognitive system, as well as verifying the information received from the feedback. This loop stops

once the correct step is performed, marking the third step of the sequence. From there, one would assume that these two scenarios would reoccur with every step—albeit perhaps with increased difficulty as one progresses with increasing sequence length—until the full sequence is performed three times correctly. Auditory and visual modalities can be used for feedback, but melodies imply a structure that binds the steps together, thus offering a superstructure in feedback and recall. Melody could facilitate the binding of actions in a sequence of actions, thus affecting both the motor and cognitive systems.

An additional factor that should not be neglected when performing this task is the extend of impairments which were present in the motor system in our PwMS. Overcoming such impairments in terms of ensuring movement control and stability could impose a certain amount of load. In other words, PwMS with balance impairments had to engage their motor system with each dynamic step, as well as cognitive control to maintain their balance and ensure safety, in addition to engaging these systems in embodied learning. In turn, one can argue that they needed to engage an additional layer of attention and control to ensure safe execution of the task. We argue that this process itself and within an embodied environment could be used to train cognitive control of movement during dynamic movements, and in turn be used to train learning. The learning can be limited to cognitive performance and may extend toward motor learning to target dynamic balance and coordination. Future studies are warranted to confirm our above proposed assumptions within a uniform selection of patients, for example, those with cognitive impairments and to expand our findings to an interventional study design. For example, to investigate the effect of multiple session training within an embodied context compared to motor, cognitive, or DT training on motor and/or cognitive functions.

Conclusion

Half of participants correctly recalled the sequence in all three conditions, while more HCs achieved correct recall within the melody condition. Balance impairment (TUG) predicted the speed of executing the sequence, where those with a higher balance impairment performed the sequence slower compared to those with a lower balance impairment. Yet, balance impairment was not a predictor for learning, indicating that all participants, irrespective of their balance impairments, had equal learning capabilities. This trend was most apparent in the melody condition, where PwMS with higher balance impairment performed the sequence faster compared to in the visual and sound condition. Information processing speed (SDMT) was a predictor effecting the speed of performing the sequence in the melody and sound conditions. Two overall trends on the motor performance were seen between learners and nonlearners. The first trend was those who learned the sequence performed it faster in the melody condition compared to those who did not learn. The second trend was those who learned the sequence performed it faster over the three consecutive trials (i.e., over time), regardless of the condition. In addition, over time, only the SDMT (and not the TUG) was found to be a significant predictor in increasing the speed of sequence performance. We engaged in a proposition of how embodied learning could expand the current context of rehabilitation of cognitive and motor control, to target symptoms of dynamic balance and coordination. This pilot work opens avenues for future proof-of-concept studies to investigate effects of using embodied learning as a training tool for cognition and motor functions in PwMS.

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Supporting information

Additional supporting information may be found in the online version of this article.

Supplementary information File S1. Familiarization check-list on the AMPEL.

Supplementary information File S2. The model specification and posterior-prediction checks.

Competing interests

The authors declare no competing interests.

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