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ORIGINAL ARTICLE

Motor imagery training promotes motor learning and brain plasticity without fatigability in people with progressive multiple sclerosis

Monica BIGGIO [1], Ludovico PEDULLÀ [2], Andrea ALBERGONI [3], Alice BELLOSTA [1], Andrea TACCHINO [2], Jessica PODDA [2], Laura BONZANO [1, 4], Laura AVANZINO [3, 4], Giampaolo BRICHETTO [2, 5], Marco BOVE [3, 4] *, Ambra BISIO [3]

[1]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics Maternal and Child Health, University of Genoa, Genoa, Italy; [2]Scientific Research Area, Italian Multiple Sclerosis Foundation, Genoa, Italy; [3]Department of Experimental Medicine, University of Genoa, Genoa, Italy; [4]IRCCS San Martino Polyclinic Hospital, Genoa, Italy; [5]AISM Rehabilitation Service, Italian Multiple Sclerosis Society, Genoa, Italy

*Corresponding author: Marco Bove, Department of Experimental Medicine, University of Genoa, viale Benedetto XV 3, 16132 Genoa, Italy.
E-mail: marco.bove@unige.it

ABSTRACT

BACKGROUND: Fatigability, defined as the activity-induced decline in performance, is common in people with multiple sclerosis (PwMS), particularly among those with progressive courses of the disease. There is a pressing need to focus on this population to identify the most appropriate rehabilitation strategies, tailored to individual characteristics, including their susceptibility to fatigability. A key objective is to develop new interventions that maximize therapeutic effectiveness while simultaneously reducing task-related fatigability.
AIM: This study investigated whether motor imagery training (MIT) could enhance motor learning and cortical plasticity without causing fatigability in progressive PwMS.
DESIGN: Randomized cross-over study.
SETTING: Outpatient clinics.
POPULATION: PwMS and healthy individuals.
METHODS: The study consisted of two experiments. Experiment 1 – Motor Training (MT): Both healthy individuals and people with multiple sclerosis (PwMS) performed motor training involving thumb-to-index opposition movements. The primary outcome was pinch strength. Secondary outcomes included finger-opposition movement rate, motor evoked potential (MEP) amplitude, and motor and cognitive Visual Analogue Scale (VAS) scores assessing fatigability. Experiment 2 investigated the effects of MIT, consisting of kinesthetically imagining thumb-to-index opposition movements, and Active Control using a cross-over design. Both groups (PwMS and healthy individuals) underwent these interven-tions in a controlled randomized order (using the RAND() function in Excel), with a one-week washout period between sessions to minimize carryover effects. Pinch strength was the primary outcome, while finger-opposition movement rate, MEP amplitude, the score of the trials mak-ing test, motor and cognitive VAS scores and the score evaluating MI ability were secondary outcome parameters. All outcome measures were assessed before, immediately after and 60 minutes after the training in both experiments.
RESULTS: MT improved motor performance and increased cortical excitability in healthy individuals, but not in PwMS, where it instead induced fatigability. Conversely, MIT enhanced motor learning and cortical plasticity in both groups without increasing fatigability. Notably, PwMS with lower motor fatigability showed greater motor learning gains.
CONCLUSIONS: MIT effectively promoted motor skill improvements and cortical plasticity without causing fatigability in progressive PwMS.

CLINICAL REHABILITATION IMPACT: These findings support MIT as a promising, low-fatigability strategy to complement traditional rehabilitation, helping to enhance motor function in progressive PwMS while minimizing fatigue-related barriers.

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KEY WORDS: Multiple sclerosis; Fatigue; Upper extremity; Rehabilitation.

Multiple sclerosis (MS) is a chronic disease characterized by motor and cognitive symptoms due to demyelination and axonal damage leading to loss of neuronal synchronization and functional disconnection among brain relays.[1] Moreover, fatigue is among the most commonly reported symptoms, affecting over 80% of people with MS (PwMS) and being perceived as highly disabling.[2] Although fatigue can be experienced throughout the course of MS, it has a higher prevalence in people with progressive courses of the disease,[3] which are characterized by gradual worsening of neurologic function and accumulation of disability over time.[4] To date, pharmacologic treatments to contrast the neurodegenerative process of progressive MS courses are limited and the main approach aiming at reducing the effects of disability relies on rehabilitation. For this reason, and in line with the International Progressive MS Alliance priorities,[5] research should focus on progressive courses to identify tailored rehabilitation treatments considering patient's fatigue status. In fact, while repetitive practice during a rehabilitation treatment improves motor performance over time, there is a point at which it also leads to fatigue and eventual deterioration in task performance.[6]

Fatigue has multiple dimensions, and the term is often used as a synonym for many fatigue-related aspects. It is important to distinguish between self-perceived fatigue, which is reported as a subjective feeling of physical, cognitive or psychosocial exhaustion and tiredness, and performance fatigability, which refers to a use-dependent decline in a demanding performance.[7] Another classification concerns the functional domain affected by fatigue/fatigability: namely, cognitive or physical/motor dimension.[8] Focusing on fatigability, the cognitive dimension consists of reduced performance on a cognitively demanding task, whereas physical/motor fatigability refers to the inability to sustain a prolonged activity.[9] Since rehabilitation could be particularly demanding, especially for progressive PwMS, an important goal would be to find new interventions that enhance the effectiveness of the rehabilitation treatment and, at the same time, reduce the fatigability associated with the task execution. In such a context, motor imagery (MI) could find its way into the rehabilitation journey of PwMS.

MI, *i.e.*, the mental rehearsal of movement without any overt motor output,[10] is a mental stimulation technique that has been shown to activate the sensorimotor system at cortical level without requiring the subject to move, and to promote motor learning and plasticity in healthy subjects.[11, 12] Based on this evidence, MI has been successfully used as an adjunct to motor practice during rehabilitation treatments in neurological patients with the aim to enhance re-learning.[13] Concerning the application of MI in PwMS,[14] recent studies have measured its effectiveness and established that MI reduces symptoms[15-17] and exerts a priming effect on action execution.[18] It should be noted that MI may be particularly indicated in patients suffering from fatigue and fatigability as it may limit the fatigability induced by physical training and boosts its effectiveness. In support of this, in healthy participants, one session of strength training based on MI alone or combined with physical practice was shown to not induce neuromuscular fatigability.[19] Another recent study provides a first hint concerning the beneficial effects of MI training in reducing the perceived fatigue as measured by the Modified Fatigue Impact Scale (MFIS) scale.[16] However, to date, studies on motor skill learning have not thoroughly explored the potential consequences of training in terms of fatigability in this population and it is currently unknown whether MI-based training induces motor and/or cognitive fatigability in both healthy adults and PwMS.

In the first experiment (Experiment 1), this study tested the effects of a motor training (MT) paradigm in progressive PwMS and healthy controls (HC). The aim was to evaluate the effects of MT on the motor performance (including strength and velocity), cortical excitability and perceived fatigability. The rationale is that, in progressive PwMS, interventions based on intensive MT could be excessively fatiguing, potentially worsening motor performance, inducing negative changes in cortical excitability, and increasing both motor and cognitive fatigability, thereby undermining the purpose of rehabilitation.

A second experiment (Experiment 2) evaluated the effects of motor imagery training (MIT), analyzing behavioral, neurophysiological, and cognitive effects before and after the intervention. The hypothesis was that, since MIT activates cortical and subcortical brain regions partially overlapping with those engaged during MT, but without requiring actual movement, it could enhance motor performance without increasing fatigability. Therefore, MIT may represent a valuable addition to conventional rehabilitation, which, by leveraging MI's effectiveness, could allow for the implementation of less demanding treatment protocols for patients. To test this, the effects of MIT were compared to those of an active control condition in which participants were engaged in a cognitive task, namely, reading.

Materials and methods

Study design

This study is composed by two experiments: Experiment 1 - Motor Training (MT) and Experiment 2 - MIT. The timeline of the experiments is represented in Figure 1A. Experiment 1 presents an experimental design with two groups of participants (HC and PwMS) performing one intervention (MT). Experiment 2 consists in a cross-over design with two groups of participants (HC and PwMS) performing two interventions (MIT and active control condition) in a controlled randomized order (using the RAND() function in Excel, which generated random numbers that were then used to sort and allocate subjects evenly), with a wash out period between them of 1 week. Randomization was performed by a researcher involved in the project, and participants were assigned to an intervention sequence during the initial visit, during which clinical assessments were conducted by the clinical staff. Participants were blinded to the intervention sequence; however, the researchers administering the interventions were not blinded to either the sequence or the group allocation of the participants.

In both experiments evaluations were performed in the same day of the intervention, before, immediately after and 60 minutes after the end of the intervention.

The recruitment was performed from January 2021 and December 2022.

The study was not registered because it did not involve a clinical trial or long-term rehabilitative interventions. Instead, it focused on the immediate behavioral and neurophysiological effects of brief, acute sessions, each lasting approximately 10 minutes.

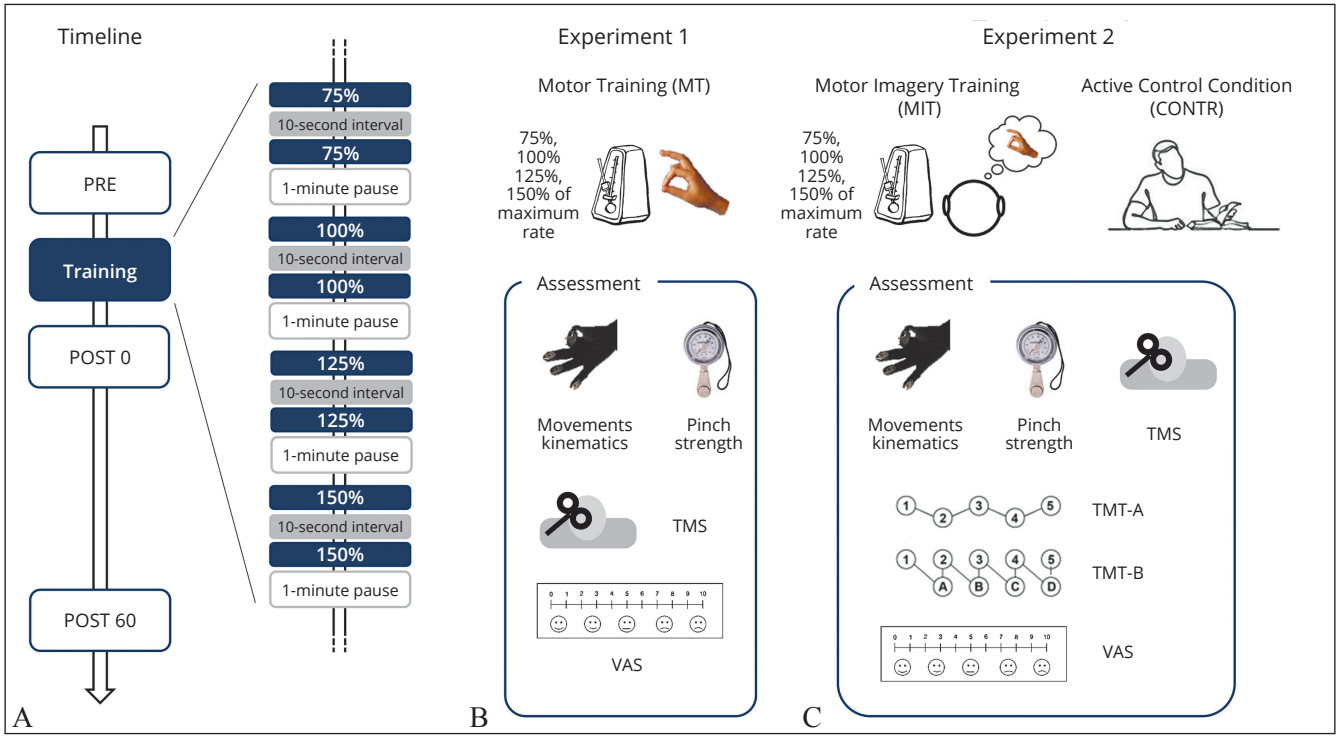

Figure 1.—Experimental paradigm. A) In both experiments assessments were made at baseline (PRE), immediately after (POST 0), and 60 minutes after (POST 60) the training. The timeline of the training conditions including movement phases, interval and pause is represented. B) During Experiment 1 participants performed a Motor Training (MT) paradigm in which they were required to perform a thumb-to-index opposition movement in synchrony with the sound of a metronome set to 75%, 100%, 125% and 150% of the previously determined maximum rate (100%). Motor assessments consisted of a thumb-to-index opposition movement at maximum rate and pinch strength. Neurophysiological assessments were performed using transcranial magnetic stimulation (TMS), which measured motor evoked potential and cortical silent period. People with multiple sclerosis were required to judge both motor and cognitive fatigability on a visual analogue scale (VAS). C) Experiment 2 consisted of two types of intervention: Motor Imagery Training (MIT) and Active Control Condition (CONTR). During MIT, participants were asked to kinesthetically imagine their hand performing a thumb-to-index opposition movement to a metronome-marked rhythm at 75%, 100%, 125%, and 150% of the previously determined maximum rate. During CONTR, participants had to read a short story. The assessments were the same as in Experiment 1 with the addition of the Trials Making Test (TMT A TMT and B).

Participants

All PwMS were followed as outpatients at the Italian MS Society (AISM) Rehabilitation Service Ligure in Genoa (Italy). The study was approved by the local ethical committee (Comitato Etico Regionale Liguria N. 338/2020, 21/01/2021) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki. Before starting the experiment, all participants gave their written informed consent.

Sample size calculation

Sample size was calculated using the pinch strength score as primary outcome considering data from a previous study[20] suggesting a difference of 1.9 ±1.2 kg in pinch strength score following a paradigm inducing fatigue in PwMS. Assuming similar levels of variability in our study, to have 90% power to detect a 1.9 kg difference in pinch strength as significant at the 1% (two-sided) level would require a minimum of 11 subjects per group. Given that the evaluation involved neurophysiological measurements using transcranial magnetic stimulation (TMS), which can yield particularly variable data, especially in the PwMS population, a larger number of participants than that required by the sample size calculation were recruited. Specifically, the target was at least 16 participants per group in both experiments.

Inclusion criteria and clinical evaluation

Clinical inclusion criteria were: 1) a diagnosis of (primary or secondary) progressive MS; 2) Mini Mental State Examination >24 to exclude people with severe cognitive dysfunction;[21] 3) lack of significant anxiety or depression levels as assessed by the Hospital Anxiety and Depression Scale (score <8 in each sub-scale); 4) a negative history for psychotropic drug use or significant co-morbidities including: non-MS neurological conditions and psychiatric disorders; and 5) MFIS score below 38.[22] All the included patients were evaluated with the following clinical scales: Expanded Disability Status Scale;[23] Nine Hole Peg Test;[24] MFIS to assess perceived fatigue;[25] Symbol Digit Modality Test to evaluate cognitive function.[26] Inclusion criteria for HC were: 1) Mini Mental State Examination > 24 to exclude people with severe cognitive dysfunction;[21] and 2) a negative history for psychotropic drug use, absence of neurological conditions and psychiatric disorders. For both groups, functional inclusion criteria were: 1) normal or corrected-to-normal vision; 2) preserved ability to correctly perform a finger-opposition movement task; 3) no major contraindication to TMS.

Experiment 1 - MT

The aim of this experiment was to evaluate the efficacy of a motor training paradigm in improving the motor performance and inducing motor cortical plasticity, and to test the fatigability associated to the task (Figure 1B).

Assessments

Assessment timepoints

Motor and neurophysiological assessments were conducted at baseline (PRE, before the intervention), immediately after (POST0), and 60 minutes post-training (POST60) in both groups (Figure 1A). Given that PwMS experience fatigability, they were also asked to self-report their perception of it.

Behavioral outcome measures – Motor assessment

The most affected side was chosen *a priori* for assessment and training, as it would be the primary focus of rehabilitation. In case of bilateral impairment and in HC the non-dominant side was selected. In the following, we will refer to this hand as the test hand.

The tri-pod pinch strength was the primary outcome of this experiment, and it has been assessed with an analog dynamometer (Baseline® Hand Evaluation Set, Fabrication Enterprises Inc., USA). A decrease in pinch strength is taken as an index of fatigability.

Moreover, finger-opposition movements kinematic parameters have been assessed. Participants were seated on a chair wearing a sensor-engineered glove (GAS, ETT S.r.l., Genoa, Italy) on their test hand.[27] An eye-close paradigm was adopted to avoid confounding effects due to visual input. A brief familiarization phase, consisting of two 30-second tasks involving thumb-to-index opposition movement at spontaneous rate, was performed by participants. To assess motor performance at baseline, participants executed a thumb-to-index opposition movement task at their maximal speed for two trials, 30 seconds each, with 1-minute rest. The average rate obtained from the two repetitions was considered as the individual maximum (100%) and used to set the training parameters. The same task was repeated in POST evaluation epochs to evaluate changes in motor performance. The rate (Hz) of thumb-to-index opposition movements was considered as outcome variable. Increased movement rate is interpreted as a result of motor learning,[28, 29] whilst decreased movement rate suggests that performance fatigability occurred.[30, 31]

Neurophysiological outcome measures – Primary motor cortex excitability

TMS was performed with a single Magstim 200[2] magnetic stimulator (Magstim® Company) connected with a figure-of-eight coil with wing diameters of 70 mm. The coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° angle to the sagittal plane inducing a postero-anterior current in the brain. The optimal position for the activation of the abductor pollicis brevis (APB) muscle was determined by moving the coil in 0.5 cm steps around the presumed hand motor area of the contralateral hand. Prior to the experimental procedure, the intensity of stimulation was individually defined to reliably elicit a peak-to-peak motor evoked potential (MEP) amplitude of approximately 0.8 mV in the APB muscle at rest. MEPs were recorded from the APB muscle using silver disc surface electrodes taped to the belly and tendon of the muscle. The ground electrode was placed at the elbow. Electromyographic signals (EMG) were digitalized, amplified, and filtered (20 Hz to 1 kHz) with a 1902 isolated pre-amplifier controlled by the Power 1401 acquisition interface (Cambridge Electronic Design Limited, Cambridge, UK), and stored on a personal computer for display and later offline data analysis. Each recording epoch lasted 400 ms, of which 100 ms preceded the TMS. Participants were constantly reminded to keep their hands relaxed during the whole experiment. The EMG signal was monitored visually by the experimenter and trials with background EMG activity were excluded from the analysis.

During the three evaluation epochs, 20 MEPs were recorded from the APB muscle at rest to assess changes in primary motor cortex excitability. To avoid participants' discomfort, TMS was not performed when the stimulation intensity to evoke a MEP amplitude at baseline of approximately 0.8 mV was greater than 80%. Increased MEP amplitude would suggest the occurrence of motor learning, whilst its decrease would be considered as a sign of central motor fatigability (*i.e.*, post-exercise depression).[30]

Fatigability outcome measures – Perception of fatigability

Motor and cognitive fatigability associated to the training procedures were assessed in PwMS through a visual analogue scale (VAS) where 0 indicated "not at all fatigued" and 10 indicated "extremely fatigued".

Intervention – Motor training protocol

MT consisted in performing thumb-to-index opposition movements and was chosen on the basis of a previous study showing that the proposed protocol induced motor learning and motor cortical plasticity in healthy subjects.[28]

From each participant's individual maximal finger movements rate obtained during PRE (see *Behavioral outcome measures – Motor assessment)*, hereafter referred to as 100%, three further target speeds were calculated, as a percentage of individual maximal finger movements rate: 75%, 125% and 150%. During training, participants sat on a chair and executed the thumb-to-index opposition movement tasks following the rhythm marked by a metronome, adjusted on the four percentages calculated before. At each target speed, participants completed two 20-second tasks, separated by a 10-second rest interval. The procedure began with two tasks at 75%, followed by two at 100%, two at 125%, and finally two at 150% of the individual maximal rate. After completing the two tasks at each target speed, a 1-minute pause was provided before proceeding to the next target speed. Starting at 75% of each participant's maximal speed also served to familiarize them with the task (Figure 1A).

Experiment 2 - MIT

The aim of this experiment was to test the efficacy of a training based on MI in improving the motor performance and inducing motor cortical plasticity without causing motor and/or cognitive fatigability. Results of MIT were compared with those of an active control condition (CONTR) (Figure 1C).

Assessments

Assessment of MI ability

The short version of the Kinesthetic and Visual Imagery Questionnaire (KVIQ-10) was administered to assess MI ability of PwMS and HC.[32] The short KVIQ is a questionnaire that assesses MI ability in relation to actions performed with both upper and lower limbs in healthy participants and individuals with sensorimotor impairments. It is a five-point ordinal scale that measures the clarity of the image (visual: V subscale) and the intensity of the sensations (kinesthetic: K subscale) that the subjects can imagine from the first-person perspective. Higher values correspond to a clearer motor image; lower values correspond to a weak mental image/sensation.

Motor and neurophysiological outcome measures

The same procedure described in Experiment 1 was adopted in Experiment 2 to perform the motor and neurophysiological assessments.

Cognitive outcome measures – Executive functions

Since MI relies on cognitive abilities, such as working memory,[33] MIT could negatively impact on cognitive performance due to the occurrence of cognitive fatigability. For this reason, executive function components such as working memory, inhibition control, and set-switching abilities were evaluated using the Trail Making Test A and B (TMT-A and TMT-B).[34] Both parts of the TMT consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the participant should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the participant draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (*i.e.*, 1-A-2-B-3-C, etc.). The participant was instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. The time to complete the test was recorded. The difference between the time to complete part A and B was calculated (TMT B-A, seconds), and data were corrected for age and education. An increase in TMT B–A after training suggests an increase in cognitive fatigability (excluding the influence of the motor output), whilst a decrease may be here interpreted as an effect of task learning than might occur in absence of cognitive fatigability.[35]

Fatigability outcome measures – Perception of fatigability

Motor and cognitive fatigability related to MIT and CONTR was assessed in PwMS in the same way as in Experiment 1, using VAS.

Interventions – MIT and active control condition

MIT

The training procedure was identical to that used in Experiment 1 (see Figure 1A) except that, during MIT, participants were instructed to kinesthetically imagine their test hand while executing a thumb-to-index opposition movement following the rhythm marked by a metronome. Kinesthetic MI involved the sensation of how it feels to perform the action, including the force and effort involved in movement, and spatial location.

Active control condition (CONTR)

During this condition, participants had to read a short story (the paragraph "*Concerning Hobbits*", prologue of "*The lord of the rings*" for about 8 minutes, which corresponds to the total duration of MIT. This represented the active control condition (Figure 1).

Statistical analysis

Shapiro-Wilk Test was applied to evaluate data distribution and Levene's test was used to evaluate the equality of variances. In the text, normally distributed data are reported as mean value±standard error (SE), while not-normally distributed data are given as median (interquartile range [IQR]). Significance level was set at 0.05 unless otherwise specified. Statistical analyses were performed with IBM SPSS Statistics 26 software.

Experiment 1

Pinch strength (kg) was considered as primary outcome, while finger-opposition movement rate (Hz), MEP amplitude (mV), motor and cognitive VAS scores were considered as secondary outcome parameters. Finger-opposition movement rate and MEP amplitude were normally distributed, whilst pinch strength and VAS scores were not. Normally distributed data were analyzed by means of repeated measure ANOVA with TIME (PRE, POST0, POST60) as within subject factor, and GROUP (PwMS, HC) as between subject factor. Significant main effects and interactions were interpreted with Bonferroni post hoc tests. Mann-Whitney Tests were applied to compare pinch strength between groups. Friedman tests, followed by post hoc, were applied to assess the effect of TIME within group on pinch strength, for both groups, and on VAS scores only in PwMS.

Experiment 2

Pinch strength (kg) was considered as primary outcome, while finger-opposition movement rate (Hz), MEP amplitude (mV), corrected TMT B-A scores, motor and cognitive VAS scores and KVIQ-10 score were considered as secondary outcome parameters. Finger-opposition movement rate and MEP amplitude were normally distributed, whilst pinch strength, TMT B-A, VAS scores and KVIQ-10 score were not. Normally distributed data were analyzed by repeated measures ANOVA with TIME (PRE, POST0, POST60) and TRAINING (2 levels: MIT and CONTR) as within subject factor, and GROUP (PwMS, HC) as between subject factor. Significant main effects and interactions were interpreted with Bonferroni post hoc tests.

Mann-Whitney Tests were applied to compare pinch strength, TMT B-A and KVIQ-10 scores between groups.

In order to avoid unwanted statistical comparisons that could affect the results of the analysis, the effect of TIME on TMT B-A was analyzed in each group using Wilcoxon tests, considering the following comparisons: MIT PRE *vs.* POST0/60, MIT POST0 *vs.* POST60, CONTR PRE *vs.* POST0/60, CONTR POST0 *vs.* POST60, MIT PRE vs. CONTR PRE, MIT POST0/60 *vs.* CONTR POST0/60. As there were 3 multiple comparisons for each data set, the Bonferroni correction was applied, and the new level of significant difference was P=0.05/3=0.017. The same method of analysis was adopted for VAS scores to evaluate the effect of TIME (PRE, POST0, POST60) and TRAINING (MIT and CONTR) on PwMS data.

In PwMS, an index of motor learning was computed using finger-opposition movement rate values as [(POST-PRE)/PRE*100] at both POSTs epochs, and changes in motor and cognitive fatigability were calculated as the difference between the POST and PRE VAS (deltaVAS=VAS_{POST} – VAS_{PRE}) in both POST0 and POST60. To assess the role of fatigability on motor learning in PwMS, Spearman correlations were calculated between the index of motor learning and deltaVAS at both POSTs epochs. Lastly, to evaluate the impact of imagery ability on motor learning, Spearman correlations between the index of motor learning and KVIQ score were performed in both POST0 and POST60.

Results

Demographic characteristics, handedness and MI ability of both groups, and clinical details of PwMS are provided in Table I.

Experiment 1

Twenty PwMS and twenty HC were screened for Experiment 1. Eighteen PwMS and seventeen HC met the inclusion criteria and accepted to take part to the experiment. They completed all parts of Experiment 1, except for the neurophysiological evaluation, which was completed by eleven PwMS and seventeen HC. There was no significant difference in age between groups (Table I).

TABLE I.—*Demographic characteristics, handedness and motor imagery ability (only in Experiment 2) of people with multiple sclerosis (PwMS) and healthy control participants (HC), together with clinical details of PwMS who participated in Experiment 1 – Motor learning (MT) and Experiment 2 – Motor imagery learning (MIT).*

	Experiment 1 - MT		Experiment 2 - MIT	
	PwMS (N.=18)	HC (N.=17)	PwMS (N.=21)	HC (N.=20)
Sex (W/M, %)	50.0/50.0	68.4/31.6	52.4/47.6	68.8/31.25
Age (years, mean, SD)	55.06±7.21	54.81±12.25	55.76±6.88	56.11±11.77
MS phenotype (PP or SP, N.)	PP: 4 SP: 14	---	PP: 4 SP: 17	---
EDSS (median, range)	6 (4.5 – 6.5)	---	6 (4.5 – 6.5)	---
Disease duration (years, mean±SD)	16.24±9.74	---	16.32±10.22	---
Handedness	R=17 L=1	R=17	R=20 L=1	R=20
Affected limb	R=5 L=9 Bilateral=4	---	R=7 L=9 Bilateral=5	---
MFIS total score (mean±SD)	30.71±3.85	---	36.19±3.53	---
KVIQ-10 score (median, IQR)	---	---	57 [44, 66]	76.5 [58.5, 85.5]

W: women; M: men; SD: standard deviation; IQR: interquartile range; PP: primary progressive course; SP: secondary progressive course; EDSS - Expanded Disability Status Scale; NHPT: nine-hole peg test; SDMT: symbol digit modality test; MFIS: modified fatigue impact scale; KVIQ - kinesthetic and Visual Imagery Questionnaire.

TABLE II.—*Experiment 1 – Motor training: numerical values of the outcome parameters of people with multiple sclerosis (PwMS) and healthy control participants (HC) evaluate before (PRE), immediately after (POST0) and 60 minutes after the end of the motor training. According to data distribution, data a given as mean value±standard error (SE), or median [interquartile range].*

	PwMS			HC		
	PRE	POST0	POST60	PRE	POST0	POST60
Movement rate (Hz)	3.46±0.18	3.42±0.18	3.44±0.2	4.26±0.19	4.6±0.18	4.64±0.2
Pinch strength (kg)	3.5 [2.68, 5.03]	3.25 [2.50, 4.81]	3 [2.49, 4.56]	3.30 [2.65, 3.87]	3.35 [2.77, 3.92]	3.35 [2.40, 3.85]
MEP amplitude (mV)	0.63±0.05	0.60±0.07	0.71±0.06	0.81±0.03	0.99±0.07	0.89±0.06
Motor VAS score	2 [1, 5]	5 [2.5, 7]	5 [2.35, 6.5]	---	---	---
Cognitive VAS score	2 [1, 4]	3 [2, 4]	3.5 [1,5]	---	---	---

VAS: Visual Analog Scale.

Numerical values of the primary and secondary outcome parameters are reported in Table II.

Behavioral outcome measures – Motor assessment

Results are represented in Figure 2A, B. Results of ANOVA on movement rate showed significant main effect of TIME ($F(2,66)=3.81$, $P=0.027$) and post hoc revealed a significant increase from PRE to POST0 and to POST60. Furthermore, a significant main effect of GROUP ($F(1,33)=17.25$, $P=0.0002$) was obtained indicating that PwMS' rate was significantly lower than those of HC. At last, a significant TIME*GROUP interaction ($F(2,66)=4.84$, $P=0.001$) emerged and the post hoc tests showed that, in HC, movement rate in POST0 and POST60 increased significantly with respect to PRE (always $P=0.001$). Such an increase was not observed in the PwMS group.

Mann-Whitney Tests comparing the pinch strength of PwMS and HC showed no significant difference between the groups. In PwMS, Friedman tests showed a significant effect of TIME ($\chi^2(2,18)=9.18$, $P=0.01$) and post hoc uncovered a significant reduction of pinch strength from PRE to POST60 ($P=0.014$). No changes in pinch strength were observed in HC.

Neurophysiological assessment – Primary motor cortical excitability

A significantly lower MEP amplitude was observed in PwMS with respect to HC (GROUP: $F(1,26)=13.81$,

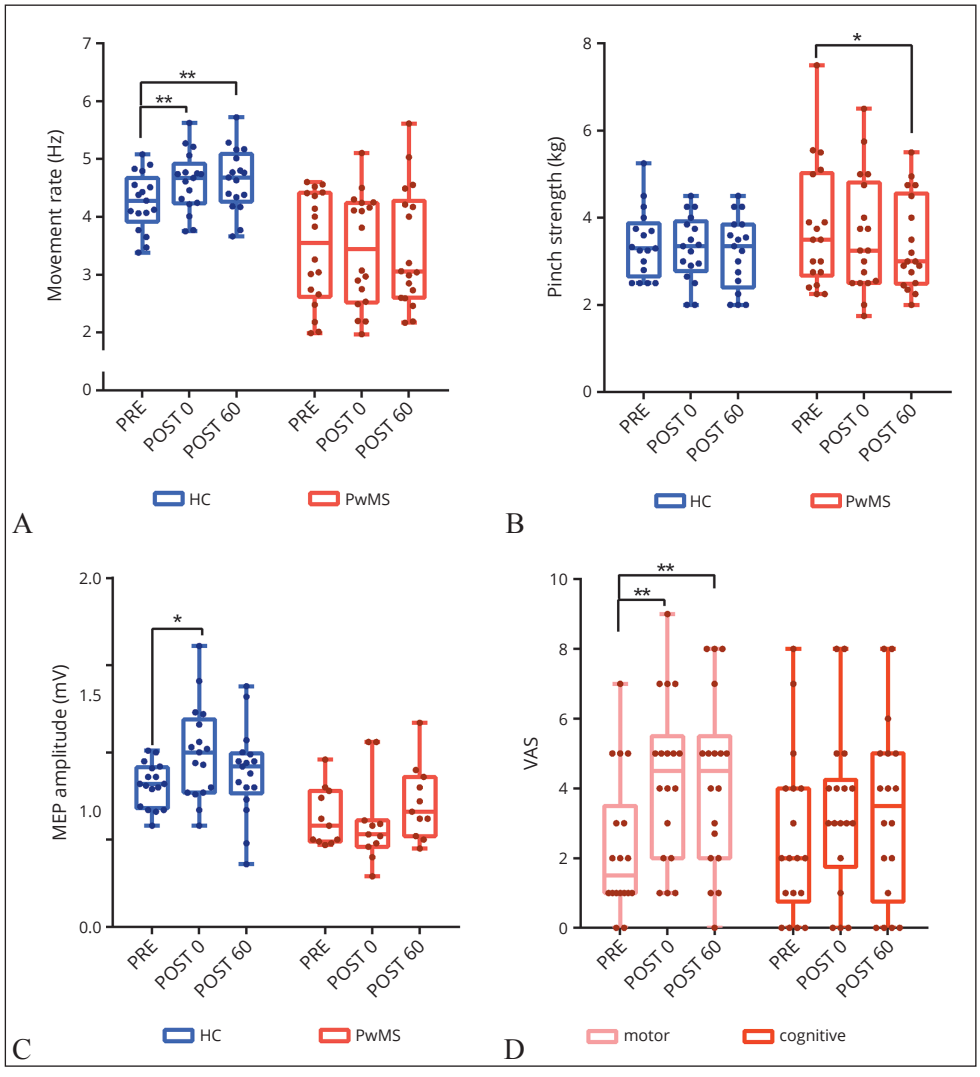

Figure 2.—Experiment 1: motor training. Results of the motor evaluations (A, B), neurophysiological assessments (C) and self-reported fatigability (D) before (PRE), immediately (POST 0) and 60 minutes (POST 60) after the end of the training. The box shows the interquartile range, with the horizontal line indicating the median values, the bars showing the maximum and the minimum values and the dots representing each participants' data. *P<0.05; **P<0.01 (A-C) The color codes the group: data from healthy control participants (HC) are shown in blue and data from people with multiple sclerosis (PwMS) are shown in red. (d) Visual analogue scale (VAS) score reported for motor (light red) and cognitive (dark red) fatigability by PwMS.

P=0.001). Furthermore, the significant interaction TIME*GROUP (F(2,52)=4.12, P=0.02) indicated that, in HC, MEP amplitude significantly increased from PRE to POST0 (P=0.013), whilst no changes occurred in PwMS. Data are shown in Figure 2C.

Fatigability outcome measures – Perception of fatigability

The statistical analysis on motor VAS scores reported by PwMS showed a significant effect of TIME (χ^2(2,18)=20.77, P=0.0003) and indicated a significant increase in motor fatigability from PRE to POST0 (P=0.001) and POST60 (P=0.003). No significant effect of MT was observed in cognitive fatigability (cognitive VAS score). The motor and cognitive VAS scores obtained in the PwMS group are represented in Figure 2D.

Experiment 2

Since Experiment 2 required two sessions, we initially screened a higher number of participants than in Experiment 1, namely twenty-two PwMS and twenty-two HC to account for potential dropouts between sessions. Twenty-one PwMS and twenty-one HC met the inclusion criteria. Ultimately, twenty-one PwMS and twenty HC completed all parts of Experiment 2, except for the neurophysiological evaluation, which was completed by fourteen PwMS and twenty HC.

There was no significant difference in age between groups (Table I).

The results of the statistical analysis on KVIQ-10 scores showed that HC had significantly higher scores than PwMS (Z=2.86, P=0.004). Numerical values of the outcome parameter are reported in Table III.

Behavioral outcome measures – Motor assessment

Pinch strength changed neither after MIT nor after CONTR in both groups.

The results of the statistical analysis on movement rate showed a significant main effect of GROUP (F(1,39)=30.13, P<0.0001), indicating that movement rate was significantly lower in the PwMS than in the HC. A significant GROUP*TIME*TRAINING interaction was found (F(2,78)=3.75, P=0.028). In PwMS, after MIT, a significant increase of movement rate was observed (P=0.027). However, at POST60, the movement rate of PwMS returned to its initial values (POST0 vs POST60: P=0.004). In HC, after MIT, movement rate significantly increased from PRE to POST0 (P=0.04) and POST60 (P=0.02). No changes in the movement of both groups were observed after CONTR. Results are shown in Figure 3A.

Cognitive outcome measures – Executive functions

Mann-Whitney test evaluating TMT B-A did not find any significant effect of the factor GROUP. In PwMS, Wilcoxon tests found a significant decrease in TMT B-A from PRE to POST60 in MIT (P=0.013). In HC, a significant decrease in TMT B-A from PRE to POST60 was observed after both MIT (P=0.006) and CONTR (P=0.001) (Figure 3B).

Neurophysiological assessment – Primary motor cortex excitability

ANOVA on MEP amplitude showed a significant main effect of TIME (F(2,62)=6.78, P=0.002), indicating a significant increase in MEP amplitude values (PRE vs. POST0: P=0.0006; PRE vs. POST60: P=0.03). No main effect of GROUP was found. Furthermore, the significant

TABLE III.—*Experiment 2: Motor imagery training: numerical values of the outcome parameters of people with multiple sclerosis (PwMS) and healthy control participants (HC) evaluate before (PRE), immediately after (POST0) and 60 minutes after the end of the motor imagery training (MIT) and active control condition (CONT). According to data distribution, data a given as mean value±standard error (SE), or median [interquartile range].*

	PwMS						HC					
	MIT			CONTR			MIT			CONTR		
	Pre	Post0	Post60	Pre	Post0	Post60	Pre	Post0	Post60	Pre	Post0	Post60
Movement rate (Hz)	3.44±0.14	3.63±0.14	3.33±0.16	3.40±0.19	3.32±0.20	3.39±0.17	4.53±0.14	4.75±0.15	4.78±0.16	4.48±0.19	4.59±0.20	4.55±0.17
Pinch strength (kg)	3.00 [2.50, 4.62]	3.25 [2.47, 4.42]	3.25 [2.32, 4.70]	3.09 [2.22, 4.87]	3.20 [2.40, 4.62]	3.06 [2.37, 4.50]	3.37 [2.77, 4.50]	3.41 [2.64,3.97]	3.25 [2.51,4.09]	3.05 [2.56,4.47]	3.12 [2.77, 3.94]	3 [2.50,3.60]
TMT B-A duration (s)	15.76 [7.1, 37.9]	8.91 [-6.02, 26.79]	7.88 [0.25, 20.67]	21.59 [2.27, 45.31]	13.41 [5.76, 36.70]	7.78 [-5.35, 40.47]	9.68 [-13.11, 38.34]	5.39 [-7.25, 27.83]	5.53 [-14.92, 25.48]	15.47 [-9.93, 38.89]	12.88 [1.73, 27.17]	7.71 [-13.1, 27.27]
MEP amplitude (mV)	0.70±0.05	0.83±0.10	0.82±0.09	0.81±0.09	0.79±0.09	0.81±0.10	0.76±0.05	1.02±0.09	0.92±0.06	0.81±0.03	0.85±0.05	0.80±0.06
Motor VAS score	5 [1, 6]	5 [3, 7]	5 [3, 6]	2 [1, 5]	3 [2, 6]	4 [2, 6]	---	---	---	---	---	---
Cognitive VAS score	2 [1, 5]	3 [2, 6]	3 [2, 6]	3 [1, 5]	3 [2, 5]	3 [2, 5]	---	---	---	---	---	---

TMT: Trial Making Test, VAS: Visual Analog Scale.

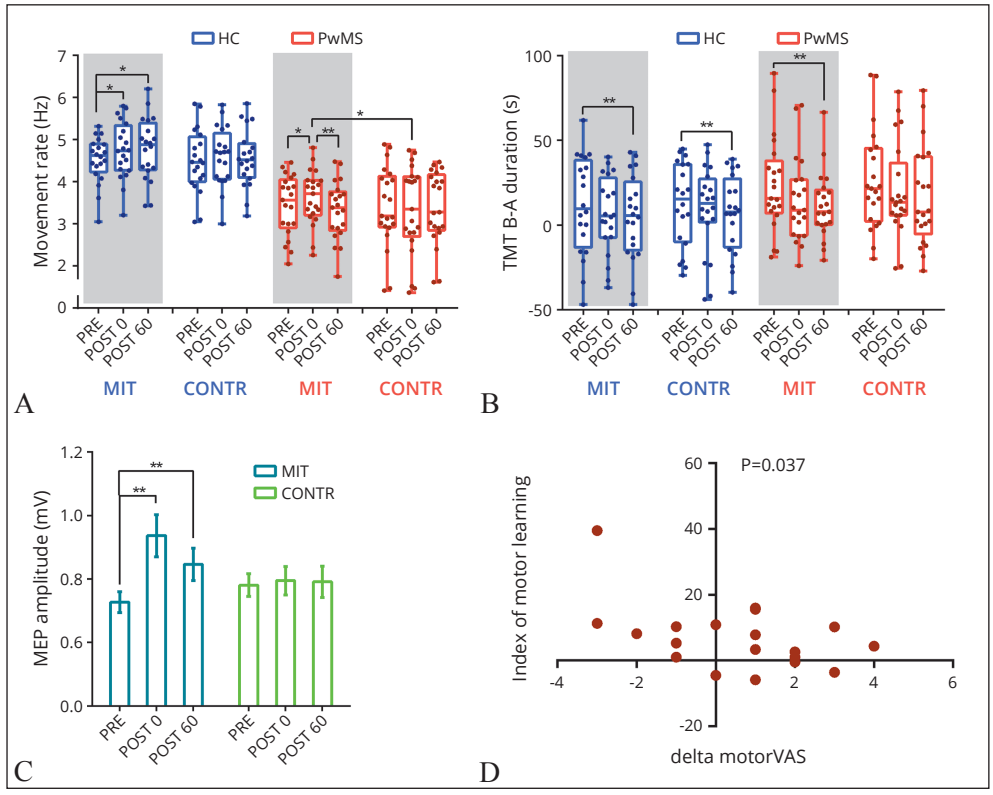

Figure 3.—Experiment 2: motor imagery training. A) The movement rate and (B) the difference between the time to complete the trial-making test B and A, before (PRE), immediately (POST 0) and 60 minutes (POST 60) after the end of the training conditions (motor imagery training: MIT, control condition: CONTR), are shown with different colors that code the group: data from healthy control participants (HC) are shown in blue and data from people with multiple sclerosis (PwMS) are shown in red. The box shows the interquartile range, with the horizontal line indicating the median values, the bars showing the maximum and the minimum values and the dots representing each participants' data. C) Motor evoked potential amplitude (mean±standard error value) in the training condition (light blue: MIT, green: CONTR) resulting from the significant TIME*TRAINING interaction. Panel (d) displays the relationship between the index of motor learning and the changes in the perception of fatigability from PRE to POST 0 assessed with motor VAS. *P<0.05; **P<0.01.

TIME*TRAINING interaction (F(2,62)=6.87, P=0.002) indicated that the significant MEP amplitude increment pertained only MIT and not CONTR. Indeed, only in MIT, post hoc tests showed a significant increase of MEP amplitude from PRE (0.73±0.03 mV) to POST0 (0.94±0.07 mV, P=0.0001) and to POST60 (0.85±0.05 mV, P=0.008). Results are represented in Figure 3C.

Fatigability outcome measures – Perception of fatigability

No changes in motor and cognitive VAS scores were observed after both MIT and CONTR in PwMS self-reported evaluations.

In PwMS, Spearman analysis revealed a significant negative correlation between the index of motor learning and the changes in motor VAS score at POST0 (ρ(21)=-0.46, P=0.037), suggesting that patients who benefited from MIT were those who reported less motor fatigability immediately after the training (Figure 3D).

Discussion

The results of Experiment 1 showed that MT was not effective in increasing movement rate in the PwMS group, whereas the increase was observed in HC. In PwMS, motor learning failure was associated with a decline in pinch strength from PRE to POST60, an increase in self-reported motor fatigability (reflected by higher motor VAS scores from PRE to POST), and an absence of enhanced excitability in the primary motor cortex. In Experiment 2, different findings were observed following MIT. Both groups showed a significant increase in movement rate after MIT, but not after CONTR. Additionally, MEP amplitude was significantly higher, while motor and cognitive VAS scores remained unchanged. Finally, in PwMS, the motor learning index significantly correlated with motor VAS scores: higher indexes of motor learning were associated with lower increases in the motor VAS score.

Motor training did not result in motor learning in PwMS with progressive course

In this study, participants were asked to perform a thumb-opposition movement at maximal velocity before and after an auditory-guided motor training, which consisting of moving faster and faster. In healthy participants, behavioral data revealed an improvement in motor performance, as indicated by an increase in movement rate. These find-

ings align with those previously described by Bonassi *et al.*,[28] whose study inspired the current training protocol, confirming its effectiveness in enhancing the motor performance of healthy adults. No changes in pinch strength were observed, suggesting that motor fatigability did not occur in this population.[36] Looking at the neurophysiological data, a significant increase of MEP amplitude was observed immediately after the end of the training (POST0) in agreement with Bonassi *et al.*[28] and also with other researches showing a task-induced MEP facilitation after a short period of motor practice.[37]

Motor performance in PwMS did not improve after motor training as evidenced by the unchanged thumb-to-index opposition movement rate. The scientific literature has shown conflicting results regarding the efficacy of motor training paradigms in promoting motor learning in this population.[38-40] This variability might be partly explained by the varying methodology used to test motor learning. In the present study, PwMS were required to perform a manual dexterity task pushing themselves to the limit of their motor skills. Thus, this task might have been perceived as extremely difficult and fatiguing. The occurrence of motor fatigability was demonstrated both by the quantitative assessment of pinch strength, which was significantly lower at POST60 than at PRE, and by the self-reported evaluation of motor fatigability (*i.e.*, motor VAS scores), which increased significantly after motor training. Furthermore, no significant changes were observed in MEP amplitude. Although looking at the present results it is difficult to understand whether the origin of the fatigability is mainly due to central or peripheral mechanisms, it is presumable that fatigability referred by PwMS impairs motor learning. This aspect needs to be carefully considered when planning rehabilitative intervention.

MIT promoted motor learning in PwMS with progressive courses

Although with differences from physical practice, MIT has been shown to activate a neural network superimposed on that activated during movement execution, to improve motor performance, and to induce use-dependent plasticity in healthy individuals (for a review on this topic, see[41]). A further potential advantage of MIT is its ability to induce performance changes similar to actual movement execution, but without requiring repeated movement execution, thus potentially minimizing fatigability. In healthy adults this issue has been tackled by two studies which came up with opposing results. Rozand *et al.* compared one session of MIT with physical practice or physical practice combined with MIT, finding that MIT did not cause post-exercise depression and reduce force production.[19] In contrast, Nakashima *et al.* reported increased muscle and mental fatigability, along with decreased cortical excitability after MIT, similar to the effects observed following physical training.[42] The differences in the results of these studies might relay in the different features of the training protocols.

Based on the promising evidence on MIT effectiveness in promoting motor learning in healthy adults, several studies explored the efficacy of MIT as add-on therapy to conventional rehabilitation procedures in neurologic patients such as stroke[43] and Parkinson's disease patients,[44] showing encouraging results. The scientific literature on the effectiveness of MIT in the rehabilitation of people with MS is sparse compared to the aforementioned pathologies.[14] A quite recent mini-review suggested MIT as promising rehabilitation tool for reducing fatigue in PwMS.[45] MIT combined with rhythmic cues was shown to have a greater beneficial effect on walking, fatigue, and quality of life than MIT alone. However, some researchers pointed out limitations in using MIT in PwMS mainly related to disease severity, cognitive impairment and cognitive fatigue.[46, 47]

The present study has made a step forward in understanding the possibility of using MIT to improve motor performance and evoke cortical plasticity without causing motor and cognitive fatigability in progressive PwMS. The present results confirmed the effectiveness of MIT in improving the motor performance in both groups of participants, despite the reduced imagery ability of PwMS compared to HC. Indeed, a significant increase of movement rate was found immediately after MIT in both HC and PwMS, but not after the active control condition. A plausible explanation for the efficacy of MIT over MT is that MIT did not induce either cognitive or motor fatigability in PwMS, as suggested by the unchanged cognitive and motor VAS scores, whereas MT in Experiment 1 was shown to cause motor fatigability. The role of the self-reported motor fatigability in motor skill improvement is supported by the significant negative relationship between the index of motor learning and changes from PRE to POST0 in the motor VAS score; participants who improved their performance more were those who showed no increase, or even a decrease, in motor fatigability. Interestingly, cognitive fatigability also did not increase after MIT. In PwMS, this can be explicitly evinced from the cognitive VAS scores, which remained unchanged after MIT. Furthermore, the significant reduction in the difference between the time

taken to complete the TMT B and A in both groups may indicate the absence of cognitive fatigability. This test is one of the most widely used instruments measuring cognitive processing speed and cognitive control and a recent study showed a positive relationship with perceived fatigue in PwMS.[48] Thus, an increase in the TMT B-A score would be expected if cognitive fatigability were present. However, this was not observed in the present study, as the TMT B-A score significantly decreased from PRE to POST. This may reflect a learning effect, that would be unlikely in the presence of fatigability, therefore suggesting that cognitive fatigability did not occur.

Another element that may help explain the efficacy of MIT is the observation that pinch strength did not significantly change after either MIT or CONTR. In this context, pinch strength was used as a quantitative indicator of motor fatigability. We hypothesized that, in the presence of motor fatigability, pinch strength would decrease following the training. The absence of differences between PRE and POST 0 evaluations in Experiment 2 suggests that MIT did not induce motor fatigability, in contrast to what was observed after MT. This absence of motor fatigability may represent an additional factor supporting the efficacy of MIT in enhancing PwMS' kinematic motor performance.

In HC, the gain in movement rate was maintained at POST60, whereas in PwMS, it returned to baseline levels. This effect may be attributed to an impaired consolidation mechanism of the newly acquired temporal movement features in PwMS. Studies investigating consolidation after motor learning in PwMS have yielded mixed results.[49, 50] Future studies specifically focused on the different phases of motor learning and involving different kinds of paradigms are needed to unveil this issue.

Looking at the neurophysiological data, results showed a significant increase in MEP amplitude after MIT that lasted up to 60 minutes after the end of the training, and that was not observed in the active control condition. Statistical analysis showed no difference between groups, suggesting that MIT was successful in stimulating plasticity in the primary motor cortex even in PwMS, a result that may be due to the absence of motor fatigability.

The results in healthy adults are consistent with those of Rozand and colleagues,[19] while differing from those of Nakashima *et al.*[42] Nevertheless, it is quite difficult to compare the present training protocol with those used in both studies, as they proposed a strength training, whereas here the training focused on manual dexterity. Further research is therefore needed to understand how different types of training affect the results of MIT in terms of fatigability.

A final observation is that, although PwMS exhibited significantly lower MI ability compared to healthy participants, their performance still benefited from MIT. Several factors, such as cognitive impairment, cognitive fatigue, and disability, have been identified as potential contributors to the reduced MI ability observed in patients relative to controls.[51] Furthermore, it is worth noting that a previous study of our group on healthy individuals has shown that those with higher MI ability tend to experience greater performance improvements from MIT compared to those with lower MI ability.[37] Furthermore, studies involving athletes and PwMS have shown that imagery ability can improve following MIT.[52-54] Taken together, the present and previous findings suggest that, even when MI ability is not optimal, as in individuals with progressive PwMS, MIT can still lead to significant improvements in motor performance. Moreover, MIT may contribute to enhancing individuals' own MI ability, but further studies are needed to confirm this latter effect.

These findings may have important clinical implications. Incorporating MIT into standard rehabilitation protocols may be particularly beneficial for progressive PwMS, potentially due to its reduced physical demands and its ability to leverage neuroplasticity. Furthermore, since MI does not require physical movement, it could be seamlessly integrated into digital or remote rehabilitation programs. As highlighted by a recent review[55] a significant portion of MI-based interventions has been conducted as self-training at home with successful results, making it a cost-effective approach that could reduce healthcare expenses.

Limitations of the study

Nonetheless, this study has some limitations. First, although the sample size meets the required threshold, the number of participants remains relatively small. Therefore, further research is needed to confirm these findings in a larger cohort. Additionally, the movement used in this study does not reflect typical daily activities. It would thus be valuable to replicate these results using more ecological tasks, as this would better demonstrate the effectiveness of MIT in real-world contexts.

Conclusions

This study is the first to show improved motor skills and induction of cortical plasticity through MIT without inducing motor or cognitive fatigability in progressive PwMS.

However, its effectiveness varied with self-reported motor fatigability. Therefore, these results are promising for the use of MI as an effective adjunct to rehabilitation for progressive PwMS who do not report fatigability associated with it. A preliminary assessment of MIT's impact on fatigability is recommended before starting a rehabilitation program that includes it.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Ambra Bisio, Ludovico Pedullà, and Marco Bove: conceptualization; Monica Biggio, Ludovico Pedullà, Andrea Albergoni, Alice Bellosta: data acquisition; Monica Biggio, Andrea Albergoni, Ludovico Pedullà, Alice Bellosta, Ambra Bisio: data curation; Ludovico Pedullà, Ambra Bisio, Monica Biggio: Formal analysis; Ambra Bisio: funding acquisition; Andrea Tacchino, Jessica Podda, Laura Bonzano, Laura Avanzino, Giampaolo Brichetto, Marco Bove, Ambra Bisio: methodology; Monica Biggio, Ludovico Pedullà, Laura Bonzano, Marco Bove: visualization; Monica Biggio, Ludovico Pedullà, Ambra Bisio: writing – original draft; Andrea Albergoni, Andrea Tacchino, Jessica Podda, Giampaolo Brichetto, Laura Avanzino, Laura Bonzano, Marco Bove: writing – review and editing. All authors have seen and approved the final version of the manuscript being submitted. All authors read and approved the final version of the manuscript.

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