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Preservation of motor skill learning in patients with multiple sclerosis

Valentina Tomassini[1,2], Heidi Johansen-Berg[1], Laura Leonardi[2], Luis Paixão[1], Saad Jbabdi[1], Jackie Palace[1], Carlo Pozzilli[2] and Paul M Matthews[1,3,4]

Abstract

Background: Several studies have demonstrated benefits of rehabilitation in multiple sclerosis (MS). However, the neuroscientific foundations for rehabilitation in MS are poorly established.

Objectives: As rehabilitation and motor learning share similar mechanisms of brain plasticity, we test whether the dynamics of skill learning are preserved in MS patients relative to controls.

Methods: MS patients and controls learned a repeating sequence of hand movements and were assessed for short-term learning. Long-term learning was tested in another cohort of patients and controls practising the same sequence daily for two weeks.

Results: Despite differences in baseline performance, the dynamics and extent of improvements were comparable between MS and control groups for both the short- and long-term learning. Even the most severely damaged patients were capable of performance improvements of similar magnitude to that seen in controls. After one week of training patients performed as well as the controls at baseline.

Conclusions: Mechanisms for short- and long-term plasticity may compensate for impaired functional connectivity in MS to mediate behavioural improvements. Future studies are needed to define the neurobiological substrates of this plasticity and the extent to which mechanisms of plasticity in patients may be distinct from those used for motor learning in controls.

Keywords

multiple sclerosis, disability, MRI, motor learning, brain plasticity, recovery, rehabilitation

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Introduction

Several studies have demonstrated a beneficial role for rehabilitation in recovery in patients with multiple sclerosis (MS) at different stages of the disease.[1] However, while supporting the efficacy of rehabilitation interventions, these studies highlight the paucity of evidence underpinning current practice,[2] underline methodological challenges of randomized controlled trials for rehabilitation[3] and identify the need for more scientifically informed studies in the area of restorative neurology.[4,5]

Rehabilitation-driven recovery involves changes in brain function and structure.[6,7] Spontaneous recovery after brain injury or rehabilitation is mediated by multiple mechanisms of brain plasticity (i.e. the ability of the brain to adapt to environmental changes or injury through changes in its function and structure).[8] Some of these mechanisms also mediate motor adaptation and learning in the healthy brain.[8,9] During the learning of new skills, cortical regions associated with sensorimotor function of the body parts most utilized for the skilled task are represented over larger cortical

[1]Oxford Centre for Functional MRI of the Brain (FMRIB), Department of Clinical Neurology, University of Oxford, Oxford, UK.
[2]Department of Neurological Sciences, 'La Sapienza' University, Rome, Italy.
[3]GSK Clinical Imaging Centre, Hammersmith Hospital, London, UK.
[4]Department of Clinical Neuroscience, Imperial College, London, UK.

Corresponding author:
Dr Valentina Tomassini, FMRIB Centre, The University of Oxford, Dept of Clinical Neurology, John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU, UK
Email: valentt@fmrib.ox.ac.uk

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territories.[8] Learning-related brain plasticity, therefore, should provide insights into mechanisms of clinical recovery after damage that are modulated through rehabilitation.[10]

Studies in MS have tested aspects of motor learning and demonstrated improvements in upper limb performance,[11,12] gait[13,14] or head control[15] during variable lengths of training (from minutes to a few days of practice). These studies suggest that the ability of MS patients to learn motor skills is preserved in the early phases of the disease,[11]but may be impaired progressively with higher levels of disability,[12] especially when a complex integration of sensory information is required.[12] If disease progression is associated with progressive impairment of the potential for adaptation and learning, benefits of rehabilitation are expected to diminish as MS disability increases. Alternatively, if plasticity remains relatively unimpaired despite progression of pathology, patients may be expected to derive some benefits from skill training throughout the course of the disease. Distinguishing these possibilities has important implications for clinical resource allocation.

Here, we characterize the performance changes and time course of short- and long-term motor learning in MS patients and matched controls and assess the impact of disability and brain lesion load on motor skill learning. We hypothesized that, although MS pathology may affect baseline motor performance, mechanisms of brain plasticity elicited by learning and limiting disability[16–18] will compensate for this pathology, allowing for behavioural improvements to occur with practice. We predicted that the time courses of learning could reflect this process of compensation by showing a delay in performance improvements in patients as a consequence of impaired structural connectivity.[19] Our hypothesis was that increasing levels of disability reflecting greater tissue damage would be associated with a progressive failure of brain plastic mechanisms, smaller changes in performance and delayed learning.

Materials and methods

Participants

A total of 66 right-handed clinically definite MS patients and 35 healthy volunteers participated in this two-centre study. Two centres were used to enable more efficient recruitment. A single investigator (VT) supervised work at both centres to ensure comparable approaches were employed. Forty-three MS patients and 18 matched controls recruited prospectively at the MS Clinic of 'La Sapienza' University, Rome, Italy, took part in *experiment 1* (a cross-sectional study of short-term motor learning during a single testing session). Twenty-three MS patients and 12 matched controls recruited at the Department of Clinical Neurology, Oxford University, UK, participated in *experiment 2* (a longitudinal behavioural study of long-term motor learning over two weeks of home training). For patients of both experiment 1 and experiment 2, clinical disability was recorded at the beginning of the study and quantified by using the Expanded Disability Status Scale (EDSS)[20] score. Patients participating in experiment 2 also had their right arm/hand dexterity tested using the 9-Hole Peg (9-HP) test, which is part of the Multiple Sclerosis Functional Composite.[21] All subjects gave informed consent according to the protocol approved by the local research Ethics Committees.

Study design

Two phases of motor skill learning were assessed in separate experiments. Experiment 1 assessed short-term learning in patients and controls over 26 minutes of the learning task. In this cohort, we also tested for the effect of disability on short-term learning. Experiment 2 assessed long-term learning in a separate cohort of patients and controls who were given the equipment to practise the same task at home daily for at least 2 weeks.

Experimental set-up

An isometric visuomotor tracking task was developed from a previously described visuomotor learning task.[22] In this modified version of the task, the handle has been designed to investigate the upper limb motor function in a more physiological semipronated position, which can be held comfortably. This new task has been tested successfully to investigate the functional and structural bases of normal motor learning[23] (Figure 1A). Subjects were asked to track the vertical movements of a computer-controlled bar (the target bar) displayed on a laptop screen by altering the amount of pressure applied to a hand-held plastic rod (with a diameter of 40 mm) containing a strain gauge located between its two halves. The maximum distance between the two halves of the rod was 5 mm. The arm was held in a semipronated position, supported by an armrest. The isometric force exerted by the subjects was represented in real-time on the computer screen by the height of a second bar representing grip pressure generated that was presented next to the target bar. The subject was asked to match the height of the pressure sensitive bar to that of the target bar. The target bar moved in a smooth oscillatory fashion with the amplitude or rate changing in either a repetitive (Sequence) or randomly varying (Random) fashion. Feedback on performance

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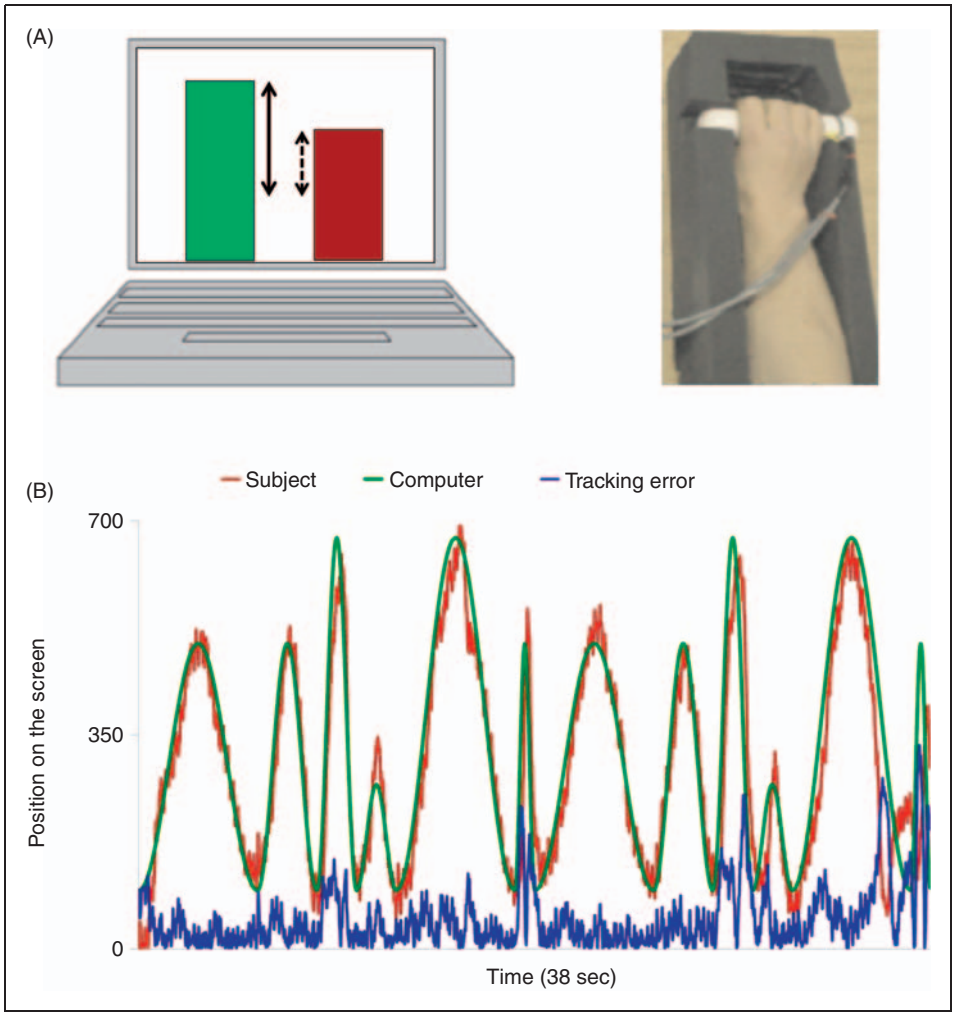

Figure 1. In this visuomotor tracking task[23] subjects were asked to track with their bar (red) the vertical movements of a computer-controlled bar (green) displayed on a screen (left) by altering the amount of pressure applied to a hand-held pressure sensor (right) (A). During a block of the Sequence condition, the subject (red line) performed two repeats of the sequence (green line). The absolute distance between the subject- and the computer-controlled bar at any time point represented the tracking error (blue line) (B).

was provided by the colour of the subject's bar changing from red to blue when the difference between the heights of the two bars fell below 10 mm (40 pixels). Instructions on the task were standardized between subjects and across centres.

Experiment 1 (short-term learning)

The experiment was implemented as a 'block' design with three conditions: Sequence, Random and Rest. During each of the 38-second Sequence blocks, subjects performed two repeats of the smoothly varying sequence (Figure 1B). In the Random blocks, subjects followed 38 seconds of pseudo-random sequence. The pseudo-random sequence was created by randomly permuting the amplitude and rate parameters of sinusoidal segments presented in the Sequence blocks. Random and Sequence conditions tested the acquisition of a skill alone (Random) or in combination with learning of a specific sequence of movements (Sequence). During the Rest blocks, subjects made no movements and were shown a newly generated random sequence of movements with random variation of the response bar to simulate subject performance. Rest blocks were designed to match the visual stimulation the Sequence and Random blocks and to prevent rehearsal of the sequence. At the beginning of each block a word ('Sequence', 'Random' or 'Rest') was presented for one second to indicate the condition that would follow. Ten blocks of each condition were performed, giving a total experimental duration of about 26 minutes. Subjects had a practice session before the start of

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the experiment, with two blocks of random sequences, to ensure that they fully understood the task.

Experiment 2 (long-term learning)

The experiment required participants to perform 10 blocks of the Sequence condition only at home once per day for 15 days. Each daily session lasted about 13 minutes. Before commencing with home training, participants in experiment 2 practised the short-term version of the task (as for experiment 1) during a single imaging session. Those short-term data will not be considered here due to potential confounds of comparing behavioural data collected in different testing environments.

Measures of learning

Experiment 1 (short-term learning). We recorded the tracking error (defined as the distance between the target bar and the pressure-sensing bar) (Figure 1B) throughout the experiment at a frequency of 30 Hz (half the screen refresh rate). The 90th percentile (p_{90}) of the absolute tracking error for Sequence and Random conditions was chosen as a summary measure of error across each block in each subject. This was expected to reduce over time with learning.

Short-term learning was quantified by a reduction of the p_{90} over 10 blocks of Sequence or Random. In each subject we used the slope of the individual tracking error changes over 10 blocks of Sequence or Random as a measure of the *rate of short-term learning*. We also calculated the mean tracking error across blocks to represent the *overall motor performance* for Sequence or Random. We considered the difference between mean tracking error in block 1 vs. block 10 as the *overall motor improvement* in Sequence or Random.

Experiment 2 (long-term learning). For each subject, the mean across blocks of the tracking error during each day of the home Sequence practice represented the daily *overall motor performance*, which was tested for changes over two weeks and quantified the long-term learning. The *rate of long-term learning* was summarized in each subject by the slope of the individual learning curve over 15 days. The difference between mean tracking error in day 1 vs. day 15 represented the *overall motor improvement* with long-term practice.

Structural MRI acquisition and analysis

Patients of experiment 2 underwent a structural MRI scan on a 1.5 Tesla Siemens Sonata scanner, with maximum gradient strength of 40 $mT \cdot m^{-1}$. A T1-weighted 3D FLASH sequence ($TR = 12$ ms, $TE = 5.65$ ms, flip angle $= 19^\circ$, with elliptical sampling of k space, giving a voxel size of 1 mm × 1 mm × 1 mm) and a turbo spin echo sequence ($TR = 3000$ ms, $TE = 22/87$ ms, $FOV = 256$ mm, slice thickness 3 mm, giving proton density and T2-weighted images) were acquired. Hyperintense lesions on proton density images and hypointense lesions on T1-weighted images were identified to quantify the T2-lesion volume (T2-LV) and T1-lesion volume (T1-LV), respectively. Lesion identification and volume calculation was performed using a semi-automated segmentation software (Jim, Xinapse Systems, UK, http://www.xinapse.com) by a researcher (LP) blind to the behavioural assessments of the study.

Statistical analysis

Individual right arm/hand dexterity was quantified by averaging two consecutive trials of the 9-HP test.

Between-group differences in disability scores were calculated using the Mann–Whitney test.

In the short-term, changes in mean tracking error were tested by using repeated measures ANOVA with group (controls, patients) or subgroups (controls, patients with EDSS <4.0, patients with EDSS ≥ 4.0) as between-subject factor, and block (1 to 10) and condition (Sequence, Random) as within-subject factors.

To test the effect of increasing disability on rate of learning, overall motor performance or overall motor improvement in the short-term univariate analysis of variance was used separately for the two experimental conditions, with subgroups (controls, patients with EDSS <4.0, patients with EDSS ≥ 4.0) as the fixed factor, and slope of tracking error changes, overall motor performance or difference between block 1 and block 10 for Sequence or Random as dependent variables. To correct for multiple comparisons, we first tested for equality of error variances in the three subgroups using Levene's test. Then, we applied Bonferroni correction to assess the significance of between-group differences.

Relationships between baseline characteristics (age, disability, T2-LV and T1-LV) and short- or long-term behavioural measures (overall motor performance and learning slope) were assessed using Spearman correlation, which is relatively robust to the effects of potential outliers and sensitive to any monotonic association among variables.[24] Spearman correlation was also used to test the relationships between short-term measures of learning (mean tracking error block 1 vs. block 10, and mean tracking error block 1 vs. slope), and between day 1 of home training and long-term learning changes (mean tracking error day 1 vs. day 15, and mean tracking error day 1 vs. slope).

The two-tailed unpaired t-test was used to test for significant between-group difference in the mean age,

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disability, days of practice and rate of long-term learning. The paired *t*-test was used to assess within group changes in mean error of block 1 vs. block 10, as well as of day 1 vs. day 15 representing the overall motor improvement in the short-term and in the long-term, respectively.

Repeated measures ANOVA was used to assess changes in the daily mean tracking error during home practice, with group as between-subject factor and days of practice as within-subject factor.

For all the statistical tests, differences were considered significant at the $p < 0.05$ level, two-tailed. Values are quoted as mean ± standard error (SE) unless stated otherwise.

Results

Demographic and clinical characteristics

Experiment 1 (short-term learning) included 43 patients (26 females, age 44.0 ± 1.37 years, disease duration 12.5 ± 1.3 years, median EDSS 4.0, range 1.0–7.5) and 18 age- and sex-matched controls (8 females, age 41.9 ± 3.50 years). Out of 43 patients, 23 were relapsing–remitting MS (RRMS) (16 females, age 40.0 ± 1.50 years; median EDSS 2.0, range 1.0–5.5) and 20 secondary-progressive MS (SPMS) (10 females, age 48.6 ± 2.0 years; median EDSS 6.0, range 3.5–7.5). There was a significant difference between RRMS and SPMS patients in EDSS score ($U = 23.500$, $N_1 = 23$, $N_2 = 20$, $p < 0.0001$).

Experiment 2 (long-term learning) studied 23 patients (18 females, age 45.1 ± 1.8 years; disease duration 12.0 ± 1.5 years; median EDSS 4.0, range 0–7.0) and 12 matched controls (9 females, age 43.1 ± 2.6 years). Out of the 23 patients, four had SPMS.

The patient groups in the two experiments did not differ in age ($p = 0.61$) or EDSS score ($p = 0.79$). Patients participating in experiment 2 had less right arm/hand dexterity than did matched healthy controls (controls, mean ± SE 18.2 ± 0.5 s; patients, mean ± SE 25.3 ± 3.1 s, $p < 0.04$).

Short-term motor skill learning (experiment 1)

Overall, patients showed significantly greater mean tracking error across conditions than did the matched healthy controls (controls, 105.7 ± 13.3; patients, 155.5 ± 8.6; $p < 0.004$). This between-group difference was evident in both the Sequence (controls, 104.9 ± 13.4; patients, 154.0 ± 8.7, $p < 0.004$) and Random (controls, 106.5 ± 13.3; patients, 157.1 ± 8.6, $p < 0.003$) conditions.

Repeated measures ANOVA showed a significant effect of block ($F = 15.4$, $df = 3.1$, $p < 0.0001$) and a significant block*condition interaction ($F = 3.1$, $df = 5.7$, $p < 0.008$), but no effect of condition ($F = 1.8$, $df = 1.0$, $p = 0.19$). No significant block*group interaction ($F = 1.0$, $df = 3.1$, $p = 0.41$) and no condition*group interaction ($F = 0.2$, $df = 1.0$, $p = 0.67$) was observed during 10 blocks of learning. The mean Sequence tracking error decreased more rapidly over the first two blocks of learning in controls (−23%) than in patients (−9%), although this difference was not statistically significant ($p = 0.24$).

Short-term training led to a significant reduction in mean tracking error in Sequence for both patients (191.8 ± 14.8 vs. 129.0 ± 7.3, $p < 0.0001$) and controls (154.9 ± 14.5 vs. 87.4 ± 8.3, $p < 0.0001$). Patients showed a significant reduction in mean tracking error in the Random condition (180.9 ± 15.2 vs. 139.7 ± 7.3, $p < 0.003$), whereas controls only showed a trend (126.7 ± 11.7 vs. 105.6 ± 15.8, $p = 0.098$).

Effect of disability on short-term motor skill learning (experiment 1). To assess the impact of disability on short-term learning we stratified the patient group on the basis of their disability levels, using 4.0 as the cut-off between the group with mild/moderate disability (EDSS < 4.0, 'low-EDSS' group) and the group with severe disability (EDSS ≥ 4.0, 'high-EDSS' group).

Univariate analysis showed a significant between group difference in the mean tracking error across blocks for Sequence ($F = 8.1$, $df = 2$, $p < 0.002$) and Random ($F = 8.8$, $df = 2$, $p < 0.0001$) conditions (Figure 2A). The 'high-EDSS' group had higher mean Sequence tracking error than the 'low-EDSS' group (169.5 ± 10.5 vs. 127.8 ± 13.7, $p = 0.056$). While the mean Sequence tracking error across blocks was significantly higher in the 'high-EDSS' group than in the control group (169.5 ± 10.5 vs. 104.9 ± 12.9, $p < 0.002$), low-EDSS patients did not differ significantly from the control group (127.8 ± 13.7 vs. 104.9 ± 12.9, $p = 0.68$). Similarly, patients with high EDSS had significantly higher mean tracking error across blocks in the Random condition than did patients with low EDSS (173.1 ± 10.4 vs. 130.1 ± 13.5, $p < 0.05$) or the matched healthy controls (173.1 ± 10.4 vs. 106.5 ± 12.7, $p < 0.0001$). Patients with low EDSS did not differ significantly in the Random condition from the control group (130.1 ± 13.5 vs. 106.5 ± 12.7, $p = 0.62$).

Results of repeated measures ANOVA testing for short-term learning in patients at different levels of disability are shown in Figure 2B. There was a significant effect of block ($F = 18.4$, $df = 3.0$, $p < 0.0001$) and a significant block*condition interaction ($F = 2.5$, $df = 2.5$, $p < 0.03$), but no effect of block*group interaction ($F = 0.78$, $df = 6.0$, $p = 0.59$). There was no effect of condition ($F = 2.3$, $df = 1.0$, $p = 0.14$) and no condition*group interaction ($F = 0.14$, $df = 2.0$, $p = 0.87$).

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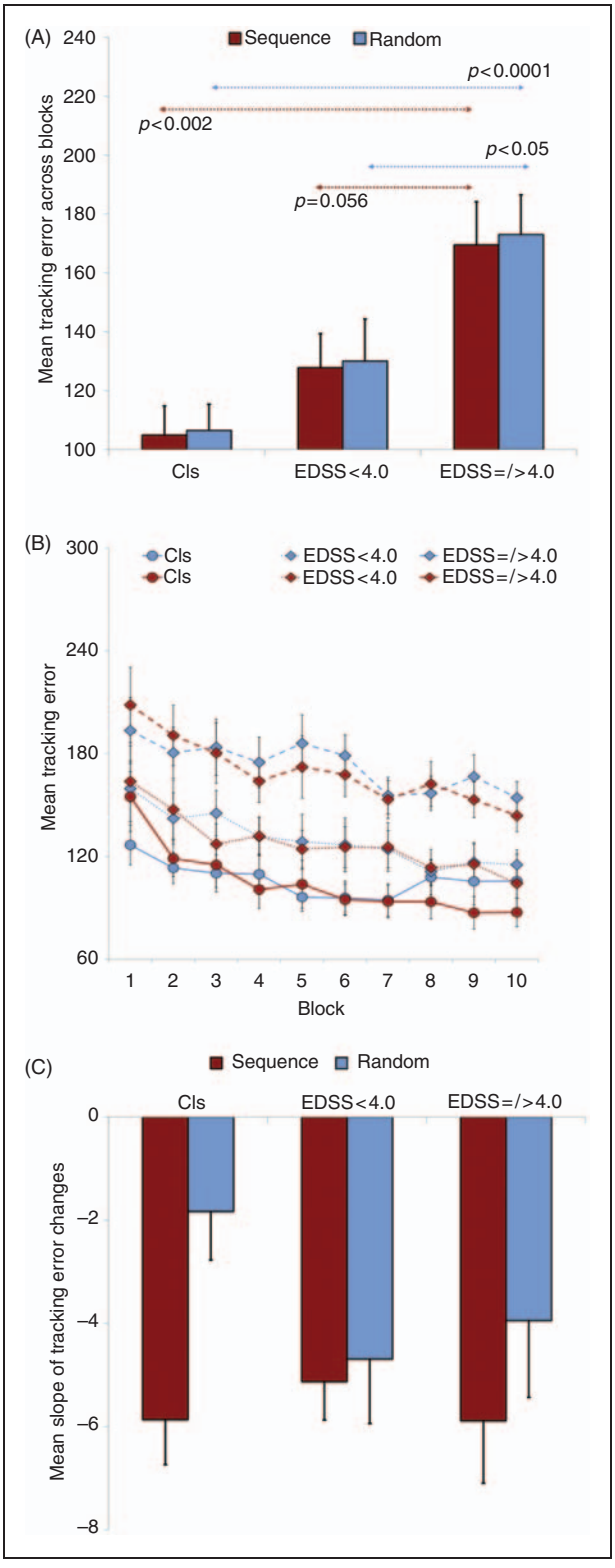

Figure 2. Overall motor performance in the short term (calculated as the mean tracking error across blocks) differed between patients with severe disability (Expanded Disability Status Scale (EDSS) $\geq$4.0, $n = 27$), patients with mild/moderate disability (EDSS $<$4.0, $n = 16$) and controls (CIs, $n = 18$) both in the Sequence and Random conditions. The 'high-EDSS' group had higher mean tracking error than the 'low-EDSS' group. While the mean tracking error across blocks was significantly higher in the 'high-EDSS' group than in the control group, 'low-EDSS' group patients did not differ significantly from the control group (A). Mean tracking error was reduced during short-term learning with time courses and degree of reduction similar in controls, patients with EDSS $<$4.0 and patients with EDSS $\geq$4.0 for both Sequence (red) and Random (blue). Between condition differences in the dynamics of changes were preserved at higher levels of disability (B). The rate of short-term learning (and thus the overall motor improvement) did not differ significantly between the three groups for both the Sequence and Random conditions (C). Error bars represent standard errors for each condition within each group. *p* values are corrected for multiple comparisons (Bonferroni correction).

Univariate analysis showed that the rate of short-term learning (Figure 2C) as well as the overall motor improvement did not differ significantly between the three groups for either the Sequence (*rate of short-term learning*: controls, -5.9 ± 1.5; 'low-EDSS' group, -5.1 ± 1.6; 'high-EDSS' group, -5.9 ± 1.2, $F = 0.08$, $df = 2$, $p = 0.92$; *overall motor improvement*: controls, 67.5 ± 17.2; 'low-EDSS' group, 59.6 ± 18.2; 'high-EDSS' group, 64.6 ± 14.0, $F = 0.05$, $df = 2$, $p = 0.95$) or Random conditions (*rate of short-term learning*: controls, -1.8 ± 1.5; 'low-EDSS' group, -4.7 ± 1.5; 'high-EDSS' group, -3.9 ± 1.2, $F = 1.02$, $df = 2$, $p = 0.37$; *overall motor improvement*: controls, 21.1 ± 17.7; 'low-EDSS' group, 44.5 ± 18.8; 'high-EDSS' group, 39.2 ± 14.5, $F = 0.48$, $df = 2$, $p = 0.62$).

Relationships between baseline demographic or clinical characteristics and short-term motor learning (experiment 1). There was no significant relationship between performance and age for the healthy controls in either condition (Sequence: rho $= 0.23$, $p = 0.36$; Random: rho $= 0.40$, $p = 0.10$), or for patients (Sequence: rho $= 0.25$, $p = 0.11$; Random: rho $= 0.23$, $p = 0.14$) when controlling for disease duration.

In the patient group, we found a significant correlation between disability score and mean tracking error across blocks for both the Sequence (rho $= 0.40$, $p < 0.009$) and Random (rho $= 0.42$, $p < 0.007$) conditions (Figures 3A and 3B, respectively). However, there was no correlation between disability score and rate of short-term motor skill learning for either the Sequence (rho $= -0.12$, $p = 0.45$) or Random conditions (rho $= 0.01$, $p = 0.95$).

Patients showed consistent relative performance throughout the short-term training period. The mean tracking error during block 1 correlated significantly with the mean tracking error during block 10 of both Sequence (rho $= 0.62$, $p < 0.0001$) and Random (rho $= 0.76$, $p < 0.0001$) conditions. This relationship held even when correcting for disability scores

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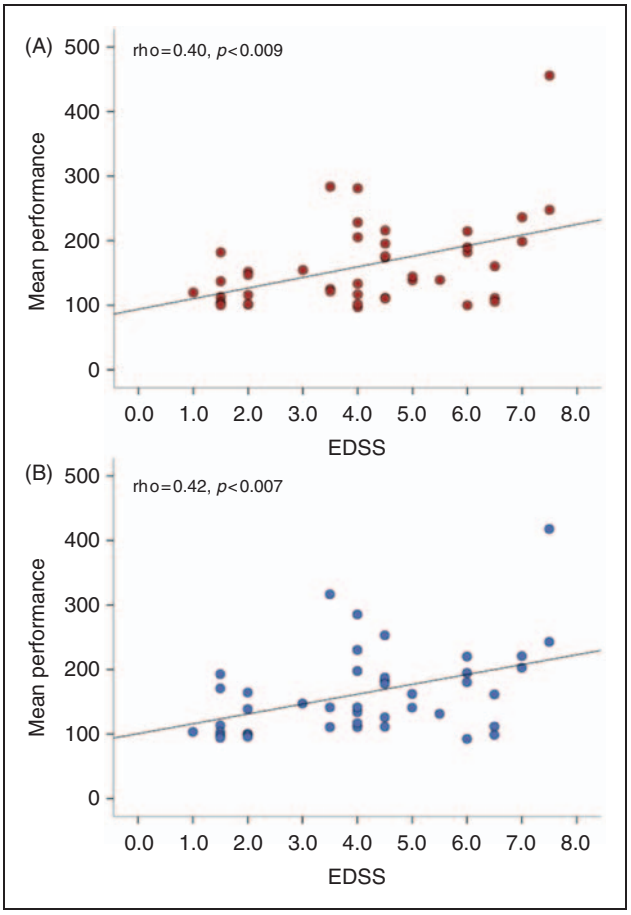

Figure 3. Relationship between Expanded Disability Status Scale (EDSS) score and overall motor performance (calculated as the mean tracking error across blocks) in experiment 1 (short-term study) for Sequence (A) and Random (B). In both conditions, there was a significant positive correlation between disability levels and overall motor performance, that is, worse performance was associated with higher disability levels. The significance of these correlations held after removing the extreme value (Sequence, rho = 0.45 $p = 0.002$; Random, rho = 0.37 $p = 0.02$).

in both Sequence (rho = 0.50, $p = 0.001$) and Random (rho = 0.52, $p < 0.0001$). By contrast, the controls did not show a significant correlation between tracking errors in block 1 and in block 10 for Sequence (rho = 0.40, $p = 0.10$) and for Random (rho = 0.17, $p = 0.50$).

There was a significant correlation between mean tracking error in block 1 of Sequence and the subsequent rate of short-term Sequence learning both in controls (rho = −0.81, $p < 0.0001$) and in patients (rho = −0.62, $p < 0.0001$). Similarly, both controls (rho = −0.52, $p < 0.03$) and patients (rho = −0.46, $p < 0.003$) showed a correlation between mean tracking error in block 1 of Random and the subsequent rate of short-term Random learning.

Long-term motor skill learning (experiment 2)

The mean number of days of training did not differ between patients and controls (controls, 17.3 ± 0.8; patients, 17.7 ± 0.7, $p = 0.64$). However, as the exact length of training differed between subjects (median days in controls 17 [range 13–21 days] and in patients 17 [range 9–24]), in the following analysis we assessed performance changes only over the first 15 days of practice. Two subjects were excluded from each group because they had fewer than 15 days of practice.

The mean tracking error across Sequence blocks during day 1 of home practice did not differ significantly between groups (controls, 61.5 ± 4.1; patients 68.8 ± 4.2, $p = 0.22$). Repeated measures ANOVA showed an effect of days of practice ($F = 12.5$, $df = 5.5$, $p < 0.0001$), but no days*group interaction ($F = 0.6$, $df = 5.5$, $p = 0.71$) (Figure 4A). There was no significant difference in the slope of long-term learning between controls and patients (controls, −1.1 ± 0.6; patients, −1.3 ± 0.9, $p = 0.39$) (Figure 4B). After two weeks of practice, there was a significant overall motor improvement both in patients (day 1, 70.5 ± 4.4; day 15, 50.2 ± 3.7, $p < 0.0001$) and in controls (day 1, 61.2 ± 4.6; day 15, 41.3 ± 4.0, $p < 0.002$) (Figure 4C).

Relationships between baseline characteristics and long-term motor skill learning (experiment 2). There was no correlation between age and long-term learning performance in controls (rho = 0.08, $p = 0.81$) or in patients (rho = 0.03, $p = 0.90$) when controlling for disease duration.

There was a trend for a correlation between disability and mean tracking error across days of practice in the patients (rho = 0.36, $p = 0.09$). However, no significant relationship was found between disability and the rate of motor skill learning (rho = −0.30, $p = 0.17$). While patients showed a significant correlation between 9-HP test performance and mean tracking error across the practice period (rho = 0.58, $p < 0.005$), controls did not (rho = −0.24, $p = 0.27$). However, there was a significant relationship between 9-HP performance and rate of long-term learning in controls (rho = −0.59, $p < 0.05$), which was not found in patients (rho = −0.37, $p = 0.24$).

Performance in the Sequence condition during day 1 of practice correlated significantly with Sequence performance after 15 days of practice in patients (rho = 0.88, $p < 0.0001$), but not in controls (rho = 0.48, $p = 0.16$). The correlation in patients was not improved when controlling for disability scores (rho = 0.75, $p < 0.0001$).

Performance during the first day of practice correlated significantly with the rate of long-term learning (rho = −0.55, $p < 0.008$), that is, poor initial performance was associated with faster tracking error

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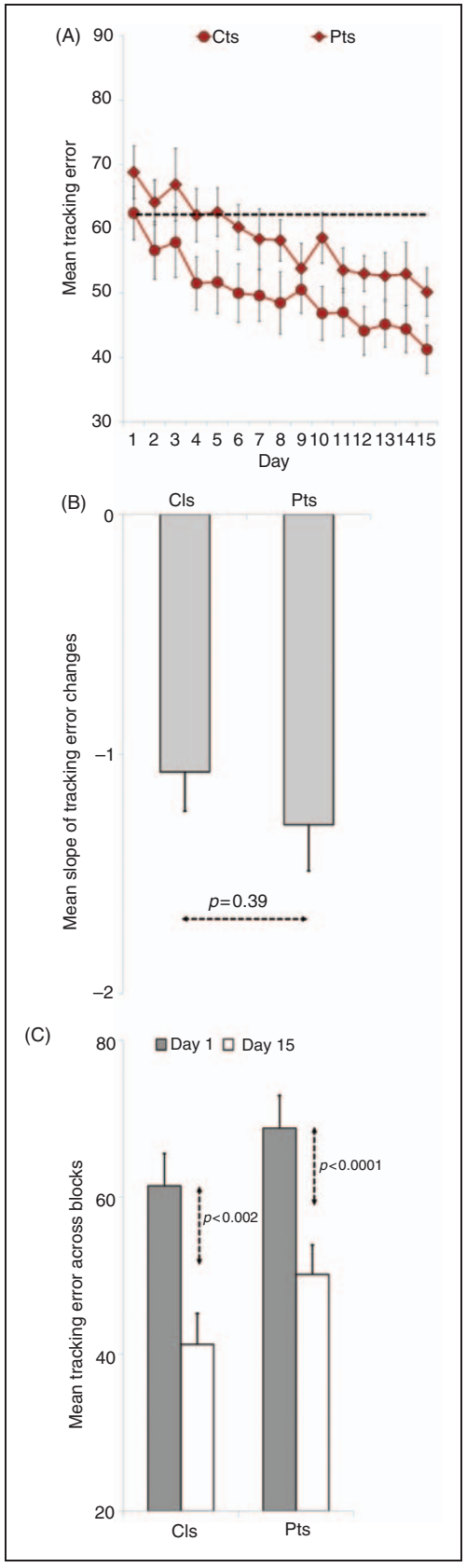

Figure 4. Reduction in mean tracking error during 15 days of practice in patients (Pts) and in controls (Cls) (A). There was no significant difference in the slope of long-term learning between controls (Cls = 10) and patients (Pts = 21) ($p = 0.39$) (B). There was a significant overall motor improvement (shown as mean tracking error across blocks for day 1 and day 15) with long-term practice both in patients ($p < 0.0001$) and in controls ($p < 0.002$) (C). Error bars represent standard errors within each group.

changes over time for the patients. Healthy controls only showed a trend in the relationship between performance on the first day and speed of learning (rho = −0.54, $p = 0.07$).

Relationships between brain lesion load, motor performance and long-term motor skill learning (experiment 2). In the patient group, mean ± SE T2-LV and T1-LV were 18234.0 ± 2875.1 and 14389.8 ± 2445.8 mm^3, respectively.

Performance in the 9-HP test significantly correlated with both T2-LV (rho = 0.44, $p < 0.05$) and T1-LV (rho = 0.45, $p < 0.04$). A significant relationship was found between mean tracking error across days of practice and both T2-LV (rho = 0.66, $p < 0.002$) and T1-LV (rho = 0.66, $p < 0.002$) (Figure 5). No significant relationship was found between the rate of long-term learning and T2-LV (rho = −0.05, $p = 0.82$) or T1-LV (rho = −0.06, $p = 0.79$) (Figure 5).

Discussion

Using behavioural measures of motor skill learning in MS, we have shown that the potential to learn a new motor skill in both the short- and long-term is preserved in MS patients across a wide range of disability and brain tissue damage. Although patients differed from controls in their baseline performance, the rate and the extent of improvements with short- and long-term training were comparable between groups, with preserved time courses of short-term condition-specific changes in patients. While disability and brain lesion load were reflected in the level of task-related motor performance, they both did not predict the rate of learning or performance outcome. After only one week of home training, patients achieved performance levels identical to those for healthy controls at baseline. If we postulate that this motor skill learning task probes mechanisms of brain plasticity that underlie recovery of function in MS,[25] our results do not support the hypothesis that plastic mechanisms responsible for recovery of function are substantially impaired in MS patients within the disease burden and the disability range studied here.

Short-term motor skill learning

We found that patients and healthy controls had similar rates of short-term motor skill learning. Our results

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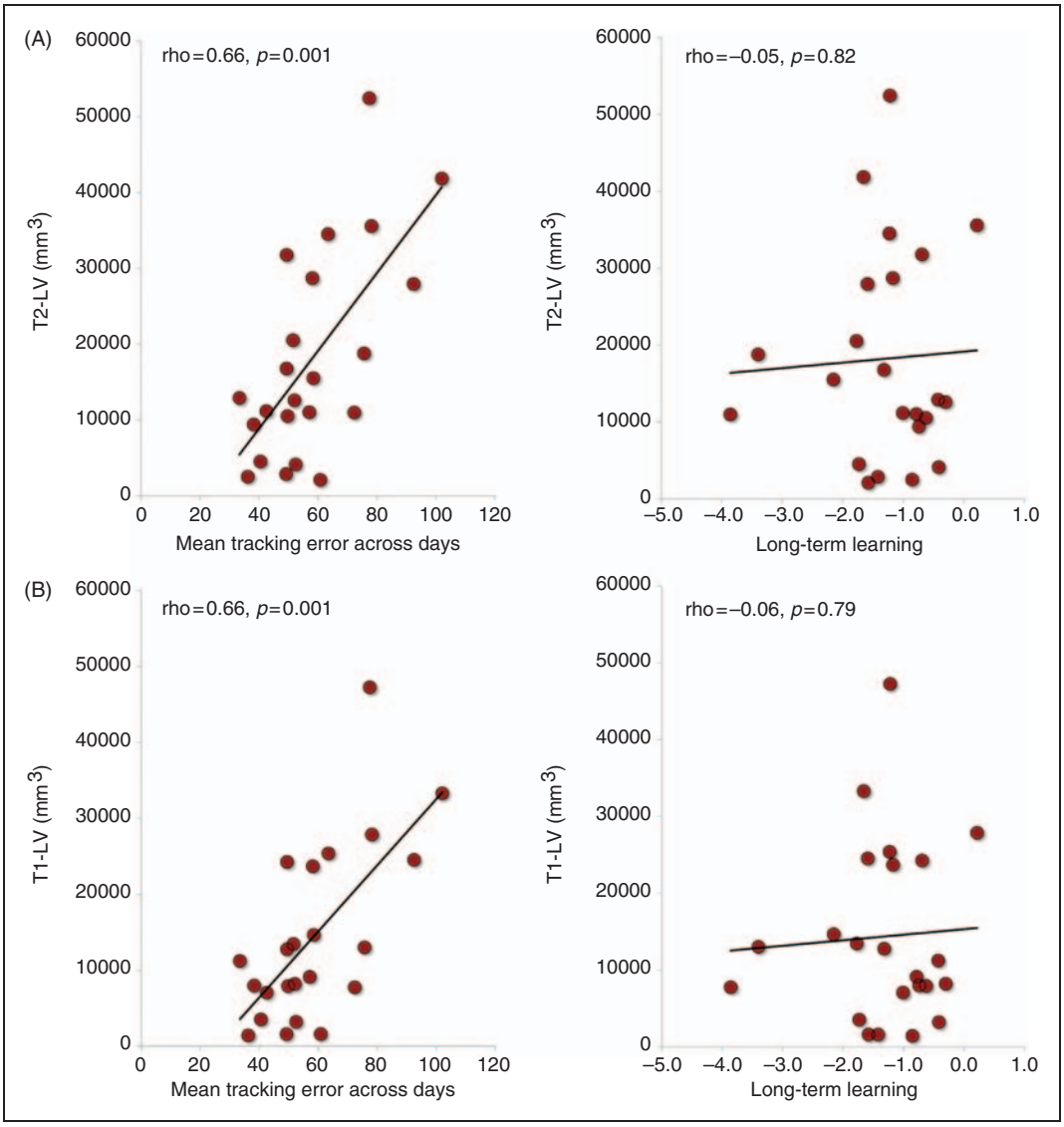

Figure 5. Relationship between T2-hyperintense lesion volume (T2-LV) (A) or T1-hypointense lesion volume (T1-LV) (B) and mean tracking error across days of practice (left) or rate of long-term learning (right) during Sequence in patients ($n = 21$). Higher T2-LV and T1-LV were significantly associated with worse motor performance, but not with the rate of long-term learning.

confirm previous findings suggesting intact short-term sensorimotor adaptive capabilities despite impaired motor execution in MS patients with normal motor performance.[11]Our results extend previous observations both with the use of a different task and by demonstrating that the potential to learn a new motor skill is preserved even in disabled MS patients. Refuting our motivating hypothesis and in line with previous findings of preserved short-term motor learning and rapid-onset motor plasticity in MS,[26] we have shown that motor skill learning is intact even in patients with higher levels of disability. We suggest that this may reflect relatively unimpaired brain plasticity for motor control.[25] Previous functional imaging studies have suggested specific mechanisms for this by demonstrating increased recruitment of higher-order sensorimotor and multimodal integration areas as the burden of disease rises across patients with well-preserved levels of motor performance.[27,28]

By showing a similar temporal profile of learning and magnitude of changes, patients confirmed the predicted delay in learning compared with controls, along with a tendency towards slower initial mean short-term learning rates. MS pathology could impair processes of neural signal summation required for learning-related synaptic plasticity to occur[29] and limit the efficiency of the learning process. Indeed, the initial improvements in task performance require rapid motor adaptation[30,31] and rely on an efficient stimulus–response coding for action selection.[32,33] The relatively

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slow early changes in patients may reflect the impairment of long-range connectivity supporting sensorimotor transformations[34] and is consistent with previous findings showing impaired short-term learning of task features requiring a complex integration of sensory information.[12] Alternatively, learning of new skills could demand a qualitatively different type of motor functional adaptation in patients relative to healthy controls. Previous imaging studies[28] show that brain activation patterns associated with *simple* motor tasks in patients resemble those engaged in healthy controls for executing *complex* motor tasks. Further functional studies are needed to elucidate mechanisms of skill learning in MS.

The effect of disability on skill learning

Different levels of disability were consistently reflected in the relative differences in task-related motor performance. At baseline, patients performed more poorly than controls and this difference was consistent across conditions. Within the patient group, we also observed consistent differences in the overall motor performance between patients with severe vs. mild/moderate levels of disability. However, even the most disabled patients were able to reduce their errors with learning. Although the relatively small sample size may have limited our ability to detect a between group difference in learning, these findings may overall suggest that behavioural changes with visuomotor learning may be smaller in more disabled patients because of the more limited motor resources.[27,28] In our cohort, patients with higher levels of disability ($\geq$4.0) are either in a secondary-progressive phase of MS (as suggested by the clinical characteristics) or suffer from motor impairment (as defined by EDSS scores greater than 4.0). This suggests that in more disabled patients skill learning may be affected particularly by increasing damage to the relevant sensorimotor effector pathways. Therefore, we speculate that patients with more severe disability could benefit from the use of neural prosthetic devices bypassing damaged efferent paths[35,36] or from augmentation of fundamental mechanisms of repair, for example, by enhancing neurite outgrowth[37,38] or remyelination.[39]

Our results show that disability levels do not predict the rate of error reduction and thus the actual skill learning process. In this study disability was quantified by the EDSS scoring system. The EDSS is a widely used scale for quantifying MS disability in clinical trials as well as in daily clinical practice, but it is biased towards the impairment of lower limbs.[40] We suggest that limitations in EDSS scoring may have contributed to our findings and the application of a more specific measure of upper limb disability might have revealed some relationship with performance improvement.

Behavioural evidence for specific systems-level plasticity in MS

We explicitly tested different aspects of learning of the visuomotor task in our study: subjects learned the visuomotor skill alone (in Random) or in combination with a specific sequence of movements (in Sequence). The two aspects of motor skill learning probed by these tasks both play roles in normal motor function.[41] Brain functional sub-systems mediating general skill and sequence-specific learning can be distinguished.[42] Improved performance with the Sequence condition demands both motor system 'feed-forward' adaptations[33] and reinforcement of a specific procedural memory over successive trials.[43] The cortical–subcortical systems (particularly cortical–cerebellar and cortical–striatal circuits) that are implicated in both of these aspects of motor learning[42,44] are affected by MS pathology.[45] By demonstrating relatively unimpaired dynamics of motor skill learning in our patients, we provide indirect evidence that specific systems-level brain plasticity must occur.[45] This conclusion could be made more secure by additional studies testing the relation between individual differences in lesion distribution or neuroaxonal injury and individual variation in motor learning.

Restoring impaired motor performance in MS patients with long-term skill practice

We observed a significant reduction in mean Sequence errors with practice both in controls and in patients, with the amount of change over time comparable between groups. The unexpected similarity in the temporal profile of long-term learning between healthy controls and patients is consistent with short-term learning results. The different composition of patient groups in the two experiments of the study demands caution when relating the short- to the long-term results. However, our behavioural evidence for long-term motor learning in patients with increasing tissue damage strengthens the hypothesis of preserved mechanisms for brain plastic reorganization [42] in MS even in the longer term and in more damaged patients.[26]

On average patients reached the level of performance shown by healthy controls at their baseline after a few days of practice of the Sequence condition and continued improving in the subsequent week. Although no 'Random-trained' group was used to compare with our 'Sequence-trained' group and we cannot disambiguate effects of sequence-specific vs. pure skill learning on long-term practice, we interpret this observed 'normalization' of motor performance in patients as *learning*-related, rather than just *use*-related. Motor cortical plasticity in normal adult brains indeed appears to be learning-dependent or skill-dependent, and not simply

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use-dependent.[46] Our learning task, therefore, may be informative about changes occurring with rehabilitation, which often involve retraining of sequences of movements to allow for goal directed tasks to be carried out.

With long-term practice, patients improved consistently by about 30% relative to baseline performance. Previous findings on spontaneous recovery showed behavioural and neuronal functional changes two weeks after a MS relapse.[47,48] We suggest that two weeks of home training improved motor performance by altering motor representations. This time scale of behavioural and hypothesized functional changes is consistent with previous experimental[49,50] and clinical[10] evidence. In clinical settings, however, rehabilitation involves longer periods of therapeutic intervention than that explored here. Longer-term studies, therefore, are needed to explore later phases of motor learning in MS.

Consistent with results of short-term learning, we observed a correlation between initial and final mean tracking error in patients but not in the healthy controls. While this between-group difference may reflect a smaller range of performance differences within the control group, it may also represent different functional substrates for learning in patients and controls. While in controls motor representation of a new pattern of movements may build immediately on previous motor experiences,[43] in patients learning a novel motor skill may initially demand the establishment of a sensorimotor framework in which new motor representations can be subsequently consolidated.[27] If our findings can be extrapolated to rehabilitation outcomes, we expect that in patients the relative performance level achieved by an intervention may be predicted from baseline performance.[51]

Conclusions and implications

Our results demonstrate that learning of new motor skills can adaptively drive the motor abilities in MS patients. Although pathological changes in MS impair signal summation and adaptation,[12] compensatory mechanisms maintain a potential for both short- and long-term motor plasticity.[52] This finding along with previous electrophysiological and metabolic evidence[26] suggests that MS rehabilitation should focus on mechanisms supporting the later stages of motor learning.

Our observations suggest that brain plasticity contributes to the potential for functional recovery despite an increasing burden of disease and disability. Progression of disability in MS, therefore, must arise predominantly from increasing damage to the relevant sensorimotor effector pathways and limitations in their repair, rather than from limitations of plasticity.

The presence of a relationship between initial motor performance and learning outcomes along with relatively slower initial motor adaptation with short-term learning in patients suggest that learning may involve different mechanisms in MS with respect to healthy controls. Further studies are needed to elucidate these mechanisms.

Finally, our approach to the study of rehabilitation in MS by using motor learning as a probe to characterize and quantify behaviourally meaningful plastic changes offers ways to develop and test novel recovery-oriented strategies using a controlled and reproducible experimental probe.[5]

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Conflict of interest statement

PMM is a full-time employee of GlaxoSmithKline, which is engaged in the development of new drugs for multiple sclerosis.

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