

Investigating the clinical pattern of motor relearning in people with multiple sclerosis

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ABSTRACT

Introduction: Understanding how people with multiple sclerosis (PwMS) acquire motor skills during rehabilitation is essential for optimizing treatment strategies. Motor learning theory suggests that skill acquisition follows predictable trajectories, but the time course and variability of learning during task-oriented rehabilitation remain poorly defined in PwMS. The aim was to investigate the learning trajectory and performance variability in PwMS undergoing task-oriented rehabilitation, using mathematical modeling of behavioral changes over time.

Methods: This longitudinal prospective study included 44 PwMS admitted to a rehabilitation unit. Participants received either balance-specific or non-specific motor impairment treatments. Balance performance was assessed with the Berg Balance Scale (BBS) after each session. Session-to-session changes were analyzed using linear and exponential models to characterize the learning pattern, and residuals were examined to quantify variability.

Results: An exponential mixed model (Akaike information criterion (AIC) = 2514.1) best described learning trajectories and provided more accurate estimates of pre-to-post improvement compared to a linear model (AIC = 2672.1). Performance variability decreased across sessions, from 1.16 to 0.75 points. Participants receiving specific balance treatment reached the minimal clinically important difference after three sessions, while participants receiving non-specific treatments achieved MCID only after 7 sessions.

Conclusions: Motor performance changes in PwMS during rehabilitation resemble motor learning in healthy individuals: improvements follow an exponential function and are accompanied by reduced variability. Treatment specificity enhances the velocity and magnitude of learning, underscoring the importance of targeted interventions in neurorehabilitation.

Keywords: Balance, Berg Balance Scale, Multiple sclerosis, Motor learning, Rehabilitation

What is already known about the topic?

- Motor performance changes in PwMS during rehabilitation resemble motor learning in healthy individuals.

What does the study add?

- This study models session-to-session changes in balance, using BBS, demonstrating exponential learning, decreasing variability, and higher asymptotic scores with balance-specific treatment.

Introduction

Balance impairments, defined as difficulties in maintaining an upright position during static, challenging, and reactive conditions of postural control, are common in People with Multiple Sclerosis (PwMS) (1,2) leading to falls in 46% of them over six months (3). In the last twenty years, several papers and meta-analyses have been published on the effects of balance rehabilitation in PwMS, suggesting that

the specificity of the intervention within a task-oriented paradigm is a key ingredient to induce motor learning and improve balance (4).

Motor learning is described as the process that produces *relatively permanent* improvements in movement skills, accompanied by reduced variability in performance (5). In healthy individuals, learning curves typically follow a nonlinear trajectory: performance improves rapidly at first, then the rate of improvement decreases as skill acquisition progresses (6-9). Monitoring performance changes over time during rehabilitation offers valuable insights into motor learning in people with neurological disorders. Importantly, mathematical modeling of these trajectories can also capture variability in performance, thereby improving our understanding of how and when learning occurs and informing the therapy dose-response relationship (10). Variability, measured across repeated trials, is often considered a random error within the

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motor system (11). While promoting variability during training can facilitate exploration and adaptability, a hallmark of skilled learning is the progressive reduction of errors and increased consistency of performance (7).

In healthy participants, analyses of learning curves have guided the development of mathematical models to describe the time course of learning (8,9). However, it remains unclear whether these models can adequately characterize motor learning in people with neurological disorders, such as PwMS. For example, the large early improvements often observed in healthy subjects may be attenuated in PwMS due to neurological impairments that limit the emergence of skilled movement (12). Research findings are mixed: Leocani et al. (13) reported impaired learning in PwMS during an upper limb tracking task, whereas Carpinella et al. (14) and Bonzano et al. (15) demonstrated preserved learning using robotic training or a finger serial reaction time task.

Even though task-oriented rehabilitation for balance and mobility is grounded in motor learning principles, there is still limited and inconsistent evidence regarding the learning capacity of PwMS and the evolution of performance across treatment sessions. Understanding the nature and mechanisms of learning in this population is critical for developing effective rehabilitation strategies (12). Furthermore, modelling behavioral changes and performance variability over time may allow comparisons between healthy individuals and PwMS, providing both theoretical insights into the learning process and practical clinical information about the dose—response relationship.

Therefore, the aim of the present study is to assess the time course of behavioral changes, performance variability, and the role of treatment specificity in motor learning during rehabilitation, using a well-established clinical outcome measure. This approach seeks to generate clinically relevant information about the nature of motor relearning in PwMS.

Methods

We recruited a sample of 44 PwMS from the [masked] with the following inclusion-exclusion criteria: MS diagnosis, a score ≤ 53 at the Berg Balance Scale, and age > 18 years old. We excluded PwMS unable to walk, EDSS > 7.5 , with severe joint and/or bone disorders and cardiovascular diseases. Written informed consent was provided by all subjects in accordance with the International Declaration of Helsinki.

Assessments and treatments

The outcome variable was the Berg Balance Scale (BBS) (16) rating of balance disorders, with a good test–retest reliability (17,18).

The BBS was evaluated at baseline and before the beginning of each treatment session over a period of three weeks, with ≥ 3 points improvement being defined as the minimal clinically important difference (19). The Timed Up and Go Test (TUG) was measured every session (data not shown) as a transfer test.

The details of treatment methods can be found elsewhere and in the supplementary material (20-22). In the

balance-specific group, treatment was based on a task-oriented approach with emphasis on the static and dynamic control of the center of mass, quality of performance of the tasks retrained and impacting on the underlying impaired sensory system. In the non-balance specific group, treatments were not specifically aimed at balance rehabilitation and were based on the recovery of motor impairments with a non-task-oriented specific approach.

Assessment of the best function fitting of the learning curve

The progression of the BBS scores over the rehabilitation period was used to study day-to-day learning by measuring the retention of skills achieved during the previous session.

First, we verified if the learning curves showed systematic changes over time. To do so, we used the augmented Dickey-Fuller test (ADF) to test stationarity of each individual time series. Then, we fitted the session-by-session BBS learning trajectories to study the pattern of changes over time.

The trajectories were analyzed using a nonlinear mixed-effects model fitted with the nlme R package (see Supplementary Material for the R code). We modelled BBS scores as a linear and an exponential function of session (Equation 1), consistent with previous literature (9,10). At the population level, parameters a , b , and α were estimated as fixed effects. To capture inter-individual variability, we included subject-specific random effects for parameters a , b , and α , assuming a compound-symmetry covariance structure at the subject level. Within-subject serial dependence across sessions was accounted for by specifying a residual correlation structure.

To assess model fit, we reported the RMSE: Root Mean Squared Error, AIC: Akaike information criterion, and BIC: Bayesian Information Criterion.

$$\text{Equation 1, } E(BBS_N)_e = a_e + b_e e^{-\alpha N}$$

- $E(BBS_N)_e$ is the expected BBS score at session N .
- a_e is the maximum (asymptotic) BBS value that a PwMS would eventually reach if rehabilitation continued indefinitely.
- b_e indicates the expected change in BBS values from the initial to the asymptotic values. Finally, the amount of nonlinearity displayed by the learning function is controlled by its rate parameter α . A positive value of α results in trends depicted in Supplementary Figure 3 showing small changes over the first rehabilitation sessions. Conversely, a negative α results in trends with the largest changes occurring at the beginning, levelling out towards the end of the rehabilitation sessions.

Assessment of intra-individual variability

We calculated intra-individual variability (IIVar) as the root-mean-square residual around the population-level (fixed-effects) model predictions, i.e., the typical deviation between the observed and predicted BBS scores across sessions for each PwMS (see Fig. 2, right panel, where these deviations are shown as vertical red segments).

We computed IIVar for individual j as:

$$\text{Equation 2, } IIVar_j = \sqrt{\frac{\sum(y_{j,N} - E(BBS_{j,N}))^2}{T_j - 1}}$$

where $y_{j,N}$ is the observed BBS score for PwMSj at session N , $E(BBS_{j,N})$ is the corresponding model-predicted score, and T_j denotes the total number of treatment occasions for PwMSj. This metric is the square root of the mean squared residual and reflects the consistency of a subject's performance over time. We fitted IIVar with the same exponential function described above using a nonlinear mixed model (see Supplementary Material)

Summarizing;

ae: represents the expected final BBS score as rehabilitation duration approaches infinity; larger values indicate better outcomes.

be is the expected magnitude of change from the beginning of the treatment to the asymptotic values; larger values mean correspond to greater improvement.

α estimates the rate of change (learning speed), higher values indicate a steeper curve – upward for negative values, downward for the positive ones. See supplementary material.

Note that the estimated initial BBS values can be obtained as $a + b$.

IIVar represents the consistency of scores for each subject over the treatment period. Thus, PwMS with smaller variability across the 13 sessions will have lower IIVar values.

Assessment of the difference between balance-specific and non-specific treatment

We also investigated whether different learning trajectories were associated with different overall outcomes. Specifically, we verified if PwMS showing a large amount of learning at the beginning of the training sessions exhibited better final outcomes compared to those showing delayed learning changes. To this end, PwMS were classified as responders (≥ 3 -point improvement on BBS) or non-responders. A chi-squared test was used to test the association between the status (responder/not responder) and the sign of α . Furthermore, a t-test was used to compare mean BBS differences between responders and non-responders. The Pearson correlation coefficient was used to explore the relationship among model parameters.

Finally, we tested differences between specific and unspecific treatment using a baseline-adjusted nonlinear mixed-effects model. Baseline BBS (session 1) was included as a standardized covariate on parameter a (see Supplementary Material, Model 4). Group differences were tested on the rate parameter α , and a subject-specific random effect was included on a .

Results

Table 1 shows the descriptive statistics of the sample including 25 (60%) women and 19 men. PwMS had (mean \pm standard deviation) 16.0 ± 3.0 treatment sessions resulting in BBS changes from 42.31 ± 7.44 to 48.75 ± 5.66 points.

BBS mean total score values and standard deviations across sessions are depicted in Figure 1. The TUG also showed statistically significant improvement ($p < 0.001$), median [25th-75th percentile], pretreatment 17.01 sec [14-21] to post-treatment 13.41 sec [10.35-18.03].

TABLE 1 - Descriptive statistics of the sample, $n = 44$

	mean	sd	median	min	max
Age (Years)	51.2	13.4	52.0	27.0	72.0
Onset (Years)	16.5	10.1	14.0	1.0	38.0
EDSS (points)	5.8	0.9	6.0	3.5	7.0

EDSS: Expanded Disability Status Scale; TUG: Timed Up and Go test.

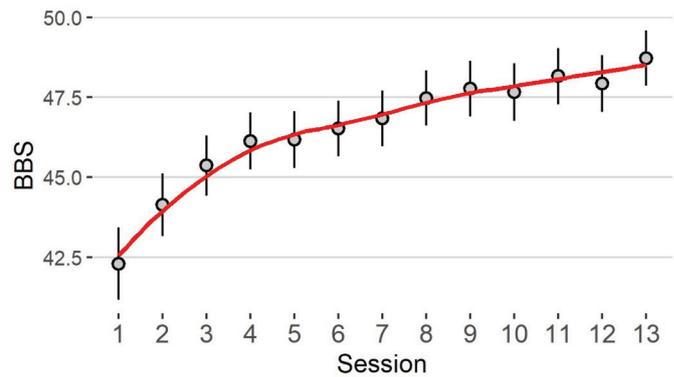


FIGURE 1 - Nonlinear trend of the learning curve, $n = 44$. BBS: Berg Balance Scale. Dots represent mean scores; bars represent standard errors of mean.

Fitting of the learning curve

The results from the ADF tests ($p < 0.01$) and inspection of the plots indicate that the learning curves were not stationary, showing a nonlinear trend with large (>1 point) improvements in the first two sessions followed by small changes later (Fig. 1).

Table 2 and Supplementary Figures 1 and b report results from the nonlinear model showing better fitting (smaller AIC, BIC, and RMSE) compared with the linear model. In the exponential model, all parameters were statistically significantly different from 0. The expected asymptotic BBS score was 48.98 points, with an expected change of 8.61 points from pre to post rehabilitation. The negative value of the α parameter indicates that, as a whole, the sample showed larger improvements during the early stage of the treatment.

Intra-individual variability

Mean Inter-Individual Variability across sessions was 0.93 points with a large between-subject difference of ± 0.13 points. Figure 2 shows differences between two representative subjects with inconsistent (large variability, right bottom panel) and consistent (small variability, right top panel) performances. Modeling variability (left panel of Fig. 2) shows a reduction from 1.16 points at the first treatment session to 0.75 points (-35%) after session 13, following an exponential trend ($a = 0.41 \pm 1.10$, $b = 0.81 \pm 0.98$, $\alpha = -0.07 \pm 0.15$). Compared with the intercept-only



TABLE 2 - Parameters of the linear and exponential models, n = 44

	Value	Std. Error	t	p
LINEAR				
<u>Fixed effects</u>				
Intercept	43.20	0.98	43.66	<0.001
Slope	0.46	0.06	7.62	<0.001
<u>Random Effects (SD)</u>				
Intercept	6.02			
Slope	0.38			
RMSE	1.85			
AIC	2672.12			
BIC	2657.63			
EXPONENTIAL				
<u>Fixed effects</u>				
a	48.98	1.02	47.6	<0.001
b	-8.61	1.33	-6.44	<0.001
α	-0.21	0.04	-5.70	<0.001
<u>Random Effects (SD)</u>				
a				
b	6.24			
α	8.35			
	0.16			
RMSE	1.421			
AIC	2514.1			
BIC	2561.9			

SD: standard deviation, RMSE: Root Mean Squared Error, AIC: Akaike information criterion, BIC: Bayesian Information Criterion

(null) model, the model fit improved significantly (likelihood ratio test, $p < 0.02$). However, none of the individual fixed-effect parameter estimates were statistically significant (all $p > 0.42$; see Supplementary Material for full model details).

Of note, PwMS with worse baseline scores resulted in increased IIVar ($r = -0.50$, $p = 0.01$).

Clinical implications

In this section, we fitted data using the exponential function to represent the time course of learning for each subject. Six out of 44 PwMS were non-responders with a BBS change < 3 points showing higher fitted baseline scores ($a + b$, $n = 6$, score = 49.36 ± 3.31 points) compared to responders ($n = 38$, baseline score = 41.34 ± 7.03 points, t -test = -4.83 , p -value ≤ 0.001 , see also Supplementary Figure 2).

We also found a statistically significant correlation between the asymptotic score (a) and the estimated initial values ($a + b$, $r = 0.44$, $p < 0.001$, see Supplementary Figure 3). To note, there was also a significant association ($r = 0.51$, $p = 0.01$) between the learning rate (α) and the b parameter (estimated pre to post changes in BBS). This suggests that PwMS who showed greater improvements early in treatment (i.e., those with a large negative α) tended to experience larger overall gains in their BBS scores. In fact, PwMS in the group with large initial improvements (negative α) achieved an expected pre-to-post change of 10.0 points, compared to

only 2.32 points in the group showing improvement later in the intervention. This difference remained statistically significant even after adjusting for baseline scores (beta: -3.9 , Std. Error: 1.45, t -test = -2.75 , $p = 0.01$).

Finally, we checked whether including a training specifically aimed at improving balance results in larger learning across sessions compared with subjects that received rehabilitation not specifically aimed at improving balance. Pre scores for the two groups are presented in Supplementary Table 1a. When comparing the specific group vs the unspecific group, we observed a faster learning of the specific group, meaning that PwMS who underwent specific balance training needed a reduced number of sessions to arrive at a clinically important difference on the BBS with continuing improvement in the rest of the sessions. This remains significant after adjusting for baseline BBS, the specific group showed a significantly faster learning rate than the unspecific group (group effect on the rate of change (α): $\beta = -0.19$, $SE = 0.05$, $p = 0.0002$, Figure 3 and Supplementary Table 1b). Additionally, the baseline-adjusted group-rate model fit significantly better than the null model (likelihood-ratio = 52.94, $p < 0.0001$).

Discussion

The most cardinal finding of this study is that changes in motor performance of PwMS during neurological rehabilitation parallel changes in performance observed in healthy subjects according to the key principles of motor relearning:

- 1) Improvements during rehabilitation follow an exponential function.
- 2) Improvements are associated with increased consistency, i.e., a decrease in performance variability.
- 3) The amount and rate of learning are associated with treatment modalities.

Our results are consistent with other studies in healthy subjects showing that learning curves are best fitted by an exponential function rather than a linear function (9).

The form of the learning law has important implications for understanding the nature of learning since the exponential function implies a constant rate of learning relative to the amount left to relearn (9). In our study, this rate was approximately 20% of what was left to learn. Motor learning has also been studied in PwMS. Although studies on PwMS did not address the form of the learning law, visual assessment of published data shows nonlinear evolution. Gera et al (3) investigated the learning of postural control in PwMS during surface translations, reporting greater improvements at the beginning of training compared to later stages. Similarly, Hatzitaki et al (4) studied the ability of PwMS to learn a novel visuo-postural coordination task, showing a nonlinear reduction of spatial errors across trials, although at a slower rate of performance compared with healthy subjects.

Learning can be the result of a sum of time-varying component processes or the result of a mixture of processes (25). For instance, faster improvement in the first phase can be attributable to cognitive processes involved in the cognitive-verbal phase of learning (26), in which subjects

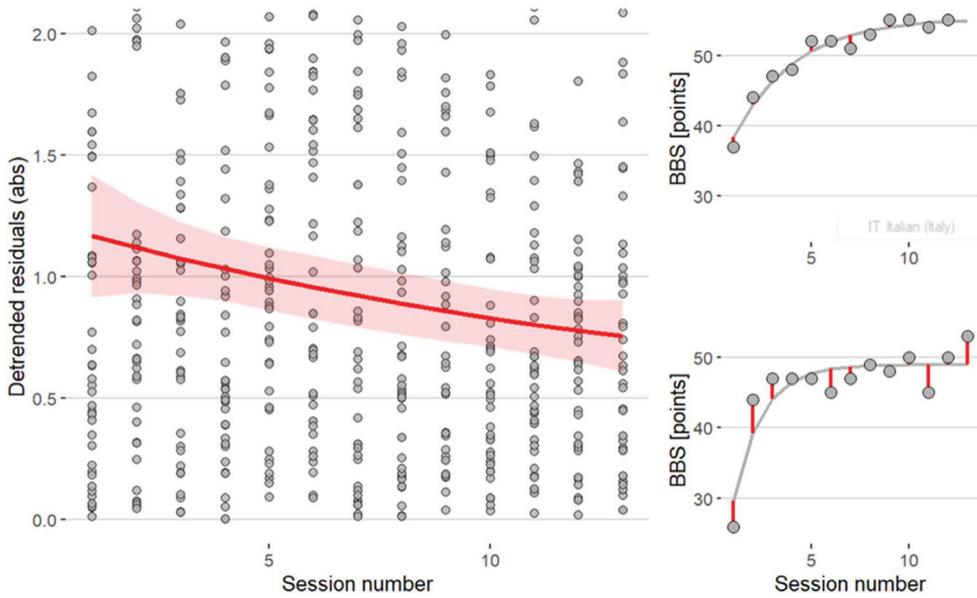


FIGURE 2 - Evolution of variability across sessions, n = 44. Left panel, evolution of variability across sessions computed as the root mean square of detrended residuals (Eq. 2). Top and bottom right panels, example of two PwMS showing low and large variability.

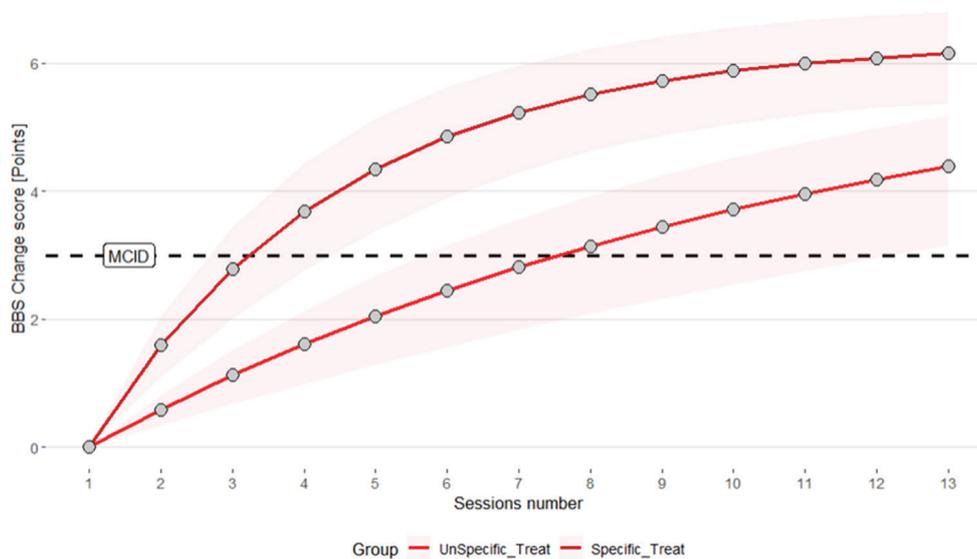


FIGURE 3 - Trends of BBS change scores for positive and negative α parameter, n = 44. MCID: minimal clinically important difference

learn the best strategies for performing BBS, while later, slower improvements are more likely associated with the associative phase of learning. In addition, we know that balance control is comprised of complex multivariate systems where sensory, motor, and cognitive adaptation play a role in improving performance (27). The present study cannot characterize the time course of how these subcomponents influence balance. Further studies are needed to clarify their relative contributions during motor relearning, and any mechanistic claims would require targeted physiological or neuroimaging evidence.

Besides changes in motor performance, we also observed changes in intra-individual variability; however, model fit was suboptimal, and more extensive data and further analyses are needed to fully characterize patterns of variability.

Variability can be considered detrimental, indicating a suboptimal learning (28) as a result of sensory-motor impairments. Our results are consistent with motor learning principles (29), which state that a good performance is reproducible to optimize the movement accuracy and efficiency when the context is constant. To note, the greater the baseline balance impairment, the higher the variability, underlining the relationship between motor variability and sensory-motor impairment (5). Similar results were observed by Hatzitaki et al., showing that PwMS with an EDSS score greater than 4 and cerebellar dysfunction failed to reduce performance variability over one day of practice (24). It is important to note that in this study, increased consistency within PwMS does not imply better movement reproducibility but rather an increased ability to perform the task successfully. Further



studies examining session-to-session changes in motor and neural subcomponents during rehabilitation will be important for clarifying the mechanisms underpinning improvements in participants' performance.

The modeling of the learning curves revealed that more than 3 sessions are needed to achieve a minimal clinically important change (18) when a balance-specific treatment is provided, while further sessions are needed when training is non-specific. This knowledge is helpful in defining the dosage of the intervention, which also depends on the treatment approach. However, it is important to note that repeated exposure to BBS items may promote item-specific learning and that assessor bias is also possible, as assessors were not blinded to group allocation or prior results.

Due to the nature of our non-randomized controlled study, our data cannot provide information on the most effective options for improving balance. Nevertheless, our results are consistent with the descriptive notion of treatment specificity, suggesting that specific interventions are associated with faster and greater improvements in balance performance. We observed a 20% higher learning rate in PwMS who received balance-specific treatment compared to those who did not. The greater improvements observed in the first few training sessions in the specific group may reflect the use of hierarchical balance-specific reinforcement learning. In balance-specific reinforcement learning, therapists break down complex balance tasks into smaller, manageable components and guide patients toward the most effective strategies. This structured approach likely promotes faster progress than a trial-and-error method (31).

Finally, we observed better outcomes at the end of the sessions in subjects with poorer baseline performance, as already reported elsewhere (32). This is in line with the exponential model in which subjects improve a fixed amount of what was left to improve, implying that PwMS with greater baseline impairments have a higher capacity for improvement. The amount of learning is also modulated by the pattern of changes. PwMS with a large negative learning rate parameter, indicating greater improvements at the beginning of the treatment, showed larger improvements. This means that subjects showing small or no improvement during the early sessions will likely result in poorer outcomes in terms of change, perhaps requiring the adoption of alternative approaches, especially for subjects with good baseline balance performance. Further studies are needed to understand whether modeling changes in the first two-three sessions may better predict the mid-term effect of treatment.

Limitations

First, a strength of our approach was adopting a widely known outcome measure having an established cut-off point distinguishing between clinically or not clinically relevant changes. However, the BBS is known for having ceiling effects; it does not assess dynamic balance in depth and is ordinal in nature. Because of this, we also used Rasch-transformed continuous BBS scores (33) (Supplementary Material) in a further analysis, which still showed better fitting of the exponential function compared to the linear function. Second, the nonlinear behavior observed may be due to

the nature of the BBS in which the total score is the sum of the items, thus total score gains are reduced as subjects approach the scale's maximum score, with the easiest items saturating, leading to smaller gains at the end of the treatment. However, in this sample, most subjects had a poor initial score and thus many items to improve even at the end of the rehabilitation regimen. Moreover, nonlinear improvement can also be observed in single items (data not shown). Third, skilled learning may be better studied by outcomes measuring movement quality through the use of kinematic and kinetic measures to assess improvement in coordination across sessions. These measures were not available in the present study but should be included in future studies. Fourth, we studied motor learning using a well-known nonlinear equation to compare our results with those of other studies. However, other equations may better explain learning. Finally, group comparisons should be interpreted with caution. This was not a randomized controlled trial, and assessors were not blinded. Moreover, the group-comparison models converged only after removing the within-subject correlation structure (see Supplementary Materials), which may have introduced bias. Finally, no a priori sample-size calculation was performed; therefore, the results may differ in a larger sample.

Conclusion

This study demonstrates that motor relearning in persons with multiple sclerosis (PwMS) during neurological rehabilitation follows the same fundamental principles observed in healthy individuals, with improvements best described by an exponential learning model. This pattern underscores that rehabilitation-induced gains occur at a constant rate relative to the remaining potential for improvement, highlighting the dynamic nature of motor learning in PwMS. The findings also emphasize the importance of treatment specificity, as balance-focused interventions yielded faster and greater learning compared to non-specific training. Furthermore, improvements in motor performance were accompanied by decreased intra-individual variability, reflecting enhanced movement consistency and control. Notably, participants with poorer baseline performance exhibited greater relative improvements, aligning with the exponential model's predictions. These insights have practical implications for optimizing rehabilitation dosage and tailoring interventions according to individual learning trajectories. Nevertheless, future research may extend this modelling to other functional metrics, more sensitive kinematic and kinetic measures, and explore the contribution of sensory, cognitive, and motor subsystems to better understand the mechanisms underpinning motor relearning in PwMS.

Disclosures

Conflict of interest: The authors declare no conflict of interest.

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Data availability statement: Data are available upon reasonable request.



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