Predictors of training-related improvement in visuomotor performance in patients with multiple sclerosis: a behavioural and MRI study

Ilona Lipp[1,2,3], PhD, Catherine Foster[2], PhD, Rachael Stickland[2], PhD, Eleonora Sgarlata[1,2], MD, Emma C. Tallantyre[1,4], MD, PhD, Alison E. Davidson [1,2], Neil P. Robertson[1,4], MD, Derek K. Jones[2], PhD, Richard G. Wise[2,5], PhD, Valentina Tomassini[1,2,4,5], MD, PhD

[1]Division of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, United Kingdom; [2]Cardiff University Brain Research Imaging Centre (CUBRIC), School of Psychology, Cardiff, United Kingdom; [3]Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; [4]Helen Durham Centre for Neuroinflammation, University Hospital of Wales, Cardiff, United Kingdom; [5]Institute for Advanced Biomedical Technologies (ITAB), Department of Neurosciences, Imaging and Clinical Sciences, University "G. d'Annunzio" of Chieti-Pescara, Chieti, Italy.

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Corresponding author

Dr Valentina Tomassini, MD, PhD

Institute for Advanced Biomedical Technologies (ITAB)

Department of Neurosciences, Imaging and Clinical Sciences, University "G. d'Annunzio" of Chieti-Pescara

Via Luigi Polacchi, 66100 Chieti, Italy

Tel. +39 (0)871 3556926; email: valentina.tomassini@unich.it

Abstract

Background. The development of tailored recovery-oriented strategies in multiple sclerosis requires early identification of the individual's potential for functional recovery.

Objective. To identify predictors of visuomotor performance improvements, a proxy of functional recovery, using a predictive statistical model that combines demographic, clinical and MRI data.

Methods. Right-handed multiple sclerosis patients underwent baseline disability assessment and MRI of brain structure, function and vascular health. They subsequently undertook 4 weeks' right upper limb visuomotor practice. Changes in performance with practice were our outcome measure. We identified predictors of improvement in the *training set* using lasso regression; we calculated the best performing model in the *validation set* and applied this model to the *test set.*

Results. Patients improved their visuomotor performance with practice. Younger age, better visuomotor abilities, less severe disease burden and concurrent use of preventative treatments predicted improvements. Neuroimaging localised outcome-relevant sensory-motor regions, whose microstructure and activity correlated with performance improvements.

Conclusion. Initial characteristics, including age, disease duration, visuo-spatial abilities, hand dexterity, self-evaluated disease impact and the presence of disease modifying treatments, can predict functional recovery in individual patients, potentially improving their clinical management and stratification in clinical trials. MRI is a correlate of outcome, potentially supporting individual prognosis.

INTRODUCTION

Prediction of the individual patient's capacity for functional improvements is relevant for patient management in multiple sclerosis (MS), as it allows personalised recovery interventions, rationalisation of health resource allocation and improved stratification of patients in clinical trials[1]. Currently, prediction of functional recovery in the individual case is based solely on clinical experience and thus remains largely variable and inaccurate[2].

The individual's potential for functional recovery results from the complex interaction of age, MS damage and disability, residual abilities and pre-morbid reserve, all of which can be captured by clinical measures and by MRI features[3]. Indeed, characteristics such as age and disease severity can play a role in disability development and worsening[4, 5], as well as in determining individual outcomes during recovery-oriented interventions[6-8]. Brain damage and reserve, as assessed by MRI, can also influence the individual's functional potential[3].

In this study, we combined demographic with baseline clinical and MRI measures to identify predictors of functional recovery in patients with MS. We used upper limb performance improvements on a visuomotor task as a proxy for functional recovery[3, 9]. *Firstly*, in a cohort of MS patients, we employed exploratory statistical modelling by combining measures of initial disability with functional and structural neuroimaging metrics, acquired before 4 weeks' home practice of a standardized upper limb visuomotor task[10]. *Secondly*, using this predictive model of functional recovery, we identified predictors of individual performance improvements. *Thirdly*, we validated our predictive model and results in an independent patient cohort.

METHODS

Patients and study design

We recruited right-handed MS patients[11] aged 18-60 years, with retained use of their right upper limb, no relapse or change in treatment for at least three months before study entry; no other neurological or psychiatric conditions. Patients were recruited within the Helen Durham Centre for Neuroinflammation, University Hospital of Wales, Cardiff, UK. The study was approved by the NHS South-West Ethics Committee. All patients provided written informed consent.

At baseline, we collected demographic and clinical measures (**Table 1)**, as well as functional and structural MRI (**Table 2**). Patients were instructed to practise a visuomotor task at home and subsequently returned to be clinically assessed.

Visuomotor task and home practice

We used a serial reaction time (SRT) task to probe recovery experimentally at baseline, while undergoing a brain MRI scan, and subsequently at home, on a laptop, daily for five days/week, for four weeks, with each practice session lasting for about 15 minutes (**Fig. 1A** and **Supplementary material** for details on the SRT task design and presentation). For the home practice, patients were asked to complete a practice log sheet on paper and weekly phone calls by the study team were made to ensure compliance. During the home-practice, the SRT task was presented on a laptop, on which the patient's responses were recorded to be used for the analysis of performance improvements.

During the SRT task, stimuli were presented in "Sequence", "Random" or "Rest" condition. For each block of the SRT task, the number (accuracy) and median latency (reaction time, RT) of correct responses were calculated. For each day of practice, the accuracy and RT across blocks

were calculated (**Fig. 1B, left**). As accuracy can rapidly reach a plateau, we used RT to describe changing performance with home practice. Only patients who completed at least 50% of the scheduled sessions (10 days) were included in the analysis.

For each participant and day of practice, we compared RT in Sequence *versus* Random blocks using an unpaired *t*-test in order to generate a contrast measure that represented Sequence-specific performance changes. For each participant, a linear model was fitted using *robustfit* of Matlab, with practice day as the independent variable and the Sequence-specific contrast measure as the dependent variable. We used the individual slope of practice-related Sequence-specific RT changes as our outcome measure of visuomotor performance changes with home practice (**Fig. 1B, right**).

Demographic and clinical characteristics

Demographic and clinical characteristics are indicated in **Table 1**. Disease duration was defined as the time (in years) between the onset of the first symptoms and the time of the study assessment. The date of disease onset was established from the patient's clinical notes (whenever available) and confirmed during the study interview. Expanded Disability Status Scale (EDSS)[12] and MS Impact Scale 29 items (MSIS-29)[13] assessed disability and disease impact; Beck Depression Inventory (BDI)[14], State Trait Anxiety Inventory (STAI)[15] scale and Modified Fatigue Impact Scale (MFIS)[16] quantified mood, anxiety and fatigue; 9-hole peg test (9-HPT)[17] and timed 25-foot walk (T25-FW)[17] characterised limb function; Rao's Brief Repeatable Battery[18] probed cognition.

MRI acquisition and analysis

We acquired brain MRI scans on a 3T MRI system (GE Medical Systems, Milwaukee, WI) using an 8-channel receive-only head RF coil. Detailed descriptions of the MRI protocols and analysis pipelines are in **Fig. 2** and in **Supplementary material**.

MRI measures that entered the predictive modelling were selected to capture as many aspects of MS damage as possible in a single scan session. We considered lesional and non-lesional damage, functional responses and cerebral blood flow (CBF). For all MRI modalities, we extracted measures from predefined regions of interest (ROI-based MRI measures); functional MRI (fMRI) measures were defined in task-relevant ROIs. For all MRI modalities, we also extracted measures from areas of significant correlations with home-practice outcome (outcome-relevant MRI measures, **Table 2**) for use in the models of prediction.

Predictive modelling

To predict performance improvements from baseline data, we employed a statistical learning approach that included a random assignment of the patients to three groups: a training set (60%) to establish statistical models, a validation set (20%) to select the best performing model in independent data, and a test set (20%) to evaluate the performance of the selected model. The three statistical sets underwent the same study procedures, including home practice.

Five groups of variables were established in the training set: *group A*, that included demographic and clinical variables; *group B*, that included ROI-based MRI measures; *group C*, that included demographic and clinical, as well as ROI-based MRI measures; *group D*, that included outcome-relevant MRI measures; *group E*, that included demographic and clinical, as well as outcome-relevant MRI measures.

Data preparation

Prior to modelling, all variables were z-standardized using the mean and standard deviation from the training set. Missing values were mean-imputed. Patients with a home-practice outcome 1.5 interquartile ranges below the first quartile or above the third quartile of the distribution were excluded from modelling. Patients unable to complete the T25-FW were assigned the value of the slowest patient who was able to complete the test. Variables with an absolute skewness >2 were log transformed: the scores of 9HPT and T25FW, the measures of lesion volume and the CBF in the putamen and globus pallidus.

Statistical modelling

Lasso regression was used for the linear modelling in the training set [Matlab (v R2015a) function: *lasso*]. This method performs variable selection and parameter estimation simultaneously[19]. Lasso regression overcomes the overfitting problems that are associated with traditional multiple linear regression analyses, by employing a regularisation of hyperparameter lambda that penalizes for the number of non-zero regression coefficients. Here, the optimal lambda was estimated by 7-fold cross-validation (repeated and averaged over 5 times) within the training set, finding lambda that minimises the mean squared error in the left-out folds. Correlations between predicted and actual outcome were calculated using Pearson correlation coefficients.

Lasso regression was applied to each of the five groups of variables in the training set for linear modelling (**Fig. 2**), generating five linear regression models (models A-E), which consisted of a number of retained variables along with their parameter estimates (regression coefficients). To obtain an index of the predicted home-practice outcome for each patient, we applied the

regression coefficients of each of the five models to the baseline demographic, clinical and MRI data. Selection of the best performing regression model occurred by comparing the mean squared error (MSE) across models in the validation set. The MSE quantifies how well the predicted home-practice outcomes matched the measured home-practice outcomes, with a low MSE indicating a small difference between predicted and measured outcome. Therefore, the model with the lowest MSE was deemed the model best performing in the validation set and was tested for predictive performance in the test set by quantifying the amount of variance (R^2) in the actual home-practice outcome that could be explained by the predicted home-practice outcome.

Data Availability Statement

Anonymized data may be shared with qualified investigators.

RESULTS

Baseline characteristics

Out of 141 recruited MS patients, 19 did not complete the study: six did not comply with baseline study procedures (e.g., claustrophobia in the scanner); 13 patients did not complete the home training programme (**Fig. 1C**). Out of 122 patients who completed the study, four patients were identified as outliers in the home-practice outcome and thus not considered for the modelling purposes (**Fig. 1C**). **Fig. S1** shows the distributions of the demographic and clinical characteristics for the whole cohort of patients. **Table 1** summarizes the characteristics of the whole cohort (n=118), as well as of the three groups of patients. There was no difference among the training, validation and test sets in their baseline demographic and clinical characteristics. Patients were on average in their mid 40s, mainly women and mildly to moderately disabled[20], as suggested by measures of global disability, limb function, cognition, anxiety, mood and fatigue. They had a wide range of disease duration, with many patients being untreated, but (as requested by the eligibility criteria) in a stable phase of their disease course.

Changes in behavioural measures with home practice

Patients completed 18.8±2.2 days of home practice (min = 11, max = 24). A two-way ANOVA showed a significant interaction between time and condition, indicating stronger visuomotor performance improvements in the Sequence than in the Random for both RT [$F(1,117) = 115$, $p < 0.001$] and accuracy [$F(1,117) = 82$, $p < 0.001$]. There were significant Sequence-specific RT improvements with practice in the whole cohort of patients (mean±SD -0.45±0.33; $t[117] = -15$, $p < 0.0001$). The 3 groups did not differ in the mean±SD Sequence-specific RT changes (training set: -0.41±0.32; validation set: -0.52±0.37; test set: -0.49±0.30; $p = 0.29$).

With practice, patients showed better performance in the 9-HPT and cognitive tests, as well as improved levels of mood and fatigue (**Table 3**). This improvement did not correlate with the extent of home training related improvements (**Table 3**).

Baseline MRI measures and their relationship with practice-related visuomotor improvements

Functional MRI. In the training set, we identified SRT task-relevant regions, i.e., bilateral motor, premotor, visual and somatosensory cortices, as well as the right cerebellum (**Fig. 3A, top**). Sequence-specific signal changes were observed in the posterior parietal and visual cortices (**Fig. 3A, bottom**).

When testing the relationship between functional responses in the SRT task>Rest contrast and Sequence-specific RT changes, i.e., the home training outcome, we found a significant correlation in the left cerebellar lobule VI (peak voxel coordinates in MNI space: -36, -60, -24; cluster size: 722 voxels), where BOLD signal change at baseline correlated with faster performance improvements (**Fig. 3B, top)**. We did not find regions that showed the opposite relationship.

Structural MRI and resting perfusion MRI. In the training set, there was no significant correlation between baseline MRI measures of GM integrity [GM volume and magnetisation transfer ratio (MTR)] or CBF and Sequence-specific RT changes. However, higher fractional anisotropy (FA) values in a wide range of WM tracts, including cortico-spinal tract, corpus callosum and longitudinal fasciculi, correlated significantly with home-practice outcome, i.e., higher FA values were associated with faster improvements in RT with practice (**Fig. 3B, bottom**).

Predictors of performance improvements with home practice

Variable selection and parameter estimation (training set). **Tables 1** and **2** list the clinical and MRI variables that were considered in the five modelling approaches for the predictive analysis. In each resulting model, between three and 13 variables were retained and contributed to the model to varying extents (**Fig. 4**).

Model selection (validation set). For each model, we calculated the model error (MSE). The lowest model error in the validation set was found in model A (model A: 1.16, model B: 1.33, model C: 1.28, model D: 1.63, model E: 1.23).

Model evaluation (test set). Model A was applied to the independent test set. The home-practice outcome predicted by model A significantly correlated with the actual outcome ($r[21]=0.66$, $p<0.0001$, **Fig. 5**) and could explain 44% of the variance.

Based on these model parameters (regression coefficients in **Fig. 4**), the variables in model A predicted individual improvements with practice in upper limb performance according to the relationship:

predicted outcome (z score) $Y = X\beta$

where X is a row vector of predictor values and β is a column vector of their respective beta coefficients (**Table 4**).

DISCUSSION

By combining baseline demographic, clinical and neuroimaging data, this study identified predictors of visuomotor performance improvements with training in individual MS patients. The strongest predictors were age, clinical characteristics such as disease duration, visuo-spatial abilities, upper limb dexterity and self-evaluated disease impact, and the presence of DMT. MRI metrics did not predict the training outcome over and above these measures, but variation in brain activity and WM microstructure in regions relevant to the practised task explained individual differences in training outcome.

Visuomotor training to probe upper limb functional recovery

A four-week standardised visuomotor training intervention probed brain plasticity underlying functional recovery. Compliance was high, with a dropout rate of less than 20%. Patients varied in the number of trained days, but this did not affect the outcome measure.

Interventional studies rely on the patient's compliance with the intervention procedures. We monitored compliance by recording the log file of each session of intervention and by asking the patients to complete a diary to record specific deviations from the daily protocol or factors affecting the practice. We mitigated the effect of variability in task execution by defining an outcome measure that is independent of the total number of practice sessions completed.

While, as a group, patients significantly improved performance with practice, the training outcome varied considerably between patients, reflecting the heterogeneity in functional recovery and rehabilitation outcomes observed in real-life setting. The distribution of performance improvements (**Figure 5**) suggested a *continuum* rather than distinct groups of responders *versus* non-responders. Therefore, our modelling predicted the extent of performance improvement, without attempting an arbitrary classification of patients into groups.

Our contrast-derived training outcome, i.e., slope of Sequence-specific RT changes, allowed us to limit the confounding effect of attention, fatigue or motivation on performance, thus capturing more stable changes in visuomotor performance[21]. Although our intervention was not individually tailored, as it would be in clinical rehabilitation, it facilitated generalizability and interpretability of the results by allowing all patients to experience the same, controlled training conditions. Indeed, the biological processes underlying clinically-induced or experimentally-driven improvements in performance largely overlap. Firstly, rehabilitation leads to functional recovery that, in most cases, is sub-served by brain changes similar to those occurring with skill learning[9]. Secondly, Sequence-specific improvements with training, closely reflecting task-oriented practice in rehabilitation, rely on systems involved in visuomotor integration and learning of movement sequences, functions that are relevant in rehabilitation[3]. Although this study was not designed to test explicitly a generalisation of effect of our intervention on routinely used clinical measures, changes in hand dexterity that accompanied performance improvements with practice suggest a possible, although small, clinical benefit of our experimental intervention.

Predictors of performance improvements

We used a statistical learning approach to identify predictors of visuomotor performance improvements, as a conventional linear regression could lead to overfitting, i.e., the resulting model could work well for the data that was used to establish the model, but not for independent data.

Within the most successful predictive model (model A), the strongest predictor was performance of SDMT, a measure of visuo-spatial skills and speed of processing that is considered to be

powerful tool to assess cognition in MS[22]. Patients with higher SDMT performance showed faster visuomotor performance improvements with practice, extending the relevance of cognitive reserve from normal motor learning[23] to functional recovery.

Higher levels of hand dexterity predicted performance improvements, with scores of both hands contributing independently to the model. Although right-hand dexterity is directly relevant to the execution of the study intervention, left hand dexterity in MS may also reflect the function of the left motor regions, thus contributing to explain the independent predictive role of the left upper limb function in performance improvements of the right upper limb[24].

Our results also suggest that younger age, higher pre-morbid reserve, lower disease burden, as assessed formally and by self-report, and modulation of inflammation predict patients who will improve performance with practice. Since our intervention relies on brain plasticity, these factors can also act as determinants of the intervention success, as they can be associated with building[25], maintaining[26] and exploiting[27] plastic reserve in the patients. By contrast, pathological MS changes, from brain atrophy to vascular abnormalities, can contribute to reduce plastic reserve in patients with higher disease burden, adding to the effect of age on brain health[5, 28].

MRI correlates of performance improvements

Performance improvements with training correlated significantly with baseline group-level structural and functional MRI measures. Higher FA in the longitudinal fasciculi, corticospinal tracts and corpus callosum was significantly associated with better home training outcome. These regions are important for visuomotor integration, inter-hemispheric communication and motor execution, functions all relevant to our visuomotor task[29]. These effects were widespread across white matter, suggesting that, along with the integrity of specific regions, the overall

microstructural health, which provides the substrate for local, as well as long-range connectivity and that is disrupted by MS damage[30, 31], is beneficial to support full recovery.

Patients with stronger cerebellar activation, as measured by BOLD fMRI during the SRT task, showed greater improvements with practice. A localised brain-behaviour relationship was found in cerebellar lobule VI, which is functionally connected with the contralateral higher motor control regions[32]. While the relationship between training outcomes and baseline SRT-related signal changes in the cerebellum may result from a simple modification of performance[33], it could also suggest that stronger or more intact error processing function leads to better training outcomes[34].

At least within the range of damage and length of training studied here, brain MRI data did not predict the outcome over and above demographic and clinical data, confirming the difficulty in translating directly results from MRI group-level analyses to the individual patient and clinical practice and highlighting the importance of developing novel biologically-informative MRI-based metrics to increase the potential of neuroimaging for single-subject prediction[35]. Some aspects of damage in our population, e.g., those revealed by other MRI methods (e.g., MR spectroscopy) or within other anatomical sites (e.g., spinal cord and optic nerve), may not have been fully captured. However, we aimed for a comprehensive, yet feasible baseline characterisation of brain function and structure in a single MRI session, and selected MRI methods and measurements, whose biological informativeness for MS damage, repair and systems-level plasticity is well established[3]. While we aimed to predict performance improvements from a single baseline assessment, it is possible that analysis of longitudinal clinical and MRI data could identify MRI predictors of functional recovery.

Conclusions

A comprehensive formal, as well as self-reported, baseline clinical assessment offers a reliable indication of the likely extent of recovery of visuomotor function in individual MS patients, at least within the range of disabilities, times and activities studied here. Residual abilities are retained functions, sub-served by the individual functional reserve, i.e., the remaining capacity of the brain to cope with an increased behavioural demand[36]. Our results highlight the importance of extending the routine clinical assessment of current disability to include measures of residual abilities relevant for recovery. Prediction of functional recovery in individual patients can provide valuable information at an early stage regarding the likelihood of response to standard rehabilitation interventions, as well as the stratification of patients for recovery-oriented clinical trials. The identification of structural and functional imaging correlates of performance improvements in a large cohort of patients provides a strong rationale for further, more targeted exploration of neuroimaging predictors of recovery.

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COMPETING INTERESTS

The authors have no conflicts of interest to report.

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