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Complementary roles of grey matter MTR and T2 lesions in predicting progression in early PPMS

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Objective: To investigate whether T2 lesion load and Magnetization Transfer Ratio (MTR) in the normal-appearing white matter (NAWM) and grey matter (GM) at study entry are independent predictors of progression and whether their changes correlate with the accrual of disability, over five years in early primary progressive multiple sclerosis (PPMS).

Methods: Forty-seven patients with early PPMS and 18 healthy controls were recruited at baseline and invited to attend clinical assessments six monthly for three years, and after five years. Patients were scored on the expanded disability status scale and multiple sclerosis functional composite subtests (25-foot timed walk test (TWT), nine-hole peg test and paced auditory serial addition test). At each time point, all subjects underwent brain MRI including T2-weighted, magnetization transfer, and volumetric sequences. T2 lesion load (T2LL), MTR histogram parameters and volumes for NAWM and GM, were calculated. Statistical analyses identified predictors of progression and correlations between MRI changes and clinical changes over time.

Results: Baseline T2LL and GM peak location and peak height MTR were independent predictors of progression, as measured by TWT; a model including these three predictors explained 91% of the variance of the progression on TWT, a significantly higher percentage than that obtained when the predictors were modelled individually (80%, 74% and 68%, respectively). Greater progression rate correlated with a steeper increase in T2LL and a faster decline in GM mean and peak location MTR.

Conclusions: The combined assessment of both visible white matter damage and GM involvement is useful in predicting progression in PPMS.

INTRODUCTION

Progression in primary progressive multiple sclerosis (PPMS) varies widely amongst patients[1], but, at present, only a few tools provide modest prediction of clinical outcome[1]. Among these tools, conventional magnetic resonance imaging (MRI), including T2-weighted imaging, is attractive, since it can easily be performed and standardised across scanners. Although T2 lesion load at study entry did not predict progression in patients with established PPMS[2,3], other features of T2 lesions, such as their increase over a short period of time, were reported to predict clinical outcome at five-year follow-up[2], suggesting that T2 lesion load may be relevant to determine disability, and, therefore, progression. Whether T2 lesion load is a predictor of disability over a longer period in patients with early PPMS has not been addressed.

Another tool is magnetization transfer imaging (MTI), which, although being dependant on the characteristics of scanners and sequences, and therefore less suitable for multi-centre studies, has a higher pathological specificity than conventional MRI. Magnetization transfer ratio (MTR) reflects demyelination and axonal loss, and can be measured in normal-appearing tissue, i.e. outside visible lesions[4]. We found that, in patients with early PPMS, MTR of the normal-appearing white matter (NAWM) and grey matter (GM) at baseline were the best predictors of clinical outcome at one and three-year follow-up, respectively[5,6]. Since MTR of GM predicted disability over a longer period than that of NAWM, and had, in addition, a steeper rate of change over time[6], MTR of the GM

appears the more promising candidate for predicting long-term progression in early PPMS. Although not yet confirmed, it has been suggested GM MTR abnormalities reflect axonal damage[7] and, to a greater extent, demyelination[4], mainly within GM lesions[8,9], since little is known about pathological findings outside GM lesions[9]. Moreover, GM lesions have been found to play an important part in determining disability in other forms of MS[10,11]. These findings prompted investigation of the MTR of GM as a potential measure to predict disability in PPMS.

We hypothesised that T2 lesion load and MTR of the GM at study entry were independent predictors of clinical progression over a five-year follow-up in early PPMS. We also assessed whether T2 lesion load and MTR of the normal-appearing brain correlated with progression over five years. We investigated the cohort of patients with early PPMS previously studied[5,6] and, in order to ensure that the effect of the imaging measures were independent of brain atrophy[12], our statistical analyses controlled for the NAWM and GM brain volumes. Clinical progression was measured by the expanded disability status scale (EDSS)[13], and, since this measure is known to have limitations in reflecting accumulation of disability over time[14,15], we also used the subsets of the multiple sclerosis functional composite (MSFC)[16], which is potentially more sensitive to clinical worsening[15].

METHODS

Subjects

Forty-seven patients with definite or probable PPMS[17] within five years of symptom onset and 18 healthy controls (10 female, mean age 34.56yrs., range 27-52) were studied at baseline (see their clinical and demographic characteristics in **table 1**). All subjects were then invited for clinical and radiologic assessment at baseline and every six months for three years, and again at five years. The number of individuals studied at each time point is shown in **supplemental table 1.** Although not all patients attended all time points, the use of linear mixed effect models allowed us to take into account all the clinical and radiologic data acquired at each time point for statistical analysis (see below), which corrected for the difference in age between patients and controls.

Regarding the five-year follow-up visit, 42 patients (16 female, mean age 44.38yrs., range 19-63) and 10 controls were assessed. The reasons for not being assessed, in patients, were: death for causes unrelated to MS (two cases); withdrawal from the study (three cases).

None of the patients was taking disease-modifying medication. Two patients had received a single course of intravenous corticosteroids for a deterioration of symptoms (two males, who received steroids at three and between three and five-year follow-up, respectively). Two patients were taking oral corticosteroids every three months (two males). One male patient took five courses of mitoxantrone between three and five-year follow-up.

The study was approved by the Joint Medical Ethics Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology, London, England.

Clinical assessments

At every visit, patients were scored on the EDSS[13]. Where possible, patients were also scored on the MSFC subtests (i.e., the timed 25-foot walk test [TWT], the nine hole peg test [NHPT] and the paced auditory serial addition test [PASAT])[16]. At the last follow-up visit, the EDSS was obtained in person in 27 patients; the EDSS of the remaining 15 patients was assessed by phone[18], since they were too disabled to undergo MRI, and declined the invitation to attend in person. The MSFC scores were obtained in 26 patients (out of those 27 who attended their last appointment).

Image acquisition and processing

At each time point, all subjects underwent the whole brain sequences described below, acquired using a 1.5-Tesla GE Signa scanner (General Electric Co, Milwaukee, Wisconsin). The scanner was upgraded during the study, increasing the maximum gradient strength from 22 mTm−1 to 33 mTm−1, and changing the imager software version from 5x to 11x.

1) Magnetization transfer (MT) dual echo spin-echo sequence, including PD and T2-weighted images, acquired with and without a MT presaturation pulse to calculate the MT ratio (MTR) images[19]. T2 lesions were contoured, and T2 lesion load (T2LL) and lesion masks were obtained[20]. GM and NAWM MTR histograms were generated (bin width, 0.1 percentage unit [PU]; smoothing window, 0.3 PU), and the histogram mean, peak location (PL) and peak height (PH) were calculated[6].

2) 3D inversion prepared fast spoiled gradient recall (FSPGR) images. Segmentation was carried out using SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology), for consistency with previous studies in the same patient cohort. For each tissue class, the output of the algorithm is an image, whose voxel intensity represents the probability (from 0 to 1) of belonging to that class. To obtain binary masks for NAWM and GM, we set a threshold of 0.75 for the NAWM and GM map, meaning that only those voxels with a 75% or more likelihood of being NAWM and GM, respectively, were retained)[6,21]. In patients, binary lesion masks were applied to the tissue probability maps to obtain NAWM, lesions, and GM maps. GM and NAWM volumes were divided by the total intracranial volume (sum of GM, NAWM, lesion and cerebrospinal fluid volumes), to obtain normalised volumes. These resulting volumes were multiplied by 100 to produce percentage GM and NAWM fractions[6].

Statistical analysis

Analysis was carried out with Stata 9.2 statistical software (Stata-Corp, College Station, Texas).

Assessment of clinical progression over five years

To assess changes in EDSS over time, the EDSS scores at baseline and at five years were compared using the Wilcoxon matched-pairs signed rank test, given its non-normal distribution. Changes in EDSS scores from baseline to five-year follow-up were then converted into steps by considering 1 step change equal to 1 point increase for values of EDSS of 5.5 or lower, and 0.5 increase in the EDSS for values of EDSS higher than 5.5, as previously described [5,6]; this unequal step size helps to overcome the intrinsic limitation of the EDSS in depicting real clinical changes at different levels of the scale. To assess changes in z-scores over time, scores of 180secs. and 300secs. were assigned to the TWT and NHPT of patients who were unable to perform these tests[22]. Then, all the MSFC subtests were transformed into z-scores (z-NHPT, z-TWT, and z-PASAT), using our baseline sample as reference[23]. Finally, rather than perform paired t-tests which lose data on patients not present at both baseline and final follow-up, changes over time were assessed using linear mixed regression models[24], which maximise the efficient use of all available data. In particular, each z-score recorded at each time point and for each subtest was used, in turn, as the dependent variable, and time was entered as the independent variable[25].

Prediction of clinical progression over five years

To identify predictors of progression, a multiple proportional odds ordinal logistic regression was used for the EDSS, and a multiple linear regression was used for the z-TWT, z-NHPT and z-PASAT. The EDSS step changes, and the z-score of each MSFC subtest at five-year were used as dependent variables, and age, gender, baseline z-scores (where appropriate) and baseline MRI measures were used as explanatory variables. To predict progression on the z-TWT, data from those unable to walk at baseline were excluded from the analysis, since their score at baseline would predict perfectly the score at five years, as both would be 180secs.

First, each MRI measure (i.e., MTR mean, PL and PH for GM and NAWM, percentage of GM and NAWM fractions, T2 lesion load) was entered singly into the model. Secondly, to assess the best MRI predictor of progression, the significant MRI measures were included together in a new regression model, and the significant variables retained, although a correlation between the MRI measures might contribute to a possible loss of significant association when they are put together into the model. Thirdly, to assess the proportion of variance of progression explained by the best MRI predictors (R-squared x100), final models were created considering only the MRI measures which were significant in the previous step.

Concurrent MRI and clinical changes over five years

To make the most efficient use of the data points, and to avoid bias from excluding subjects not present at both baseline and five years, associations between clinical and MRI changes were assessed using linear mixed longitudinal models[24], which estimated rates of change using all of a subject's available data points. When the MRI measure was the response variable, and 'group' and time were the explanatory variables, the groupxtime interaction term coefficient assessed the extent to which the group variable was associated with rate of MRI change over time, and estimated the difference in rates between different groups. 'Group' variables were both subject type, and, within patients only, clinical progression category. Additional explanatory variables were age, gender, and an additional indicator for whether a data point was observed before or after April 2004, to adjust for a scanner upgrade at that time.

To assess the correlations between MRI changes and clinical changes over time, similar models were used in patients only, but with clinical change and clinicalxtime interaction replacing the subject terms. The EDSS clinical change variable had three categories: minimal progression (deterioration ≤ 0.5 steps, 13 patients), moderate progression (deterioration of 1-2.5 steps, 13 patients), and considerable progression (deterioration ≥ 3 steps, 16 patients). For MSFC components the continuous Z scores were used.

Residuals from the final models, in both prediction and correlation analyses, were checked for normality and outliers.

RESULTS

Predictors of clinical progression over five years

Patients showed a significant increase in their disability during the follow-up, as measured by EDSS, z-TWT and z-NHPT (**table 2**). Progression on the EDSS was predicted by T2LL, NAWM PL MTR and percentage NAWM fraction measured at baseline (**table 3**). However, when these variables were put together into the same regression model to assess the best MRI predictor, none remained significant.

Worsening on z-TWT was predicted by T2LL, all the GM MTR histogram parameters, NAWM mean and PL MTR, and both percentages of GM and NAWM fractions ($p<0.001$) (**table 3**). When these variables were modelled together, T2LL, GM PL and PH MTR were significantly associated with progression (T2LL: Regression coefficient (RC, in z-TWT unit/mL) -0.04, 95%CI: -0.08, -0.01, p=0.007; PL: RC (z-TWT unit/pu) 1.73 z-TWT, 95%CI: 0.53, 2.93, p=0.007; PH: RC (z-TWT unit/pv) 527.4, 95%CI: 227.09, 827.73, p=0.002). The final resulting model, including, baseline T2LL, GM PL and PH MTR, together with z-TWT at baseline and age, explained 91% of the variance, which was significantly higher than the percentages obtained when the MRI variables were modelled individually (from 68% for GM PH MTR, to 80% for T2LL).
None of the MRI measures predicted changes in the z-NHPT and z-PASAT.

Concurrent MRI and clinical changes over five years

In patients, T2LL significantly increased over five years follow-up and all the MTR histogram parameters (except GM PH and NAWM PH), and both percentages of GM and NAWM fractions, significantly decreased (**Supplemental table 2**). T2LL increased by about 3mL (95%CI 2.1–3.9, p<0.0001) every year. Of the MTR measures, GM mean and PL MTR had the highest rate of reduction (RC: -0.384 and -0.235 per year, respectively). Of the volumetric measures, the percentage GM fraction decreased more than the percentage NAWM fraction (RC: -0.686 and -0.415 per year, respectively). In controls, none of the MRI measures changed over time. The rates of changes in all MRI measures, except GM and NAWM PH and PL MTR, were significantly greater in patients than in controls (**Supplemental table 2**).

In patients, a greater progression rate**,** as measured by EDSS, z-TWT, z-NHPT, and z-PASAT, correlated significantly with a steeper increase in T2LL (p<0.0005, p=0.001, p=0.009 and p=0.017, respectively). In addition, a greater decline in z-TWT and z-NHPT correlated with a faster rate of decline in GM mean MTR (p=0.008 and p=0.043, respectively); a steeper reduction in z-NHPT and z-PASAT correlated with a faster rate of reduction in GM PL MTR (p=0.045 and p=0.016, respectively). Finally, a greater rate of decline in z-NHPT correlated with a steeper reduction in NAWM PL MTR (p=0.025) (**Supplemental table 3**).

DISCUSSION

In this study of early PPMS we found evidence supporting the hypothesis that T2LL and GM MTR were independent predictors of the accumulation of disability, as measured by changes in TWT, considered a more responsive clinical endpoint in PPMS than the EDSS[15]. We found that T2LL and GM MTR had complementary roles, since the model including them together with age and TWT at baseline, explained 91% of the variance of the progression (as measured by changes in TWT). This was significantly higher than the percentages obtained by T2LL and GM MTR histogram parameters alone. A possible explanation for this finding is that combining T2LL and GM MTR provides a comprehensive assessment of the visible damage occurring in the white matter and of the "occult" involvement of the GM. However, the finding of a significant role of T2LL in predicting progression independently from the other MRI measures is in contrast with the results of the MAGNIMS studies performed in patients with well established PPMS[2,3], which reported that baseline T2LL did not predict progression after five and ten years. This may suggest the relevance of the T2LL to the accrual of disability declines in the later stages of PPMS. A similar finding has also been reported in the 20-year follow-up study of patients with relapse onset MS[26].

With regard to the GM damage, GM lesions are mostly undetected on conventional images[27], so that the damage in this tissue compartment, which has been reported to be extensive[9], cannot be assessed with conventional scans.

Instead, MTI has a higher histopathological specificity than T2 scans[28], although both normal-appearing GM damage and GM lesions may contribute to the observed abnormal GM MTR. Our findings, therefore, extend the results of our three year follow-up study performed in the same patient cohort[6], by highlighting the relevance of GM damage in determining disability, and therefore long-term progression, in patients with early PPMS. Due to the method used to segment the GM tissue, both cortical GM MTR and deep GM MTR contributed to the final MTR values. Thus, it is plausible that structures such as the thalamus, which is known to be affected by atrophy in PPMS[29] that correlates with disability[30], plays a role, in addition to the cortical GM damage, in contributing to progression. The prominent role of GM damage in determining disability in PPMS has been also suggested by other authors, who reported that GM damage quantified by means of diffusion tensor MRI at study entry was the best MRI predictor of clinical progression over the following five years[31].

Another important finding of our study was the strong correlation between clinical progression and changes in T2 lesion load and GM MTR over five years. However, while T2 lesion load changes correlated with clinical deterioration measured by all the clinical scales, the GM MTR decline strongly correlated with MSFC subtests decrease and only a trend was achieved for the correlation with EDSS changes. These findings highlight the higher sensitivity of the MSFC in detecting clinical changes[15] when compared with the EDSS, and extend the

results of the 10-year MAGNIMS study in patients with PPMS[3], which showed that the TWT at baseline predicted clinical progression, whilst EDSS did not.

We also found that the T2 lesion load and GM mean and PL MTR showed dynamic changes over time in patients, and distinguished between patients and controls, in agreement with previous reports[6,32]. Also, rates of GM MTR changes over time were higher than those of NAWM, suggesting that GM pathology changed more rapidly than the NAWM. Since a similar result has been reported in patients with early relapsing-remitting MS[32], one possible conclusion is that GM abnormalities develop faster than NAWM changes in the early stages of the disease.

We found that although NAWM MTR and percentage of NAWM and GM fractions predicted progression, especially if this was measured by TWT, when they were entered individually into the model, they became non-significant when they were modelled together and with the other MTR histogram parameters, suggesting that their role is less important than that of the T2 lesion load and the GM damage. The presence of strong correlations between the MRI measures may well have also contributed to the loss of correlation when they were combined. However, a recent paper reported that brain and spinal cord atrophy and GM MTR, when combined together, correlated with EDSS in patients with PPMS, who had a mean disease duration of 9.6 years[33], suggesting that the role of CNS

atrophy may be important if spinal cord atrophy is included, especially when patients with well-established PPMS are studied.

From the clinical point of view, patients significantly deteriorated over time on all the EDSS, TWT and NHPT, suggesting that progression in this cohort of early PPMS mainly related to the deterioration of motor function. Interestingly, the two MSFC subtests which reflected motor function (TWT and NHPT) showed stronger and more frequent correlations with the MRI measures than the EDSS. Despite the lack of progression on the PASAT over time in our cohort as a whole, probably due to a learning effect[6], we found that people with higher cognitive decline over five-years had steeper decline of GM MTR and higher lesion load increase, suggesting that these radiological measures have an impact on cognition in PPMS, as previously reported[34-36]. However, this finding should be taken cautiously, and further studies are needed to clarify the relative contribution of GM MTR changes to cognitive decline in PPMS.

Although a number of statistical tests are reported in this paper, we did not feel it was appropriate to adjust for multiple comparisons, as a number of separate null hypotheses was examined, rather than one single null hypothesis, whose error rate is affected by every reported test[37,38].

A possible limitation of this prospective, longitudinal study is that the number of patients who underwent the MRI scan and were assessed on the MSFC subtests

at five years was lower compared to the number of patients studied at baseline. However, we used mixed effects models[24] which estimate the mean rate of change of the response variable over time using information from all available data points in each subject. This minimises the bias which can result from excluding patients with missing data at the last time point (such patients may have higher or lower individual rates than other patients). Another limitation is that we did not take into consideration the involvement of the spinal cord, which may play a role in the development of disability in PPMS[39,40].

Finally, this study has the longest follow up of a cohort of early PPMS comprehensively investigated by means of MTI. We showed that combining measures that reflected both GM and WM damage improved on the currently available tools to predict the accrual of disability in PPMS. This combined assessment is more accurate in predicting clinical progression than previous approaches, which focused mainly on the WM damage, and, in particular, on the lesion load. Thus this approach may be of benefit either to monitor treatment effects or to identify patients with a higher risk for developing irreversible disability, for whom more aggressive therapeutic approaches might be offered.

In conclusion, a comprehensive assessment of the damage occurring in the WM and GM is an attractive approach that offers insights into the pathological mechanisms underlying progression in MS and may help to predict clinical progression.

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Table 1. Clinical and demographic characteristics of subjects at the study entry. Results are mean (SD) unless otherwise stated.

Clinical and demographic characteristics	**Patients** **N = 47**	**Controls** **N = 18**
Age	45.13 (10.66)	34.56 (5.79)
Gender, Female N (%)	19 (40.4%)	10 (55.6%)
Disease duration	3.38 (.8736)	-
EDSS, Median (range)	4.5 (1.5–7.0)	-
z-TWT	-0.099 (1.224)	-
z-NHPT	-2.25×10^{-7} (1)	-
z-PASAT	2.51×10^{-6} (1)	-

Table 1 (footnote). EDSS: expanded disability status scale; z-TWT: timed 25-foot walk test z-score; z-NHPT: nine hole peg test z-score; z-PASAT: paced auditory serial addition test z-score. SD: standard deviation.

Table 2. Clinical data in patients at baseline and at five years follow-up, and clinical changes over time.

Clinical measures				
	Baseline Median (range)	**Five years Median (range)**	**Change from baseline to five years follow-up p[a]**	
EDSS	4.5 (1.5–7.0)	6.5 (1.5–8.5)	**<0.00005**	
	Baseline Mean (SD)	**5 years Mean (SD)**	**Yearly rate of change, from baseline to five years follow-up RC (95%CI)**	**p[b]**
z-TWT	7.71×10^{-7} (1)	-1.451 (2.725)	-0.215 (-0.284, -0.022)	**0.007**
z-NHPT	-2.25×10^{-7} (1)	0.051 (1.145)	-0.096 (-0.132, -0.054)	**<0.0005**
z-PASAT	2.51×10^{-6} (1)	0.414 (1.159)	0.013 (-0.037, 0.064)	0.615

Table 2 (footnote). [a]: Wilcoxon matched-pairs signed rank test; [b]: Longitudinal model (see text for further details). EDSS: expanded disability status scale; z-TWT: timed 25-foot walk test z-score; z-NHPT: nine hole peg test z-score; z-PASAT: paced auditory serial addition test. SD: standard deviation; RC (95%CI): regression coefficient (given as z-score unit change/year) (95% confidence interval), which represents the annual change of each z-score; p: p value.

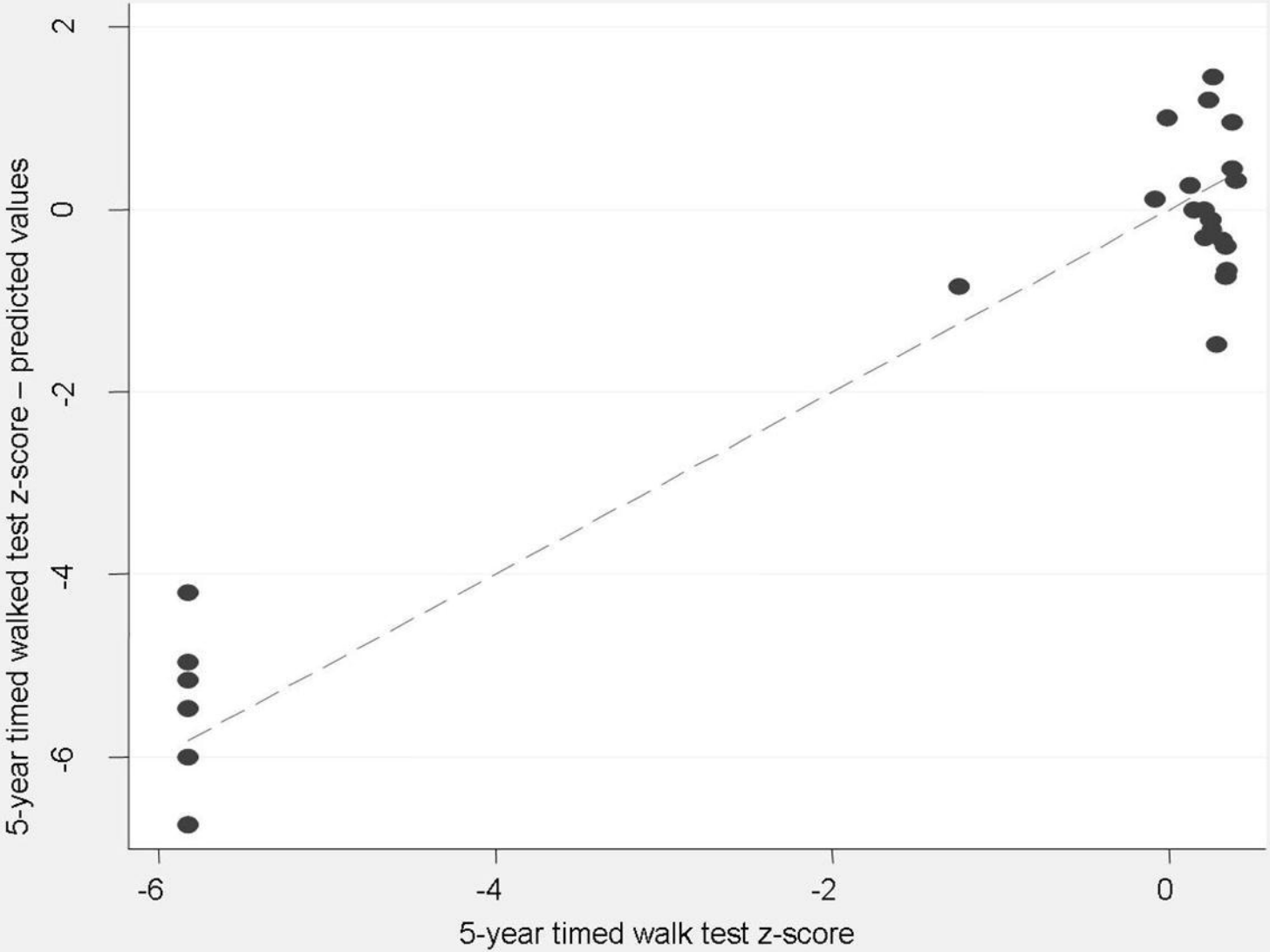
Table 3. Results of the regression models used to predict progression when MRI measures were entered individually into the model.

MRI MEASURES MODELLED INDIVIDUALLY (*FIRST STEP*)												
Baseline MRI measures	**EDSS**			**z-TWT**			**z-NHPT**			**z-PASAT**		
	OR (95%CI)	p^a	R^2	RC (95%CI)	p^b	R^2	RC (95%CI)	p^b	R^2	RC (95%CI)	p^b	R^2
T2LL	1.03 (1.01, 0.05)	**0.015**	0.09	-0.09 (-0.12, -0.06)	**0.0001**	0.80	-0.01 (-0.03, 0.002)	0.080	0.77	-	0.131	-
GM mean MTR	0.61 (0.36, 1.02)	0.057	0.08	1.52 (0.90, 2.14)	**0.0001**	0.76	-	0.450	-	-	0.120	-
GM PL MTR	-	0.255	-	3.29 (1.81, 4.77)	**0.0001**	0.74	-	0.293	-	-	0.705	-
GM PH MTR	-	0.154	-	858.12 (381.44, 1334.81)	**0.001**	0.68	-	0.447	-	-	0.263	-
NAWM mean MTR	0.58 (0.30, 1.1)	0.093	0.07	2.15 (1.2, 3.09)	**0.0001**	0.74	-	0.371	-	-	0.270	-
NAWM PL MTR	0.44 (0.21, 0.92)	**0.029**	0.08	2.11 (1.13, 3.1)	**0.0001**	0.73	-	0.407	-	-	0.249	-
NAWM PH MTR	-	0.324	-	266.4 (-1.93, 534.72)	0.052	0.56	-	0.952	-	-	0.444	-
PGMF	-	0.165	-	0.63 (0.28, 0.97)	**0.001**	0.69	-	0.116	-	-	0.138	-
PNAWMF	0.78 (0.61, 0.99)	**0.037**	0.08	0.70 (0.35, 1.05)	**0.0001**	0.71	-	0.183	-	-	0.278	-

Table 3 (footnote). [a]: Multiple proportional odds ordinal logistic regression (results adjusted by age and gender); [b]: Multiple linear regression analysis (results adjusted by age, gender, and baseline z-scores). EDSS: expanded disability status scale; z-TWT: timed 25-foot walk test z-score; z-NHPT: nine hole peg test z-score; z-PASAT: paced auditory serial addition test. OR (95%CI): odds ratio (95% confidence interval); RC (95%CI): regression coefficient (95% confidence interval), which indicates the amount of change in the clinical score (in z-score units) per unit of change in the MRI variable (see below). R^2: R-squared, which indicates the proportion of variance of the dependent variable which is explained by the model. T2LL: T2 lesion load. GM: grey matter; NAWM: normal appearing white matter. MTR: magnetization transfer ratio; PL: peak location; PH: peak height; mean, PL and PH are MTR histogram parameters (see text for further details). PGMF: percentage grey matter fraction; PNAWMF: percentage normal appearing white matter fraction. Units of MRI measures are: mL, for T2 lesion load; percentage units, for mean and PL MTR; percentage volumes (x1000), for PH MTR; and percentage units (%), for PGMF and PNAWF.

Legend

Figure 1. Predicted versus real z-TWT scores at five years. This graph represents the correlation between timed 25-foot walk test z-scores (z-TWT) at five years (x-axis) and the predicted z-TWT (y-axis) according to our regression model, which included z-TWT at baseline, age, baseline T2 lesion load, GM peak location (PL) and peak height (PH) MTR.



dotted line is line of equality (perfect fit)