Changing Associations Between Cognitive Impairment and Imaging in Multiple Sclerosis as the Disease Progresses

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The authors explored cross-sectional associations between MRI parameters (lesion metrics, brain volumes, magnetization transfer ratio histograms, and metabolite concentrations) and cognition in 61 patients who experienced clinically-isolated syndromes (CIS) 7 years earlier. IQ decline and poorer overall cognition were associated with T2 white-matter lesions, and slow information-processing with both T2 lesions and gray-matter atrophy. In a previous study of the same cohort, gray-matter atrophy measured shortly after CIS failed to predict development of cognitive impairment years later. Our findings suggest that gray-matter pathology, reflected by atrophy measurements, becomes increasingly important in determining cognition as MS progresses.

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Cognitive impairment occurs in 40%–65% of patients with multiple sclerosis (MS),[1] including those with clinically isolated syndromes (CIS).[2] Information-processing speed, attention, memory, and executive functions are commonly impaired.[3] Correlating magnetic resonance imaging (MRI) abnormalities with measures of cognitive functioning is important both in elucidating pathological mechanisms underpinning cognitive impairment and in predicting early in the disease those likely to develop cognitive impairment later.[4–6] Focal inflammatory lesions on conventional MRI correlate only modestly with cognitive impairment,[1] and the role of diffuse pathology in normal-appearing brain tissue is increasingly recognized. Several cross-sectional studies have reported that measures of atrophy,[7,8] changes in magnetization transfer ratio (MTR),[9,10] and in 1H-MRS (magnetic resonance spectroscopy) metabolite concentrations[11] are more closely correlated with cognitive impairment than lesion metrics. The contribution of gray-matter pathology to physical and cognitive disability[12] is increasingly recognized, and gray-matter atrophy has been described in association with cognitive impairment.[13]

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In a previous study, using imaging data obtained shortly after the initial CIS, we reported that T1- and T2-weighted and Gad-enhancing lesion metrics and increase in myo-inositol concentration in normal-appearing white matter (NAWM) were the best predictors of cognitive impairment in patients assessed 7 years later, whereas the volume of the gray matter was not an independent predictor.[5] Using the same longitudinal cohort, we examine here the associations between a wide range of imaging parameters and neuropsychological data obtained contemporaneously, 7 years after the initial CIS, using a cross-sectional design. We aimed to explore whether the imaging parameters associated with cognitive impairment in this cross-sectional study were the same as those from baseline imaging that predicted future cognitive impairment in our earlier study.[5]

PATIENTS AND METHODS

Subjects

Sixty-one patients (38 women, 23 men) with a mean age of 40.4 years (range: 25 to 57) took part in the study. Patients were part of a larger longitudinal cohort (N=178) recruited within 3 months of presentation with a CIS;[14] 47 had optic neuritis, 1 had an optic tract lesion, 10 had brainstem, and 3 had spinal cord syndromes. We selected patients for the present study from among those who had reached the 7-year follow-up and, therefore, had undergone neuropsychological testing and imaging (mean interval from baseline: 6.9 years; range: 4.7–9.8). Exclusion criteria were the presence of other neurological or systemic illness, psychiatric illness, head injury leading to loss of consciousness, and substance abuse. We used the 2005 McDonald criteria[15] to diagnose MS. At the time of the study 19 still had CIS; 34 had clinically-definite MS (32 relapsing–remitting, 2 secondary progressive), and 8 met MRI criteria[15] for MS, although they had not experienced further clinical events. Fifty-one of these subjects had taken part in our earlier study predicting later cognitive impairment from imaging obtained at the time of the initial CIS.[5] The same cognitive data were used in both this and our previous study. The study was approved by local ethics committees, and patients gave informed written consent.

Clinical Examination

We used the Expanded Disability Status Scale (EDSS)[16] and the Hospital Anxiety and Depression Scale (HADS).[17] Scores of ≥11 on the HADS subscales were considered indicative of anxiety or depression. A history of use of disease-modifying treatment (DMT) was recorded, based on patient self-report and clinical records.

Cognitive Assessment

Two trained psychologists (SP and MS) administered a comprehensive neuropsychological battery in one 2-hour session within a month of the clinical and MRI assessment. It was not possible to obtain a valid result for all patients on all tests, for a variety of reasons, including physical impairment, dyslexia, English not being the first language, and time constraints. The total number of patients who completed each test is shown in Table 1.

We assessed the following cognitive domains:

1. **General intellectual functioning**, using the Wechsler Adult Intelligence Scale–Revised (WAIS–R).[18] Four verbal subtests (Vocabulary, Digit Span, Arithmetic, Similarities) and three performance subtests (Picture Completion, Picture Arrangement, Block Design) were used to pro-rate Verbal and Performance IQ (VIQ and PIQ) scores. Premorbid intellectual functioning was estimated with the National Adult Reading Test (NART).[19] The WAIS–R IQ was subtracted from the NART IQ to provide an index of IQ decline for both verbal and performance IQs. Thus, a positive IQ change score indicated a decline in current IQ from the premorbid estimate. IQ decline was defined as a difference of ≥15 points between current and premorbid IQ.
2. **Verbal and visual recall memory**, using the immediate and delayed conditions of the Story and Figure Recall subtests of the Adult Memory and Information Processing Battery.[20]
3. **Attention/speed of information processing**, using the PASAT (Paced Auditory Serial Addition Test, 3-second version)[21] and the written version of the Symbol Digit Modalities Test (SDMT).[22]
4. **Executive functions**, using the Hayling Sentence Completion Task,[23] a test of verbal response-generation and inhibition, and the Brixton Spatial Anticipation Test,[23] a spatial reasoning, rule-detection, and rule-change task.

Raw test scores were compared with those of published, age-matched, healthy controls. Scores ≤ the 5th percentile of the norms were considered to indicate impairment, except for the SDMT, for which normative centile data were not available, where the cut-off point was a z-score ≤1.5 standard deviations (SD) below the

TABLE 1. Neuropsychological Test Scores and Number of Patients Impaired

Measure	Mean	(SD)	Range	Number Impaired/Tested[ab]
General intellectual functioning				
Current Verbal IQ	97.92	(15.06)	72 to 134	3/61
Current Performance IQ	99.70	(16.07)	74 to 140	2/61
Verbal IQ decline[c]	4.71	(8.13)	−19 to 24	7/55*
Performance IQ decline[c]	3.42	(11.23)	−24 to 24	13/55**
Memory				
Story Recall: immediate (max. score: 56)	34.85	(11.07)	2 to 53	4/61
Story Recall: delayed (max. score: 56)	33.08	(11.57)	0 to 52	3/59
Figure Recall: immediate (max. score: 80)	65.44	(13.08)	17 to 80	1/59
Figure Recall: delayed (max. score: 80)	64.91	(13.31)	32 to 80	1/57
Attention/speed of information-processing				
PASAT (max. score: 60)	40.81	(16.23)	0 to 60	13/52**
SDMT	47.67	(10.89)	10 to 78	10/59**
Executive functions				
Hayling Part 2: errors (max. score: 50)	4.86	(8.02)	0 to 38	6/57†
Hayling: total of scaled scores (max. score: 23)	17.93	(2.70)	7 to 22	4/57
Brixton: errors (max. score: 54)	16.31	(8.83)	4 to 50	7/55*

PASAT: Paced Auditory Serial Addition Test; SDMT: Symbol Digit Modalities Test.
[a]It was not possible to obtain a valid result for all patients for all tests for a variety of reasons, including patients' physical impairments and time constraints, dyslexia, and English not being the native language.
[b]Binomial single-proportion exact test comparing the proportion of subjects actually impaired with the expected 5%.
[c]A positive value indicates decline.
*$p < 0.01$; **$p < 0.001$; †$p = 0.0833$.

mean of the published norms.[22] Patients were considered to be cognitively impaired if they failed in two or more tests, a criterion used in previous studies.[2,10] Also, we converted raw test scores of all the measures included in Table 1 except current IQ and Hayling error score to z-scores, so that a lower score always indicated poorer performance. Z-scores were then averaged to produce an index of overall cognitive performance/impairment.

Magnetic Resonance Imaging (MRI)

MRI was performed on a 1.5-tesla Signa scanner. The details of the MRI sequences have been previously reported.[24] The following classes of MRI variables were measured at 7 years:

1. **Hyperintense T2 lesions** were identified on both proton-density and T2-weighted images and were contoured by a research neurologist (JS) on the proton-density images, using a semi-automated contouring technique (D. L. Plummer; University College London; London, U.K.).[25] The total number and volume of these lesions were calculated. *Hypointense T1 lesions* were identified and contoured on post-contrast T1-weighted spin-echo images, and their volumes were calculated.
2. **Gray- and white-matter volumes and total brain volume** were measured with a 3D, fast spoiled, gradient-recall sequence (TR: 10.9 msec, TE: 4.2 msec, TI: 450 msec, 128×1.5-mm contiguous coronal slices). A mask of lesions in T2-weighted images was created to avoid misclassification. The T1 images were segmented, using SPM99, and results were expressed as fractions of total intracranial volume.
3. **MTI:** An interleaved 2D sequence[26] was used to carry out generation, lesion-masking, segmentation, normalization, and histogram analysis of MTR maps,[24] yielding the mean, peak height, and location for NAWM and NAGM.
4. **1H-MRS metabolite concentrations (total N-acetyl aspartate, myo-inositol, choline, creatine, and glutamate–glutamine)** were measured in a voxel manually placed in the NAWM of the posterior parietal/centrum semiovale region. This large, white-matter region was selected to facilitate the exclusion of lesions, gray matter, and cerebrospinal fluid from the voxel. The mean voxel size was 2.00 ml (SD: 0.71). A point-resolved spectroscopy sequence (PRESS) was used, and metabolites were measured by use of the linear combination model.[27]

Statistical Analysis

We used binomial, single-proportion exact tests to compare the number of patients failing a specific neuropsychological test with the expected number in the general population (i.e., 5%). Patients who had converted to MS and those

who had not were compared with regard to demographic and clinical variables by use of χ^2 tests, *t*-tests, and Mann-Whitney rank-sum tests, as appropriate. For comparisons of neuropsychological scores, we entered a binary group indicator into a multiple linear-regression model for each cognitive measure, with age, gender, premorbid IQ, and years of education as covariates.

Only MRI and neuropsychological variables with significant associations in Spearman's correlations were entered into regression models. We used the following staged strategy in multiple linear regressions for each neuropsychological dependent variable:

1. We identified independent predictors from among age, gender, premorbid full-scale IQ, and level of education by entering these variables singly and retaining those with $p < 0.10$. These relevant covariates were then retained in the models at all subsequent stages.
2. We identified independent predictors within an MRI class by entering the variables identified by Spearman's correlations singly and retaining those with $p < 0.05$.
3. Where relevant, we identified overall, independent predictors by entering singly the variables identified in #2.
4. We added baseline EDSS and HADS scores and a binary variable signifying whether the patient had ever had DMT, singly, to the model generated in #4, as they may have been related to the MRI abnormalities.
5. We checked residuals from the final models in #3 and #4 for normality and outliers.

All tests used were two-tailed. No corrections were made for multiple comparisons, because these would have assumed independence in cognitive scores.

RESULTS

At follow-up, median EDSS was 1 (range: 0–6); 59 patients were able to work; 58 lived independently; and 1 was in residential care; 10 patients were receiving, or had previously received, disease-modifying treatment (DMT), and 3 were on antidepressant medication.

Of the 54 patients for whom ratings of anxiety and depression were obtained, 16 (29.6%) scored above the cut-off point for anxiety, and 4 (7.4%) were over the cut-off point for depression. All patients were included in the analysis, but we controlled for HADS scores.

There were no differences between patients whose diagnosis was still CIS and those who had converted to MS in age, years of education (overall mean: 13.8 years; SD: 3.10), premorbid IQ (overall mean: 104.2; SD: 14.0) or depression ratings (overall mean: 4.87; SD: 3.83), but those with MS had higher EDSS (median [interquartile range, or IQR]: MS: 1.5 [1], CIS 1 [1]; $p < 0.001$) and anxiety ratings (median [IQR]: MS: 9.5 [6], CIS 5.5 [4.5]; $p < 0.05$).

Pattern of Cognitive Impairment

Neuropsychological results are detailed in Table 1. Fifty-seven patients had completed most or all tests. Of these, 29 (50.9%) were not impaired on any test, and 17 (29.8%) scored below the 5th percentile on at least two tests and were considered to be "cognitively impaired." Compared with the normative data, more patients than expected had significant Verbal and Performance IQ decline and were impaired on tests of attention/speed of information-processing (PASAT and SDMT) and executive functioning (Brixton Test and a trend for Hayling Test; see Table 1 for proportions impaired and significance levels).

Four out of 22 CIS patients (18.2%) were "cognitively impaired," versus 13 out of 35 MS patients (37.1%); this difference failed to reach statistical significance (χ^2=2.3205; NS). Cognitive scores were lower in MS than CIS patients, but these differences also failed to reach statistical significance. Older age at disease onset predicted poorer performance on the Brixton Test (p=0.018) and on the delayed Story Recall test (p=0.043).

MRI Correlates of Cognitive Performance

Only performance on the SDMT, decline in verbal IQ, and overall cognitive performance were predicted by MRI parameters independently of demographic covariates (age, gender, premorbid full-scale IQ, and level of education; Table 2). For the SDMT, a model incorporating the number of T2 lesions, GM volume, premorbid IQ, and educational level explained 63% of the variance. For Verbal IQ decline, the best model included the number of T2 lesions and female gender; this model only explained 14% of the variance. For the overall cognitive performance index, a model including number of T2 lesions, male gender, and premorbid IQ explained 26% of the variance.

T2 lesion metrics were the most significant MRI parameters in all three models, but it was not possible to separate the independent effects of number, volume, or location of lesions, as these variables were closely related. T1 lesion metrics were not independently associated with

TABLE 2. Regression Models

	Regression Models		
Dependent Variables	**Verbal IQ Decline**	**Symbol Digit Modalities Test**	**Overall Cognitive Performance**
Model data	N=52; adjusted R^2=0.137	N=47; adjusted R^2=0.626	N=51; adjusted R^2=0.264
Gender	β=4.10; p=0.059 (CI: –0.16 to 8.36)	NS	β = –0.21; NS; (CI: –0.49 to 0.06)
Premorbid full-scale IQ	NS	β=0.49; p=0.016 (CI: 0.10 to 0.88)	β=0.147; p=0.049 (CI: 0.00 to 0.29)
Educational level	NS	†β: No GCSE/equivalent: 0; GCSE/equivalent: 0.87; A-levels: 1.02; degree: 0.37; postgraduate: 1.64; p=0.055	NS
Number of T2 lesions	β=2.45; p=0.023 (CI: 0.36 to 4.55)	†β: 0=0; 1 to 10=0.47; 11 to 50=0.45; 51+ = –0.86; p=0.029	†β: 0=0; 1 to 10=0.17; 11 to 50=0.08; 51+ = –0.52; p=0.007
Gray-matter fraction	NS	β=0.36; p=0.038 (CI: 0.02 to 0.70)	NS

†Entered as a categorical indicator because of evidence of nonlinearity; therefore, confidence interval (CI) not available.
β: standardized regression coefficient (gives the change in raw units of the cognitive measure for a one-SD increase in the predictor variable) with the exception of gender (0: male; 1: female), educational level, and number of T2 lesions when entered as a categorical variable, where β is unstandardized; A-level, advanced level; CI: 95% confidence interval; GCSE: General Certificate of Secondary Education; NS, not a significant predictor.

cognitive performance after controlling for T2 lesion metrics and/or demographic variables. 1H-MRS metabolite concentrations, MTR changes, and WM volume loss were not associated with cognitive performance.

DISCUSSION

The salient finding of this cross-sectional study of patients examined 7 years after their initial CIS is the association between cognitive deficits, in particular attention and speed of information-processing, and T2 lesion metrics and loss of gray-matter volume in contemporary imaging. Changes in white-matter volume, MTR, or 1H-MRS metabolite concentrations were not significantly associated with the presence of cognitive impairment.

Two-thirds of our patients met criteria for MS 7 years after experiencing a CIS, in keeping with the findings of several longitudinal studies,[28,29] and, therefore, our sample can be seen as representative of the natural history of the disease. Patients who had not converted to MS did not differ significantly in their cognitive performance from those who had, although they tended to perform better, and fewer were "cognitively impaired." This finding is in keeping with our earlier report in a different patient cohort,[30] and the presence of cognitive impairment in CIS patients is the more likely explanation.[31]

One-third of our patients were cognitively impaired, by use of standard criteria,[2,10] and their cognitive profile was similar to that described by others,[2,4,32] with impairment in attention/speed of information-processing and executive functions. This pattern has been attributed to disturbed connectivity resulting from white-matter damage,[33] as these cognitive functions require the rapid transfer of information between different cortical regions along white-matter tracts. Decline in Verbal and Performance IQ was also present in our patients, a finding previously considered to be uncommon in MS populations,[34] but in keeping with a recent meta-analysis reporting intellectual decline of a small-to-moderate effect size.[32] High premorbid IQ and educational history predicted better cognitive performance, suggesting, as in our previous study,[5] that "cognitive reserve" influences compensatory reorganization of cognitive networks.

In our previous study of an almost-identical patient sample,[5] cognitive performance at the 7-year follow-up was predicted by T1 and T2 lesion metrics, but not by the loss of gray-matter volume, measured at the time of the initial CIS. By contrast, in the cross-sectional study presented here using imaging data obtained at the 7-year follow-up, loss of gray-matter volume was more closely, and independently, associated with cognitive performance. The reasons for the differences between these two studies are unclear. Gray-matter atrophy reflects demyelination and neuroaxonal damage due to intrinsic cortical pathology and/or secondary to white-matter damage,[12] and it has been observed to increase over time[35] and to be associated with impaired cognitive performance early in the disease[13,36–38] and to predict early conversion to MS.[39] A possible explanation for our findings is that whereas white-matter lesions are the main pathology in CIS, gray-matter pathology becomes increasingly evident over time and increasingly contributes to cognitive impairment. The relative contribution

of primary and secondary gray-matter pathology to cognitive impairment remains to be determined.

1H-MRS metabolite concentrations were not associated with contemporaneous cognitive impairment, although, in our previous study,[5] increases in myo-inositol, a marker of glial and inflammatory cells, shortly after the initial CIS, predicted poor executive functioning years later. There is no obvious explanation for this discrepancy, although serial metabolite concentrations appear to be a poor indicator of progressive pathology in relapsing–remitting MS.[40]

The major limitation of our study is that patients in this longitudinal cohort were not tested neuropsychologically when recruited after their initial CIS, and, therefore, it has not been possible to compare baseline cross-sectional MRI–cognitive associations with those presented here. It remains possible that gray-matter volume would have been associated with contemporaneous cognitive performance at baseline. Furthermore, we did not control for levels of fatigue, a potential confounder of the association between MRI parameters and cognitive impairment. Future studies using imaging methods more able to detect intrinsic cortical pathology and subtle abnormalities in normal-appearing brain tissue will increase our understanding of the neuropathological mechanisms that determine cognitive impairment over the course of the illness.

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