Posterior fossa lesion volume and slowed information processing in multiple sclerosis

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Summary
The relationship between performance on information processing efficiency measures and MRI-derived lesion volume including global and regional T2 and T1 lesion volumes was investigated in 20 patients with relapsing--remitting multiple sclerosis (RRMS) and secondary progressive multiple sclerosis (SPMS). Processing speed, as measured by the Sternberg Memory Scanning Test, was significantly correlated with posterior fossa lesion volume and slowed reaction time in seven out of eight patients (six out of seven with SPMS) with any lesion volume in the posterior fossa suggesting a ‘threshold effect’. Processing capacity as measured by the Salthouse Keeping Track Test was not significantly correlated with the MRI measures. Cognitive performance did not correlate with Expanded Disability Status Scale score, depression or fatigue, and patients performed within normal limits on tests of attention/concentration ability. The significant relationship between posterior fossa lesion volume and memory scanning speed in this study suggests that pathological damage in the posterior fossa may contribute to slowed cognitive processing and may be an important direction for future studies of cognitive function in multiple sclerosis. Lack of correlation of cognitive measures with the other MRI measures may be due to low lesion volume relative to other studies, sample composition, and limited pathological specificity of the MRI measures.

Keywords: multiple sclerosis; MRI; cognition; cerebellum; brainstem

Abbreviations: RRMS = relapsing--remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; EDSS = Expanded Disability Status Scale; PASAT = Paced Auditory Serial Addition Test; WMS-R = Wechsler Memory Scale-Revised


Introduction
Information processing efficiency, conceptualized to require cognitive speed, complex attention and working memory capacity, is an important domain of cognitive dysfunction in patients with multiple sclerosis (Thornton and Raz, 1997; Fisher, 2001; Benedict et al., 2002). Although not uniformly impaired, a significant proportion of multiple sclerosis patients have shown impaired performance on neuropsychological tests of information processing efficiency such as the Oral Symbol–Digit Modalities Test (Beatty et al., 1988; Franklin et al., 1988; Swirsky-Sacchetti et al., 1992; Camp et al., 1999; Sperling et al., 2001) and the Paced Auditory Serial Addition Test (PASAT) (Litvan et al., 1988; DeLuca et al., 1993, 1994, 1998; Kujala et al., 1995, 1997; Camp et al., 1999; Demaree et al., 1999; Archibald and Fisk, 2000). Impairment has also been reported with laboratory-based paradigms such as choice reaction time (Jennekens-Schinkel et al., 1988, 1990; Kujala et al., 1994; Kail, 1998), the Sternberg Memory Scanning Test (Rao et al., 1989, 1991; Archibald and Fisk, 2000), the Salthouse Keeping Track Test (Archibald and Fisk, 2000) and dual-task/Baddeley methodology (Grant et al., 1984; Beatty et al., 1988; Rao et al., 1993; Grigsby et al., 1994; Ruchkin et al., 1994; D’Esposito et al., 1995, 1996).

The Sternberg Memory Scanning Test (Sternberg, 1966) and the Salthouse Operational Working Memory Capacity Test or Keeping Track Test (Salthouse et al., 1991) are useful...
for the assessment of processing efficiency in this patient population. The Sternberg Test requires the participant to determine whether a test number (ranging from 1 to 9) was or was not a member of a previously presented set of numbers (memory set) that varied in size across trials (1–6 numbers/set). Although the dependent measure in the Sternberg task is reaction time (RT), it controls for perceptual–motor abnormality that may confound measurement of cognitive speed, a common problem in neuropsychological studies of multiple sclerosis, through the use of the slope of the RT function. The RT slope is a measure of serial comparison or memory scanning speed, while the y-intercept value reflects the speed of perceptual and motor processes. The Salthouse Keeping Track Test (Salthouse et al., 1991) is a measure of complex attention and working memory capacity that requires the participant to keep track of from one to four parallel sequential timed arithmetic operations (Archibald and Fisk, 2000). The Salthouse task measures performance in terms of accuracy not RT, thereby eliminating the potential confound of the time required to execute a motor act. It is designed to assess central processing capacity rather than specific working memory functions such as the articulatory loop assessed with the Brown–Peterson test (e.g. Grigsby et al., 1994), and does not suffer from limitations of task inequivalence common to dual-task approaches (Hegarty et al., 2000).

The Salthouse task also affords advantages compared with the PASAT, a commonly employed test in studies of multiple sclerosis. The PASAT is a serial addition task in which the participant is required to add consecutively orally or visually presented numbers in pairs. In the PASAT, the participant provides an answer before adding the next number in the sequence to the number just before it, not to the answer. The number sequences are presented at different rates, to vary processing demands. While the PASAT taxes the working memory system by varying the stimulus presentation rate, it requires an invariant number of processing operations in every trial. Alternatively, the Salthouse task permits systematic measurement of operational working memory capacity by varying the amount of processing (operations). Finally, the PASAT has been shown to be amenable to strategy use that makes the task a test of simple addition rather than a working memory test, and thus ‘artificially’ elevates total correct scores (Snyder et al., 1993, 2001; Archibald and Fisk, 2000).

In a previous study (Archibald and Fisk, 2000), cognitive processing speed measured by the Sternberg Memory Scanning Test was significantly slowed in multiple sclerosis patients relative to matched, neurologically intact controls. However, on the Salthouse measure, only the secondary progressive multiple sclerosis (SPMS) patients had an additional decrement in working memory capacity as task demands increased. These differences occurred in the absence of impairment on standardized neuropsychological tests and were not related to depression, fatigue or physical disability as measured by the Expanded Disability Status Scale (EDSS). As the sample was comprised of relapsing–remitting multiple sclerosis (RRMS) and SPMS patients with mild to moderate neurological disability, these findings suggested that the Sternberg and Salthouse tests were sensitive measures of mild (early) memory dysfunction.

To investigate further the utility of the Sternberg and Salthouse tasks as markers of disease progression in multiple sclerosis, the present pilot study was conducted to examine the relationship between performance on these tests and MRI measures. Evidence that impaired performance on these tasks correlates with MRI measures would provide justification for a larger scale study to assess their value as sensitive outcome measures of disease progression in multiple sclerosis. MRI measures included total lesion volume and frontal lesion volume, due to previous reports that they are associated with working memory impairment in multiple sclerosis (D’Esposito et al., 1995). Also included was measurement of lesion volume in the posterior fossa due to conflicting reports in the literature about a relationship with performance on neuropsychological tests (Baumhefner et al., 1990; Rao et al., 1990; Sperling et al., 2001). An abbreviated battery of clinical measures and questionnaires was included to aid interpretation of test findings.

Methods

Subjects

Twenty patients from the University of Calgary Multiple Sclerosis Clinics were recruited to participate in this study. Eligibility criteria included: (i) diagnosis of clinically definite multiple sclerosis (Poser et al., 1983); (ii) diagnosis of either an RRMS or SPMS course of multiple sclerosis; and (iii) mild to moderate neurological impairment as determined by board-certified multiple sclerosis neurologists using the EDSS (Kurtzke, 1983). Patients were excluded from the study if they were experiencing an exacerbation of symptoms, had received corticosteroid treatment within 4 weeks of testing, or had reported disabling pain. They were also excluded from the study if they reported a history of drug or alcohol abuse, major psychiatric disorder, learning disability, seizures, head trauma, or neurology disorder other than multiple sclerosis. Six patients reported use of antidepressants (fluoxetine, desipramine, amitriptyline, venlafaxine and bupropion), two reported use of a sedative–hypnotic (zopiclone), five reported use of hormone replacement therapy, and four patients reported use of anti-fatigue medication (amantadine). As data collection occurred prior to the introduction of disease course-modifying therapy, no patients were taking these medications. For each patient, all the cognitive tests were performed in one session, and sessions occurred within 2 weeks prior to the MRI scan. Seven patients with RRMS and 13 patients with SPMS met all of the inclusion and exclusion criteria and were involved in the study. Fifteen of the patients were female and five were male, and the mean age was 48.5 ± 7.8 years (mean ± SD). The EDSS scores ranged from 1.5 to 6.5 (4.2 ± 1.9). Disease duration ranged from <1 year to 12 years (4.6 ± 3.8). Mean years of formal education were 14.6 ± 3.1 (mean ± SD). In the absence of normative data and a control group, performance data were compared with data from a sample of healthy participants from the Archibald and Fisk (2000) study. The samples were comparable in terms of gender composition (3 : 1) and years of formal education, but the patient sample was older (48.5 ± 7.8 versus 38.0 ± 13.0 years, P = 0.002). The study was approved by the
Informed consent was obtained from all study participants in agreement with institutional policies after the nature of the procedures had been fully explained.

**MRI acquisition and analysis**

All brain MRIs were acquired on a GE Signa 3.0 T MRI system (GE Medical Systems, Milwaukee, WI) at the Seaman Family MR Research Centre, Foothills Medical Centre, Calgary, Alberta, Canada. For each patient, the following sequences were performed in a single session: (i) spin echo (SE) T1-weighted [repetition time (TR)/echo time (TE) = 500/9 ms, NEX = 2, matrix = 512 × 256]; and (iii) fluid attenuated inversion recovery (FLAIR) [TR/TE/inversion time (TI) = 12002/135/2500 ms, NEX = 0.5, matrix = 512 × 192]. To cover the entire brain, 19 axial 5 mm thick slices with 2 mm gaps were obtained for all the sequences. The field of view (FOV) was 220 × 220 mm and the image reconstruction matrix was 512 × 512, thus an in-plane resolution of 0.4348 × 0.4348 mm was obtained. A standard patient set-up and slice orientation procedure was used to minimize patient motion during the scans (Mitchell et al., 1997).

Global lesion volumes were obtained using a semi-automatic image segmentation program that classifies image voxels into predefined lesions and non-lesions based on their characteristics of signal intensity pattern and connectivity properties (Mitchell et al., 1994). The accuracy and reproducibility of this program had been evaluated extensively (Mitchell et al., 1996). Initially, a radiologist (J.N.S.), who was blinded to the results of cognitive testing and the clinical characteristics of the patients, labelled several small non-lesion regions (normal appearing white matter, grey matter and CSF) to ‘train’ the program. Next, the radiologist viewed the images again and identified individual lesions. A T2 lesion was defined as an area of increased signal on T2-weighted images and which appeared bright on FLAIR, and a T1 lesion was an area with signal intensity between those of grey matter and CSF on T1-weighted images and also appeared bright on T2-weighted images. Such T1 lesions were also called ‘black-holes’ (Truyen et al., 1996). After one or more locations within an identified lesion were labelled, the program performed multispectral segmentation that automatically labelled the entire single lesion (Fig. 1). This step was repeated for each lesion in the whole brain.

Regional lesion volumes were also measured in addition to global lesion volumes. The frontal lobe was demarcated using standard cortical landmarks on a case-by-case, slice-by-slice basis. The deep white matter of frontal regions was separated from other tissue by a line drawn from the innermost points of bilateral central sulci in more cranial slices (A), or a line connecting the anterior-most points of the bilateral lateral fissure on more caudal slices (B). The areas in blue (A) are segmented lesions, and the areas in green (B) are marks of normal tissue for program training.

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lesion volume was then calculated in the same manner as total cerebral lesion load for each patient. The posterior fossa lesion included those lesions within the cerebellum and visible brainstem structures (Fig. 1).

Cognitive tests
The experimental tasks included the original varied-set procedure of the Sternberg task (Sternberg, 1966) as a measure of information processing speed, and a task adapted from Salthouse et al. (1991) to assess working memory capacity.

As previously discussed, the Sternberg task requires the participant to determine whether a test number (ranging from 1 to 9) was or was not a member of a previously presented set of numbers (memory set) that varied in size across trials (1–6 numbers/set). No number appeared twice in a memory set and the frequency and order of a number’s occurrence were balanced across trials. Each number of a set was presented individually and sequentially for 1200 ms in the centre of a computer screen. Following the last number of a set, there was a 2000 ms delay. A 500 Hz warning tone was then presented for 1000 ms, after which a test number appeared and remained on the screen until a response was made. Participants were asked to answer yes or no by depressing one of the two keys on an external keypad of the computer as quickly and accurately as possible. Feedback was displayed on the computer screen after every response for 1000 ms. The inter-trial interval was 2000 ms. Positive and negative trials occurred with equal probability across the memory set sizes. There were 24 practice trials, and the 144 experimental trials were broken into four blocks of 36 trials, with three positive and three negative trials for each memory set size in each block. Total test time was ~30 min.

The measure of interest for the Sternberg task was the response speed across the memory set size. Previous research has consistently found a positive linear relationship between RT and memory set size (Sternberg, 1966). The slope of the RT/memory set size function provides a measure of the time that a participant takes to compare the test stimulus with the representation of that stimulus in memory (serial comparison or scanning) that is independent of primary perceptual or motor system functioning. The zero-intercept (or y-axis intercept) of this function provides an estimate of how long it takes to encode the test stimulus, make a binary decision and organize a response, and is therefore influenced by disruption in perceptual processing and/or motor functioning. Thus, the slope of the RT function was of primary interest as an estimate of speed of cognitive processing (Archibald and Fisk, 2000).

A second task was adapted from the work of Salthouse et al. (1991). This task used up to four parallel sequential timed arithmetic operations to tax working memory capacity (Archibald and Fisk, 2000). In order to perform the task accurately, participants had to keep track of each set of arithmetic operation(s), since no information was provided about which set of operations would be prompted for an answer. The task required only simple addition and subtraction and an answer between zero and nine. Participants were provided with as much time as they needed to produce their response, and the trials were self-paced. For this study, a maximum of four arithmetic operations were required in up to four different, mutually exclusive number sequences for 12 conditions. There were four experimental blocks of 60 trials each, run at a stimulus duration of 2400 ms. Although the dependent measure was accuracy, i.e. the proportion of correct responses for each condition, analyses focused only on the error rates for the most difficult condition (i.e. four windows–four operations condition).

As depression can be a common feature of multiple sclerosis, and depression has been shown to impair performance of effortful, capacity-demanding cognitive tasks (Arnett et al., 1999), a measure of depression, the Beck Depression Inventory II (Beck et al., 1996), was included in the protocol. Fatigue is another significant symptom of multiple sclerosis that could affect cognitive performance (Fisk et al., 1994; Krupp and Elkins, 2000); thus, we included a 10-point visual analogue rating of fatigue severity at the beginning and end of the test session. Finally, the Attention/Concentration Index subtests of the Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987) were included to assess attention and working memory capacity and to provide comparative data.

Statistical analysis
Data were analysed using descriptive statistics, Student’s t tests, and correlation coefficients with alpha level adjusted to reduce error associated with multiple comparisons (Bonferroni correction). Correlations between the EDSS score and lesion volume were done with Spearman rank correlation analysis, while Pearson correlation analysis was used for other parametric data.

Results

The MRI lesion volume measurements

Table 1 Descriptive statistics of the MRI lesion volume measurements

<table>
<thead>
<tr>
<th>Lesion volume (ml) mean (SD)</th>
<th>Overall</th>
<th>RRMS</th>
<th>SPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain T2 lesion</td>
<td>11.04 (8.86)</td>
<td>17.52 (10.58)</td>
<td>7.55 (5.53)</td>
</tr>
<tr>
<td>Frontal T2 lesion</td>
<td>4.15 (3.80)</td>
<td>6.26 (5.20)</td>
<td>3.02 (2.30)</td>
</tr>
<tr>
<td>Posterior fossa T2 lesion</td>
<td>0.10 (0.16)</td>
<td>0.04 (0.07)</td>
<td>0.14 (0.19)</td>
</tr>
<tr>
<td>Whole brain T1 lesion</td>
<td>3.44 (3.03)</td>
<td>3.74 (3.94)</td>
<td>3.27 (2.54)</td>
</tr>
<tr>
<td>Frontal T1 lesion</td>
<td>1.26 (0.88)</td>
<td>1.13 (0.63)</td>
<td>1.34 (1.02)</td>
</tr>
</tbody>
</table>

The MRI lesion volume measurements are summarized in Table 1. EDSS scores were not significantly correlated with either whole brain T2 lesion volume [Spearman rank correlation coefficient (r) = -0.11, P = 0.64] or whole brain T1 lesion volume (Spearman r = 0.32, P = 0.16). Frontal T2 lesion volume accounted for 42.7% of whole brain T2 lesion volume on average, while frontal T1 hypointense lesion volume accounted for 47.3% of whole brain T1 hypointense lesion volume. EDSS scores also did not correlate significantly with frontal T2 lesion volume (Spearman r = -0.03; P = 0.90) or T1 frontal hypointense lesion load (Spearman r = 0.18; P = 0.47). Eight patients had T2 lesions in the posterior fossa. Of these, two had lesions in both the brainstem and cerebellum, four had lesions in the brainstem only and two had lesions in the cerebellum only. No significant relationship between EDSS scores and T2 poster-
ior fossa lesion volume was found (Spearman $r = 0.39$, $P = 0.09$).

**Sternberg Memory Scanning Test and correlation with MRI measurements**

The mean slope for the overall sample was 67.5 ± 44.5 ms/digit (mean ± SD), which is higher (slower) than a comparison sample of healthy controls (47.9 ± 24.2 ms/digit) (Archibald and Fisk, 2000). The Sternberg slope of patients with RRMS (59.3 ± 48.2 ms/digit) did not differ from that of SPMS patients (72.0 ± 43.7 ms/digit) ($P = 0.56$). The level of impairment was assessed in terms of standard deviations from the comparison sample mean slope, with mild slowing defined as ≥1 SD from the comparison sample mean slope. According to this cut-off, nine patients had mild slowing, representing 45% of the patient sample. [Although ≥1.5 or 2 SDs are normally used to define impairment, the ≥1 SD criterion was used to capture evidence of mild difficulty (or the beginning of difficulty) in patients with relatively early and/or mild disease.] Within this category, five patients (20%) were 2 SD slower than the comparison sample mean slope (129.6 ± 24.0 ms/digit).

Posterior fossa T2 lesion volume distinguished patients with slowed information processing from those who performed equivalently to the comparison sample of healthy controls ($P = 0.008$) (Fig. 3). There was also a significant correlation between posterior fossa T2 lesion volume and processing speed (Pearson correlation coefficient $r = 0.58$, $P = 0.008$) (Fig. 3). Processing speed was slowed in seven out of eight patients with any T2 lesion volume in the posterior fossa and one out of 12 patients with no lesion volume detected in the posterior fossa. The Sternberg slope was not detected in the posterior fossa. The Sternberg slope was not significantly correlated with the WMS-R Attention/Concentration Index (Pearson $r = -0.28$, $P = 0.24$).

**Fig. 3 Relationship between the Sternberg cognitive speed measure and posterior fossa T2 lesion volume. A slope of 72.1 ms/digit, which is ≥1 SD from the mean slope of a healthy comparison sample, represents the threshold of ‘impairment’ or mild slowing (solid line).**

≥50% errors in this condition, and one patient made 90% errors, which was 2 SD above the comparison sample mean. There was no difference between patients on the basis of disease course ($P = 0.67$). There was also no difference between the nine patients who had high Sternberg slopes (≥1 SD) versus those 11 patients with low Sternberg slopes (<1 SD) ($P = 0.33$).

Correlations with T2 and T1 total and frontal lesion volume were not significant ($r = 0.003, 0.03, 0.01, -0.10, P > 0.05$). Likewise, the correlation with T2 posterior fossa volume was not significant ($P = 0.22, P = 0.35$).

Performance in the most difficult condition did not correlate significantly with EDSS score (Spearman $r = 0.32; P = 0.17$), disease duration (Pearson $r = 0.03, P = 0.99$), depression (Pearson $r = -0.23, P = 0.33$), initial fatigue (Pearson $r = -0.38, P = 0.10$) or self-perceived change in fatigue over the course of the test session (Pearson $r = 0.42, P = 0.07$). Performance was significantly related to the Digits Forward subtest (Pearson $r = -0.57, P = 0.009$) such that higher numbers of errors were associated with reduced immediate memory span, and with the Digits Backward subtest (Pearson $r = -0.51, P = 0.023$), suggesting that higher numbers of errors were associated with reduced complex attention and working memory. These relationships were evident for the other demanding four windows conditions (correlations ranged from −0.32 to −0.57).

**Salhouse Operational Working Memory Test and correlation with MRI measurements**

The patients made a mean of 50% errors (SD = 19%), which is higher than that of the comparison sample in the most difficult ‘four windows–four operations’ condition (36 ± 20%, mean ± SD) (Archibald and Fisk, 2000). Nine patients made

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**Measures of depression, fatigue and attention/concentration ability**

The mean Beck Depression Inventory II score was 9.7 (SD = 6.8) and, although the mean is not clinically significant, there were five (three SPMS) patients who scored in the mild or moderate severity range. There was no difference between patients based on disease course ($P = 0.84$).
Mean initial fatigue rating was 5.7 ± 3.9 (mean ± SD). Although the SPMS patients had marginally higher (worse) scores at the beginning of the test session (6.8 ± 3.6) compared with the RRMS patients (3.6 ± 3.6, \(P = 0.07\)), there was no difference in their perception of change in fatigue from the beginning to the end of the test session (RRMS 4.6 ± 2.9, SPMS 4.0 ± 3.9, \(P = 0.72\)).

Attention/concentration ability in the sample was assessed using the WMS-R Attention/Concentration Index subtests. The index scores were at average levels relative to the normative standardization sample mean (i.e. 100; Wechsler, 1987). All scores were above the 25th percentile of the standardization sample. There was no difference between patients on the basis of disease course (RRMS 85.4 ± 18.7, SPMS 92.9 ± 23.8, \(P = 0.48\)).

**Discussion**

The present study investigated the relationship between performance on experimental measures of cognitive processing speed, working memory and total lesion volume. Although the sample size was small, it was representative of the Calgary Multiple Sclerosis Clinic population in terms of gender composition and educational level. The sample was comprised of RRMS and SPMS patients within the mild to moderate EDSS disability range. There were more SPMS patients than RRMS patients, and the SPMS patients were older and had greater neurological symptom severity as measured by the EDSS. None of the patients were taking disease course-modifying or corticosteroid treatment that may have affected cognitive function. While depression can affect performance on capacity-demanding tasks in multiple sclerosis (Arnett *et al.* 1999), our study criteria excluded clinically depressed patients. There were no significant correlations between the depression measure and performance on any cognitive test. The SPMS patients also reported more fatigue prior to testing, but there was no difference in their perception of change in fatigue over the course of the cognitive test session. Like depression, fatigue was not significantly associated with performance on the cognitive tasks. Attention/concentration ability of the sample was also within normal limits compared with the WMS-R standardization data, and there was no difference between patients on the basis of disease course.

Prior to a discussion of the findings, it is necessary to address important methodological limitations. This was a pilot study, and the cost of imaging prevented inclusion of a matched healthy control group and more participants in the patient sample. In the absence of a control group, data were interpreted relative to a comparison sample from a previous study. This sample was similar in terms of gender composition and educational level, but the patients examined in this study were older, on average. Further, the small sample size reduced statistical power and the ability to examine the effect of age. Ideally, a sample size of 25 participants in each group would be needed to detect a significant change (\(\geq 2\) SDs from the control sample mean) with 90% power at \(\alpha = 0.01\). For these reasons, our findings must be considered as preliminary, but worthwhile to explore in further research.

With one exception, correlations between the T2 and T1 lesion volumes and cognitive performance measures were non-significant. There was a significant positive correlation between T2 posterior fossa lesion volume and cognitive processing speed, but non-significant relationships with the remainder of the cognitive performance measures. However, the lack of a significant correlation with the other MRI measures does not argue against the use of the Sternberg and Salthouse tasks as sensitive outcome measures. Patients performed comparably with a previous multiple sclerosis patient sample and were different from a sample of healthy control participants (Archibald and Fisk, 2000), suggesting that these measures were sensitive to changes associated with mild to moderate disease. The results we obtained may be a function of insufficient lesion volume, sample composition, and limited pathological specificity of the MRI methodology employed. Our lesion volumes were less than what has been obtained in other studies, and greater lesion volumes have correlated with neuropsychological measures (Foong *et al.*, 1997; Rovaris *et al.*, 1998; Sperling *et al.*, 2001). For example, in the study of Foong *et al.* (1997), cognitive impairment (\(\geq 2\) SD from the normative mean) was evident on tests of verbal and spatial working memory in patients with a mean T2 total lesion volume of \(\geq 33\) ml. Sample composition, notably the inclusion of RRMS patients, may also have been an important factor. Although Hohol *et al.* (1997) reported lesion volumes that were smaller than those obtained in our sample, there were no significant correlations with cognitive measures at baseline for the RRMS and relapsing–progressive groups in their study, whereas the chronic–progressive group, comprised of both primary progressive and SPMS patients (with presumably more severe/active disease), showed the most robust correlations with MRI measures. Finally, measures of focal macroscopic damage such as conventional lesion volume measurements may not reflect subtler, diffuse microscopic changes in the brain (Arnold, 1999; Bammer *et al.*, 2000; Cercignani *et al.*, 2001; DeStefano *et al.*, 2002) that may have a stronger association with performance on cognitive tests, especially in the absence of a critical level of lesion accumulation.

The experimental cognitive tasks used in this study measured speed and capacity of cognitive processing. The finding of slowed cognitive processing is consistent with previous studies (Rao *et al.*, 1989, 1991; Archibald and Fisk, 2000) using standard methods in multiple sclerosis patients with mild to moderate neurological disability, but not with other studies, which departed from the standard method (Litvan *et al.*, 1988; Janculjak *et al.*, 1999). Litvan *et al.* (1988) used a faster stimulus presentation rate than is typically used with the Sternberg task, which may have obscured group differences. In the study of Janculjak *et al.* (1999), the participants did not make the motor responses themselves, rather their verbal responses were registered by
the examiner who pressed the ‘Y’ or ‘N’ keys. While they argued that the same procedure had been used with the controls, both the y-intercept and slope values were based on the examiner’s responses, and do not reflect the true reaction times of the participants in the experiment. Further, our findings showed that 45% of our sample had mildly slowed cognitive processing that was significantly related neither to clinical variables such as EDSS score or disease duration, nor to common symptoms of multiple sclerosis such as depression, or fatigue.

The Salthouse task was included as a measure of complex attention and working memory capacity, shown previously to reveal impairment in SPMS patients (Archibald and Fisk, 2000). Consistent with this study, we found that patients made significantly more errors in the more complex task conditions than a healthy comparison sample. That performance on this task correlated with a measure of immediate memory span (Digits Forward subtest) and complex attention/working memory (Digits Backwards subtest) supports its construct validity. Lack of correlation with performance on the Sternberg task suggests that working memory capacity and memory scanning speed are separable functions, at least in patients with mild to moderate disease burden.

An important finding in the current study was the strong correlation between cognitive processing speed and T2 posterior fossa lesion volume, while no significant correlations were found between Sternberg slope and whole brain and frontal T2 lesion loads, or whole brain and frontal T1 hypointense lesion loads. There also appeared to be a ‘threshold effect’ in which the presence of any T2 lesion volume in the posterior fossa was associated with slowed processing efficiency. Our results revealed that seven out of eight (87.5%) patients with slowed processing had visible T2 lesions in their posterior fossa; yet only one out of 12 (8.3%) patients without slowing had visible T2 lesions in their posterior fossa. This result is surprising since the posterior fossa (especially the cerebellum) are generally thought to be associated with motor learning, motor planning and temporal processing, not cognitive functions such as memory scanning speed. A great deal of effort has gone into the design and construction of the Sternberg test to isolate and separate cognitive and motor function effects. The y-intercept of the Sternberg RT function is presumed to reflect the time required for processes of motor function, stimulus registration, perceptual analysis, decision and response selection, while the Sternberg RT slope is considered to reflect memory scanning speed, independent of motor function (Sternberg, 1966). The significant positive correlation between T2 posterior fossa volume and Sternberg slope could be explained by damage to the reciprocal cerebellocortical pathways that provide the neuroanatomical basis for cerebellar involvement in cognition (Schmahmann, 1997, 2001).

In recent years, there has been a re-emergence of interest in the role of the cerebellum in cognitive and emotional processes (Schmahmann, 1997, 2001). Schmahmann argued that reciprocal cerebellocortical pathways have been identified and may provide the neuroanatomical basis for cerebellar involvement in cognition. The cerebellum receives projections from the posterior parietal cortex, the superior temporal sulcus and from frontal regions via corticopontocerebellar pathways. Efferent projections from the dentate nucleus of the cerebellum lead back to these same cortical regions. In the multiple sclerosis literature, few studies have included measurement of lesions in the posterior fossa. Performance on a measure of complex auditory attention (the oral version of the Symbol–Digit Modalities Test) was inversely correlated with lesion area in the brainstem and cerebellum (Baumhefner et al., 1990), but no significant correlations were found between this and other tests in the Brief, Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis (Rao et al., 2000) and T2 lesions in a posterior region that included the occipital lobe, cerebellum and brainstem (Sperling et al., 2001). The contradictory findings may be due to the limitation of early lesion quantification techniques [e.g. lesion area rather than lesion volume was measured (Baumhefner et al., 1990)] or the non-specific study of the cerebellum and/or brainstem (Sperling et al., 2001).

In conclusion, performance decrements on the processing efficiency measures were found in a small sample of multiple sclerosis patients with a relapsing–remitting or secondary progressive disease course and relatively mild disease, as assessed by the EDSS, consistent with previous reports. These findings suggest that the Sternberg and Salthouse tasks may be useful in future evaluation of disease burden. However, correlations with T2 and T1 lesion volumes were mostly non-significant, with the exception of posterior fossa lesion volume. Lack of correlation with the MRI measures may have been a function of insufficient lesion volume, sample composition and/or limited pathological specificity of the MRI methodology employed. A provocative finding was the significant correlation between cognitive information processing speed and posterior fossa lesion load. This finding, although preliminary, suggests that posterior fossa damage may contribute to slowed cognitive processing in patients with multiple sclerosis, and that examination of the posterior fossa should be included in studies of cognition in multiple sclerosis.

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