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Cognitive function in primary progressive and transitional progressive multiple sclerosis
A controlled study with MRI correlates

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Summary
The relative rarity of primary progressive (PP) and transitional progressive (TP) multiple sclerosis has meant that little documentation of cognitive function in such patients is currently available. The aim of this study was to investigate the cognitive skills of patients with PP and TP multiple sclerosis relative to matched healthy controls, and to examine the relationship of this impairment to MRI parameters. Sixty-three patients (43 PP, 20 TP) were individually matched with healthy controls, who undertook the same cognitive tasks as the patient group. The neuropsychological assessment comprised Rao's brief repeatable battery, a reasoning test, and a measure of depression. Patients also underwent T_1- and T_2-weighted brain MRI. These patients were taken from a larger cohort (158 PP, 33 TP) in whom it had been demonstrated that there were no significant differences between the mean scores of the PP and TP groups on any of the cognitive variables. The 63 patients were therefore taken as one group for comparison with the healthy controls. These patients performed significantly worse than the controls in tests of verbal memory, attention, verbal fluency and spatial reasoning. An impairment index was constructed and applied to the patient data. This correlated modestly with T_2-lesion load ($r = 0.45$, $P = 0.01$), T_1-hypointensity load ($r = 0.45$, $P = 0.01$) and cerebral volume ($r = –0.35$, $P = 0.01$). Thus, PP and TP multiple sclerosis patients demonstrate significant cognitive dysfunction when compared with matched healthy controls. The relationship between this impairment and MRI parameters is moderate, suggesting that cognitive dysfunction in PP and TP multiple sclerosis has a complex and multifactorial aetiology, which is not adequately explained by pathology as demonstrated on conventional MRI.

Keywords: multiple sclerosis; primary progressive; transitional progressive; cognitive function; MRI

Abbreviations: BRB = Brief Repeatable Battery; EDSS = Expanded Disability Status Scale; MADRS = Montgomery and Asberg Depression Rating Scale; PP = primary progressive; SP = secondary progressive; TP = transitional progressive; VESPAR = Verbal and Spatial Reasoning Test

Introduction
Cognitive impairment is a common occurrence in multiple sclerosis, detected in 40–60% of patients (McIntosh-Michaelis *et al*., 1991; Rao *et al*., 1991). Deficiencies tend to be more prevalent in the later stages of the disease (Heaton *et al*., 1985; Beatty *et al*., 1988), although they may be detectable at initial presentation (Feinstein *et al*., 1992), during the early phase (Grant *et al*., 1984; Lyon-Caen *et al*., 1986) or in the presence of limited physical disability (Van Den Burgh *et al*., 1987). Impairments are typically demonstrated in memory, conceptual/abstract reasoning, attention, speed of information processing and visuo-spatial functions (Rao, 1986; Ron *et al*., 1991). Several attempts

have been made to understand the pathology underlying cognitive deficits in multiple sclerosis utilizing MRI. Poor neuropsychological performance has been correlated with total lesion load (Huber *et al*., 1992; Hohol *et al*., 1997; Rovaris *et al*., 1998), atrophy of the corpus callosum (Huber *et al*., 1992; Comi *et al*., 1993), ventricular dilation (Clark *et al*., 1992; Comi *et al*., 1993) and magnetization transfer ratio (Rovaris *et al*., 1998; Van Buchem *et al*., 1998).

Recent studies examining cognitive function in multiple sclerosis have focused on patients with either relapsing–remitting or chronic progressive forms of the disease. The latter term lacks specificity (Lublin and Reingold, 1996), typically including patients with both a purely progressive course, i.e. primary progressive (PP) multiple sclerosis, and those who become progressive after an initial period of relapses and remissions, i.e. secondary progressive (SP) multiple sclerosis. Patients with PP disease not only demonstrate a distinctive clinical course (Thompson *et al*., 1997), but also pathological (Revesz *et al*., 1994) and MRI differences (Thompson *et al*., 1991; Filippi *et al*., 1995*a*) have been noted when compared with relapsing–remitting or SP multiple sclerosis. In the only study to date examining cognitive function in PP multiple sclerosis, the cognitive abilities of PP and SP multiple sclerosis patients were compared (Comi *et al*., 1995). Cognitive dysfunction was reported in 7% of PP patients, compared with 53% in patients with SP multiple sclerosis, of similar physical disability.

In the present study, neuropsychological tests and MRI techniques were used to investigate the pattern and pathology of cognitive dysfunction in PP multiple sclerosis. The same methodology was also applied to transitional progressive (TP) multiple sclerosis patients, who have been shown clinically to be very similar to the PP group (Stevenson *et al*., 1999). TP patients differ from the group termed 'progressive-relapsing' by Lublin and Reingold (Lublin and Reingold, 1996) in that they have a predominantly progressive course with only a single relapse. Progressive-relapsing patients will not be considered in the current research.

The main aim of this study was to investigate the pattern of cognitive dysfunction in PP and TP multiple sclerosis patients, in comparison with matched healthy controls, and to examine these findings in the context of their MRI features.

Methods

Subjects

One hundred and ninety-one patients with clinically or laboratory supported PP or TP multiple sclerosis were recruited from six European centres (Amsterdam, Barcelona, Bordeaux, Lisbon, London, Milan). Of this group, 63 of the UK patients were compared with an equal number of individually matched healthy controls and form the main focus of this paper. The controls were included in the study if they had no history of neurological or psychiatric disturbances.

All patients gave informed consent to participate in the study, which had been approved by the ethics committee of the Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK.

Neurological assessment

A careful history was taken from each patient to exclude individuals with any relapses, for a diagnosis of PP multiple sclerosis, or more than one such episode, for a diagnosis of TP multiple sclerosis. All patients underwent a full neurological examination. Impairment and disability were measured by a single observer at each centre, using the Expanded Disability Status Scale (EDSS), 10 m timed walk and Nine Hole Peg Test.

Neuropsychological tests

The neuropsychological battery comprised tests of memory, attention, verbal fluency and reasoning. The Brief Repeatable Battery (BRB) (Rao, 1990) assessed verbal immediate and delayed recall memory, using the Selective Reminding Test (SRT) (Buschke and Fuld, 1974). Spatial immediate and delayed recall memory were examined by the 10/36 Spatial Recall Test (10/36) (Rao, 1990). Complex attention, concentration and speed and accuracy in visual search and scanning were assessed by the Symbol Digit Modalities Test (SDMT) (Smith, 1982) and sustained attention by the Paced Auditory Serial Addition Task (PASAT) (Gronwall, 1977). The Word List Generation Task (WLG) (Rao, 1990) measured verbal associative fluency. The BRB concentrates on memory and attention, and this narrow focus has been noted (Basso *et al*., 1996). In particular, complex reasoning and semantic processing are hardly addressed. Therefore, in addition to the BRB, the Verbal and Spatial Reasoning Test (VESPAR) (Langdon and Warrington, 1995) was administered. In this test the inductive reasoning skills of categorization, analogy and series completion, for both verbal and spatial domains were examined. The Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) was also included, to assess emotional distress. Only one patient declined to complete the whole neuropsychological assessment. In Bordeaux, Lisbon and Milan the VESPAR test was not administered.

UK patients and controls completed an additional measure, that of the National Adult Reading Test—Revised (NART) (Nelson and Willison, 1992) in which optimum intellectual function is estimated (Paque and Warrington, 1995) and this was used for the purposes of matching with the healthy controls. Patients were matched according to sex, age (within 5 years) and NART IQ (within 5 IQ points).

MRI

MRI examinations were performed at each of the six European centres (3 mm T_2-weighted fast spin echo and T_1-weighted

Table 1 *The demographic and clinical characteristics of the patient sample*

	PP multiple sclerosis (n = 158)	TP multiple sclerosis (n = 33)
Sex (male : female)	81 : 77	14 : 19
Mean age in years (SD)	50.7 (10.3)	46.5 (10.2)
Mean age of onset in years (SD)*	40.2 (9.0)	34.9 (10.7)
Mean disease duration in years (SD)*	10.9 (7.0)	12.3 (7.1)
Median EDSS (range)	6.0 (2.0–8.5)	5.5 (2.5–8.5)
Mean T_1-hypointensity load (SD) in cm^3	4.30 (6.33)	6.00 (10.74)
Mean T_2-lesion load (SD) in cm^3	12.02 (13.77)	17.58 (22.33)
Mean cerebral volume (SD) in cm^3	264.82 (23.70)	267.50 (23.69)

*For TP patients, onset and disease duration taken from first symptoms.

spin echo images of the brain). A detailed account of the imaging protocol employed can be found in the paper by Stevenson *et al*. (Stevenson *et al*., 1999). All electronic data were transferred to London for analysis by a single observer (V.L.S.). Total brain T_2-lesion load and T_1-hypointensity load were obtained using a semi-automated contour technique. The measure of cerebral volume, reflecting atrophy, was taken from a series of six, 3 mm consecutive slices, with the most caudal at the level of the velum interpositum cerebri (Losseff *et al*., 1996). This site was chosen as it covers a large proportion of the lateral ventricles and cortical sulci and the velum interpositum cerebri is thought to be a stable landmark despite ongoing atrophy, allowing repositioning for serial assessment.

Statistical analyses

Non-parametric statistics were employed for all analyses because the score distributions were not uniformly normal, and a Bonferroni correction for multiple tests (Bland and Altman, 1995) was applied where appropriate. The cognitive abilities of the PP and TP patients were compared using the Mann–Whitney test, while the differences in the performance of the patients and individually matched controls were examined by the Wilcoxon signed rank test. Spearman rank correlation coefficients were employed to investigate the relationship between the cognitive impairment index and the MRI parameters.

The cognitive impairment index was constructed by calculating the mean and standard deviation for the control data, on each cognitive variable. A grading system was then applied to each patient score on every given cognitive test, dependent on the number of SDs below the control mean. For example, the patient was given zero if he/she scored at or above the mean of the controls. Grade 1 was assigned if the patient scored below the control mean, but at or above 1 SD below that mean. Grade 2 was allocated if the patient achieved a score $>$1 SD below the control mean, but $\geqslant$2 SDs below that mean. This grading was continued until all patient scores had been accommodated. These grades were summed across all variables to give one overall measure of cognitive dysfunction for each patient. Hence, the higher the figure, the greater the patient's impairment. The impairment index takes aging into account by individually matching each patient with a control of similar age, thus incorporating the variance in cognitive performance related to age.

The method of analysis and chosen threshold determine the prevalence reported. With this in mind, the number of patients scoring at least 2 SDs below the control mean on three or more tests in this study was calculated. This was to facilitate a broad comparison with the previous study of cognitive function in PP multiple sclerosis (Comi *et al*., 1995) where performance of 2 SDs below the published means on three or more neuropsychological tests was taken as indicating cognitive impairment.

Results

Table 1 shows the demographic and clinical characteristics of the 158 PP and 33 TP patients recruited in the European study. There were no significant differences between the mean scores on the cognitive tasks carried out by the PP and TP patients (Table 2). In addition, there was no significant difference in their level of depression. It was therefore considered appropriate to combine the two groups for the main analyses of the study, i.e. the comparison of 63 patients from the UK cohort with individually matched healthy controls.

Sixty-three patients (43 PP, 20 TP) in the UK sample were individually matched with healthy controls. Of those unmatched, five did not complete the relevant test to estimate optimum intellectual function, whilst the remaining 12, middle-aged, unskilled workers, possessed a combination of sex, age and IQ which proved too difficult to find suitable controls. The male : female ratio of the 63 matched patients and their controls was 34 : 29 in each case. The mean age (SD) of the patient group was 47.7 (9.9) years, whilst for the controls it was 45.8 (10.3) years. The mean (SD) NART IQ was 107.5 (11.4) for patients and 108.0 (12.1) for the control group. Patients performed significantly below that of the controls on tests of verbal memory, attention, verbal fluency and spatial reasoning (Table 3).

The cognitive impairment index produced a range of scores from 0 to 35 (where 0 reflects no impairment), with a mean

Table 2 *Descriptive statistics of the cognitive tasks for primary progressive and transitional progressive patient groups*

	PP multiple sclerosis (n = 157)	TP multiple sclerosis (n = 33)
Verbal memory SRT: long-term storage over six trials		
Mean (SD)	38.4 (16.0)	42.5 (13.4)
Median (range)	38.5 (5–70)	43.0 (8–70)
Verbal memory SRT: consistent long-term retrieval over six trials		
Mean (SD)	27.0 (16.0)	29.3 (14.7)
Median (range)	26.0 (0–70)	26.0 (1–70)
Verbal memory SRT: delayed recall		
Mean (SD)	7.5 (3.0)	7.7 (2.4)
Median (range)	8.0 (0–12)	8.0 (2–12)
Spatial memory 10/36: immediate recall over three trials		
Mean (SD)	18.3 (5.4)	20.1 (6.1)
Median (range)	18.0 (5–30)	21.0 (8–29)
Spatial memory 10/36: delayed recall		
Mean (SD)	6.6 (2.4)	7.2 (2.2)
Median (range)	7.0 (1–10)	7.0 (3–10)
Attention SDMT		
Mean score (SD)	39.5 (15.1)	41.0 (14.2)
Median (range)	41.0 (9–74)	41.0 (11–68)
Attention PASAT 3 s rate		
Mean score (SD)	36.6 (14.8)	35.7 (16.3)
Median (range)	37.0 (2–60)	37.0 (8–59)
Attention PASAT 2 s rate		
Mean score (SD)	27.0 (12.8)	27.8 (14.0)
Median (range)	26.0 (0–57)	27.0 (4–56)
Verbal fluency WLG		
Mean score (SD)	23.5 (7.8)	22.7 (7.1)
Median (range)	23.0 (7–51)	23.0 (7–43)
Reasoning verbal VESPAR: score over three subtests		
Mean (SD)	44.3 (11.3)	44.5 (11.7)
Median (range)	44.0 (18–68)	44.0 (21–64)
Reasoning spatial VESPAR: score over three subtests		
Mean (SD)	48.9 (10.5)	52.3 (9.7)
Median (range)	51.0 (26–71)	53.5 (34–68)
Depression MADRS: total score		
Mean (SD)	7.5 (6.4)	9.7 (7.2)
Median (range)	5.0 (0–31)	9.0 (0–30)

A range of descriptive statistics are given for comparison with other work.

value of 16.1 (8.7). This measure correlated significantly with the T_2-lesion load ($r = 0.45$, $P = 0.01$), T_1-hypointensity load ($r = 0.45$, $P = 0.01$) and with the measure of cerebral volume ($r = –0.35$, $P = 0.01$) (Table 4). When the cognitive impairment index was broken down into two components—the impairment indices assigned for performance on the BRB and those on the VESPAR—the MRI measures of T_2-lesion load and T_1-hypointensity load correlated better with impairment on the BRB, whilst the measure of cerebral volume gave a higher coefficient with impairment on the VESPAR.

The percentage of patients who scored >2 SD below the control mean on the individual cognitive tests varied from 4.8 to 42.9 (Table 5). Adopting the categorical approach of patients classified as cognitively impaired if they scored at least 2 SD below the control mean on three or more tests (as in Comi *et al*., 1995), 28.6% of patients in this study were designated cognitively impaired.

Discussion

This study demonstrates that patients with PP and TP multiple sclerosis exhibit cognitive deficits in the areas of verbal memory, attention, verbal fluency and spatial reasoning, when compared with individually matched healthy controls. The lack of significant depression in the patient group as a whole, according to the MADRS (Montgomery and Asberg, 1979), suggests that the patients' poor performance on the cognitive tasks was unlikely to be due to affective factors. Not all tests showed cognitive dysfunction. The fact that patients in this study were not deficient on the spatial memory task may have been due to the low ceiling level of the 10/36 (Rao, 1990). Of the 63 patients 33.3% achieved the maximum score on the delayed assessment of the 10/36, whilst for the controls 49.2% were at ceiling level. It is possible that the task did not prove sufficiently demanding to assess this skill at the higher end of the ability scale. Patients whose memory may have been slightly impaired may not have been tested

Table 3 *Descriptive statistics of the cognitive tasks for patients and matched controls*

	Multiple sclerosis patients (n = 63)	Controls (n = 63)
Verbal Memory SRT: long-term storage over six trials		
Mean (SD)	40.4 (14.5)	50.6 (10.8)*
Median (range)	40.0 (5–70)	51.0 (21–69)
Verbal Memory SRT: consistent long-term retrieval over six trials		
Mean (SD)	26.3 (14.7)	40.7 (14.4)*
Median (range)	25.0 (2–70)	42.0 (13–69)
Verbal Memory SRT: delayed recall		
Mean (SD)	7.5 (2.6)	9.5 (2.0)*
Median (range)	8.0 (1–12)	10.0 (4–12)
Spatial Memory 10/36: immediate recall over three trials		
Mean (SD)	20.3 (5.9)	22.6 (4.6)
Median (range)	21.0 (8–30)	24.0 (11–29)
Spatial Memory 10/36: delayed recall		
Mean (SD)	7.1 (2.4)	8.1(1.9)
Median (range)	7.0 (1–10)	8.0 (3–10)
Attention SDMT		
Mean score (SD)	43.4 (13.9)	60.2 (9.3)*
Median (range)	43.0 (12–74)	61.0 (43–85)
Attention PASAT 3 s rate		
Mean score (SD)	38.2 (15.0)	50.1 (10.7)*
Median (range)	43.0 (8–60)	53.0 (5–60)
Attention PASAT 2 s rate		
Mean score (SD)	28.4 (12.8)	38.5 (11.6)*
Median (range)	27.0 (4–55)	38.0 (18–59)
Verbal Fluency WLG		
Mean score (SD)	22.7 (7.8)	27.5 (7.3)*
Median (range)	21.0 (7–43)	26.0 (14–46)
Reasoning Verbal VESPAR: score over three subtests		
Mean (SD)	48.0 (10.1)	51.9 (9.5)
Median (range)	48.0 (21–68)	56.0 (24–66)
Reasoning Spatial VESPAR: score over three subtests		
Mean (SD)	52.6 (9.0)	58.2 (6.3)*
Median (range)	54.0 (31–71)	60.0 (38–70)
Depression MADRS: total score		
Mean (SD)	7.0 (6.4)	4.2 (3.4)
Median (range)	5.0 (0–22)	3.0 (0–15)

A range of descriptive statistics are given for comparison with other work. *Significant difference (P = 0.004, Bonferroni correction).

at the level of difficulty required to expose any deficits. Also patients did not demonstrate any deficits in verbal reasoning, as assessed by the verbal sections of the VESPAR (Langdon and Warrington, 1995). This did not reflect a ceiling effect and may indicate that verbal semantic skills tend to remain intact in PP and TP forms of multiple sclerosis.

The findings reported in this paper do not support the only previous study of this patient group (Comi *et al*., 1995), which reported cognitive impairment in PP multiple sclerosis to be rare. In that study patient scores were considered abnormal only when they differed by >2 SD from the mean of the healthy population and three or more of these abnormal scores had to be recorded in order for a patient to be categorized as cognitively impaired. Adopting a close approximation of the Comi criteria (the difference being only that the current study used individually matched, contemporaneous controls rather than published norms) the incidence of cognitive impairment was 28.6%, compared with the 7% previously reported. The demographic and clinical characteristics of the patients were similar. Therefore, it is possible that the sensitivity to the detection of cognitive dysfunction in the earlier study may have been reduced due to the correction of neuropsychological scores for age and education according to published norms, followed by the transformation into Z scores rather than using matched controls, and to the small numbers involved (PP 14, SP 17). This could either be due to a sampling difference or a chance effect due to small numbers.

In this study the correlations of the cognitive impairment index with the MRI parameters are moderate. The impairment index takes account of the effects of aging on cognitive skills and the mental deterioration of each individual patient. It produces a single figure to correlate with the MRI parameters, which increases the power of the statistical analysis. However, possible limitations of the index are that it assumes the cognitive functions measured are independent, that each

Table 4 *The correlations of the cognitive impairment index with the MRI parameters*

	Cognitive impairment index	Cognitive impairment index—BRB	Cognitive impairment index—VESPAR
T_2-lesion load	0.45**	0.43**	0.35**
T_1-hypointensity load	0.45**	0.47**	0.27*
Cerebral volume	–0.35**	–0.32*	–0.40**

Correlations significant at $^{**}P = 0.01$, $^{*}P = 0.05$.

Table 5 *Percentage of patients that are cognitively impaired on each cognitive task*

	No. (%) of patients impaired
Verbal memory SRT: long-term storage over six trials	12 (19.0)
Verbal memory SRT: consistent long-term retrieval over six trials	10 (15.9)
Verbal memory SRT: delayed recall	12 (19.0)
Spatial memory 10/36: immediate recall over three trials	8 (12.7)
Spatial memory 10/36: delayed recall	9 (14.3)
Attention SDMT	27 (42.9)
Attention PASAT 1	20 (31.7)
Attention PASAT 2	12 (19.0)
Verbal fluency WLG	5 (7.9)
Reasoning verbal VESPAR: score over three subtests	3 (4.8)
Reasoning spatial VESPAR: score over three subtests	15 (23.8)

Cognitive impairment is taken as having a score more than 2 SD below the control mean.

contributes equally in an additive fashion and that the cognitive tasks are uniformly sensitive to MRI pathology. Patients in this study had relatively low lesion loads on MRI, which is consistent with previous studies in which PP multiple sclerosis patients showed fewer cerebral MRI lesions than patients with SP or benign multiple sclerosis. Those that are detected tend to be smaller (Thompson *et al*., 1990) and rarely enhance with gadolinium–DTPA (Thompson *et al*., 1991). Similar MRI characteristics have also been reported in TP multiple sclerosis patients (Filippi *et al*., 1995*b*; Stevenson *et al*., 1999). The fact that enhancement is infrequent supports the pathological observation that PP multiple sclerosis appears to be a less inflammatory form than that of other subgroups (Revesz *et al*., 1994). PP patients are also the group in whom the discrepancy between physical disability and MRI appearance is most marked (Kidd *et al*., 1996). In this study, the cognitive impairment index has given moderate correlations, not only with cerebral volume, but also with T_2-lesion load and T_1-hypointensity load. It has been suggested that T_1-hypointensity may be a more specific marker of tissue destruction (axonal loss) than T_2-load (Van Walderveen *et al*., 1998). However, no difference was seen in this study in the correlations with the cognitive impairment index. Although these correlations are encouraging, they suggest there is still much variance to be explained. The focal effect of lesions is only a partial explanation suggesting a multifactorial aetiology. Conventional MRI techniques poorly demonstrate microscopic changes in the normal appearing white matter. The evidence for these changes comes from studies in both MRI spectroscopy (Fu *et al*., 1998) and magnetization transfer imaging (Filippi *et al*., 1995*c*). The integrity of cortical tracts is another issue hardly addressed by conventional MRI.

Despite the limitations of present MRI techniques, the correlations of the components of the cognitive impairment index with the MRI parameters could be taken to suggest that performance on the BRB (Rao, 1990) is more closely associated with identifiable white matter lesions, as shown on T_2- and T_1-weighted images. The BRB is heavily loaded towards tasks of attention and concentration, and such skills could be impaired by the cumulative effect of many discrete areas of pathology. In contrast, the VESPAR (Langdon and Warrington, 1995) gives a slightly higher correlation with the measure of cerebral volume. Because this test requires high level and extended serial and parallel processing for reasoning, it places more demands on distributed cortical functions. This inevitably involves a number of different integrated pathways, in part because there may be several different approaches to each solution. Deficits in performance on the VESPAR reflect a breakdown in more global mental processing, which is most accurately captured by the six slice measure of cerebral volume, a more comprehensive measure of brain pathology. It is not clear how this finding might relate to more detailed pathology. Both white and grey matter are included (and not separable) within the volume analysis. However, as both white and grey matter are involved in the disease process, both are likely to contribute (Kidd *et al*., 1999).

This study shows that PP and TP multiple sclerosis patients do not appear to differ in terms of their cognitive abilities. Despite identifiably different courses, the underlying pathology of PP and TP multiple sclerosis does not seem to

impact on cognitive function in a detectably distinct manner. This reflects the similarities in MRI and clinical characteristics reported between the two groups (Stevenson *et al*., 1999). The study by Kremenchutzky and colleagues (Kremenchutzky *et al*., 1998) also supports these findings, as they have reported that patients who were originally categorized as progressive-relapsing did not comprise a clearly defined subgroup and had a similar long-term outcome to PP patients.

The relatively high frequency of cognitive dysfunction in PP and TP multiple sclerosis needs to be considered within the context of other studies conducted at established research centres, where the patients recruited tend to be pre-selected, often having greater physical disability or more active disease (Nelson *et al*., 1988). Despite this, the demographic characteristics of the current patient group correspond to those noted by other researchers who have investigated multiple sclerosis patients according to geographical location (Confavreux *et al*., 1980; Weinshenker *et al*., 1989), suggesting that the findings reported in this study would be applicable to most PP and TP patients. An inability to match 12 patients in the UK sample limits the capacity to generalize from the cognitive results, as a particular set of demographic characteristics were not represented. However, it is unlikely that their exclusion would greatly influence the comparative analysis because individuals at the lower end of the intelligence continuum, as these were, can, by definition, demonstrate only a limited decline in ability.

As an additional investigation, it would be interesting to compare the PP group with SP patients. Matching PP and SP patients is problematic (Thompson, 1998) as the groups inevitably differ either in levels of physical disability or disease duration. In the only study where this comparison has been attempted (Comi *et al*., 1995) patients with PP and SP multiple sclerosis were similar in terms of age and degree of disability but differed significantly in duration of disease. It may be more productive, therefore, to identify cognitively impaired and intact patients from both PP and SP groups, by reference to matched controls, and to compare their clinical and MRI characteristics (Camp *et al*., 1998).

The current study is the only one to date to examine cognitive function in PP and TP multiple sclerosis patients, relative to individually matched healthy controls. Advancements in imaging techniques, particularly those examining normal appearing white matter and the cortex, where lesions are often missed by conventional scanning, together with more sensitive cognitive tests, will help elucidate the pathophysiology of cognitive dysfunction in these forms of the disease. It is also anticipated that further insights will be gained by serial evaluation of this cohort.

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