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# Executive function in multiple sclerosis
## The role of frontal lobe pathology

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## Summary
*Deficits in executive function and the relationship to frontal lesion load as detected on MRI were investigated in 42 multiple sclerosis patients. A battery of neuropsychological tests examining executive skills including computerized tests of planning and spatial working memory was administered to all subjects. Performance on these tests was impaired in the patient group when compared with a group of matched controls, but not all executive skills were affected to the same extent. Although a number of executive test scores correlated with the severity of frontal lesion load, it was difficult to disentangle the specific contribution of frontal lobe pathology to the impairment on executive tasks. This study highlights the difficulties in attempting to attribute specific cognitive abnormalities to focal brain pathology in the presence of widespread disease such as in multiple sclerosis.*

**Keywords**: executive function, multiple sclerosis, lesion load, MRI, frontal lobe pathology

**Abbreviation**: APM = Advanced Progressive Matrices

## Introduction
It has been recognized since the writings of Charcot (1877) that cognitive impairment occurs in multiple sclerosis, but it is only in recent years that there have been more accurate prevalence estimates. It is now generally accepted that ~40% in community samples (Rao *et al*., 1991) and 50–60% of hospital samples (Ron *et al*., 1991) have some degree of cognitive impairment. Although it is usually a feature of advanced disease, cognitive impairment can occur early even in the absence of severe physical disability.

The type of cognitive deficits commonly seen in multiple sclerosis have been well characterized. Attention deficits are known to be present early in the disease, even in patients with clinically isolated lesions (optic neuritis) in whom brain lesions are already detectable on MRI and are likely to represent the early neuropsychological manifestation of multiple sclerosis (Feinstein *et al*., 1992). Cognitive deficits are especially severe in patients with chronic progressive disease in whom memory and executive deficits, with a relative preservation of high level visuoperceptual and language functions, are commonly seen (Litvan *et al*., 1988; Beatty *et al*., 1989; Rao *et al*., 1989). Executive or supervisory processes as defined by Shallice and Burgess (1991) are required in situations which involve decision making or planning, error correction, novel sequences of action and overcoming strong habitual responses. Therefore, the different components of executive function can include working memory, initiation and inhibition of responses, problem solving, strategic planning and conceptual ability.

Euphoria, a well-recognized albeit rare symptom in multiple sclerosis patients, is likely to be a clinical expression of executive dysfunction and has been found to correlate well with total MRI lesion load (Ron and Logsdail, 1989). However, it is only recently that the presence of executive deficits in multiple sclerosis has been addressed in neuropsychological studies. Some have reported poor performance on measures of abstract reasoning such as the Category Test and Wisconsin Card Sort Test (Heaton *et al*., 1985; Rao *et al*., 1987; Mendozzi *et al*., 1993), whilst others have reported deficits in verbal working memory (Litvan *et al*., 1988). To date, other executive skills such as spatial working memory, planning and use of strategy have not been investigated.

The interest in demonstrating executive deficits has been coupled with attempts to correlate them with the severity

and site of lesions on MRI. This has proved problematic for a number of reasons, the main one being the difficulty in assessing the contribution of focal pathology in the presence of widespread brain abnormalities. The quantification of lesion load is also not without problems and it is only recently that more reliable automated methods for quantification have become available. Moreover, it is difficult to determine the impact that lesions at different stages of evolution and with different underlying pathology may have on function (Kermode *et al*., 1990; McDonald *et al*., 1994). In addition, it may be erroneous to assume that impairment in tests of executive function signals frontal lobe disease or is exclusively due to its presence (Anderson *et al*., 1991). Rao *et al*. (1989) have suggested that there may be a critical threshold of lesion load that must be crossed before cognitive deficits can be detected. Using a similar rationale, Swirsky-Sacchetti *et al*. (1992) and Arnett *et al*. (1994) have reported that poor performance on the Wisconsin Card Sort Test is closely related to the severity of frontal lesion load. The results of these studies cannot be seen as conclusive because they were performed in small samples and the sensitivity of the Wisconsin Card Sort Test to focal frontal lesions in the presence of widespread pathology may be questioned.

The aims of the present study are twofold. Firstly, to examine executive skills in multiple sclerosis patients in a more systematic way than has been attempted hitherto and secondly to try to establish the contribution of frontal lobe lesion load to these deficits using sensitive techniques in MRI lesion quantification.

## Methods

### *Subjects*

Forty-two patients (16 male, 26 female) with clinically definite multiple sclerosis according to the criteria of Poser *et al*. (1983) were selected for the study. They were recruited from the out-patient clinics and the neurorehabilitation unit at the National Hospital for Neurology and Neurosurgery. Their ages ranged between 24 and 50 years. Patients were excluded if their visual acuity was less than 6/12 or if there was motor impairment that would interfere with accurate use of a computer touch screen. Patients were also excluded if they were experiencing a clinical relapse (defined as the development of new signs or worsening of existing signs within the past month), at the time of evaluation. Patients who appeared to be severely depressed on clinical interview were not selected for the study. With respect to disease category, 28 patients had secondary progressive, 10 had relapsing–remitting, three had primary progressive and one had benign multiple sclerosis, using a classification reported elsewhere (Miller *et al*., 1991).

Forty healthy controls (20 male, 20 female) were chosen to match the patient group as closely as possible with respect to age and estimated premorbid IQ. Any subject whose alcohol intake exceeded the recommended levels (21 units for males and 14 units for females per week) was excluded from the study. The study was approved by the Ethics Committee of the National Hospital of Neurology and Neurosurgery, London, UK. Informed consent was obtained from all subjects.

### *Physical disability*

All the multiple sclerosis patients had a neurological examination at the time of the study and physical disability was assessed on the Kurtzke Expanded Disability Status Scale (Kurtzke, 1983).

### *Psychiatric symptoms*

The Hospital Anxiety and Depression Questionnaire (Zigmond and Snaith, 1983) was administered to all subjects. This self-rating scale has subscales for anxiety and depression (range of scores 0–21 for each). Scores $>10$ on each subscale are indicative of 'caseness'.

### *Neuropsychological tests*

A battery of neuropsychological tests to assess level of general intellectual ability and executive skills was administered to each subject. It included the following:

#### *National Adult Reading Test (Nelson and Willison, 1991)*

This test provided an estimate of premorbid IQ and was used to match the controls to the patient group.

#### *Advanced Progressive Matrices, Set 1 (Raven, 1958).*

A set of 12 non-verbal abstract reasoning tests was presented. The number of problems correctly completed was converted to an age adjusted scaled score which was used as a measure of current intellectual functioning.

#### *Verbal Fluency Test*

The subject was required to generate as many words as possible (excluding proper nouns) beginning with the letter S in 90 s and as many animals as possible in 90 s. The two scores obtained were the total number of acceptable words generated for each condition.

#### *Cognitive Estimates (Shallice and Evans, 1978).*

Each subject was required to make estimates in response to 10 questions such as 'What is the length of the average man's spine?' or 'What is the largest object normally found in a house?' Estimates were scored according to normative

data (range 0–3) and higher scores reflected worse performance.

### *Stroop (Stroop, 1935)*

A computerized version of this test was administered to each subject. Two control conditions were presented prior to the test to determine the subject's accuracy of reading words and identifying colours. In the first condition, each subject was required to read 24 printed words of colours (four rows of six words) on the screen and in the second one, to name the colours of 24 squares (four rows of six boxes) shown on the screen. In the test condition, 24 names of colours printed in a different colour ink were presented on the screen. The subject was required to name the colour in which each word was printed and not read the words denoting names of the colours. The time taken to complete this task and the number of errors made were recorded.

The next three tests were taken from the Cambridge Neuropsychological Test Automated Battery (Sahakian and Owen, 1992). The Cambridge Neuropsychological Tests were selected as they have been found to be sensitive in assessing frontal lobe dysfunction in patients with focal frontal pathology (Owen *et al*., 1990, 1991) and in patients with more widespread brain disease involving the frontal lobes such as in Korsakoff's syndrome, Parkinson's disease and HIV (Joyce and Robbins, 1991; Robbins *et al*., 1994; Sahakian *et al*., 1995). The tests were run on a personal computer with an Intasolve touch-sensitive screen and subjects were instructed to respond to stimuli by touching the screen.

### *Spatial Span Test*

This is a computerized version of the Corsi Block Tapping Task (Milner, 1971) and assesses the ability to remember a sequence of squares lighting up on the screen. For each trial, nine randomly arranged white squares are shown on the screen. Some of the squares light up in colour, one by one, in a variable sequence and subjects were instructed to remember the sequence. At the end of the presentation, the subject is required to touch each of the boxes that had lit up in the same order as they were originally presented. The task begins with the simplest level of a two box sequence. After each successful trial, the number of boxes in the sequence was increased by one to a maximum of nine. If the subject's response was incorrect at any particular level, an alternate sequence of the same length was presented. This continued until the subject failed three consecutive trials at any one level whereupon the test was terminated. The spatial span was calculated as the longest sequence that the subject could recall accurately on at least one trial.

### *Spatial Working Memory*

In this test, the subject was required to search for a blue token hidden within a number of boxes shown on the screen. The test started with two practice trials of two boxes. Levels of three, four, six and eight boxes were presented and there were four trials at each of the levels. The subjects were instructed that at any one time, there would be a single blue token hidden in one of the boxes. The subject was required to 'open' each box by touching the boxes in turn until the blue token was located and to place it in an empty column on the right hand side of the screen. When this has been completed, the next token would then be hidden. The subjects were instructed that once a blue token had been found within a particular box, then that box would not be used again to hide a token for that particular trial. Since every box was used once, on each trial the total number of blue tokens hidden corresponded to the number of boxes on the screen.

Two types of possible search errors were recorded at each level of difficulty. The 'between errors' score referred to the number of returns to a box in which the blue token had previously been located in earlier searches, whereas the 'within errors' referred to the number of returns to a box previously opened and shown to be empty during the same search sequence. Both scores are a measure of spatial working memory but the 'between errors' is a more stringent one as the subject has to remember, across searches, which boxes had contained the blue tokens while conducting a new search (Joyce and Robbins, 1991). An index for an efficient strategy termed as 'strategic count' was also recorded and reflected the use of a pre-determined search sequence beginning with a particular box and then returning to start each new sequence with the same box as soon as a token has been found. This was estimated from the number of search sequences starting with the same box, within each of the trials at the more difficult six- and eight-box levels. The total of these scores provided a single measure of strategy with a high score (many sequences beginning with a different box) representing low use of strategy and a low score (many sequences starting with the same box) representing more extensive usage of strategy.

### *Planning task*

This spatial planning task is based on the Tower of London Task developed by Shallice (1982). Two displays, each of three coloured balls held in suspended socks, are presented, one in the top half of the screen and the other in the bottom half. The subject was instructed to rearrange the balls in the lower display to copy the pattern shown in the upper one. The balls had to be moved one at a time by touching the required ball and then the intended position.

A minimum of two, three, four or five moves was required to solve each problem. Subjects were instructed to attempt to solve the problem in the minimum number of moves and to think about the solution prior to executing the sequence. There were two blocks of test trials with six problems each. The first block contained two problems at each of two, three and four minimum move solutions and the second block contained two problems at four moves and four at five

minimum move solutions. The computer recorded the number of moves made and the time taken to initiate the first move, select the subsequent ball and to complete the problem for each test trial. This was used to estimate initial and subsequent thinking/planning times.

After each block of test trials, a block of 'yoked control' trials was presented. On each trial, the computer moved one ball at a time in the upper display which was a replication of the moves made by the subject in the corresponding previous block of test trials. The subject was instructed to follow the moves made in the upper display by moving the balls in the lower display. The selection and execution latencies recorded from the 'yoked control' trials provided baseline estimates of motor initiation and execution times. The maximum number of moves allowed corresponded to twice the number of the minimum number possible plus one, or plus two in the 'five-move' problems. If the maximum number of moves was exceeded, the trial was terminated and the next one would be presented. The three measures that were evaluated in this task were movement times, thinking times and accuracy.

### *MRI*

Imaging was performed on a NMR 1.5 Tesla GE Signa System. Axial slices were obtained using a pulse sequence VEMP 35/90/2400. A series of 36 contiguous, axial slices (3 mm thickness) with a TR of 2400 ms and TE of 35 ms was selected for measurement of lesion volume.

A neuroradiologist (G.Q.), who had no clinical or neuropsychological information about the patients, identified and delineated the lesion areas on hard copies. With reference to these, one single rater (J.F.) obtained measurements of lesion load using a semi-automated contouring technique to mark the images displayed on a SUNSPARC station. This technique has been shown to be highly reproducible and objective in segmenting lesions on MRI (Grimaud *et al*., 1996). A software lesion volume measurement program was utilized to compute the total cerebral lesion load by summing the lesion volumes measured for each slice. A protocol based on neuroanatomical landmarks was used to delineate the frontal regions on each slice. First, the central sulcus, in the most superior slice in which it appears, and the Foramen of Munro in the inferior slices, were identified. A line drawn through the central sulcus was used to delineate the frontal regions. This line was adjusted for each slice by measuring the distance between these two landmarks and dividing it equally by the number of slices. Lesions anterior to this line, but excluding those in the insula and temporal lobes, were considered to be in the frontal region. Total frontal lesion volume was then calculated in the same manner as the total brain lesion load for each patient.

### *Statistical analysis*

The data were analysed using the Statistical Package for the Social Sciences. Independent *t* tests and ANOVA for repeated measures were applied to examine group differences. Where appropriate, non-parametric tests (Mann–Whitney) were used. Logarithm (base 10) transformation was applied to latency data to reduce skewness prior to statistical analysis. Spearman's correlation analysis was used to examine the relationship between MRI frontal lesion volumes, neuropsychological scores and physical disability.

**Table 1** *Demographic and clinical data for patients and controls: group means (SDs)*

| | MS patients ($n$ = 42) | Controls ($n$ = 40) |
|---|---|---|
| Age | 38.64 (7.99) | 35.75 (6.49) |
| Sex (M/F) | 16/26 | 20/20 |
| EDSS | 6.26 (1.45) | |
| Disease category | | |
| Primary progressive | 3 (7.1%) | |
| Secondary progressive | 28 (66.7%) | |
| Relapsing–remitting | 10 (23.8%) | |
| Benign | 1 (2.4%) | |

MS = multiple sclerosis; EDSS = Expanded Disability Status Scale.

## Results

The demographic and clinical data for patients and controls are shown in Table 1. There was no significant difference between the multiple sclerosis and control groups with respect to age or gender.

There was no significant group difference in premorbid IQ as estimated by the National Adult Reading Test. Performance on the Advanced Progressive Matrices (APM) was shown to be significantly worse in the multiple sclerosis group compared with controls ($Z = –6.36$, $P < 0.001$), as seen in Table 2, suggesting that current intellectual functioning was impaired in patients. The performance on APM was used as a covariate in the analysis of the data to determine the extent to which the patients' impaired intellectual functioning had affected their performance on tests of executive function (*see* below).

On the Verbal Fluency Test, the multiple sclerosis group generated significantly fewer words than the control group for both conditions (i.e. words beginning with 'S' and the category for animals).

Cognitive estimate scores were significantly higher in the multiple sclerosis patient group than controls, indicating worse performance.

In the test condition for the Stroop test, multiple sclerosis patients took significantly longer time to complete the task and made more errors than the controls although the mean number of errors was very small.

The results of these tests are summarized in Table 2.

### *Cambridge Neuropsychological Tests*

#### *Spatial span*

There was a significant difference in spatial span between patients and controls (Table 3).

**Table 2** *Tests of general ability and executive function: group means (SDs)*

| Tests | MS patients ($n$ = 42) | Controls ($n$ = 40) | $t$ test/Mann–Whitney |
|---|---|---|---|
| NART | 109.40 (9.27) | 113.15 (8.14) | n.s. |
| APM | 7.24 (2.68) | 9.73 (2.04) | $Z = -6.36$ ** |
| Verbal fluency | | | |
| 'S' words | 16.31 (7.37) | 25.08 (7.52) | $t = -5.33$ ** |
| Category (animals) | 20.05 (8.51) | 33.35 (7.13) | $t = -7.65$ ** |
| Cognitive estimates | 6.64 (3.49) | 3.58 (2.59) | $Z = 4.47$ ** |
| Stroop time (s) | 39.16 (12.92) | 23.14 (6.31) | $Z = -6.36$ ** |
| Stroop errors | 1.59 (3.44) | 0.23 (1.13) | $Z = -3.25$ * |

NART = National Adult Reading Test. *$P < 0.01$; **$P < 0.001$; n.s. = not significant.

**Table 3** *Spatial span and spatial working memory tests: group means (SDs) and statistical analysis*

| Tests | MS patients ($n$ = 42) | Controls ($n$ = 40) | Mann–Whitney/ANOVA | | |
|---|---|---|---|---|---|
| Spatial span | 4.83 (1.15) | 6.48 (1.24) | $Z = -5.39$, $P < 0.001$ | | |
| Spatial working memory | | | Effect of group | Level of difficulty | Group×difficulty interaction |
| Between errors | | | | | |
| Four boxes | 2.90 (3.48) | 0.4 (0.84) | $F(1,78) = 44.82$, | $F(2,158) = 242.77$ | $F(2,158) = 38.94$, |
| Six boxes | 15.34 (7.45) | 4.33 (4.87) | $P < 0.001$ | $P < 0.001$ | $P < 0.001$ |
| Eight boxes | 29.56 (11.76) | 11.80 (8.93) | | | |
| Within errors | | | | | |
| Four boxes | 0.29 (0.90) | 0.15 (0.43) | $F(1,79) = 4.62$, | $F(2,158) = 10.61$, | $F(2,158) = 3.16$, |
| Six boxes | 0.27 (0.63) | 0.18 (0.50) | $P < 0.05$ | $P < 0.001$ | $P < 0.05$ |
| Eight boxes | 1.00 (1.47) | 0.38 (0.74) | | | |
| Strategic score | 36.66 (4.25) | 30.80 (6.05) | $Z = -4.56$, $P < 0.001$ | | |

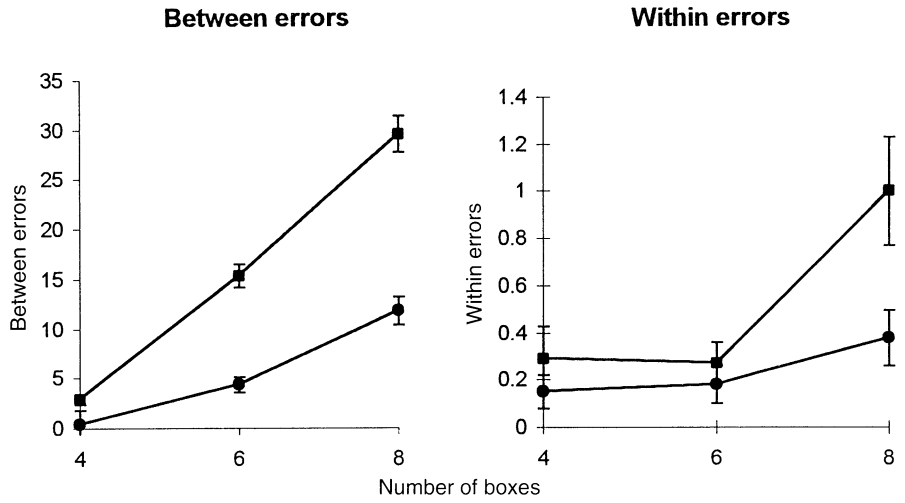


**Fig. 1** Group mean number of between and within errors on the spatial working memory task. Error bars represent SEM. Closed squares represent multiple sclerosis group. Closed circles represent controls.

## *Spatial working memory*

The group mean scores for between search and within search errors at each level of difficulty are shown in Table 3 and Fig. 1. Patients made more between and within errors than controls at every level of difficulty and the number of errors also increased as the level of difficulty increased for both groups. There were very few within errors in comparison with the number of between errors for both groups. ANOVA for repeated measures was used to analyse the data (Table 3). For both the between and within errors, there were significant effects of group and level of difficulty at four, six and eight boxes. group×difficulty interactions were also significant, particularly for the between errors, indicating that the differences between multiple sclerosis patients and controls became greater as the level of difficulty increased.

Strategy scores were significantly different between patients and controls and the latter obtained a lower mean score indicating greater usage of strategy. The strategy score was highly correlated with the between errors score (summed at six and eight boxes) for the control group ($r$ =

0.711, $P < 0.001$) as well as the patient group ($r = 0.714$, $P < 0.001$) suggesting greater usage of strategy at the more difficult levels for both groups. Using the strategy score as a covariate in the ANOVA analysis of between errors at the six and eight levels, significant group differences persisted indicating that the patients' poor performance on this test could not be solely accounted for by poor use of strategy [$F(1,78) = 34.45$, $P < 0.001$]. Similarly, using the spatial span as a covariate in the analysis of the between errors, significant group differences also persisted, indicating that the impaired immediate recall in the multiple sclerosis patient group was not a major contributing factor in their poor performance on the working memory task [$F(1,78) = 27.08$, $P < 0.001$].

## *Planning task*

*Movement times.* In analysing the data, motor initiation and motor execution times were extracted from the yoked trials of the Tower of London Test. The motor initiation time refers to the time taken to select the first ball for each level of difficulty. The motor execution time represents the time taken between making the first move to completing the problem. As this varied with the number of moves taken, the total execution time was divided by the number of moves to give an estimate of motor execution time per move.

The motor initiation and execution times were significantly longer for patients compared with controls, as shown in Table 4. None of the group×difficulty interactions were significant (Table 5). This suggests that overall, the multiple sclerosis patients were slower at initiation and execution times but the group differences did not change significantly with the increasing level of difficulty.

*Thinking times.* The initial thinking time was calculated by subtracting the motor initiation time as calculated on the 'yoked control' task from the copying initiation time. Subsequent thinking time was the time taken between selection of the first ball and the completion of the problem minus the motor execution time from the corresponding control task. As this measure varied with the problem length, the subsequent thinking times were divided by the number of moves to give an estimate of thinking time per move. Any negative value produced from the subtractions was reduced to 0 indicating minimal thinking time. The group mean latencies are summarized in Table 4.

There was no significant group difference in initial thinking times or group×difficulty interaction when all problems were considered (Table 5). This indicates that patients did not differ from controls in the time taken to initiate the first move in attempting to solve the problem. There was, however, a significant effect of task difficulty with longer initial thinking times as the level of difficulty increased.

Subsequent thinking times per move were analysed for (i) all problems and (ii) problems solved in the minimum number of moves. For both conditions, there were no significant group differences but there was a significant effect of difficulty. The group×difficulty interactions were significant for both conditions (Table 5). Further analysis comparing the groups at each individual level showed that group effects were significant only for the more difficult four- and five-move solutions when all problems were considered and for level 5 when only minimum move solutions were considered. Overall, the multiple sclerosis patient group did not take significantly longer time than controls to solve the problems except at the most difficult levels.

**Table 4** *Planning task: group means (SDs)*

| Planning task | MS patients ($n = 42$) | Controls ($n = 40$) |
|---|---|---|
| Motor initiation times (s) | | |
| Three moves | 3.05 (1.91) | 1.47 (2.98) |
| Four moves | 3.04 (2.34) | 1.53 (0.44) |
| Five moves | 2.78 (1.99) | 1.44 (3.25) |
| Motor execution times (s) | | |
| Three moves | 3.12 (2.60) | 1.42 (0.25) |
| Four moves | 2.96 (1.89) | 1.57 (0.37) |
| Five moves | 2.98 (2.96) | 1.50 (0.24) |
| Initial thinking times (s) | | |
| Three moves | 5.74 (4.37) | 4.85 (3.28) |
| Four moves | 8.86 (9.78) | 8.67 (5.91) |
| Five moves | 8.31 (25.48) | 10.39 (6.84) |
| Subsequent thinking times per move (all solutions) (s) | | |
| Three moves | 1.78 (4.50) | 0.34 (0.53) |
| Four moves | 3.76 (5.93) | 1.08 (1.02) |
| Five moves | 2.35 (1.99) | 1.10 (1.19) |
| Subsequent thinking times per move (minimum move solutions)(s) | | |
| Three moves | 0.25 (0.73) | 0.30 (0.51) |
| Four moves | 1.53 (3.02) | 0.33 (0.56) |
| Five moves | 0.96 (1.78) | 0.35 (0.70) |
| Excess moves | | |
| Three moves | 0.47 (0.63) | 0.1 (0.26) |
| Four moves | 1.52 (0.97) | 0.98 (0.88) |
| Five moves | 2.66 (2.00) | 1.33 (1.26) |
| Problems solved in minimum number of moves | 6.8 (2.17) | 8.98 (1.76) |

*Accuracy.* The different aspects of accuracy were assessed by two measures: (i) the proportion of problems solved in the minimum number of moves which reflect efficient planning ability; (ii) the number of excess moves (mean number of moves above the minimum possible) which is a more general measure of problem solving ability. The group mean scores are shown in Table 4. The control group solved a significantly greater number of problems with the minimum number of moves allowed than the patient group ($Z = -4.46$, $P < 0.001$). At each level of difficulty, patients tended to take more moves in solving the problems ('excess moves') than controls. There was a significant effect of group and level of difficulty. The group×difficulty interaction was also

**Table 5** *ANOVA for planning task*

| Planning task | Effect of group | Level of difficulty | Group×difficulty interaction |
|---|---|---|---|
| Motor initiation times | $F(1,75) = 43.71$*** | n.s. | n.s. |
| Motor execution times | $F(1,72) = 48.00$*** | $F(3,216) = 23.07$*** | n.s. |
| Initial thinking times | n.s. | $F(2,146) = 25.68$ | n.s. |
| Subsequent thinking times (all solutions) | n.s. | $F(3,219) = 33.96$*** | $F(3,219) = 3.95$** |
| Subsequent thinking times (minimum move solutions) | n.s. | $F(3,192) = 5.52$*** | $F(3,192) = 3.92$** |
| Excess moves | $F(1,75) = 12.53$*** | $F(2,152) = 49.52$*** | $F(2,152) = 4.44$** |

**$P < 0.01$; ***$P < 0.001$; n.s. = not significant.

**Table 6** *Covariance of current intellectual functioning (APM) with tests of executive function*

| Tests | Contribution of APM | Main group effect |
|---|---|---|
| Verbal fluency ('S' words) | $P < 0.01$ | $P < 0.001$ |
| Category (animals) | $P < 0.001$ | $P < 0.001$ |
| Cognitive estimates | n.s. | $P < 0.001$ |
| Stroop | $P < 0.05$ | $P < 0.001$ |
| Spatial span | $P < 0.05$ | $P < 0.001$ |
| Spatial working memory (between errors) | $P < 0.001$ | $P < 0.001$ |

n.s. = not significant.

significant (Table 5). The results indicate that the multiple sclerosis patients were less efficient in their performance than the controls on this task.

## *Covariance of current intellectual functioning with tests of executive function*

In order to examine the contribution of current intellectual functioning, as determined by the APM, to the patients impaired performance on tests of executive function, analysis of covariance was carried out using APM as a covariate. Results indicated that although APM made a significant contribution in most of the tests, the main group effects were not affected, as shown in Table 6. This suggests that the executive deficits in the multiple sclerosis patients cannot be solely attributed to general cognitive decline.

## *Physical disability*

There was no correlation between physical disability as measured by the Expanded Disability Status Scale and any of the neuropsychological variables.

## *Psychiatric symptoms*

The difference between the two groups was significant on the depression scale ($t = 3.35$, $P < 0.001$) but not on the anxiety scale. However, group mean scores on the depression scale did not reach 'caseness' (score >10) with mean scores of 4.88 for multiple sclerosis patients and 2.61 for controls. Only one multiple sclerosis patient reached caseness on the depression scale with a score of 13. This patient had a 2-year history of depression and was on antidepressant treatment. A further three multiple sclerosis patients and three controls reached 'caseness' on the anxiety scale (scores of 11–15). The neuropsychological test scores for each of these subjects did not differ significantly from their group mean scores.

**Table 7** *Correlation between MRI frontal lesion load and neuropsychological test scores*

| Neuropsychological tests | Correlation coefficient ($r$) | $P$ |
|---|---|---|
| Verbal fluency | | |
| 'S' words | −0.32 | * |
| Category (animals) | −0.42 | ** |
| Cognitive estimates | 0.33 | * |
| Stroop time | 0.48 | *** |
| Spatial working memory | | |
| Between errors 4 | 0.29 | n.s. |
| Between errors 6 | 0.65 | *** |
| Between errors 8 | 0.42 | ** |
| Within errors 4 | 0.12 | n.s. |
| Within errors 6 | 0.15 | n.s. |
| Within errors 8 | 0.16 | n.s. |
| Strategic score | 0.32 | * |
| Spatial span | −0.15 | n.s. |
| Tower of London | | |
| Subsequent thinking times | | |
| Five moves (all solutions) | 0.35 | * |
| Five moves (minimum move solutions) | 0.34 | n.s. ($P = 0.058$) |
| Minimum move solutions | −0.36 | * |

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; n.s. = not significant.

## *Correlation with MRI frontal lesion load*

Most patients were found to have widespread lesions especially in the periventricular white matter which is the usual pattern seen in multiple sclerosis. Total lesion load ranged from 1089 to 135 951 $mm^3$ and the frontal lesion load ranged from 177 to 65 019 $mm^3$ which represented a mean of 42.4% of the total lesion load. The frontal lesion

load correlated highly with the total lesion load ($r = 0.96$, $P < 0.001$).

Neither frontal nor total lesion load correlated with physical disability as measured on the Expanded Disability Status Scale or with ratings of anxiety and depression.

Correlations between MRI frontal lesion load and neuropsychological scores are shown in Table 7. We selected the neuropsychological variables in which significant group differences were found. Scores on tests of Verbal Fluency, Cognitive Estimates and Stroop were significantly correlated with frontal lesion load. On the Spatial Working Memory Test, the between error scores, particularly at the more difficult levels, and the strategy score correlated significantly with frontal lesion load. On the planning task, subsequent thinking times at the most difficult level (when all solutions were considered) correlated significantly with frontal lesion load and there was a trend towards a significant correlation between the subsequent thinking times at the most difficult level and frontal lesion load when only minimum move solutions were considered. Scores for the number of solutions solved in the minimum number of moves also correlated significantly with frontal lesion load. In order to dissect the specific contribution of frontal lesion load in these correlations, the analysis was repeated, controlling for total lesion load. This resulted in all the previous significant correlations becoming non-significant.

Using forward multiple regression analysis, the significant ($P < 0.05$) neuropsychological variables predicting frontal lesion load were the Spatial Working Memory between errors scores (summed at levels 6 and 8) and the Stroop test times. The same variables also significantly predicted total lesion load.

In order to explore further the contribution of frontal lesion load to the impairment of executive skills, a grading system, was devised to examine the patients' level of performance in the Spatial Working Memory between errors scores (summed at levels 6 and 8) and the Stroop test based on the performance of the control group. The scores on each of these tests were available in 40 patients and assigned grades as follows: Grade 0 = within 1 SD from the group mean score of controls; Grade 1 = within 2 SDs; Grade 2 = >2 SDs.

The grades for the two tests were summed to give an overall measure of performance (impairment index). The patients ($n = 40$) were divided into four groups based on their impairment index: Group A = impairment index of 0–1 (eight patients); Group B = impairment index of 2 (nine patients); Group C = impairment index of 3 (seven patients); Group D = impairment index of 4 (16 patients)

Group A was considered to be the unimpaired group. ANOVA revealed a significant difference in frontal lesion load between the groups with a much lower frontal lesion load for the unimpaired group (Group A) compared with the other groups [$F(3) = 4.39$, $P < 0.01$] and there were no significant differences between the other groups. Total lesion load of Group A was also significantly smaller than that of the other three groups [$F(3) = 4.27$, $P < 0.01$], which did not significantly differ between each other, although total lesion load tended to increase with severity of cognitive impairment. The results are shown in Table 8 and Fig. 2. Frontal lesion load accounted for 37% of total lesion load in Group A and 43.3% in the three other groups combined.

Further analysis of the data was conducted using a similar method to that of Arnett *et al.* (1994), excluding the eight patients who had a low total lesion volume (<10 000 $mm^3$). The remaining 32 patients were divided into two groups of 16 each based on a median split of the frontal to total lesion volume ratio. There was a significant difference in the frontal: total lesion volume ratio between the two groups ($t = –7.90$, $P < 0.001$) with group mean ratios (and standard deviations) of 0.35 (0.04) and 0.49 (0.06). However, we were unable to find any significant differences between these two groups in their performance on the executive tasks.

## Discussion

The results of this study suggest that patients with multiple sclerosis present with deficits in executive function which cannot be fully explained as a result of general intellectual decline. On the other hand, the contribution of frontal lobe pathology to this aspect of cognitive impairment is difficult to delineate and according to the present findings is less significant than previously reported.

Previous studies of executive function in multiple sclerosis patients have mainly focused on measuring abstract ability or verbal working memory in isolation (Litvan *et al.*, 1988; Swirsky-Sacchetti *et al.*, 1992; Mendozzi *et al.*, 1993; Arnett *et al.*, 1994). Patients in this study were found to have abnormalities in verbal fluency, Stroop, cognitive estimation, spatial span, spatial working memory, use of strategy and planning, although not all of these skills were impaired to the same extent. This applies, in particular, to planning ability which appears to be relatively preserved in our group of multiple sclerosis patients as exemplified by the fact that differences in the subsequent thinking (planning) times between multiple sclerosis patients and controls were only significant at the most difficult levels of the task.

The neuropsychological tests adopted in this study allowed us to dissect various executive deficits. Thus, we were able to demonstrate that the impaired performance on the Spatial Working Memory task could not be explained by less efficient use of strategy or poor immediate recall but indicated a specific impairment of working memory. These results are analogous to earlier studies in which impairment of verbal working memory in patients with multiple sclerosis were found (Litvan *et al.*, 1988; Grafman *et al.*, 1990). There are overall similarities in the pattern of performance on the Cambridge Neuropsychological Tests between our group of multiple sclerosis patients and those with frontal lobe excisions, Huntington's disease, Multiple system atrophy and HIV (Owen *et al.*, 1990; Robbins *et al.*, 1992; Lange *et al.*, 1995; Sahakian *et al.*, 1995) even if the underlying mechanisms leading to these deficits may have been different.

**Table 8** *Frontal and total lesion load for multiple sclerosis patient groups: group means (SDs)*

| Groups | Impairment index | Frontal lesion load ($mm^3$) | Total lesion load ($mm^3$) |
|---|---|---|---|
| A ($n$ = 8) | 0–1 | 4058.63 (4412.42) | 11109.75 (11687.73) |
| B ($n$ = 9) | 2 | 12421.67 (7013.08) | 32918.56 (19125.18) |
| C ($n$ = 7) | 3 | 17250.86 (21700.64) | 39677.14 (43775.90) |
| D ($n$ = 16) | 4 | 23062.31 (12321.35) | 51604.69 (25636.86) |

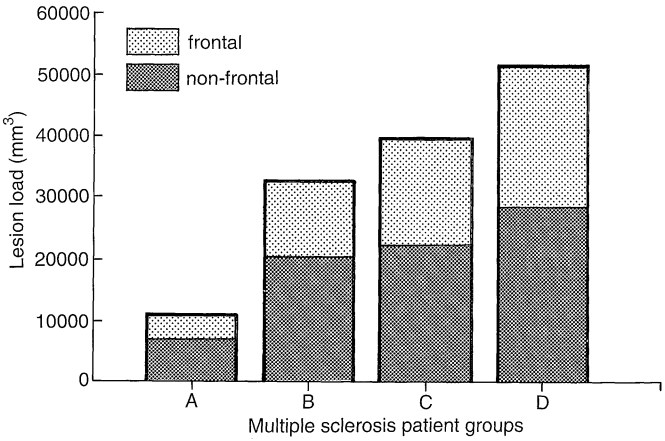


**Fig. 2** Lesion load in the multiple sclerosis patient groups.

Indeed, the similarities in their performance contrast with the different clinical presentation of these patients. The performance of multiple sclerosis patients in these tests most closely resembles that of HIV infected patients (Sahakian *et al*., 1995), whilst patients with more extensive frontal lobe pathology (i.e. frontal lobe excisions) (Owen *et al*., 1990) had greater impairment on planning tasks.

Although we only focused on tests of executive function, which included spatial working memory, in this study, it would be misleading to assume that other neuropsychological deficits were absent in our patients, especially in a widespread disease such as multiple sclerosis. It has been well documented in previous studies (Rao *et al*., 1991; Ron *et al*., 1991) that a range of neuropsychological deficits can be detected in multiple sclerosis patients, including attentional and memory deficits, and it would therefore be unusual to observe executive deficits in isolation. It is now recognized that some aspects of executive function may fractionate and can be more severely affected than others in the same individual. This has led to arguments about the association or dissociation of these executive skills. Our results would support the hypothesis that different aspects of executive function may be subserved by different distributed systems (Burgess and Shallice, 1992).

The executive deficits in our patients cannot be attributed to coexisting psychiatric symptoms or primary visual impairment as we used strict exclusion criteria in our selection of patients for the study. It is also unlikely that the patients' poor performance on the tests reflected a general decline in intellectual ability as the significant differences in the group mean scores on tests of executive function persisted when APM scores were used as a covariate. Although APM has been used in the past as a specific measure of abstracting ability, performance on this task was not found to be impaired in a study of patients with widespread frontal lobe dysfunction (Kartsounis *et al*., 1991) suggesting that its use as a measure of current intellectual functioning is more appropriate.

In our measurement of lesion load, we used an automated program which calculated the volume of lesions in thinner slices (3 mm). This represents an advance over previous studies in which lesion load was calculated by measuring the area of the lesions (Rao *et al*., 1989; Huber *et al*., 1992; Arnett *et al*., 1994). The contouring technique used in our study has also been shown to have greater intra- and inter-rater precision when compared with manual outlining and global threshold techniques in measuring multiple sclerosis lesion load on MRI (Grimaud *et al*., 1996). A number of the executive test scores were found to correlate significantly with frontal lesion load, although it was only at the more difficult levels on the spatial working memory and planning task. Similar findings have been reported by others (Swirsky-Sacchetti *et al*., 1992; Arnett *et al*., 1994), who have postulated a close relationship between frontal lobe pathology and executive deficits. In our study, however, it proved impossible to disentangle the specific contribution of frontal lobe pathology to cognitive impairment in the presence of widespread lesions and, although frontal pathology may be crucial in causing the executive deficits, it seems unlikely to be the sole cause. This was illustrated by our findings that the significant correlation of impaired executive skills with frontal lesion load disappeared when total lesion load was controlled for. This was further supported by the finding that frontal lesion load did not differ significantly between the subgroups of multiple sclerosis patients with increasing impairment of executive function (Groups B, C and D). It is possible that the impairment on executive tasks may be secondary to a more diffuse process affecting the general functioning of the brain or causing a disconnection between prefrontal, limbic and association cortices which has been suggested in traumatic brain injury patients (Levin *et al*., 1987; Stuss *et al*., 1992). Some support for this possibility accrues from an earlier PET study (Brooks *et al*., 1984) in which generalized rather than focal reduction of cerebral oxygen utilization, regional cerebral blood flow and oxygen extraction was found in multiple sclerosis patients. It may also be important to consider that visible lesions on conventional MRI may not be the only measure of the extent

of disease process in multiple sclerosis as recent studies using proton magnetic resonance spectroscopy have indicated that abnormalities can be detected in normal appearing white matter (Davie *et al*., 1994). These abnormalities in normal appearing white matter have been attributed to the presence of microscopic demyelination (Allen, 1991) but the precise contribution to cognitive dysfunction remains to be determined.

Using a similar method of analysis, our findings were in contrast to Arnett *et al*. (1994) who found a significant correlation between frontal lobe pathology and the Wisconsin Card Sort Test. They compared seven patients with predominant frontal lesions with seven patients with similar total lesion load, but more evenly distributed and although not statistically significant, there were trends for the frontal group to be older and to have a longer duration of illness. Although this correlation may be present in patients with predominantly frontal lesions, it was not possible to identify such a subgroup in our sample which contained patients who had a more widespread distribution of lesions or who had as low a frontal to total lesion volume ratio as reported in their study. Our findings also differ from those of Swirsky-Sacchetti *et al*. (1992) who entered a variety of test scores and regional lesion loads in a step-wise regression analysis. No attempt was made to control for total lesion load in that study, but the fact that the frontal lesion load predicted performance in a variety of tests of language and memory suggests that the overall lesion load may have explained some of these results.

Our study highlights the difficulties in trying to attribute specific cognitive abnormalities to focal brain pathology in the presence of widespread brain disease. This model, which stems from earlier observations of patients with single lesions, is being superseded by functional imaging studies that highlight the contribution of several brain regions to the performance of a given task. In this context, functional imaging studies using the Stroop test have reported that not only the right orbitofrontal and anterior cingulate but also parietal structures are involved (Bench *et al*., 1993). As the lesions in multiple sclerosis are widespread, it is possible that our patients' impairment on the Stroop task is partially accounted for by lesions elsewhere and not solely due to frontal lesions. A similar observation has been made by Mellers *et al*. (1995) who found activation of anterior and posterior parasagittal cortex, left parietal cortex and left dorsolateral prefrontal cortex in normal subjects during a working memory task using functional MRI. It is evident that the specific patterns of brain activity during the performance of these tasks in patients with similar executive function deficits, but different localizations of brain pathology will need further investigation.

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