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Cognitive deficits in multiple sclerosis correlate with changes in fronto-subcortical tracts

M Roca[1], T. Torralva[1]*, F Meli[2], M Fiol[1], ML Calcagno[3], S Carpintiero[2], G De Pino[2], F Ventrice[2], ME Martín[1], L Vita[1]*, F Manes[1]* and J Correale[1]*

Cognitive function and diffusion tensor imaging were assessed in a group of 12 patients with early relapsing–remitting multiple sclerosis (disease duration ≤3 years), and mild clinical disability (expanded disability status scale ≤2), as well as in 12 control subjects. Patients showed impairment in immediate logical memory and delayed recall with the Rey auditory verbal learning test. No significant differences in classical executive tests were observed. In contrast, differences were found for specific executive tests including IOWA Gambling Task, multiple errands test hospital version (MET) and Hotel Task, as well as in Paced-Auditory Serial Addition Test (PASAT). Significant correlation was found between PASAT performance and FA measures ($r = 0.64$, $P = 0.03$), the apparent diffusion coefficients and the MET ($r = 0.72$, $P = 0.01$), as well as in one subtask of Hotel ($r = -0.68$, $P = 0.02$). Thus, executive deficits can best be appreciated at early stages of MS when a more specific battery of tests is used for patient evaluation. In this series, test failures observed correlated with changes in fronto-subcortical fiber tracts. *Multiple Sclerosis* 2008; **14**: 364–369. http://msj.sagepub.com

Key words: Multiple Sclerosis, Frontal lobe, Cognitive functions, Diffusion tensor MRI

Introduction

Only a few decades ago, cognitive impairment was considered rare among multiple sclerosis (MS) patients, mostly confined to those with severe disability. However, with the use of more sophisticated neuropsychological evaluations, it is currently accepted that 50–65% of MS patients have some level of cognitive dysfunction. Although the pattern is not homogeneous, a specific frontal-subcortical impairment has been described presenting with memory, problem solving, abstract reasoning, attention and information processing speed deterioration. The pathophysiology underlying this neuropsychological profile is unclear. Studies using conventional magnetic resonance imaging (MRI) indicate that cognitive impairment in MS patients cannot be fully explained on the basis of T2 lesional disease burden alone. Diffusion tensor MRI (DT-MRI) has enabled researchers to obtain reliable *in vivo* estimates of brain damage, showing that it is not limited to lesions visible on T2-weighted images, but can also involve regions that appear normal on conventional MRI. Diffusion tensor MRI provides the basis for tractography, a technique used to trace pathways responsible for anatomical connectivity in the CNS [1]. To the best of our knowledge, only one study has explored the correlation between cognitive deficits and changes in measures derived from DT-MRI, without establishing a conclusive relationship between them [2]. In this study, specific executive deficits in patients were studied at an early stage of relapsing–remitting MS (RRMS), in order to evaluate whether potential correlation was present between fronto-subcortical DT-MRI results and the presence of cognitive impairment.

[1]Department of Neurology, Dr Raúl Carrea Institute for Neurological Research (FLENI), Buenos Aires, Argentina
[2]Department of Radiology, Dr Raúl Carrea Institute for Neurological Research (FLENI), Buenos Aires, Argentina
[3]Department of Statistics, School of Pharmacy and Biochemistry, Buenos Aires University, Buenos Aires, Argentina
Author for correspondence: Jorge Correale, MD, Department of Neurology, Dr Raúl Carrea Institute for Neurological Research (FLENI), Montaneses 2325, 1428 Buenos Aires, Argentina. E-mail: jcorreale@fleni.org.ar; bairesla@fibertel.com.ar
*Present address: Institute of Cognitive Neurology (INECO), Buenos Aires, Argentina.
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Materials and methods

Patients

Twelve consecutive RRMS patients, six women and six men, fulfilling Poser and McDonald criteria and referred to our MS clinic for routine follow-up, underwent neuropsychological and MRI evaluation for the present study. All had mild clinical disability [Expanded Disability Status Scale (EDSS) <2], without visual deficit or upper limb impairment potentially affecting neuropsychological test performance or history of alcohol or drug abuse, major psychiatric disorder, head trauma or other neurological disorder or systemic illness. All tests were performed at least 90 days after the most recent relapse episode, and with all patients off steroid treatment for at least three months. Mean age was 32.5 ± 7.97 years (range 18–43 years) and mean disease duration 29.5 ± 12.04 months (range 11–36 months). Physical disability was assessed using EDSS [3] and MS Functional Composite (MSFC) score [4]. Twelve subjects matched for age, gender and educational level recruited from a local volunteer group served as controls.

MRI method

Magnetic resonance images of the brain were obtained using a standard quadrature birdcage head coil operating at 1.5T (GE Medical System, Milwaukee, WI, USA). Diffusion tensor MRI images were obtained from patients and controls using 25 noncollinear orientations in the axial plane. Fractional anisotropy (FA) and apparent diffusion coefficients (ADC) were measured along frontal lobe white matter bundles. White matter parameters were registered for both frontal lobes in patients and normal subjects in the following regions: orbito-frontal (OF) (Figure 1A), fronto-lateral (FL) (Figure 1B), fronto-medial (FM) (Figure 1C) and gyrus cinguli (GC) (Figure 1D). The four frontal regions were defined using DTI mapping [5], and FA and ADC were registered for normal appearing brain tissue in all cases. Regions of interest enclosed by white matter bundle areas from each region were recorded including approximately 90 pixels for each. Magnetic resonance imaging was performed within one week of neurological evaluation and neuropsychological testing, by observers blinded to neuropsychological test results.

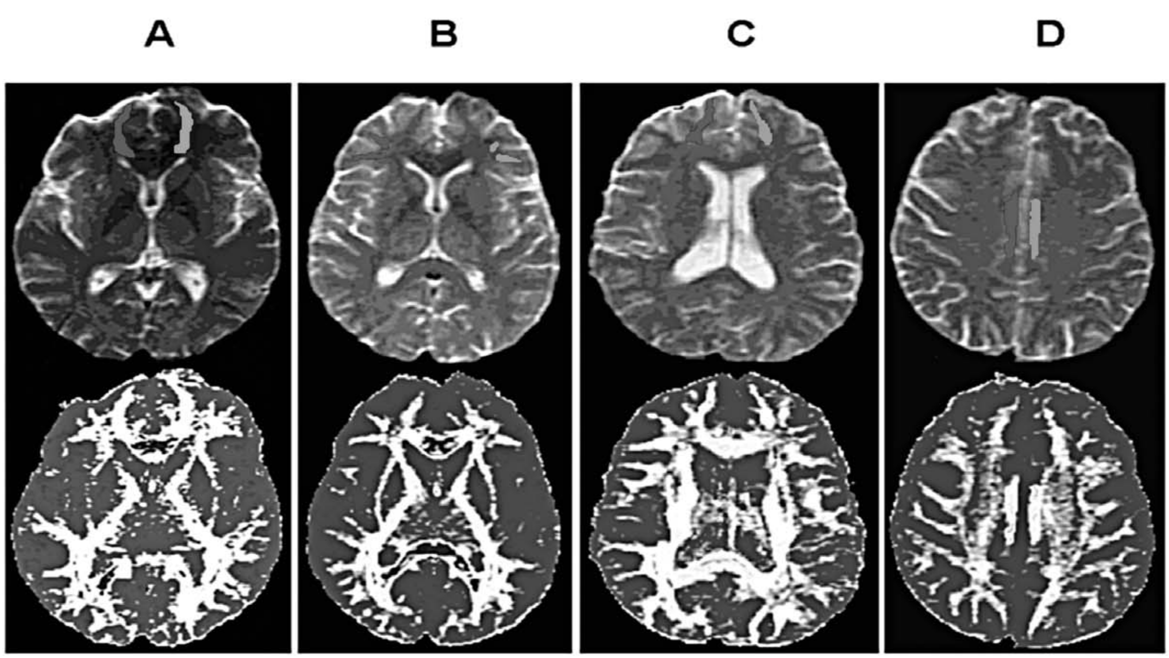

Figure 1 Fractional anisotropy and ADC measures in different frontal lobe regions. All figures show anatomical T2-image corresponding to DT-MRI images on top, and DT-MRI area of interest images below for (A) orbito-frontal region; (B) fronto-lateral region; (C) fronto-medial region and (D) gyrus cinguli region.

Neuropsychological evaluation

All subjects underwent standard neuropsychological battery and specific executive battery testing and were also screened for depression using the Beck Depression Inventory. Standard cognitive battery assessments included language, praxis, memory, executive functions, measures of general intelligence and the vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS).

Specific executive battery tests

Patients were examined using a specific executive battery consisting of a group of tests proved to be sensitive for prefrontal cortex dysfunction detection. The purpose of assessing these patients with an executive battery was to detect specific and subtle executive deficits, more closely related to every day activities. Given that these tests are not often used, a detailed description of the battery is included.

1. *The IOWA Gambling Task (IGT)* [6]. Computerized test that assesses decision-making by measuring the ability to identify from a choice of 4-card decks, the one which results in low short-term gain and better long-term benefit. Subjects make a series of decisions between four decks varying in magnitude of reward and punishment (specifically, winning and losing abstract points). Two 'risky' decks (A and B) yield large immediate wins but very large occasional losses. Two 'conservative' decks (C and D) yield smaller wins but negligible losses that result in net profit over time.
2. *The faux pas test* [7]. In this test, the subject reads 20 stories, 10 of which contain a social faux past. After each story, the subject is asked whether something inappropriate was mentioned in order to assess the theory of mind.
3. *Reading the Mind in the Eyes Test* [8]. This theory of mind task consists of 17 photographs of the eye region of faces. The subject is required to make a choice between two words, which best describe what the individual is thinking or feeling.
4. *The Hotel Task* [9]. This test assesses planning and organization in an ecological way. The subject has to complete in 15 min, five distinct activities that would plausibly need to complete in the course of running a hotel. Besides these five main tasks (compiling individual bills, sorting the charity collection, looking up telephone numbers, sorting conference labels and proofreading the hotel leaflet), subjects were asked to remember to open and close the hotel garage doors at two predefined times, for deliveries. Deviation of the assigned times were scored as 4 points.
5. *The multiple errands test hospital version (MET)* [10]. In this test, the individual must carry out a number of tasks under 'real world' conditions. It measures social interaction, personal regulation, planning and organization. Twelve separate subtasks have to be completed, following explicit and implicit rules.

Statistical analysis

Group differences were compared using Student's test and the Mann–Whitney test. Associations between numerical variables were measured using Spearman's rank correlation coefficient. Variable distribution was examined using the Kolmogorov–Smirnov test to determine whether it was normal or not. Given the many comparisons made, a P-value ≤ 0.01 was considered statistically significant, a P-value between >0.01 and ≤ 0.05 as a significance trend and P-values greater than 0.05 were not considered significant. Stepwise regression analysis was performed to examine the strongest neuropsychological test associated with patient cognitive impairment. Tests were entered and removed from the model at a significance level of 0.05. Only correlations showing moderate strength as a minimum (i.e., with r values >0.30) were reported.

Results

No statistical differences related to age, gender or educational level were observed between patients and controls. However, MSFC was reduced in MS patients ($P = 0.03$) as shown by a lower Paced Auditory Serial Addition Test (PASAT) score ($P = 0.002$), and in the 25-foot walk ($P = 0.001$), with no significant differences in the nine-hole peg test (HPT9 right $P = 0.48$; HPT9 left $P = 0.61$).

Neuropsychological results

A summary of the standard neuropsychological battery results is shown in Table 1. No significant differences were observed between groups in premorbid National Adult Reading Test IQ, current intellectual functioning (Raven's matrices and WAIS vocabulary subtests), language or praxis.

Memory

Patients showed immediate logical memory and delayed recall impairment ($P = 0.008$ and 0.002,

Table 1 Demographic data, MSFC and standard neuropsychological performance in MS patients and controls

	MS Patients (*n* = 12)	Controls (*n* = 12)
Age (years)	32.5 (7.97)	31.0 (8.49)
Education (years)	15.17 (2.33)	15.83 (2.76)
HPT9 right (seconds)	18.91 (2.05)	18.36 (1.72)
HPT9 left (seconds)	20.17 (2.74)	19.69 (1.68)
PASAT (number correct)	34.17 (11.36)	51.17 (6.16)[a]
Timed 25-ft walk (s)	5.27 (1.20)	3.57 (0.50)[a]
MSFC	−0.15 (0.66)	0.30 (0.18)[b]
MMSE	29.92 (2.89)	29.83 (5.78)
ACE	95.25 (2.42)	97.25 (2.77)
WAT-BA	38.08 (2.15)	38.83 (2.85)
Vocabulary Subscale (WAIS)	47.92 (4.87)	42.83 (8.50)
Raven Colour Progressive Matrices	32.00 (1.95)	32.33 (2.39)
Paragraph Memory (immediate)-WMS	21.08 (4.05)	27.0 (5.70)[a]
Paragraph Memory (long-term)-WMS	16.58 (3.08)	23.50 (6.41)[a]
Recognition	16.17 (2.37)	17.17 (2.04)
Rey list		
Total (Trails 1 al 5)	49.00 (10.16)	52.67 (9.20)
Distracter List	5.75 (1.42)	7.5 (3.87)
Delay	9.08 (3.45)	11.67 (3.28)[a]
Recognition	12.83 (1.85)	14.42 (1.16)
Rey figure		
Copy	35.67 (0.78)	35.58 (0.79)
Delay	19.63 (5.82)	22.04 (8.18)
Language		
Boston	19.58 (0.67)	19.92 (0.29)
FAS	17.58 (5.33)	17.42 (3.87)
Semantic Fluency	18.92 (5.09)	21.92 (6.07)
Token Test	25.42 (0.79)	24.75 (0.87)
Executive functions		
Digits Forward	7.2 (0.8)	6.8 (0.8)
Digits Backward	5.2 (1.8)	4.8 (0.4)
Trails A	33.92 (9.69)	26.17 (7.67)
Trails B	70.17 (28.13)	56.58 (16.88)
Letters and Numbers	10.08 (2.06)	10.92 (2.71)
WCST categories	6.0 (0.0)	6.0 (0.0)

Data shown are mean (SD) values.
[a]$P \leq 0.01$.
[b]P between >0.01 and ≤ 0.05.
MSFC, MS Functional Composite; HPT9, nine-hole peg test; PASAT, Paced Auditory Serial Addition Test; MMSE, Mini-Mental State Examination; ACE, Addenbrooke's Cognitive Examination; WAT-BA, Word Accentuation Test; WAIS, Wechsler Adult Intelligence Test; WMS, Wechsler memory scale; FAS, Word Fluency Test; WCST, Wiscosin card sorting test.

respectively) as well as delayed recall dysfunction using the Rey auditory verbal learning test ($P = 0.01$). No significant differences between groups were observed for the recognition phase in either test, suggesting information storage sparing with faulty visual memory acquisition and retrieval; however, recall was normal when measured using Rey's delayed Complex Figure.

Executive functions

No significant differences in classical executive tests such as the Wisconsin Card Sorting Test, the Trail Making Test, the letters and number subtest of the WAIS or the Digit Span Test were observed. Differences were found in the PASAT ($P = 0.002$), as well as for specific executive battery tests including the IGT, the MET and the Hotel Task (Table 2). Performance on the IGT was examined by analysing card selections in successive blocks of 20 cards, and net score per block was calculated by subtracting the number of risky from the number of safe card selections $[(C + D) - (A + B)]$. Significant differences were found between MS and control groups in the choice of 'advantageous' decks in the last selection block ($P = 0.41$; $P = 0.39$; $P = 0.33$; $P = 0.07$; $P = 0.01$; Figure 2). Moreover, when the entire task was considered, a trend for higher errors was found in the MS group ($P = 0.04$). In the MET, differences were found in the total number ($P = 0.02$), specific task ($P = 0.004$), and interpretation failures ($P = 0.02$). These results suggest deficits in planning and in the organization of time and tasks, in a way, which

Table 2 Executive Function Battery performance in MS patients and controls

	MS patients (n = 12)	Controls (n = 12)
Frontal Assessment Battery (FAB)	17.33 (1.43)	16.67 (4.31)
Theory of Mind		
Reading the mind in the eyes (faces)	15.42 (1.08)	15.50 (1.38)
Reading the mind in the eyes (eyes)	14.00 (0.85)	14.00 (0.95)
Faux Pas	18.08 (2.15)	18.5 (1.09)
Hotel Task		
Number of Tasks	4.75 (0.45)	4.83 (0.39)
Time deviations	380.58 (134.64)	428.08 (116.28)
Numbers of Buttons played	1.50 (0.80)	2.00 (0.0)
Button deviation times	5.08 (2.40)	6.92 (1.83)[b]
IOWA Gambling Task		
Iowa 0–20	−5.00 (5.00)	−2.58 (5.23)
Iowa 21–40	−0.83 (5.75)	1.67 (4.73)
Iowa 41–60	0.67 (6.73)	3.50 (7.77)
Iowa 61–80	2.17 (5.75)	7.50 (8.44)
Iowa 81–100	−2.58 (9.96)	6.50 (10.16)[a]
Selections of advantageous decks (A + B)	52.42 (9.11)	41.92 (13.95)[b]
Multiple Errand Test (Met)		
Interpretation Failures	0.75 (0.75)	0.17 (0.38)[b]
Tasks Failures	0.83 (0.71)	0.08 (0.29)[a]
Total Failures	4.58 (2.90)	2.08 (1.24)[b]

Data shown are mean (SD) values.
[a]$P \leq 0.01$.
[b]P between >0.01 and ≤0.05.

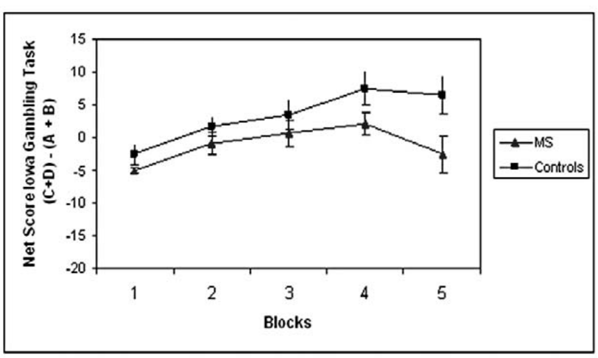

Figure 2 Performance of MS patients and controls on the IGT. Each block (1–5) represents 20 sequential card choices. Net score is calculated by subtracting number of risky deck selections from number of 'good' deck selections. Negative scores indicate poor decision-making. Bars indicate SE of the mean.

resembles everyday life much more as perceived by patients. Furthermore, when patients were asked about their performance, they referred worse results than the control group (MET competency: 6.58 + 1.16; $P = 0.01$) indicating awareness of performance related difficulties. In the Hotel Task, differences in terms of buttons pressed for opening and closing garage doors ($P = 0.03$) and deviation from task-assigned times were observed, suggesting working memory deficit. A stepwise regression analysis demonstrated PASAT performance ($r^2 = 0.823$, $P < 0.01$) and specific task failures in MET ($r^2 = 0.772$, $P < 0.01$) as the most powerful indicators of the decline in neuropsychological performance.

Diffusion tensor MRI measures

When compared with healthy controls, MS patients showed significant increase in average ADCs for FM, FL and GC areas ($P = 0.01–0.006$), but not in OF areas ($P = 0.03$). In contrast, FA values were significantly lower in MS patients when compared with controls, for FM and FL regions ($P = 0.01–0.006$), but not in OF ($P = 0.02$) and GC areas ($P = 0.05$). No significant differences were observed between right and left hemispheres for any DT-MRI values, in MS patients or controls.

Correlation between neuropsychological findings and DT-MRI results

Significant correlation was observed between PASAT performance and FA measures in the FL region ($r = 0.64$, $P = 0.03$). Correlations were also found between ADC measures in the FL region and the number of tasks achieved in the Met ($r = 0.72$, $P = 0.01$), as well as in a subtask of the Hotel Task (deviation from correct time assigned to open and close garage doors; $r = -0.68$, $P = 0.02$).

Discussion

Executive deficits are an important part of the cognitive profile observed in MS and closely linked to prefrontal cortex function. Standard neuropsychological testing is usually not sensitive enough to detect social and behavioral impairment present in prefrontal dysfunction. Consequences of this damage can best be appreciated when viewed in a more ecological context. In this exploratory study, greater complexity tasks, many applied for the first time in MS, were used to detect specific and subtle executive deficits. Results indicated the presence of cognitive deficits in a group of MS patients still at an early stage of disease, presenting a fronto-subcortical pattern with impairments in memory, decision-making, working memory and planning, as well as in goal-oriented behavior. Previous studies have demonstrated that MS is associated with delayed decision-making, which may represent an important contributing factor to poorer quality of life and to impairments seen and referred by MS patients in every day life functioning [11]. Failures observed for both MET and Hotel Task tests correlated with loss of tissue integrity and organization within fronto-subcortical fiber tracts, particularly in the FL areas. Interestingly, this area has already been specifically linked to executive cognitive dysfunction such as poor planning, or loss of inhibitory control, strategy development, cognitive flexibility and working memory [12]. The correlation observed between cognitive deficits and MR-DTI measures in MS patients may contribute to a better understanding of the pathophysiology underlying these findings and consequently to the development of better management strategies.

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