Behavioural Neurology, 1991, **4**, 129–141

Cognitive Function in Multiple Sclerosis: a Subcortical Pattern of Neuropsychological Impairment?

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In order to evaluate cognitive impairment in multiple sclerosis (MS) neuropsychological tests were administered to 25 patients with clinically definite disease. Four (16%) showed diffuse cognitive impairment, whereas the others, compared with controls showed a specific deficit on tests known to be sensitive to frontal lobe damage. These results are interpreted in the light of current hypotheses relating to subcortical contributions in cognition.

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). The pathological lesions are mostly located in the white matter although small plaques may be found in grey matter and in the white-grey matter junction (Brownell and Hughes, 1962). Phases of exacerbation and periods of remission generally characterize the clinical course of the disease and a chronic-progressive course, rarely observed in the early stages, becomes frequent in advanced stages of the disease (Silberberg, 1977). Since demyelinating plaques can be located anywhere in the CNS, neurological signs and symptoms vary considerably. The most frequently observed symptoms reflect involvement of optic nerves (unilateral or bilateral visual loss), pyramidal tracts (limb weakness and spasticity), cerebellum (ataxia) and the medial longitudinal fasciculus (internuclear ophtalmoplegia) (McAlpine *et al.*, 1955).

The occurrence of cognitive deficits is also accepted but there is disagreement about the frequency and qualitative features of mental impairment.

Values ranging from 0–3% (Cottrell and Wilson, 1926; Sugar and Nadell, 1943; Kurtzke *et al.*, 1972) to 60–70% (Ombredane, 1926; Surridge, 1969) have been reported for dementia in MS (Table 1). In these studies it has been generally observed that mental impairment is mostly seen in the advanced stages of the disease in a context of severe physical disability (McKann, 1982) and frequently associated with dysphoric and anosognosic behaviour (Ombredane, 1926; Surridge, 1969; Brown and Davis, 1922; Kahana *et al.*, 1971).

Neuropsychological studies also report variable prevalence figures for mental impairment in MS studies. Table 2 summarizes data derived from

0953–4180/91/030129 + 13 $3.50/0

TABLE 1. *Prevalence of cognitive deterioration and associated emotional behaviour in MS derived from some clinical studies*

References	*Number of MS subjects*	*% Deteriorated subjects*	*Emotional behaviour*	
Sachs–Friedman (1922)	141	15%		
Cottrell–Wilson (1926)	100	2%	euphoria depression	63% 10%
Ombredane (1929)	50	72%	eurphoria correlated to cognitive deterioration	
Sugar–Nadel (1943)	28	0%	euphoria depression	50% 36%
Surridge (1969)	108	61·1%	euphoria correlated to cognitive deterioration	
Kurtzke (1970)	572	3%		
Kahana *et al.* (1971)	295	25%	euphoria depression	5% 9%

TABLE 2. *Prevalence of cognitive impairment in MS derived from various neuropsychological studies*

References	*Number of subjects*	*% Deteriorated subjects*		*Tests*
Pratt (1951)	50		15%	Shipley Hartford test
	64		28%	Raven's P.M.
Baldwin (1952)	32		50%	Hurt–Minnesota test for organic brain damage
Parsons *et al.* (1957)	17	mildly severely	41% 29%	Grassi block substitution test
Peyser *et al.* (1980)	52		55%	Halstead Category test
De Smedt *et al.* (1984)	46	mildly severely	57% 8%	WAIS
Rao *et al.* (1984)	44	mildly severely	43% 20%	verbal and visual memory verbal and visual memory; Rush cognitive screening examination
Lyon-Caen *et al.* (1986)	30		60%	WAIS, WCST, Wechsler memory scale
Beatty *et al.* (1988)	38		75% 61% 45%	Digit symbol Word fluency Anterograde and remote memory

some of these studies together with the types of tests used and the percentages of subjects obtaining deficient performances.

Neuropsychological data concerning the relationship between cognitive deficits and clinical variables are also controversial. In particular, the claim by Canter (1951) and Fink and Houser (1961) of a significant relation between cognitive impairment and degree of physical disability has not been confirmed by Marsh (1980) and Rao *et al.* (1985). These latter authors did not even find a significant correlation between cognitive impairment and duration of illness. Heaton *et al.* (1985) have reported a greater frequency of mental impairment in MS patients with a chronic-progressive form of the disease than in those with a relapsing-remitting one.

In addition to quantitative data concerning the frequency of mental deterioration, neuropsychological studies have been reported which assess qualitative features of cognitive impairment attempting to highlight possible relationships between structural changes and pattern of cognitive deficits. WAIS IQ testing has shown that MS patients obtain higher scores in verbal subtests than in performance ones (Canter, 1951; Reitan *et al.*, 1971). On the basis of these data, the hypothesis of an asymmetrical pattern of cognitive impairment in MS patients, with more compromised visual-spatial skills than linguistic functions, has been proposed. It must be noted, however, that the reliability of WAIS to offer specific information about single cognitive functions is questionable. In fact, various subtests appear so saturated with a general intelligence factor as to make them scarcely specific in assessing single cognitive functions. Furthermore, the correct execution of performance subtests of WAIS requires manual dexterity and speed, which are frequently deficient in MS patients. For this reason Rao (1986) has suggested that the impairment of fine motor coordination is a more parsimonious explanation than an asymmetrical pattern of cognitive deterioration to account for the lower scores obtained by MS patients on performance subtests of the WAIS.

More recently, studies devoted to assess cognition of MS patients have been based on neuropsychological tests able to give specific information on a wide range of cognitive functions. The most frequently documented deficits are concerned with retrieval memory and conceptual reasoning. In particular, a deficient immediate and delayed recall (Rao *et al.*, 1984) and a deficit in the formation and shifting of concepts (Heaton *et al.*, 1985; Rao and Hammeke, 1984) have been noted. Deficits of language on the other hand have only been rarely described (Olmos-Lau *et al.*, 1977) and dyspraxia and visual-perceptual disorders have not yet been documented. Rao (1986) has suggested that a similar pattern of cognitive impairment, characterized by prevalent deficits of memory and conceptual reasoning with a preservation of linguistic, praxic and gnosic functions, occurs in subjects with prefrontal lesions. Moreover, in view of the fact that a frontal pattern of cognitive impairment has been demonstrated in demented (Pillon *et al.*, 1986) and non-demented subjects (Taylor *et al.*, 1986; Caltagirone *et al.*, 1989*a*) affected by subcortical pathologies, the same author has proposed to include

cognitive deficits observed in MS in the group of so-called subcortical dementias.

The aims of our study were:

1 to evaluate, by means of a suitable neuropsychological battery, the prevalence of diffuse cognitive impairment in a sample of subjects with definite MS;

2 to assess possible relationships between cognitive impairment and some clinical variables of the disease such as duration of illness, disability degree, clinical course and emotional behavior;

3 to verify the hypothesis that performance profile shown by MS patients is indicative of a specific impairment of such functions as concept formation and shifting aptitude generally subsumed by frontal lobes and frequently impaired in patients with subcortical pathologies.

Material and methods

In this study we have examined a sample of 25 subjects (22 females and three males) with clinical definite MS according to criteria proposed by McAlpine and coworkers (1972). Nineteen patients showed a relapsing-remitting clinical course while the remaining six had a chronic-progressive one. At the time of the neuropsychological examination none of the patients were on steroid therapy and none of the individuals with a relapsing-remitting course had an acute exacerbation. The degree of disability for every subject was established by means of the Disability Status Score (DSS, Kurtzke, 1965).

The control group was composed of 25 subjects affected by traumatic or inflammatory diseases of spinal cord not involving the Central Nervous System above the cervical region and matched according to sex, age and literacy with MS subjects. The clinical features and relative statistical comparisons between MS patients and control subjects are shown in Table 3.

The presence of dementia was established on neuropsychological grounds by means of the Mental Deterioration Battery (MDB). The MDB is composed of eight tests assessing mnesic, verbal, visuo-constructive and intellectual abilities. A detailed description of this test is described elsewhere

TABLE 3. *Clinical features of MS and control samples*

	MS (*n*=25)	*Controls* (*n*=25)	*p*
Age	40·1 (11·8)	40·3 (11·3)	n.s.
Literacy (years of schooling)	10·0 (3·8)	9·8 (3·9)	n.s.
DSS	4·9 (1·6)	4·5 (1·8)	n.s.
Duration of illness (years)	12·3 (7·3)	11·9 (6·5)	n.s.

DSS = Disability Status Score.

(Caltagirone *et al.*, 1979). A subject is considered impaired when he obtains pathological scores on four or more of the eight tests. The cut-off points which in every test distinguish normal from pathological performances are calculated subtracting one standard deviation from the mean scores obtained by a large group of healthy subjects (Caltagirone *et al.*, 1979). The MDB has been shown to be highly reliable in distinguishing between deteriorated and healthy subjects (over 90% of correctly classified patients in a population composed of 103 demented and 83 control subjects, Caltagirone *et al.*, 1979).

For a more detailed neuropsychological examination of MS and control subjects, the eight tests forming the MDB where integrated with other tests so as to provide information concerning the following cognitive fields (tests forming MDB are indicated with *):

Language	Token test (T) (De Renzi and Vignolo, 1962) Boston naming test (B) (Kaplan *et al.*, 1978) Phrases construction* (PC) (Gainotti *et al.*, 1976)
Verbal memory	Rey's 15 words (Rey, 1958): immediate recall* (RST) delayed recall* (RLT) recognition (Rec) Digit span (DS) (Wechsler, 1945) Digit span backward (DSB)
Visuospatial memory	Immediate visual memory* (IVM) (Gainotti *et al.*, 1978) Corsi test (C) (Corsi, 1969) Corsi backward (CB)
Constructional praxia	Copy drawing designs* (CD) (Gainott *et al.*, 1977) Copy designs with landmarks* (CDL)
General intelligence	Progressive Matrices '47* (PM '47) (Raven, 1949) Verbal analogies (SAT) (Tarquini and Masullo, 1981)
Frontal functions	Word fluency* (WF) (Borkowski *et al.*, 1967) Temporal rules induction (TRI) (Caltagirone *et al.*, 1982) Wisconsin card sorting test (WCST) (Nelson, 1976)

Scores obtained on different tests of MDB were adjusted for age and literacy

on the basis of normative data derived from a large population of healthy subjects.

Furthermore, MS patients underwent a depressive status evaluation using the Hamilton rating scale.

Results

Four out of 25 MS subjects (16%), on the basis of MDB were considered demented.

In order to assess possible correlations between MS patients' cognitive performances and some clinical variables of the disease, a Global Performance Index (GPI) for every subject was calculated according to standard criteria (Caltagirone *et al.*, 1987).

The correlations between GPI and the different clinical aspects were measured by means of the Spearman rho test (Table 4). Non-significant correlations were found for: GPI and DSS score (Rho = −0·24; p = n.s.), GPI and depression scale score (Rho = −0·11; p = n.s.).

A trend toward significance was found for the correlation between GPI and duration of illness (Rho = −0·38; p = 0·06).

A higher, though non significant, prevalence of diffuse cognitive impairment was detected ($\chi^2 = 1{\cdot}8$; p = − n.s.) in the chronic-progressive cases (2/6) than in the relapsing-remitting one (2/19).

To evaluate the qualitative features of cognitive impairment exhibited by MS patients, the comparison between performances of MS and control groups on single tests were submitted to statistical analysis, utilizing Student's t test. Since performance scores obtained on WCST do not fit a normal distribution, statistical analysis for this test was performed by means of a non-parametric test (Mann-Whitney U test).

As shown in Table 5, significant differences were found for Word Fluency and for the different performance scores derived from WCST (number of criteria, perseverative errors and total errors). Marginally significant differences were obtained for Simple Analogies Test and for the Immediate Visual Memory.

TABLE 4. *Correlations between Global Performance Index and clinical variables in the MS sample*

	GPI	*p*
Duration of illness	Rho = -0·38	0·06
DSS score	Rho = -0·24	n.s.
Depression scale score	Rho = -0·11	n.s.

GPI = Global Performance Index;
DSS = Disability Status Score.

TABLE 5. *Performance scores obtained on various tests of neuropsychological battery by the whole sample of MS and control subjects*

	MS (*n*=25)	*Controls* (*n*=25)	*t*	*p*
T	32·8 (2·8)	33·9 (2·0)	1·6	n.s.
B	44·7 (9·1)	48·4 (6·8)	1·6	n.s.
PC	20·0 (5·3)	21·8 (3·8)	1·3	n.s.
RST	34·0 (9·6)	38·3 (9·2)	1·6	n.s.
RLT	7·5 (3·4)	8·7 (2·8)	1·3	n.s.
Rec	12·5 (2·6)	13·1 (2·2)	0·9	n.s.
DS	5·9 (1·1)	6·0 (1·1)	0·1	n.s.
DSB	4·0 (1·0)	4·2 (1·0)	0·7	n.s.
IVM	19·3 (2·5)	20·5 (1·4)	2·1	<0·05
C	4·7 (0·6)	5·0 (1·0)	1·4	n.s.
CB	4·2 (0·8)	4·4 (0·6)	0·6	n.s.
CD	9·3 (2·3)	10·1 (1·8)	1·3	n.s.
CDL	67·3 (4·2)	68·1 (2·6)	0·8	n.s.
PM′ 47	24·1 (4·0)	25·5 (4·0)	1·3	n.s.
SAT	16·2 (4·7)	18·0 (2·1)	1·9	=0·06
WF	25·8 (7·9)	32·1 (8·1)	2·8	<0·01
TRI	37·1 (4·1)	36·7 (4·8)	0·4	n.s.
			z	
WCST criteria	3·2 (1·6)	4·6 (1·5)	2·7	<0·01
total errors	22·6 (8·0)	15·6 (7·7)	2·7	<0·01
pers. errors	9·1 (4·9)	7·5 (3·4)	2·6	<0·01

B=Boston Naming Test; C=Corsi test; CB=Corsi test Backward; CD=Copying Designs; CDL=Copying Designs with Landmarks; DS=Digit Span; DSB=Digit Span Backward; IVM=Immediate Visual Memory; PC=Phrase Construction; PM′ 47=Raven's Progressive Matrices 1947; Rec=Rey's 15 words Recognition; RLT=Rey's 15 words Delayed Recall; RST=Rey's 15 words Immediate Recall; SAT=Simple Analogies Test; T=Token test; TRI=Temporal Rules Induction; WCST=Wisconsin Card Sorting Test; WF=Word Fluency.

Brown and Marsden (1986) noted that, when pathological and healthy subjects' cognitive performances are compared, the differences found could result from the high percentage of demented subjects in the pathological group. For this reason, in order to point out the possible presence of selective cognitive deficits in MS subjects unaffected by dementia, we compared the performances of control subjects to those of 21 MS patients not showing neuropsychological features of diffuse mental impairment. Even in this case, we found significant differences for Word Fluency and for number of criteria, perseverative errors and total errors obtained at WCST (Table 6).

Discussion

A prevalence of dementia in MS higher than one would expect in a normal population of similar age was found. It is difficult to compare these results

TABLE 6. *Performance scores obtained on various tests of neuropsychological battery by non-demented MS and control subjects*

	MS (*n*=21)	*Controls* (*n*=25)	*t*	*p*
T	33·6 (2·4)	33·9 (2·0)	0·5	n.s.
B	46·2 (9·1)	48·4 (6·8)	0·9	n.s.
PC	21·1 (3·5)	21·8 (3·8)	0·6	n.s.
RST	36·4 (8·2)	38·3 (9·2)	0·7	n.s.
RLT	8·2 (3·2)	8·7 (2·8)	0·5	n.s.
Rec	12·9 (2·5)	13·1 (2·2)	0·4	n.s.
DS	6·0 (0·9)	6·0 (1·1)	0·1	n.s.
DSB	4·0 (1·0)	4·2 (1·0)	0·5	n.s.
IVM	20·0 (1·6)	20·5 (1·4)	1·1	n.s.
C	4·7 (0·6)	5·0 (1·0)	1·2	n.s.
CB	4·3 (0·8)	4·4 (0·6)	0·1	n.s.
CD	9·8 (1·9)	10·1 (1·8)	0·5	n.s.
CDL	68·2 (2·1)	68·1 (2·6)	0·2	n.s.
PM′ 47	25·1 (2·6)	25·5 (4·0)	0·4	n.s.
SAT	16·9 (4·0)	18·0 (2·1)	1·2	n.s.
WF	26·3 (7·9)	32·1 (8·1)	2·5	=0·02
TRI	37·5 (3·5)	36·7 (4·8)	0·7	n.s.
			z	
WCST criteria	3·5 (1·6)	4·6 (1·5)	2·2	=0·02
total errors	21·0 (7·4)	15·6 (7·7)	2·1	=0·03
pers. errors	8·9 (4·7)	7·5 (3·4)	2·0	=0·04

B = Boston Naming Test; C = Corsi test; CB = Corsi test Backward; CD = Copying Designs; CDL = Copying Designs with Landmarks; DS = Digit Span; DSB = Digit Span Backward; IVM = Immediate Visual Memory; PC = Phrase Construction; PM′ 47 = Raven's Progressive Matrices 1947; Rec = Rey's 15 words Recognition; RLT = Rey's 15 words Delayed Recall; RST = Rey's 15 words Immediate Recall; SAT = Simple Analogies Test; T = Token test; TRI = Temporal Rules Induction; WCST = Wisconsin Card Sorting Test; WF = Word Fluency.

with data derived from other studies. Tables 1 and 2 demonstrate the high variability of findings in previous clinical and neuropsychological studies. It is likely that the marked difference in reported prevalence of dementia in previous clinical studies reflects the use of different diagnostic parameters.

The lack of agreement even in results derived from neuropsychological studies requires further consideration. Firstly, it must be noted that many of these studies have assessed single cognitive functions (for example memory, conceptual reasoning, etc.) without more comprehensive survey of cognition, so it is impossible to determine whether deficient performance reflects a selective deficit or is indicative of a more global mental deterioration.

Furthermore, the reliability of Wechsler's intelligence scales (created to measure intelligence level in normal subjects) in assessing cognitive deterioration in pathological samples has been challenged on methodological grounds (Gainotti, 1977).

We believe the prevalence of dementia found in our sample to be a reliable estimation of reality because it was obtained utilizing a battery of tests exploring a wide range of cognitive functions and expressly created to highlight the presence of diffuse mental impairment.

In agreement with previous cross sectional studies (Marsh, 1980; Rao *et al.*, 1985) our data shows no correlation between cognitive deficits and the degree of physical disability. Similarly, the lack of negative correlation between cognitive performances and depressive scale scores are in agreement with previous reports (Peyser *et al.*, 1980). Cognitive deficits in MS are probably therefore a direct consequence of the disease and not simply an expression of visuo-motor or emotional disturbances.

Finally, in agreement with Heaton *et al.* (1985), our data seem to suggest a higher prevalence of mental deterioration in the chronic-progressive forms of MS than in the relapsing-remitting ones.

Previous neuropsychology studies in unselected groups of MS subjects have shown reduced performance in a wide range of tests. The best documented deficits concern immediate and delayed recall (Rao and Hammeke, 1984) and conceptual reasoning capacity (Heaton *et al.*, 1985; Rao and Hammeke, 1984). Comparing the performances of our MS group to those of the control group, significant differences were found only in two tests (WF and WCST) both known to be sensitive to frontal lobe damage. Marginally significant differences were noted on a test of general intelligence on verbal data (SAT) and on the Immediate Visual Memory test.

We excluded from our sample those MS patients who demonstrated neuropsychological evidence of diffuse mental impairment (dementia). However, even when these were excluded significant differences were demonstrated on "frontal" tests, confirming that a selective impairment of frontal functions is detectable in MS patients.

It is interesting to note that a similar pattern of frontal impairment has also been detected in other CNS diseases characterized by a subcortical involvement including Parkinson disease (Taylor *et al.*, 1986; Caltagirone *et al.*, 1989*a*; Pillon *et al.*, 1986; Caltagirone *et al.*, 1989*b*). Progressive Supranuclear Palsy (Pillon *et al.*, 1986), Normal Pressure Hydrocephalus (Caltagirone *et al.*, 1982; Berglund *et al.*, 1979) and "etat lacunaire" (Ishii *et al.*, 1986).

In an attempt to confirm the subcortical origin of cognitive impairment exhibited by MS patients, Beatty *et al.* (1988) have administered to a group of chronic-progressive MS patients a battery of tests expressly created to distinguish differential patterns of cognitive impairment in cortical and subcortical dementias. MS patients did badly not only on tests (such as Word Fluency, anterograde and remote memory tests) considered indicative of a subcortical dementia, but also in a naming test known to be typically compromised in cortical dementias. The authors concluded that cognitive impairment in MS shares features of both cortical and subcortical dementia. It must be pointed out, however, that when most deteriorated patients (Mini Mental State Examination score less than 28) were excluded from the MS sample, significant differences in comparison to control group were found only for Word Fluency and memory tests.

Alzheimer's disease and MS patients have been compared on an extensive neuropsychological battery. While Alzheimer's patients obtained worse performances on tests exploring memory and language, MS patients performed at lower level than Alzheimer's patients on tests of auditory and visual sustained attention (Filley *et al.*, 1989). The authors considered that these data supported the hypothesis of differential patterns of cognitive impairment in dementias caused by cortical (Alzheimer's disease) and subcortical (MS) pathological changes. The prevalent deficit in attention seen in the MS patients was interpreted as resulting from "a disruption of diffuse attentional system arising from the brain stem" and/or "a damage to pathways originating in prefrontal cortex and terminating in posterior cortical areas" (Filley *et al.*, 1989).

The selective or prevalent impairment of frontal functions in subcortical pathologies has been generally interpreted as due to a reduction of afferent pathways projecting from subcortical structures to frontal areas (Taylor *et al.*, 1986; Ishii *et al.*, 1986; Javoy-Agid and Agid, 1980; Adams, 1980).

Ventricular widening without cortical atrophy has been documented in MS both by autopsy studies (Barnard and Triggs, 1974) and neuroradiological techniques (Cala *et al.*, 1978). Moreover, Lumsden (1970) has pointed out, in a large sample of MS autopsied cases, that demyelinating areas are mainly localized in periventricular white matter and in the superior frontal gyrus. Ventricular enlargement, periventricular and prefrontal plaques could all produce damage to fibre tracts interconnecting frontal lobes and other cortical and subcortical areas of the CNS.

Our results reveal a prevalence of diffuse mental impairment among MS patients which was higher than expected and a selective frontal deficit in non-deteriorated patients. Further research, conducted on a larger population, is needed to confirm these findings.

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