Brain (1997), **120,** 289–297

The progress of cognitive decline in multiple sclerosis

A controlled 3-year follow-up

P. Kujala,[1] R. Portin[2] and J. Ruutiainen[1]

[1]*Masku Neurological Rehabilitation Centre and the*
[2]*Department of Neurology, University of Turku, Finland*

Correspondence to: Päivi Kujala, Masku Neurological Rehabilitation Centre, PO Box 15, FIN-21251 Masku, Finland

Summary

*The purpose of this study was to illustrate how cognitive functioning evolves over time in patients with multiple sclerosis. We followed the evolution of cognitive performances in two clinically and demographically similar multiple sclerosis groups, the 'cognitively preserved' (*n *= 20) and the 'cognitively mildly deteriorated' (*n *= 22), and in healthy controls (*n *= 34). We conducted the follow-up examination using the Mild Deterioration Battery, the Mini-Mental State Examination, and a set of additional neuropsychological measures after an interval of 3 years. The drop-out rate in our study was only 5%. The 'cognitively preserved' multiple sclerosis group showed substantial neuropsychological stability by performing as well as the controls both at baseline and at follow-up. By contrast, the initially 'cognitively mildly deteriorated' group demonstrated progressive cognitive decline on many neuropsychological tests. The intermediate-length screening battery, the Mild Deterioration Battery, was sensitive to this decline, whereas the briefer Mini-Mental State Examination was not. The progressive cognitive decline could not be predicted from other disease variables. The study demonstrated that intact cognitive functioning in multiple sclerosis may remain stable, whereas incipient cognitive decline seems to be widespread and progressive in nature. Thus, progressive cognitive deterioration should be considered as one of the characteristics of multiple sclerosis.*

Keywords: cognitive performance; neuropsychology; multiple sclerosis

Abbreviations: EDSS = Expanded Disability Status Scale; MDB = Mild Deterioration Battery; MMSE = Mini-Mental State Examination

Introduction

Cross-sectional studies have demonstrated that multiple sclerosis patients often perform less well than healthy controls on various neuropsychological tests (for review, *see* Rao, 1986). However, great individual variability exists in cognitive performance among multiple sclerosis patients, i.e. some patients perform as well as controls, whereas others demonstrate different degrees of cognitive deterioration (Young *et al.*, 1976; Jennekens-Schinkel *et al.*, 1990*b*; Kujala *et al.*, 1994, 1995). Although cognitive decline is admitted to be an integral feature of multiple sclerosis, very little is known about the prognosis of this decline. Only a few longitudinal studies have been aimed at elucidating this question. Signs of at least mild cognitive deterioration over time have been observed in follow-ups (Canter, 1951; Ivnik, 1978*b*; Feinstein *et al.*, 1992; Amato *et al.*, 1995). However, preservation of cognitive performance has also been reported (Fink and Houser, 1966; Filley *et al.*, 1990; Jennekens-Schinkel *et al.*, 1990*b*; Mariani *et al.*, 1991). Hence, the existing knowledge about the course of cognitive performance in multiple sclerosis is partly contradictory.

The discrepancies in the results of previous longitudinal studies on cognitive functioning in multiple sclerosis can be explained by various methodological factors. Great variation exists in follow-up times (0.5–4.5 years), in clinical variables of the subjects, and in neuropsychological methods. In most studies, the patient samples have been heterogeneous with respect to physical as well as cognitive factors, and part of the longitudinal studies have employed brief and restricted neuropsychological batteries. Furthermore, the interpretation of results has been complicated due to such methodological

problems as lack of control subjects (Filley *et al.*, 1990; Mariani *et al.*, 1991; Feinstein *et al.*, 1992), relatively high drop-out rates (Filley *et al.*, 1990; Feinstein *et al.*, 1992), and small patient samples (Ivnik, 1978*b*; Mariani *et al.*, 1991). Moreover, in the studies of Jennekens-Schinkel *et al.* (1990*a*) and Amato *et al.* (1995), patients with uncertain diagnosis were included, and in the study of Amato *et al.* (1995), the findings were based on separate analyses of baseline and follow-up results, not on the longitudinal evaluation of performance differences.

In none of the previous follow-up studies, has the predictive value of incipient cognitive decline for further cognitive development in multiple sclerosis been evaluated. In the present study, we have followed the evolution of cognitive functioning in two physically and demographically similar multiple sclerosis groups, the 'cognitively preserved' (preserved) and the 'cognitively mildly deteriorated' (deteriorated), which initially differed only with respect to cognitive status. We also included a demographically matched group of healthy controls, which performed similarly to the preserved multiple sclerosis group at baseline. The follow-up examination of the three study groups was conducted after an interval of 3 years using a wide variety of neuropsychological measures. The drop-out rate was minimal, 95% of the subjects participated in the reassessment.

The aim of this study was twofold: (i) to evaluate the performance of the study groups cross-sectionally and (ii) to determine the longitudinal change in their neuropsychological performance. Therefore, we used a controlled neuropsychological follow-up design with parallel groups. The main questions, which we tried to answer with the present study were: (i) How do the groups perform on the neuropsychological measures at follow-up? (ii) What kind of longitudinal change is present in the neuropsychological performance of the groups? Does cognitive performance evolve similarly in the two multiple sclerosis groups, or does incipient cognitive decline predict further cognitive deterioration and intact cognitive functioning further cognitive preservation?

Methods

Subjects

A comprehensive neuropsychological study was conducted on 45 multiple sclerosis patients and 35 healthy controls at the Masku Neurological Rehabilitation Centre between autumn 1991 and summer 1993 (Kujala *et al.*, 1994, 1995, 1996*a*, *b*). The subjects were re-examined after an average of 2.8 years (range 2–3.9 years), dated from their original assessment. The study sample initially comprised 80 subjects: 23 preserved and 22 deteriorated patients and 35 healthy controls. The sample at follow-up was reduced to 76 (20 preserved and 22 deteriorated multiple sclerosis patients and 34 controls). One of the preserved patients had suffered a subarachnoidal haemorrhage and was not able to perform the neuropsychological tests, and two of the preserved patients could not be reached despite several attempts. One of the controls was working abroad and could not participate. All subjects gave their informed consent for participation in this study which was approved by the local ethical committee.

At follow-up, the patients were assessed in detail by a neurologist. A history covering the intervening period was obtained and each patient underwent a thorough neurological examination. All patients had a clinically definite diagnosis according to the criteria suggested by Poser *et al.* (1983). None of the patients was in exacerbation for baseline or follow-up assessments. Physical disability was rated according to the Kurtzke Expanded Disability Status Scale (EDSS; Kurtzke, 1983). The EDSS scores of the patient groups did not differ significantly from each other at baseline: preserved 5.1 ± 1.7, deteriorated 5.5 ± 1.3; $P = 0.384$. However, the EDSS score of the deteriorated group tended to increase more than that of the preserved group during the follow-up time. EDSS at follow-up: preserved 5.7 ± 1.6, deteriorated 6.5 ± 1.1, $P = 0.075$; longitudinal change in EDSS: preserved 0.6 ± 1.1, deteriorated 1.0 ± 1.1, $P = 0.098$. No statistically significant differences between the patient groups were observed at follow-up in age at disease onset: preserved 34.9 ± 8.0, deteriorated 33.8 ± 6.7, $P = 0.425$; in disease duration: preserved 12.0 ± 5.8, deteriorated 12.1 ± 6.6, $P = 0.533$; or in the course of the disease: preserved: five relapsing–remitting/eight chronic progressive/seven secondary progressive; deteriorated: one relapsing–remitting/13 chronic progressive/eight secondary progressive, $P = 0.137$. The disease course had changed from relapsing–remitting to secondary progressive in four out of the initially preserved patients and in five out of the deteriorated patients. All three study groups were similar with respect to age at follow-up: controls 46.0 ± 9.1, preserved 46.8 ± 8.7, deteriorated 45.9 ± 7.5, $P = 0.930$; sex: controls 16 M, 18 F; preserved 10 M, 10 F; deteriorated 11 M, 11F; and education: controls 11.2 ± 3.4, preserved 11.9 ± 3.8, deteriorated 11.0 ± 3.0, $P = 0.725$. The two patient groups had significantly more depression points in the Beck Depression Inventory (Beck *et al.*, 1961) than the controls: controls 3.2 ± 4.2, preserved 6.7 ± 6.9, deteriorated 7.2 ± 4.8, $P = 0.002$. However, the two patient groups did not differ significantly from each other in the Beck Depression Inventory.

Study design

The Mild Deterioration Battery used in the classification of patients into subgroups

At the initial assessment, we included multiple sclerosis patients with either preserved or mildly to moderately deteriorated cognitive capacity (Kujala *et al.*, 1994). Patients who had clinical dementia (DSM 3rd ed., American Psychiatric Association, 1980) or severe restrictions in visual acuity, fine-motor skills or speech production, were excluded from the study. In order to classify patients as 'cognitively preserved' or 'mildly deteriorated', we assessed all subjects

with the Mild Deterioration Battery (MDB; Portin and Rinne, 1980; Revonsuo *et al.*, 1993; Kujala *et al.*, 1994, 1995, 1996*a*). The MDB consists of eight measures: raw scores of the Wechsler Adult Intelligence Scale (Wechsler, 1955): (i–iv) subtests of Similarities, Digit Span, Digit Symbol, Block Design; (v–vi) immediate recall of 20 objects and 30 Paired Word Associates; (vii) error rate of the Benton Visual Retention Test (Benton, 1963); (viii) Naming time of 20 objects. On these tests, the subjects received deterioration points if their performance on any of the tests was below –1.5 SD compared with the norms. If the subject scored below –1.5 SD compared with the norms, he/she received one deterioration point; if below –2.0 SD, two points; and below –3.0 SD, three points. Thus, the maximum deterioration score was 24 (Kujala *et al.*, 1994). At the baseline assessment, patients with 0–2 deterioration points were classified as 'preserved' and patients with 4–12 points as 'mildly deteriorated' and entered into the preserved and deteriorated groups, respectively. The inclusion criterion for the controls was also 0–2 deterioration points. All subjects in the three study groups were assessed using the MDB tests again at follow-up. For the baseline assessment, all subjects were assessed at the Masku Neurological Rehabilitation Centre, whereas at follow-up six patients of the preserved group and nine patients of the deteriorated group were tested in their homes.

Additional neuropsychological measures

In addition to the MDB tests, a set of other neuropsychological measures were included at follow-up. These measures were: delayed recall from the MDB memory tests of 20 objects and 30 Paired Word Associates; immediate and delayed recalls of the Logical Memory subtest of the Wechsler Memory Scale (Wechsler, 1945); immediate and delayed recalls, learning score and error rate of the 7/24 Spatial Recall Test (Barbizet and Cany, 1970); the category (animals) and letter (S) fluencies (Lezak, 1983); word reading time, colour naming time, colour–word naming time and interference time (colour–word naming time minus colour naming time) of the Stroop test (Stroop, 1935); attentional performance on the easy (3-s interval) and difficult (2-s interval) conditions of the Paced Auditory Serial Addition Test (Gronwall and Wrightson, 1974; Gronwall, 1977). Furthermore, the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975) was administered to all subjects.

At follow-up, in four of the deteriorated patients, moderate to severe restrictions in fine-motor functions (ataxia or muscle weakness), in speech production (dysarthria) or in understanding the instructions of the neuropsychological tests had become evident. Furthermore, one of the deteriorated patients had been re-examined 1.5 years after her initial examination and was found to be demented. She could not perform all the tests and was not recalled to the actual follow-up. These five patients were no longer able to perform the Digit Symbol, the Block Design, the Benton Visual Retention Test, the Stroop test, the Paced Auditory Serial Addition Test and some parts of the MMSE. In these tests, the results recorded for the deteriorated group were based on the performance of 17 deteriorated patients. However, we estimated the deterioration score based on just the MDB for these five patients. To avoid underestimation of their cognitive abilities, we evaluated their deterioration scores of the Digit Symbol, the Block Design and the Benton Visual Retention Test as being similar to those at baseline.

Data analyses

When the performance of two study groups was compared, χ^2 and *t* tests were used. The performance of the three study groups at baseline and at follow-up was compared using the ANOVAs and Duncan's multiple comparisons test for the parametric variables and Kruskal–Wallis test and multiple comparisons of the Kruskal–Wallis test for nonparametric variables. The longitudinal change in cognitive performance of the three groups was analysed by comparing the difference in test results between the initial (baseline) and follow-up examination. The difference was calculated for every subject and the means of the three groups were compared using the nonparametric Kruskal–Wallis test. For parametric variables, repeated measures ANOVA was used. Furthermore, some correlation analyses were carried out.

Results

Cross-sectional results

The deteriorated group performed significantly less well than the other two study groups on all neuropsychological tests both at baseline and follow-up (Table 1). By contrast, the preserved group performed almost as well as the controls on both testings. Thus, our multiple sclerosis groups differed from each other with respect to cognitive status both at baseline and at follow-up. Moreover, this difference tended to increase during the follow-up period.

Longitudinal results of the MDB

The performance of the deteriorated group diminished over time in the MDB tests of memory and visuo-motor performance: the Digit Span performance was further impaired in the deteriorated group when compared with the controls, and the Digit Symbol performance when compared with both the other groups (Table 1). At follow-up, the deteriorated patients made more errors than at baseline in the Benton Visual Retention Test when compared with the other subjects. Furthermore, the deteriorated patients showed a tendency to progressive decline on most of the remaining measures of the MDB. Consistent with the subtest findings, the deterioration score of the MDB showed neuropsychological stability in the controls and in the preserved group but progressive cognitive deficits in the deteriorated group.

Table 1 *The cognitive performance of the study groups at baseline (t1) and at follow-up (t2)*

	Controls (1)		Preserved (2)		Deteriorated (3)		*P*(t1)	*P*(t2)	*P*(d)
	t1	t2	t1	t2	t1	t2			
Mild Deterioration Battery (MDB)									
WAIS, Similarities	23.0 (2.2)	23.1 (2.3)	23.4 (1.8)	23.5 (2.0)	20.4 (2.6)	19.3 (3.3)	<0.001*	<0.001*	0.193
WAIS, Digit Span	10.8 (2.0)	11.1 (2.1)	10.5 (1.8)	10.5 (1.7)	9.0 (1.7)	8.0 (1.7)	<0.001*	<0.001*	0.014***
WAIS, Digit Symbol	52.9 (11.2)	55.4 (11.6)	43.2 (15.0)	40.3 (15.1)	22.4 (8.0)	19.2 (8.4)	<0.001**	<0.001**	0.001*
WAIS, Block Design	41.0 (6.5)	40.0 (6.9)	38.9 (6.0)	39.1 (6.1)	26.6 (8.9)	23.8 (8.5)	<0.001*	<0.001*	0.106
Immediate recall of 20 objects	14.6 (1.9)	14.2 (2.0)	13.2 (2.1)	13.5 (2.1)	9.8 (2.2)	8.9 (2.6)	<0.001**	<0.001*	0.420
Immediate recall of 30 PWA	23.7 (4.9)	22.1 (6.2)	22.9 (4.7)	23.5 (5.0)	14.5 (5.1)	12.0 (6.3)	<0.001*	<0.001*	0.086
Benton VRT (errors)	3.4 (2.4)	4.0 (2.7)	3.6 (1.7)	3.7 (2.6)	6.9 (2.5)	9.6 (3.5)	<0.001*	<0.001*	0.005*
Naming time of 20 object (s)	30.4 (7.5)	28.9 (8.8)	33.0 (9.0)	36.2 (16.6)	53.6 (9.4)	63.2 (30.7)	<0.001*	<0.001*	0.053
Deterioration score for the MDB	0.4 (0.7)	0.6 (1.1)	0.7 (0.8)	1.3 (1.9)	6.9 (1.9)	9.6 (4.1)	<0.001*	<0.001*	0.003*
Mini-Mental State Examination	29.1 (0.8)	29.4 (0.7)	29.3 (0.9)	29.2 (0.9)	27.3 (1.9)	27.3 (2.2)	<0.001*	<0.001*	0.577
Memory and learning measures									
Delayed recall of 20 objects	13.2 (2.0)	13.6 (2.1)	12.0 (2.3)	12.7 (2.6)	8.3 (2.1)	7.2 (2.9)	<0.001**	<0.001*	0.036*
Delayed recall of 30 PWA	21.6 (6.1)	20.3 (6.9)	19.4 (6.2)	21.3 (6.2)	9.9 (4.6)	8.6 (5.8)	<0.001*	<0.001*	0.016††
WMS, Story 1 (immediate)	16.0 (4.4)	16.0 (4.3)	17.4 (2.9)	16.6 (3.2)	12.1 (3.9)	9.3 (4.7)	<0.001*	<0.001*	0.011*
WMS, Story 1 (delayed)	14.8 (4.3)	15.0 (4.1)	15.1 (4.4)	15.5 (3.8)	9.1 (4.0)	7.7 (4.5)	<0.001*	<0.001*	0.125
WMS, Story 2 (immediate)	14.0 (4.1)	13.8 (5.1)	13.9 (3.5)	14.0 (3.2)	9.0 (3.9)	7.7 (4.1)	<0.001*	<0.001*	0.431
WMS, Story 2 (delayed)	12.9 (4.4)	13.4 (5.3)	12.5 (4.7)	13.1 (3.4)	6.8 (4.3)	6.4 (4.1)	<0.001*	<0.001*	0.692
7/24 SRT, immediate recall	5.0 (1.8)	5.4 (1.9)	5.4 (1.5)	5.5 (1.4)	3.9 (1.9)	3.6 (1.7)	0.021*	<0.001*	0.472
7/24 SRT, learning score	31.6 (4.0)	32.1 (4.6)	31.2 (4.4)	32.3 (3.4)	24.7 (5.7)	21.7 (6.3)	<0.001*	<0.001*	0.031*
7/24 SRT, errors, total	3.1 (3.4)	2.9 (4.5)	3.3 (3.9)	3.1 (5.3)	9.7 (6.9)	13.3 (7.2)	<0.001*	<0.001*	0.012*
7/24 SRT, delayed recall	6.4 (1.2)	6.2 (1.2)	5.6 (2.0)	5.9 (1.5)	4.6 (2.0)	4.0 (1.9)	0.001*	<0.001*	0.487
Language and frontal functions									
Reading of 100 words (s)	51.9 (9.3)	57.4 (12.1)	59.4 (11.3)	65.0 (19.7)	88.8 (26.0)	92.2 (15.3)	<0.001*	<0.001*	0.761
Naming of 100 colours (s)	63.2 (11.4)	68.1 (10.4)	72.2 (13.8)	75.6 (5.3)	101.6 (26.4)	114.4 (27.8)	<0.001*	<0.001*	0.023*
Verbal fluency (S)	17.4 (5.5)	18.1 (5.8)	15.9 (5.1)	17.5 (5.3)	10.6 (3.9)	9.3 (3.7)	<0.001*	<0.001*	0.050†
Verbal fluency (animals)	23.7 (6.1)	23.1 (5.7)	21.7 (6.4)	22.0 (5.7)	13.0 (3.9)	12.0 (4.6)	<0.001*	<0.001*	0.635
Attention and information processing									
Stroop, c-w naming (s)	104.8 (18.9)	104.5 (19.7)	112.9 (29.1)	115.0 (26.0)	162.6 (54.1)	190.6 (72.5)	<0.001*	<0.001*	0.003*
Stroop, interference time	41.6 (13.4)	36.4 (15.2)	40.7 (21.0)	39.5 (16.2)	61.0 (33.5)	76.2 (55.4)	0.006*	<0.001*	0.011***
PASAT 1 (easy), correct (total)	45.7 (12.6)	46.7 (12.0)	44.5 (10.9)	45.1 (11.3)	26.8 (7.7)	23.4 (11.1)	<0.001*	<0.001*	0.162
PASAT 2 (hard), correct (total)	34.5 (10.7)	35.8 (13.6)	31.4 (9.7)	33.3 (10.4)	22.2 (7.0)	16.9 (9.1)	<0.001*	<0.001*	0.032*

Mean (SD). The differences between the study groups in the evolution of cognitive performances from t1 to t2 are demonstrated with the *P*(d) values.
*1, 2 ≠ 3; **1 ≠ 2 ≠ 3; ***1 ≠ 3; †2 ≠ 3; ††2 ≠ 1, 3. *P*-values: *P*(t1) = baseline; *P*(t2) = follow-up; *P*(d) = longitudinal change from t1 to t2. WAIS = Wechsler Adult Intelligence Scale; PWA = Paired Word Associates; VRT = Visual Retention Test; WMS = Wechsler Memory Scale; SRT = Spatial Recall Test; PASAT = Paced Auditory Serial Addition Test.

Longitudinal results of other neuropsychological measures

The deteriorated group showed longitudinal cognitive decline compared with the controls and the preserved patients on various neuropsychological measures (Table 1). On the tests of memory and learning, progressive decline in the deteriorated group was observed on the delayed recall of 20 objects, on the immediate recall of the Wechsler Memory Scale Logical Story 1 and on the 7/24 Spatial Recall Test (learning score, total error rate) when compared with the other study groups. On language-related tests, the deterioration was evident on the naming time of 100 coloured rectangles when compared with the other two study groups and on the letter fluency test when compared with the preserved patients. On the measures of attention and information processing, the deteriorated patients performed more slowly at follow-up than at baseline on the colour–word naming of the Stroop test when compared with the other study groups and on the interference time of the same test when compared with the controls. Moreover, progressive deterioration was seen on the difficult condition of the Paced Auditory Serial Addition Test. On nearly all these neuropsychological measures, the deteriorated group tended to perform less well at follow-up than at baseline. By contrast, the controls and especially the preserved patients tended to improve their performance in the re-assessment. The preserved patients improved their performance on the delayed recall of 30 Paired Word Associates when compared with the other subjects. Although the deteriorated patients exhibited consistent performance deterioration over time on many neuropsychological measures, the MMSE performance remained stable (Table 1). The performance of the controls and the preserved patients on the MMSE ranged from 27 to 30 both at baseline and at follow-up, whereas the performance

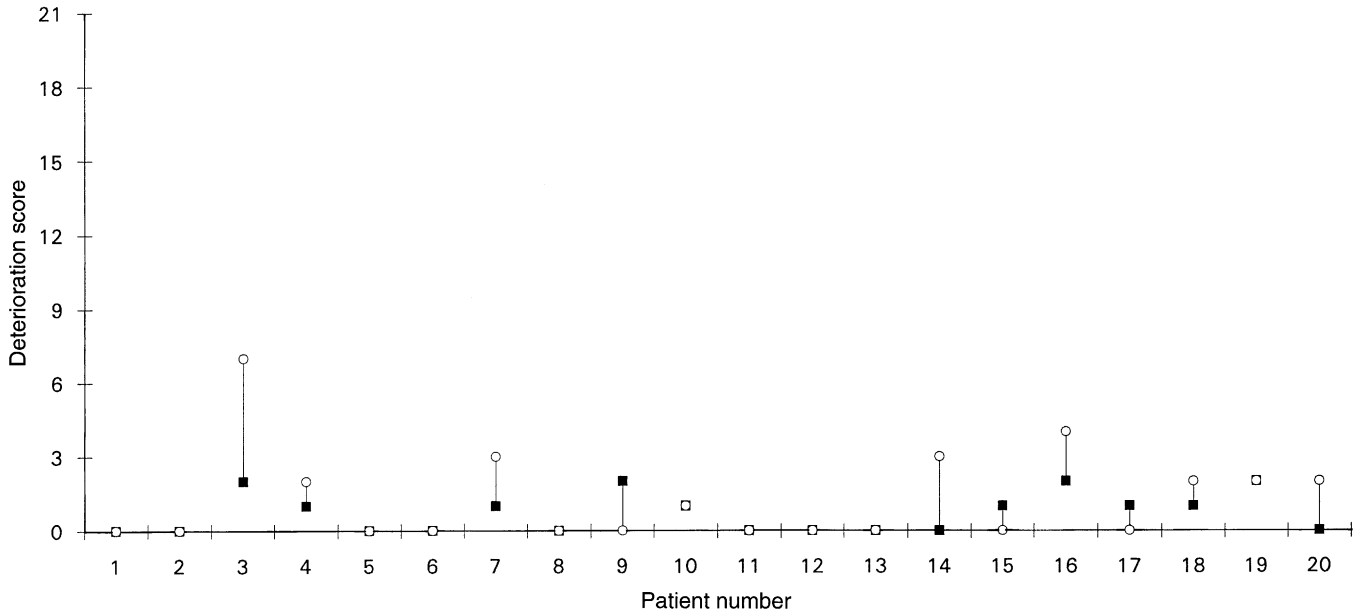

Fig. 1 The longitudinal performance change on the Mild Deterioration Battery (MDB) in the initially preserved patients. The deterioration scores of the individual patients show substantial neuropsychological stability. Closed squares represent baseline scores and open circles represent scores at follow-up.

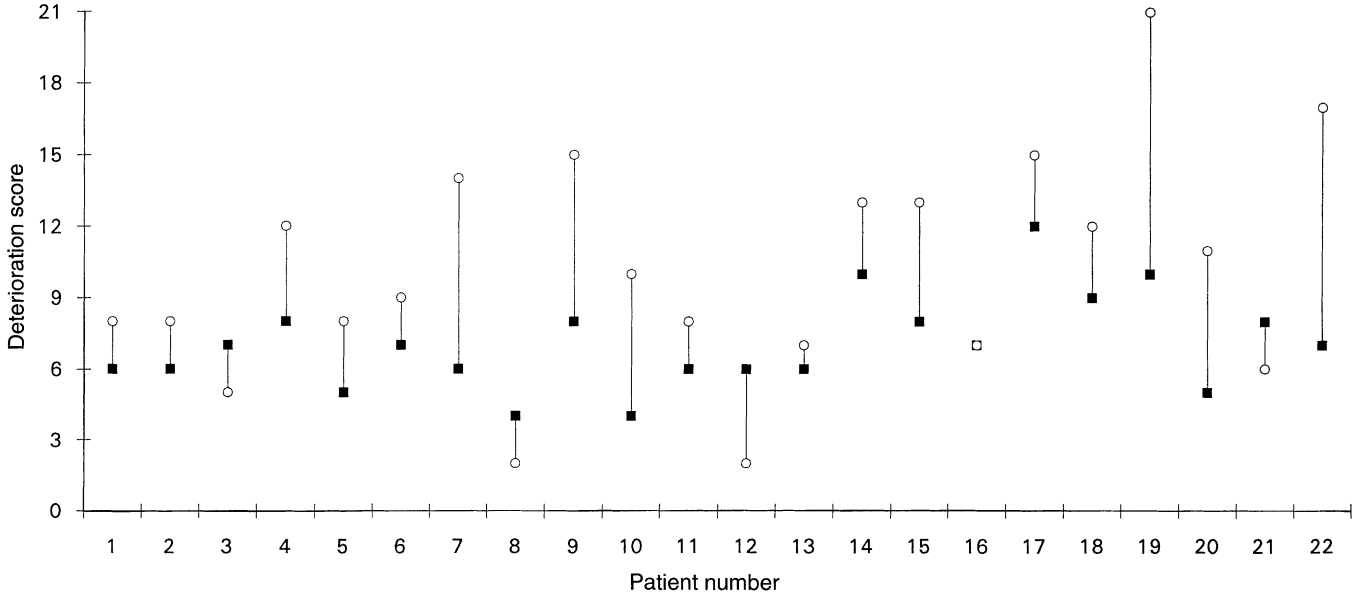

Fig. 2 The longitudinal performance change on the MDB in the initially mildly deteriorated patients. The deterioration scores of the individual patients show progressive cognitive decline. Closed squares represent baseline scores and open circles represent scores at follow-up.

of the deteriorated patients ranged from 23 to 30 at baseline and from 21 to 30 at follow-up.

Analysis of cognitive performance change in individual subjects

We evaluated the evolution of cognitive performances in individual subjects by comparing their deterioration score at baseline with that at follow-up (Figs 1 and 2). At follow-up, one of the controls scored four deterioration points, the minimum of incipient deterioration. In the other control subjects, the deterioration score remained relatively stable (0–2 points). Two of the preserved patients fulfilled the criterion for incipient decline in the retest (Fig. 1, Patients 3 and 16). However, changes in deterioration scores in other preserved patients were minimal. Of the 22 deteriorated patients, 17 had more deterioration points at follow-up than at baseline (Fig. 2). The five deteriorated patients who could

not perform all the tests showed further deterioration in their cognitive performance when evaluated with the deterioration score (Patients 1, 5, 9, 19 and 22). All deteriorated patients, apart from two (Patients 8 and 12), fulfilled the criterion for at least mild deterioration (4 points). The range of the deterioration points in the deteriorated group was 4–12 at baseline and 2–21 at follow-up.

The relationship between different variables was evaluated using correlation analyses. The correlation between physical disability (EDSS) and the Block Design test was significant in the preserved group ($P = 0.002$). In the deteriorated group, the correlations between the EDSS and the Naming time of 20 objects ($P = 0.017$), immediate ($P = 0.027$) and delayed ($P = 0.029$) recall of Wechsler Memory Scale Story 2, and the Digit Symbol test ($P = 0.020$) were significant. The correlations between the EDSS and other neuropsychological measures were nonsignificant in both patient groups. The same holds true also with respect to the correlations between disease duration and neuropsychological measures. No significant relationship was found between the longitudinal change in the EDSS score and the change in the MDB score (whole patient group, $P = 0.188$, preserved group, $P = 0.324$, deteriorated group, $P = 0.143$).

Discussion

This study is the first to illustrate how defined incipient cognitive deficits on the one hand and intact cognitive functioning on the other, evolve over time in patients with multiple sclerosis. We paid special attention to methodological factors, and, therefore, evaluated the longitudinal cognitive changes in two physically similar multiple sclerosis groups, the cognitively preserved and the deteriorated, and control subjects by using a wide variety of neuropsychological measures. The drop-out rate in our study was remarkably low, not more than 5%. The results indicated that incipient and mild cognitive deficits, observed initially in the deteriorated patients, tended to progress during the follow-up period of ~3 years. By contrast, the initially preserved but physically similarly disabled patients showed substantial neuropsychological stability over the same period.

The continuous cognitive preservation over time seemed to be obvious in the cognitively preserved subset of our multiple sclerosis patients. Cross-sectional analyses demonstrated that the preserved group performed almost as well as the controls on the neuropsychological measures both at baseline and at follow-up. Moreover, longitudinal analyses did not reveal any significant change in the cognitive performance of the preserved patients as a group over time. Actually, in the retest, a slight tendency towards improvement was observed on most neuropsychological measures. One explanation of this may be that the preserved patients could not perform maximally in the lengthy initial neuropsychological assessment and were less fatigued and more able to exploit their cognitive resources during the briefer follow-up examination. Another possibility is that some patients had learned to use cognitive strategies and, therefore, were able to show a slight performance improvement. Our results amplify the published evidence of Filley *et al.* (1990), Jennekens-Schinkel *et al.* (1990*b*), and Mariani *et al.* (1991), who have also reported longitudinal cognitive preservation in multiple sclerosis. However, in the studies of Filley *et al.* (1990) and Mariani *et al.* (1991) there is a possibility of overestimation of cognitive preservation because of the lack of controls. Furthermore, the previous findings have been mostly restricted to multiple sclerosis patients with mild functional impairment and relapsing–remitting course of the disease. Thus, our results extend the possibility of persisting cognitive preservation also to patients with more severe disability.

The mild and incipient cognitive decline in our initially deteriorated multiple sclerosis patients seemed to be progressive in nature. At baseline, they exhibited incipient cognitive deficits in many cognitive domains (Kujala *et al.*, 1994, 1995, 1996*a*, *b*), and at follow-up, their overall neuropsychological performance had further deteriorated. The progressive deterioration was observable on the tests of memory, learning, attention and visuo-motor performance, which have all previously been reported to be sensitive measures of cognitive decline in multiple sclerosis (Ivnik, 1978*b*; van den Burg *et al.*, 1987; Litvan *et al.*, 1988; Beatty *et al.*, 1989; Rao *et al.*, 1991; Ron *et al.*, 1991; Kujala *et al.*, 1995, 1996*a*, *b*). Unexpectedly, also Digit Span and naming performance, which have both been suggested to remain intact in multiple sclerosis (Heaton *et al.*, 1985; Jennekens-Schinkel *et al.*, 1990*a*; Caltagirone *et al.*, 1991; Klonoff *et al.*, 1991; Rao *et al.*, 1991), proved to be sensitive indicators of further decline. The observed progressive deterioration cannot be explained by motor-related factors because cognitively preserved patients, irrespective of their physical disability, performed as well as the non-disabled controls and tended to improve their performance over time. Moreover, most of our measures did not involve a motor component. Our observations on progressive cognitive deterioration in multiple sclerosis are consistent with the findings of Canter (1951), Ivnik (1978*b*), Feinstein *et al.* (1992), and Amato *et al.* (1995). However, in the aforementioned studies, progressive decline was observable only on a few neuropsychological measures and on motor-sensory functions. Contrary to previous suggestions, we observed the profile of cognitive decline in multiple sclerosis to be widespread and progressive rather than circumscribed.

In combination with a set of various neuropsychological tests, we evaluated the evolution of cognitive performances with an intermediate-length screening battery, the MDB (Portin and Rinne, 1980; Revonsuo *et al.*, 1993; Kujala *et al.*, 1994, 1995, 1996*a*, *b*). The results of this battery were in line with the results of the other neuropsychological measures administered. By using the deterioration score of the MDB as a measure of cognitive functioning, we were able to analyse not only group differences, but also the evolution of cognitive status in individual subjects, even in those five

who could not perform all of the tests due to their physical or cognitive restrictions. We did not underestimate the cognitive capacity of the five patients at follow-up because we evaluated their deterioration scores in the tests which they could not perform as being similar to those at baseline. As a whole, the deterioration scores showed that intact cognitive functioning predicted further preservation and that cognitive decline predicted further deterioration. However, the deterioration scores also demonstrated that some of the initially preserved patients had developed incipient cognitive decline and some of the initially deteriorated patients had improved their performance. This finding is in agreement with the previous observation about individual variability in neuropsychological performance of multiple sclerosis patients over time (Jennekens-Schinkel *et al.,* 1990*b*; Feinstein *et al.,* 1993). When analysing the evolution of cognitive performance in the five patients with extensive impairments, we noticed that all these patients showed progressive cognitive decline although the degree of deterioration on the tests which they could not perform at follow-up was evaluated as similar to that at baseline. Thus, if these patients had been treated as drop-outs, the frequency of progressive cognitive decline would have been underestimated.

The MDB consisting of tests of memory, reasoning, language and visuo-motor and visuo-constructive performance, seems to be useful in evaluation of longitudinal cognitive changes in multiple sclerosis. The properties of this battery in cross-sectional settings have already been demonstrated in our earlier studies (Kujala *et al.,* 1994, 1995, 1996*a*, *b*). We have found a relationship between cognitive deterioration determined by the MDB and cognitive slowness, attentional deficits, memory problems and language deficits. The disadvantage of the MDB is the inclusion of the Digit Symbol test which obviously is susceptible to motor-related problems (Ivnik, 1978*b*; Kujala *et al.,* 1994). Our preserved group performed less well than controls on this particular test. However, the degree of deterioration in the preserved patients on this test was low. Another shortcoming of the MDB is the lack of a measure of information processing and attentional performance. However, among the additional neuropsychological measures we included the Paced Auditory Serial Addition Test and noticed that the progressive deterioration of the deteriorated group was observable only on the difficult version of this test. As a whole, the test sample of the MDB seemed to be adequate and sensitive in mapping the course of cognitive performances in multiple sclerosis. Contrary to the MDB, the MMSE seemed to be insensitive to the longitudinal cognitive changes in the deteriorated group (cf. Beatty and Goodkin, 1990; Swirsky-Sacchetti *et al.,* 1992; Kujala *et al.,* 1996*a*). Thus, in multiple sclerosis, the MMSE is inadequate in detecting even remarkable changes in cognitive functioning.

In the present study, no direct relationship between progressive cognitive decline and overall progress of multiple sclerosis was found. First, the correlations between the EDSS and MDB scores or other neuropsychological measures were mostly nonsignificant. Secondly, no correlations were observed between disease duration and neuropsychological performance in our multiple sclerosis patients, which is in line with the observations of Ivnik (1978*a*) and Feinstein *et al.* (1992). Thirdly, no significant changes in the course of the disease in the two patient groups were observed during the follow-up period; neither did our patients with secondary progressive multiple sclerosis exhibit more cognitive deterioration over time than our patients with chronically progressive course of the disease. This is in contrast with recent findings of Comi *et al.* (1995). Fourthly, our preserved patients tended to improve their cognitive performance despite increasing physical disability, which is in line with the assumption that physical disability and cognitive functioning are not coincidental (Ivnik, 1978*b*; for review, *see* Rao, 1986). On the other hand, the EDSS score of our deteriorated group tended to grow more than that of the preserved group during the follow-up period, which suggests that cognitive deterioration and physical disability may develop in parallel. The evaluation of the relationship between cognitive decline and overall progress of the disease may, however, be confounded by such factors as the inadequacy of the EDSS to measure multiple sclerosis related impairment (Weinshenker *et al.,* 1996) and the difficulty to define the actual course of the disease. As a whole, the evolution of cognitive functioning cannot be predicted from clinical disease variables (cf. Amato *et al.,* 1995). However, in the case of cognitive deterioration in multiple sclerosis, physical disability is also usually present. In our two physically similar multiple sclerosis groups, the lesion load in the areas of spinal cord and cerebellum are probably relatively similar. In contrast to the cognitively preserved patients, the brain pathology of the cognitively deteriorated patients presumably also extends to the cerebral hemisphere areas, which are responsible for the control of cognitive abilities (cf. Brooks *et al.,* 1984; Ron *et al.,* 1991; Feinstein *et al.,* 1993; Pozzilli *et al.,* 1993; Comi *et al.,* 1995). Probably, the accumulation of demyelinative changes in wide areas of the cerebrum interferes with the function of distributed neural networks and, thereby, progressively violates several of the cognitive domains.

To conclude, both cognitive preservation and deterioration over time occur in multiple sclerosis. Our initial classification of patients into cognitively preserved and deteriorated groups demonstrated that even incipient cognitive decline predicts further deterioration, whereas intact cognitive performances, although associated with relatively high physical disability, may remain stable. Because cognitive deficits have been reported to have an integral effect on the quality of life of multiple sclerosis patients, the evolution of cognitive status should be followed, especially in patients who already have cognitive deficits. Brief neuropsychological batteries should, however, be replaced by intermediate-length batteries, like the MDB, both in initial definition of cognitive status and in evaluation of the course of cognitive performances in multiple sclerosis patients.

Acknowledgements

We wish to thank Matti Grönroos Ph.Lic. and Kimmo Hypén M.A. for their assistance with the analyses and our subjects for their time and interest in this study. This study was financially supported by the Emil Aaltonen Foundation.

References

Amato MP, Ponziani G, Pracucci G, Bracco L, Siracusa G, Amaducci L. Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. Arch Neurol 1995; 52: 168–72.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington (DC): American Psychiatric Association, 1980.

Barbizet J, Cany E. Clinical and psychometrical study of a patient with memory disturbances. Int J Neurol 1970: 7: 44–54

Beatty WW, Goodkin DE. Screening for cognitive impairment in multiple sclerosis. Arch Neurol 1990; 47: 297–301.

Beatty WW, Goodkin DE, Beatty PA, Monson N. Frontal lobe dysfunction and memory impairment in patients with chronic progressive multiple sclerosis. Brain Cogn 1989; 11: 73–86.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh JK. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561–71.

Benton AL. The Revised Visual Retention Test. New York: Psychological Corporation, 1963.

Brooks DJ, Leenders KL, Head G, Marshall J, Legg NJ, Jones T. Studies on regional cerebral oxygen utilisation and cognitive function in multiple sclerosis. J Neurol Neurosurg Psychiatry 1984; 47: 1182–91.

Caltagirone C, Carlesimo GA, Fadda L, Roncacci S. Cognitive function in multiple sclerosis: a subcortical pattern of neuropsychological impairment? Behav Neurol 1991; 4: 129–41.

Canter AH. Direct and indirect measures of psychological deficit in multiple sclerosis. J Gen Psychol 1951; 44: 3–50.

Comi G, Filippi M, Martinelli V, Campi A, Rodegher M, Alberoni M, et al. Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. J Neurol Sci 1995; 132: 222–7.

Feinstein A, Kartsounis LD, Miller DH, Youl BD, Ron MA. Clinically isolated lesions of the type seen in multiple sclerosis: a cognitive, psychiatric, and MRI follow up study. J Neurol Neurosurg Psychiatry 1992; 55: 869–76.

Feinstein A, Ron M, Thompson A. A serial study of psychometric and magnetic resonance imaging changes in multiple sclerosis. Brain 1993; 116: 569–602.

Filley CM, Heaton RK, Thompson LL, Nelson LM, Franklin GM. Effects of disease course on neuropsychological functioning. In: Rao SM, editor. Neurobehavioral aspects of multiple sclerosis. New York: Oxford University Press, 1990: 136–48.

Fink SL, Houser HB. An investigation of physical and intellectual changes in multiple sclerosis. Arch Phys Med Rehabil 1966; 47: 56–61.

Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Gronwall DMA. Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 1977; 44: 367–73.

Gronwall D, Wrightson P. Recovery after minor head injury [letter]. Lancet 1974; 2: 1452.

Heaton RK, Nelson LM, Thompson DS, Burks JS, Franklin GM. Neuropsychological findings in relapsing–remitting and chronic-progressive multiple sclerosis. J Consult Clin Psychol 1985; 53: 103–10.

Ivnik RJ. Neuropsychological test performance as a function of the duration of MS-related symptomatology. J Clin Psychiatry 1978a; 39: 304–7, 311–12.

Ivnik RJ. Neuropsychological stability in multiple sclerosis. J Consult Clin Psychol 1978b; 46: 913–23.

Jennekens-Schinkel A, Lanser JBK, van der Velde EA, Sanders EACM. Performances of multiple sclerosis patients in tasks requiring language and visuoconstruction. Assessment of outpatients in quiescent disease stages. J Neurol Sci 1990a; 95: 89–103.

Jennekens-Schinkel A, La Boyrie PM, Lanser JBK, van der Velde EA. Cognition in patients with multiple sclerosis after four years. J Neurol Sci 1990b; 99: 229–47.

Klonoff H, Clark C, Oger J, Paty D, Li D. Neuropsychological performance in patients with mild multiple sclerosis. J Nerv Ment Dis 1991; 179: 127–31.

Kujala P, Portin R, Revonsuo A, Ruutiainen J. Automatic and controlled information processing in multiple sclerosis. Brain 1994; 117: 1115–26.

Kujala P, Portin R, Revonsuo A, Ruutiainen J. Attention related performance in two cognitively different subgroups of patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 1995; 59: 77–82.

Kujala P, Portin R, Ruutiainen J. Memory deficits and early cognitive deterioration in MS. Acta Neurol Scand 1996a; 93: 329–35.

Kujala P, Portin R, Ruutiainen J. Language functions in incipient cognitive decline in multiple sclerosis. J Neurol Sci 1996b; 141: 79–86.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983; 33: 1444–52.

Lezak MD. Neuropsychological assessment. 2nd edn. New York: Oxford University Press, 1983.

Litvan J, Grafman J, Vendrell P, Martinez JM. Slowed information processing in multiple sclerosis. Arch Neurol 1988; 45: 281–5.

Mariani C, Farina E, Cappa SF, Anzola GP, Faglia L, Bevilacqua L, et al. Neuropsychological assessment in multiple sclerosis: a follow-up study with magnetic resonance imaging. J Neurol 1991; 238: 395–400.

Portin R, Rinne UK. Neuropsychological responses of parkinsonian patients to long-term levodopa treatment. In: Rinne UK, Klinger

M, Stamm G, editors. Parkinson's disease—current progress, problems and management. Amsterdam: Elsevier Biomedical Press, 1980: 271–304.

Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983; 13: 227–31.

Pozzilli C, Gasperini C, Anzini A, Grasso MG, Ristori G, Fieschi C. Anatomical and functional correlates of cognitive deficit in multiple sclerosis. [Review]. J Neurol Sci 1993; 115 Suppl: S55–8.

Rao SM. Neuropsychology of multiple sclerosis: a critical review. J Clin Exp Neuropsychol 1986; 8: 503–42.

Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis. 1. Frequency, patterns, and prediction [see comments]. Neurology 1991; 41: 685–91. Comment in: Neurology 1991; 41: 2014–15.

Revonsuo A, Portin L, Koivikko L, Rinne JO, Rinne UK. Slowing of information processing in Parkinson's disease. Brain Cogn 1993; 21: 87–110.

Ron MA, Callanan MM, Warrington EK. Cognitive abnormalities in multiple sclerosis: a psychometric and MRI study. Psychol Med 1991; 21: 59–68.

Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935; 18: 643–62.

Swirsky-Sacchetti T, Field HL, Mitchell DR, Seward J, Lublin FD, Knobler RL, et al. The sensitivity of the Mini-Mental State Exam in the white matter dementia of multiple sclerosis. J Clin Psychol 1992; 48: 779–86.

van den Burg W, van Zomeren AH, Minderhoud JM, Prange AJA, Meijer NSA. Cognitive impairment in patients with multiple sclerosis and mild physical disability. Arch Neurol 1987; 44: 494–501.

Wechsler D. A standardized memory scale for clinical use. J Psychol 1945; 19: 87–95.

Wechsler D. Manual for Wechsler Adult Intelligence Scale. New York: Psychological Corporation, 1955.

Weinshenker BG, Issa M, Baskerville J. Long-term and short-term outcome of multiple sclerosis. Arch Neurol 1996; 53: 353–8.

Young AC, Saunders J, Ponsford JR. Mental change as an early feature of multiple sclerosis. J Neurol Neurosurg Psychiatry 1976; 39: 1008–13.

Received August 6, 1996. Accepted October 11, 1996