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One-year follow-up study of relapsing-remitting MS patients' cognitive performances: Paced Auditory Serial Addition Test's susceptibility to change

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Abstract

To evaluate the progression of cognitive decline in multiple sclerosis (MS) patients and the susceptibility of the Multiple Sclerosis Functional Composite (MSFC) Paced Auditory Serial Addition Test (PASAT) to change, we conducted a 1-year follow-up with a comprehensive neuropsychological examination to 19 initially cognitively impaired and 26 cognitively intact relapsing–remitting MS patients, and to 48 healthy controls. The results indicated that the cognitive performance of MS patients remained relatively stable. Healthy controls tended to perform better on most neuropsychological measures at follow-up, the same was not observed in the MS groups. PASAT showed a significant difference between the groups: the cognitively impaired group tended to deteriorate, whereas the control group and the cognitively intact group improved. The change in PASAT could not be explained by the background variables, for example, mood, quality of life, or nervousness. Therefore, the MSFC-PASAT seems to be a sensitive measure to show clinical change in the cognitive status. (*JINS*, 2007, *13*, 791–798.)

Keywords: Cognition, Follow-up, Multiple sclerosis, Multiple Sclerosis Functional Composite (MSFC), Neuropsychological evaluation, Paced Auditory Serial Addition Test (PASAT)

INTRODUCTION

Although the presence of cognitive impairment in multiple sclerosis (MS) is well documented in cross-sectional studies, the course and evolution of cognitive performances in MS remains controversial as some studies report stable cognitive status at follow-up (Camp et al., 2005; Hohol et al., 1997; Jennekens-Schinkel et al., 1990; Mariani et al., 1991; Piras et al., 2003; Sperling et al., 2001), and some report decline (Amato et al., 1995; Amato et al., 2001; Feinstein et al., 1992; Haase et al., 2004; Kujala et al., 1997; Zivadinov et al., 2001). Various methodological factors probably explain the controversial results: variation of the follow-up times, patient samples, and neuropsychological tests has been considerable. The importance of studying cognitively homogeneous MS subgroups has been emphasized by many (Camp et al., 2005; Grossman et al., 1995; Kujala et al., 1994, 1997; Ryan et al., 1996). One study (Kujala et al., 1997) evaluated originally cognitively intact and cognitively impaired patients separately and found that the cognitively intact group remained stable at follow-up, whereas in the impaired group, the incipient cognitive decline had progressed. One restriction in some of the previous studies (Camp et al., 2005; Hohol et al., 1997; Mariani et al., 1991; Piras et al., 2003; Sperling et al., 2001) has also been the lack of an appropriate control group: subtle cognitive decline might have been obscured by undetected normal practice effects in the neuropsychological tests.

Because the main feature of MS-related cognitive decline is reduced and slowed information processing efficiency, attention tests have been found to be sensitive indicators of these deficits (Demaree et al., 1999; Hohol et al., 1997; Kujala et al., 1995). Attentional tasks may also be especially useful in detecting longitudinal changes in cognitive

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performance in patients with MS (Hohol et al., 1997). The Paced Auditory Serial Addition Test (PASAT) is a neuropsychological measure of sustained and divided attention, concentration, and information processing speed and commonly is used with MS patients (Gronwall, 1977; Gronwall & Wrightson, 1981; Lezak, 1995). The test was also included as a single measure of cognition in the widely used clinical assessment tool for MS clinical trials, the Multiple Sclerosis Functional Composite (MSFC; Cutter et al., 1999; Rudick et al., 1997). In the MSFC, the PASAT is mainly intended for longitudinal follow-up, evaluating decline or improvement in cognitive functioning in serial assessment. An important and desired factor of a clinical trial measurement tool is its ability to reflect the extent of the MS disease process and the sensitivity to show the clinical change due to MS (Rudick et al., 1996). In previous longitudinal MS studies, stability (Camp et al., 2005; Hohol et al., 1997; Kujala et al., 1997; Sperling et al., 2001) as well as decrease (Kujala et al., 1997; Ozakbas et al., 2005; Zivadinov et al., 2001) in PASAT performance have been noticed.

To increase our understanding of the progression of MS patients' cognitive deficits, and especially to clarify the MSFC-PASAT's susceptibility to change, we followed up the cognitive functioning in two demographically similar MS groups, the cognitively intact and cognitively impaired patients. Both groups consisted only of patients with relapsing–remitting form of the disease with mild motor dysfunction and relatively short duration of the illness. To evaluate the normal practice effects in neuropsychological tests during a follow-up, we also included a control group.

SUBJECTS AND METHODS

Our sample consisted of 45 clinically definite relapsing–remitting MS patients according to Poser et al. (1983) criteria admitted to Seinäjoki Central Hospital, Department of Neurology, and 48 healthy controls (hospital staff and friends or spouses of MS patients). All subjects participated in the follow-up study after 1 year from the baseline. Of the 45 patients, 44 received β-interferon treatment at the baseline and 42/45 at the time of the follow-up study. The mean Expanded Disability Status Scale (EDSS) scores did not differ between the baseline and the follow-up study among the patients [baseline 2.9 (*SD* 1.6), follow-up 2.8 (1.6); $t(44) = .270$; $p = .788$]. Exclusion criteria were drug or alcohol abuse, psychiatric history, acute MS relapses during the study period or other known neurological diseases. Controls were also free from drug or alcohol problems, psychiatric history, or any neurological disease. To verify the information obtained from both patients and controls regarding their past medical history, all available hospital records were examined.

The patients were divided into two subgroups, intact or impaired, with respect to their cognitive status on the baseline study (for the definition of impaired, see below). The three study groups were statistically comparable with respect to age, gender, and education (Table 1). All subjects provided a written informed consent before participating. The study protocol was approved by the Ethics Committee of Seinäjoki Central Hospital.

An extensive neuropsychological examination was conducted for each subject both at the baseline and at the follow-up by the same psychologist (E.R.). The same versions of the neuropsychological tests were used in both examinations to minimize the bias of varying difficulty of parallel forms. Table 2 summarizes the neuropsychological and clinical tests, their references, and the variables used. The detailed information about tests and questionnaires not publicly available can be found in our previous article (Rosti et al., 2007).

To identify cognitively impaired patients on the baseline study, raw cognitive test scores of the comprehensive neuropsychological examination were first converted to standardized residual scores (Rosti et al., 2006, 2007). The technique was adapted from Rao et al. (1991) to correct for individual differences in premorbid cognitive ability. The demographic variables for both patients and controls (age, sex, and education) were entered in a linear regression model with the 34 cognitive test variables. A product of these analyses, the standardized residual score, represents the difference between subjects' predicted and actual test scores. The fifth percentile of residual scores of control subjects was used as a cutoff point for defining the subjects who "failed" each test. The summary index for each subject was the total number of the failed tests. The fifth percentile of control subjects' summary indices (seven or more failed tests) served as a cutoff for defining a subject as "cognitively impaired."

Pearson's χ^2 test, Mann–Whitney U tests (Z), and Student's t tests were used in pairwise comparisons and the analysis of variance (ANOVA) in comparisons between three groups. The longitudinal change in cognitive performance of the three groups was analyzed 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 ANOVAs for the parametric variables and the Kruskal–Wallis test for nonparametric variables. The Tukey honest significance difference test was used for *post hoc* pairwise comparisons following ANOVAs and Mann–Whitney comparisons following Kruskal–Wallis tests. The difference between neuropsychological testing sessions within groups was compared using the paired samples t test for parametric and the Wilcoxon matched pairs signed test for nonparametric variables. Linear regression analysis was used to identify independent factors associated with the change in the PASAT scores. Furthermore, some correlation analyses were carried out.

To define a reliable change in PASAT for each individual, we calculated the mean change of correct responses of the healthy controls between two testing sessions (1.96) and used it as a cutoff point. We then conducted a 2×2 χ^2 analyses to look at the relationship between those who deteriorated (showed a decrease from baseline to follow-up of 2 or more points) *versus* those who remained stable (per-

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Table 1. Demographic and clinical characteristics of study population as measured at baseline and the differences between the groups

Descriptive variables	Controls ($n = 48$)	Cognitively intact MS ($n = 26$)	Cognitively impaired MS ($n = 19$)	Significance of the differences
Age in years, mean (range, *SD*)	42.3 (25–54, 7.4)	42.2 (22–55, 8.7)	43.5 (27–56, 7.8)	$F(2,90) = .205$, $p = .815$
Sex				
Female/Male	33/15	18/8	15/4	$\chi^2(2) = .740$, $p = .691$
Education in years, mean (range, *SD*)	13.2 (8–18, 2.5)	13.5 (8–25, 3.7)	12.5 (9–19, 3.2)	$F(2,90) = .611$, $p = .545$
BDI, mean (range, *SD*)	2.7 (0–19, 4.3)	6.6 (0–20, 5.5)	11.7 (0–30, 9.3)	$\chi^2(2) = 26.523$ $p < .001$[a]
15D, mean (range, *SD*)	.96 (.82–1.0, .0)	.86 (.68–.96, .1)	.76 (.51–.94, .1)	$\chi^2(2) = 54.858$ $p < .001$[a,b]
Nervousness Questionnaire, mean (range, *SD*)	6.0 (.9–24.8, 5.7)	11.7 (1–35.8, 9.1)	10.4 (1–36, 10.8)	$\chi^2(2) = 9.838$ $p = .007$[c]
EDSS, mean (range, *SD*)	—	2.3 (0–4, 1.0)	3.7 (1–7, 1.9)	$Z = -2.564$ $p = .01$[b]
Age at disease onset (range, *SD*)	—	34.9 (17–48, 8.7)	34.1 (18–50, 9.8)	$t(43) = .314$ $p = .755$
Disease duration (range, *SD*)	—	7.9 (1–22, 5.1)	10.7 (2–27, 6.9)	$Z = -1.326$ $p = .185$

Note. MS = multiple sclerosis; BDI = Beck Depression Inventory; 15D = Self-reported quality of life questionnaire; EDSS = Expanded Disability Status Scale.
[a]Controls ≠ intact and impaired.
[b]Impaired ≠ intact.
[c]Controls ≠ intact.

formed within 2 points of the baseline) or improved (showed an increase from the baseline of 2 or more points) in PASAT, and the cognitively intact or impaired MS patients.

RESULTS

The healthy controls tended to improve their performance in most of the neuropsychological measures. Memory tests were especially sensitive to improvement due to repeated testing. MS patients showed improvement in fewer neuropsychological tests than controls. Of the 35 cognitive test variables, 19 showed significant improvement within the control group, 8 within the cognitively intact, and only 4 within the cognitively impaired MS patient groups (see Table 2). No significant deterioration was found in any of the tests.

Only in PASAT the mean change between the first and second testing session was significantly different between the three study groups ($p = .002$), in all other neuropsychological tests, the change between the baseline and the follow-up was similar in all three groups. In the PASAT, healthy controls and cognitively intact MS patients improved their performance, whereas cognitively impaired patients tended to show a decline. In a pairwise comparison, the impaired group differed significantly from the controls [$F(2,90) = 6.864$; $p = .009$] as well as from the intact group on the PASAT change score [$F(2,90) = 6.864$; $p = .002$]. The change score of the controls and the intact group did not differ. Most of the initially cognitively impaired patients showed decline on their PASAT performance at the follow-up study compared with the baseline, whereas most of the cognitively intact patients and the controls showed improvement (Table 3). The χ^2 test between intact *versus* impaired MS patients who improved (or remained stable) *versus* deteriorated in PASAT was significant ($p = .001$).

In regression analyses, none of the background variables [change-BDI (Beck Depression Inventory; $p = .836$), change-15D (self-reported quality of life questionnaire; $p = .800$), change-Nervousness Questionnaire ($p = .784$)] explained the change on the PASAT score. Additionally, no significant correlation was found between the longitudinal change in the patients' EDSS score and the change in the PASAT (whole patient group, $p = .402$; intact group, $p = .529$; impaired group, $p = .890$).

DISCUSSION

The aim of our study was to evaluate the longitudinal change in cognitive functioning of MS patients. Therefore, we followed-up two demographically similar MS groups, cognitively intact and cognitively impaired patients, for 1 year. We were especially interested in PASAT's sensitivity to

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Table 2. The raw scores [*mean* (*SD*)] in neuropsychological tests in the follow-up assessment in healthy controls, cognitively intact, and impaired MS patients, comparisons of changes of the raw scores [*mean* (*SD*)] from baseline to 1-year follow-up within the three groups, as well as comparison of the changes between the three groups

Cognitive function and test	1 Controls (n = 48)		Change raw score within controls		2 Intact MS (n = 26)		Change raw score within intact MS		3 Impaired MS (n = 19)		Change raw score within impaired MS		p value for difference between groups
PASAT (Gronwall, 1977) (3-s interstimulus)	49.8	(9.0)	2.0	(5.1)[a]	46.0	(10.8)	3.4	(5.6)[b]	33.0	(10.0)	−2.5	(5.8)	.002[1,2≠3]
Information processing and attention													
Trail Making-A (U.S War Department, 1944) (time)	27.3	(7.4)	−.7	(7.5)	30.2	(7.8)	−.2	(7.1)	51.0	(26.2)	−.2	(27.4)	.461
Trail Making-B (U.S War Department, 1944) (time)	61.1	(18.8)	5.8	(17.3)[a]	68.7	(17.5)	4.5	(17.4)	143.4	(126.8)	−17.6	(114.9)	.255
Stroop (Stroop, 1935) (color/word interference—time)	49.1	(11.3)	1.0	(5.2)	55.2	(13.4)	−.4	(9.0)	68.7	(15.8)	−2.1	(7.6)	.501
WAIS-R (Wechsler, 1981)													
Digit Span	15.8	(3.4)	.8	(2.4)[a]	15.0	(2.4)	.2	(2.1)	12.6	(2.6)	.6	(2.2)	.556
Digit Symbol	61.0	(12.2)	1.8	(3.4)[c]	53.4	(10.7)	.9	(5.5)	38.9	(10.8)	1.6	(5.6)	.379
TEA (Robertson et al., 1994)													
Elevator Counting	7.0	(.0)	.0	(.2)	7.0	(.2)	.1	(.3)	6.7	(.7)	.2	(.5)	.246
Elevator Counting with Distraction	7.6	(2.2)	.2	(.6)[a]	7.4	(2.7)	.5	(1.5)[a]	6.0	(3.3)	−.1	(1.2)	.309
Dual Task Performance (Vilkki et al., 1996)													
(larger percentage dual task impairment)	42.5	(10.1)	2.8	(9.7)	44.6	(11.7)	2.7	(16.3)	53.1	(15.5)	5.4	(11.0)	.710
Memory and learning													
WMS-R (Wechsler, 1987)/Logical Memory													
Immediate recall	32.1	(6.3)	1.1	(4.0)	29.3	(8.0)	.8	(4.8)	26.3	(5.8)	.8	(4.0)	.936
Delayed recall	29.7	(6.0)	1.8	(3.3)[b]	26.4	(8.7)	1.3	(4.2)	22.6	(7.3)	2.2	(5.2)	.748
List Learning of 15 Words (Äikiä et al., 1995)													
Total immediate recall	43.5	(7.7)	2.1	(5.6)[a]	41.9	(6.6)	2.0	(5.8)	34.1	(8.5)	.3	(6.8)	.375
Delayed recall	9.8	(2.9)	.7	(1.8)[b]	8.7	(3.6)	.4	(2.6)	6.4	(3.3)	1.0	(2.0)[a]	.826
Delayed recognition	28.2	(1.6)	.3	(1.6)	28.5	(1.8)	.5	(1.6)	26.2	(2.1)	.4	(2.5)	.501
WMS-R (Wechsler, 1987)/Visual Reproduction													
Immediate recall	39.0	(2.4)	.3	(2.6)	29.3	(8.0)	−.9	(3.9)	30.2	(7.1)	−1.4	(4.4)	.136
Delayed recall	36.0	(6.6)	1.4	(5.0)[a]	26.4	(8.7)	2.0	(8.5)	20.3	(13.5)	3.6	(6.7)[a]	.650
Rey Osterrieth Complex Figure Test (Osterrieth, 1944)													
Delayed recall	23.8	(5.3)	1.8	(4.3)[b]	20.9	(5.6)	1.0	(3.7)	12.6	(7.3)	.5	(4.4)	.483
Immediate Recall of 20 Objects													
(Kujala et al., 1994; Portin et al., 1995)	14.1	(1.9)	.4	(1.5)[a]	13.8	(2.1)	1.0	(1.9)[a]	12.1	(3.0)	.8	(2.0)	.369
Delayed Recall of 20 Objects													
(Kujala et al., 1994; Portin et al., 1995)	12.5	(2.3)	.8	(2.2)[a]	12.8	(2.9)	1.5	(1.8)[c]	11.1	(2.6)	1.5	(2.7)[a]	.330

Executive functions												
WCST/Nelson's Modified Version (Nelson, 1976)												
Correct responses	42.0	(4.7)	2.2	(7.0)[a]	40.9	(6.6)	1.8	(3.7)[a]	38.6	(6.4)	1.3	(5.3)	.651
Categories completed	5.8	(1.7)	.2	(2.1)	5.9	(1.7)	.4	(1.1)	5.1	(1.5)	.2	(1.2)	.677
Perseverative responses	.6	(1.3)	.4	(1.6)	.9	(1.1)	.8	(1.1)[b]	2.3	(3.8)	1.0	(2.3)	.181
Semantic Verbal Fluency (animals) (Lezak, 1995)	28.7	(7.1)	1.0	(5.8)	27.2	(6.0)	.9	(5.7)	21.6	(5.4)	−.4	(5.7)	.726
Phonologic Verbal Fluency (s-words) (Lezak, 1995)	21.7	(6.2)	1.2	(4.5)	19.2	(5.7)	2.2	(3.8)[b]	15.1	(6.1)	.8	(4.7)	.503
Visual Fluency (Korkman et al., 1998)	21.2	(5.0)	1.9	(3.5)[c]	18.7	(4.0)	.7	(2.7)	14.1	(3.0)	1.2	(3.5)	.105
Visuospatial functions													
WAIS-R (Wechsler, 1981)													
Block Design	39.2	(7.5)	1.6	(5.8)	37.4	(8.2)	.9	(4.4)	28.3	(7.1)	2.6	(5.7)	.678
Picture Completion	18.9	(1.8)	.6	(1.5)[a]	18.4	(1.8)	.5	(1.4)	16.6	(2.7)	.8	(1.4)[a]	.809
Rey Osterrieth Complex Figure Test (Osterrieth, 1944)													
Copy	34.6	(1.5)	.3	(1.8)	33.8	(2.4)	.2	(3.4)	30.0	(4.1)	−.8	(3.4)	.907
Copying time	96.2	(33.9)	23.8	(31.3)[c]	107.5	(30.5)	1.1	(31.8)	172.2	(52.6)	26.7	(85.8)	.104
Language functions													
Naming time of 20 objects													
(Kujala et al., 1994; Portin et al., 1995)	22.7	(5.2)	2.2	(5.4)[a]	25.9	(11.9)	4.8	(8.1)[b]	36.6	(15.1)	4.2	(11.8)	.405
WAIS-R (Wechsler, 1981)/Similarities	29.2	(2.3)	1.1	(1.9)[c]	28.4	(2.8)	.3	(1.9)	25.5	(3.7)	−.1	(2.7)	.116
Stroop (Stroop, 1935)													
Word reading time	23.2	(3.5)	.7	(2.2)	25.6	(4.2)	−.5	(2.7)	27.8	(4.6)	1.0	(3.4)	.245
Colour naming time	29.0	(6.2)	.4	(2.6)	31.2	(4.4)	−.2	(2.7)	36.4	(7.3)	4.7	(21.6)	.622
Arithmetic functions													
WAIS-R (Wechsler, 1981)/Arithmetic	17.2	(3.9)	.1	(1.9)	16.8	(3.6)	.3	(1.7)	13.0	(4.3)	−.6	(3.1)	.214
Basic calculations (Ministry of Labour, 1969)													
(50 basic additions, subtractions, multiplications, and divisions. Correct responses in four minutes)	40.9	(8.6)	1.2	(3.9)[a]	36.5	(9.6)	.0	(3.9)	31.8	(11.3)	.6	(3.6)	.473
Background variables													
BDI (Beck et al., 1961)	2.8	(5.1)	.0	(2.7)	7.1	(6.1)	−.5	(3.5)	7.8	(4.5)	3.9	(7.6)	.107
15D (Sintonen, 2001)	.97	(.05)	.0	(.02)	.85	(.1)	−.01	(.06)	.79	(.08)	.03	(.07)	.053
Nervousness Questionnaire	8.0	(8.1)	−2.0	(5.7)[a]	13.9	(12.3)	−2.2	(8.1)	10.6	(8.5)	−.1	(9.3)	.746
EDSS (Kurtzke, 1983)	—		—		2.2	(1.3)	.1	(.8)	3.7	(1.6)	−.1	(.9)	.301

Note. PASAT = Paced Auditory Serial Addition Test; WAIS-R = Wechsler Adult Intelligence Scale Revised; TEA = Test of Everyday Attention; WMS-R = Wechsler Memory Scale Revised; WCST = Wisconsin Card Sorting Test; BDI = Beck Depression Inventory; 15D = Self-reported quality of life questionnaire; EDSS = Expanded Disability Status Scale. Sign change done when necessary that all values are in same direction; positive values indicate improvement and negative decline during follow-up. The *p* values are for the comparison of changes from baseline to follow-up between the three groups. In the EDSS, the comparison is of changes from baseline to follow-up between cognitively intact and impaired patients.

[a]Significant change within the group between baseline and the follow-up study at $p < .05$.

[b]Significant change within the group between baseline and the follow-up study at $p < .01$.

[c]Significant change within the group between baseline and the follow-up study at $p < .001$.

Table 3. The number of subjects in the three groups (controls, cognitively intact, and impaired MS patients) whose MSFC-PASAT performance deteriorated, stayed stable, or improved from baseline to follow-up

	Controls (n = 48)	Cognitively intact MS (n = 26)	Cognitively impaired MS (n = 19)
Deteriorated	10 (21%)	3 (12%)	11 (58%)
Stable	14 (29%)	6 (23%)	4 (21%)
Improved	24 (50%)	17 (65%)	4 (21%)

Note. Deteriorated = the number of correct responses on the PASAT decreased from baseline to follow-up more than the mean change on the PASAT in controls between two testing sessions (≥ 2.0); Stable = the number of correct responses on the PASAT remained stable or was less than the mean change on the PASAT in controls between two testing sessions (< 2.0) from baseline to follow-up; Improved = the number of correct responses on the PASAT increased from baseline to follow-up more than the mean change on the PASAT in controls between two testing sessions (≥ 2.0); MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; PASAT = Paced Auditory Serial Addition Test.

detect change in MS patients' cognitive performances, and in our study, we used the 3-s interstimulus version included in the MSFC (Cutter et al., 1999). Every subject participated in both examinations, the baseline and the follow-up study.

Similar to Hohol et al. (1997), we did not find clear cognitive changes among MS patients on a group level during the 1-year follow-up time. All our patients were at a relatively mild stage of the disease, and almost all of them received β-interferon treatment, which may have slowed the progression of cognitive decline. It is generally accepted that, once cognitive dysfunction develops in a patient with MS, it does not remit. However, as pathological changes within the cerebral white matter progress, both neurological and cognitive deficits are likely to emerge and increase. Neuropsychological deficits may remain stable over time (Camp et al., 2005; Hohol et al., 1997; Jennekens-Schinkel et al., 1990; Kujala et al., 1997; Mariani et al., 1991; Piras et al., 2003; Sperling et al., 2001) and are not likely to improve but may progress instead (Amato et al., 1995, 2001; Feinstein et al., 1992; Haase et al., 2004; Kujala et al., 1997; Zivadinov et al., 2001). Part of the discrepancies in the previous studies may be due to the differences in patient samples. If patients with varying amounts of initial cognitive impairment are grouped together, the results may be subdued and mild deterioration may not become evident during a short follow-up time. If one subgroup of patients is more physically and cognitively impaired than another after the same disease duration, it suggests that they have a more severe or more rapidly progressing illness. In clinical trials, for example, the evaluation of the effect of immunomodulatory drugs to cognition may be problematic, if the study groups are heterogeneous and include patients with both intact and impaired cognitive performance. By dividing patients into more homogeneous subgroups, like we did in our study, it is possible to follow separately the evolution of cognitive decline in those patients who may be more susceptible to progressive cognitive deterioration, and those with more benign course. In our study, the patients who were initially more impaired showed also more elevated scores in the depression scale, and there was a statistical trend for a difference compared with the intact MS patient group, although it did not reach full statistical significance. In this case, the depression may have been a subtle marker for initial cognitive decline. The BDI scores tended to improve slightly in the cognitively impaired group during the follow-up, which may have then counteracted the insidious cognitive decline.

When the same or even an alternative form of the same neuropsychological test is repeated, learning often occurs. We noticed that, among healthy controls, most of our neuropsychological tests, but especially the memory tests (maybe in part because of the same versions of the tests were used), were vulnerable to practice effects. When making clinical decisions based on the neuropsychological test results in repeated measurements among patient populations, the knowledge about the normal practice effects in tests should, thus, guide interpretations. Fluctuation in both directions can occur, and when analyzed individually, some controls were found to perform more poorly in second testing in PASAT, but the mean performance improved. The healthy controls tended to perform better at follow-up, and thus showed normal practice effects in several cognitive tests (in 19 tests) compared with the cognitively intact (in 8 tests) and especially with the cognitively impaired (in 4 tests) MS patients. Therefore, although the mean change in neuropsychological tests was not significantly different between the groups (except in one test), a trend was seen where the MS patients were less able to improve their performance. This finding indicates that the patients were either less able to benefit from practice than the healthy controls or that the practice effect in patients was masked by a subtle decline. Our sample sizes were, however, quite small, which reduces the generalization of our results.

The change on the MSFC-PASAT was different during the follow-up time among the three study groups: the cognitively impaired MS patients showed a declining trend and differed from the healthy controls and the cognitively intact patients, who showed improvement. Background variables such as change in mood, subjective quality of life, or nervousness could not explain the change. The change in the EDSS scores had no relationship to the change in the PASAT either. The cognitively impaired patients whose MSFC-PASAT performance showed a declining trend during 1 year reported even lower BDI scores at the follow-up compared with the baseline; the difference, however, was not significant. Additionally, the healthy controls reported significantly more anxiety and nervousness during the second testing session but were still able to improve their PASAT performance. As the observed difference in MSFC-PASAT change cannot be interpreted to be due to confounding factors, it can be suggested that the decline in MSFC-PASAT among impaired patients is due to disease progression.

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