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ORIGINAL COMMUNICATION

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Cognition in the early stage of multiple sclerosis

Abstract *Objective* Cognitive dysfunctions may contribute to limitation of everyday activities of patients with multiple sclerosis (MS). Recent studies have demonstrated that 45 to 65% of MS-patients are cognitively impaired. The profile of MS-related cognitive dysfunctions varies greatly. It includes memory and learning deficits, attention deficits, executive dysfunctions and visuo-spatial deficits. Most studies of cognition in MS examined patients in later stages, often including MS-patients with marked physical disabilities. Studies of cognitive dysfunctions in the early stage of the disease are rare. This study specifically aimed at evaluating and characterizing cognitive impairments in the early stage of MS, and determining specific patterns of cognitive dysfunction. *Methods* 21 MS patients, experiencing their first neurological symptoms not more than two years previously, and 22 healthy controls were compared. A comprehensive neuropsychological test-battery was used to evaluate MS-related cognition. The battery consisted of memory and learning tests, executive functioning tests and a visuo spatial functioning test. A computerized attention test-battery was also included, which assess accuracy and speed of test responses. In addition depression and intellectual capabilities were assessed. *Results* Compared with healthy controls, MS-patients in the early stage of the disease performed significantly lower on each neuropsychological assessment, except for verbal short-term memory. In particular, MS-patients showed a lengthened reaction time for simple and focused attention (19–38%), impaired non-verbal memory function (RVDLT recognition: 33%) and a planning deficit (24%). Associations between information processing speed and disease course and the employment situation were additionally found. However, patients did not have clinically relevant depression rates on the ADS-L and visuo spatial abilities remain preserved. *Conclusion* Our findings revealed discrete cognitive dysfunction in MS-patients within the early stage of the disease.

Key words MS · early stage · cognition · neuropsychological test-battery

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Introduction

MS is a chronic demyelinating, inflammatory and degenerative neurological disease which primarily affects younger people. Although multiple sclerosis is a physically disabling disease, many patients suffer from cognitive changes as well [53]. Recently, cognitive dysfunctions have been increasingly considered to be contributions to social and professional handicaps experienced by patients with MS.

Thirty years ago, cognitive impairment was thought to be present in only approximately 3% of MS-patients [39]. More recent studies estimated the frequency of cognitive dysfunction in MS throughout their lifetimes between 43 and 72% [12, 21, 30, 38,

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41, 46, 54, 60, 62]. Severe dementia in accordance with the criteria of the ICD–10 is relatively uncommon and is observed in 20 to 30% of cognitively impaired MS-patients, mainly in the final stages of the disease [54]. MS-related cognitive dysfunctions were traditionally described as heterogeneous in nature. However, the available studies suggest a more specific pattern of MS-related cognitive dysfunctions: The cognitive domains most commonly impaired are memory and learning, attention, executive functions, and visuo spatial abilities [51, 57]. By contrast, intellectual functions and language skills remain preserved throughout the course of the disease [52].

Memory may be broken down into several aspects. MS-related memory dysfunctions most typically affect long-term and working memory, while short-term memory is often unimpaired. Deficient performance in learning and long-term memory tasks was found in MS-patients and delayed recall was particularly affected [25, 27, 56]. The nature of the MS-related memory impairments is a topic of debate in the literature. Some studies suggest that MS-related memory dysfunctions result primarily from impaired retrieval from long-term memory, whereas encoding and storage capacity seems to remain intact [56]. By contrast, a recent study claimed that contextual encoding deficits form the core of the MS-related memory dysfunctions [63].

Deficient attention and reduced speed of information processing have also been observed in MS-patients [10, 11, 18, 19, 20, 26, 43, 47]. Comparing samples of MS-patients and healthy controls, those studies show significantly prolonged simple and choice reaction times, as well as visual information processing speeds in MS-patients. Furthermore, the results indicate deficient focused, divided and – to a smaller extent - sustained attention.

Executive functions, such as abstract reasoning, verbal fluency, planning or problem solving capabilities, have been shown to be frequently reduced in MS-patients. Various executive function measures were affected, including temporal ordering, semantic encoding, the Tower of Hanoi problem, Wisconsin Card Sorting Test (WCST), Strategy Application Test (SAT) and word fluency tasks [5, 6, 8, 13, 24, 32, 50].

Many studies suggest an influence of the course of the disease on cognitive performance: MS patients suffering from progressive MS-subtypes (primarily (PP) and secondary progressive (SP) MS) performed significantly worse on neuropsychological tests than patients suffering from relapsing remitting (RR) MS [15, 16, 39, 52]. A recent study pointed out that different courses of the disease are associated with different cognitive profiles [33]. It was shown that chronic progressive MS-patients were more likely than RRMS-patients to suffer from attention deficits, in particular reduced speed of information processing, executive dysfunctions, verbal intelligence and abstraction deficits, whereas RRMS-patients, in comparison with healthy controls, showed more memory dysfunctions [33, 66].

Recent diagnosis criteria from McDonald et al. [40] include magnetic resonance imaging (MRI), from which a diagnosis can be made before a second relapse takes place. Physical disabilities correlate only weakly with MRI findings, are fluctuating over time, and are weakly correlated with the cognitive status of MS-patients [3]. Changes in brain structure, such as total lesion area (TLA), lesion distribution and MRI measures of brain atrophy are more substantially correlated with cognitive dysfunctions [2, 6, 15, 16, 17, 23, 28, 43, 55, 64, 68]. Recent investigations showed irreversible axonal losses and cerebral atrophy in MS-patients in the earliest stages of the disease, when no or only mild signs of physical disabilities can be observed [22, 35, 62, 68]. These findings suggest that cognitive dysfunction could appear in the earliest stages of the disease as the first symptoms of MS. Thus, neuropsychological assessment of MS-patients during the earliest stages of the disease may be of particular importance for the identification of early MS [3, 4, 7, 47].

Most studies on MS-related cognitive dysfunctions were conducted during later disease stages, and most focused on groups of MS-patients which differed greatly with respect to disease duration and other clinical features. They often used brief test batteries [1] which cannot replace comprehensive neuropsychological assessment: for example, they do not sufficiently examine executive functions or use attention tests such as the Paced Auditory Serial Addition Test (PASAT), which is confounded by mathematically ability variations and working memory performance and is sometimes not well accepted by patients.

The present study aimed at investigating patterns of cognitive decline in MS-patients in the early stage of the disease. Hence a large test battery was used to analyze all major areas of cognitive functioning often affected in MS-patients, including tests with demonstrated reliability and validity. In particular, a large battery of attention tests was used to assess differences in attention patterns such as intensity and selectivity of attention and also accuracy and speed of test responses. To the best of our knowledge, such a thorough series of tests has never previously been carried out on patients in the early stages of the disease. Finally, a comprehensive approach to the assessment of cognitive dysfunctions related to early MS is provided.

Subjects and Methods

Twenty-one MS-patients were compared with twenty-two healthy participants. There were no significant differences between the groups on age ($t(41)=0.89$; $p=0.380$), gender ratio ($\chi^2(42, 0.05)=0.01$; $p=0.916$), education level ($\chi^2(42, 0.05)=3.93$; $p=0.140$), or handedness ($\chi^2(42, 0.05)=0.32$; $p=0.574$). Table 1 summarizes demographic and clinical data of the two participant groups.

Major exclusion criteria were current alcohol or substance abuse, history of head injury, or any other medical condition affecting cognition. Furthermore, participants were excluded if they had severe motor or visual impairments that might interfere with cognitive testing. The sample comprised MS-patients with definite MS according to Poser's criteria [49]. None of the patients included in the current study had experienced a clinical exacerbation at the time of the assessment. The ages of the MS-patients ranged from 20 to 56 years (M=37.00 ± 10.15 years); they were predominantly right-handed women. The disease course was relapsing-remitting in 76% of the patients (RRMS) and chronic-progressive in the remaining 24% of patients (PPMS or SPMS). Only patients with less than 24 months disease duration were included. The mean disease duration was 15 months (± 5.6) and ranged from 4–24 months. All patients were fully ambulatory and were only mildly disabled on the Expanded Disability Status Scale (EDSS [36]) (Mdn=2.0, range 1.0–7.0). The MS-patients rarely described a reduction in visual acuity (5 %), difficulty in swallowing (5 %) or bladder problems (5 %). Loss of sensitivity such as numbness and tingling sensation was experienced by 18 % of patients, cerebellar dysfunctions in the form of loss of balance by 23 % and 33 % of patients described pyramidal dysfunctions such as weakness and immobility of limbs. 33 % of patients described pains in the limbs and head and 36 % complained of fatigue. 18 % of the MS-patients described no clinical symptoms. At the time of the assessment, most MS-patients were taking disease modifying treatments: 48 % were treated with interferon-ß and 24 % with glatiramer acetate, 23 % were taking pain relief medication, 5 % used bladder control medication, 5 % took muscle relaxants, 5 % took medication to reduce high blood pressure and 5 % used asthma control medication.

Table 1 Demographic and clinical measures

		Patients	Controls
Sample	(n)	21	22
Gender (n,%)	male	7 (33%)	7 (32%)
	female	14 (67%)	15 (68%)
Age (years)	mean (± SD)	37.0 (± 10.2)	34.1 (± 11.6)
Education (n,%)	≤ 10 years	18 (86%)	13 (59%)
	10–13 years	1 (5%)	3 (14%)
	> 13 years	2 (10%)	6 (27%)
Employment (n,%)	fully employed	6 (29%)	22 (100%)
	part-time	4 (19%)	0
	unemployed	11 (52%)	0
Handedness (n,%)	right	20 (95%)	20 (91%)
	left	1 (5%)	2 (9%)
IQ (WST)	mean (± SD)	95 (± 10.9)	102 (± 7.5)
Disease duration (months)	mean (± SD)	15.1 (± 5.6)	-
Disease course* (n,%)	RRMS	16 (76%)	-
	SPMS	3 (14%)	-
	PPMS	2 (10%)	-
EDSS - score	Mdn (range)	2.0 (1.0– 7.0)	-

*relapsing remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS)

A comprehensive neuropsychological battery of tests was used to assess the cognitive performance of MS-patients and healthy participants. All participants gave informed consent prior to inclusion in the study. The present study was conducted in accordance with the Helsinki declaration.

Neuropsychological assessment

The neuropsychological test-battery was administered in two parts. The first part included attention and working memory tasks compiled in a computerized attention test battery (TAP [67]). The second part consisted of a verbal learning and memory test (VLMT [31]) and the Rey Visual Design Learning Test (RVDLT [59]). Furthermore, measures of short-term memory from the Wechsler Memory Scale (WMS-R [65]) and measures of executive functions, such as the Modified Card Sorting Test (MCST [44]) and a test for visual problem solving abilities (SLP [42]) were included. In addition, a vocabulary recognition test was used to assess the premorbid IQ (WST [61]) and the Rey-Osterrieth-Figure (ROC-Figure [59]) was applied to assess visuo spatial performance. Finally, subjects completed a handedness questionnaire (Edinburgh Handedness Inventory [45]) and depression questionnaire (ADS-L [29]), because depression may affect cognitive functions. ADS-L was used on account of low interferences between MS-specific and depressive symptoms measured by ADS-L. The serial order of the two parts was counterbalanced across participants and within each group of participants. However, the sequence of tests within each part was kept constant, with easier tests being presented before more difficult tests.

The following paragraphs provide brief descriptions of the tests:

TAP

Five subtests of the computerized attention test battery (TAP) were used:

Alertness

This test recorded participant reaction speeds to the display of a visual stimulus (a cross appearing on a monitor), which was sometimes prefixed by a warning sound. Reaction times were used as a measure of general tonic alertness, and the difference between median reaction times for stimuli with and without a warning sound was used as a measure of phasic alertness. Tonic alertness provides a reliable measure of processing speed [67]. Stimuli were presented in an ABBA pattern (A= visual stimulus; B= visual stimulus with warning sound). For those stimuli presented with a warning sound, the interval between warning sound and the relevant visual stimulus was random. 20 visual stimuli were presented to participants per block.

Go/no-go

On a monitor participants were shown squares with five possible fill-patterns and were asked to react on every occasion that they were shown one of the two fill-patterns pre-defined as relevant. In the test participants were each shown 50 squares, of which 20 were relevant.

Flexibility

Flexibility examines the ability to shift the focus of attention between two sets of targets during a choice response task. Participants were requested to alternate between selecting letters and numbers as they appeared on a monitor. Two competing stimuli

(one letter and one number) were simultaneously presented on either side of a focus point, with the key to select the letter/number located on the corresponding side of the keypad. With each display of the two stimuli the target selection alternated between letters and numbers. The program showed each participant 100 stimuli.

Divided attention

This was tested through a dual task, in which participants had to simultaneously observe the presentation of two stimuli. The optical task required recognition of a square which was composed from accumulating crosses on the monitor. The audio task required the recognition of a break in the pattern of an alternating high and low-pitched tone. 100 visual stimuli and 200 audible stimuli were presented to participants.

Working memory

This test required continuous control of information flows through the short-term memory, as participants had to compare the number shown on the monitor with the last but one shown number. On presentation of a relevant stimulus, participants were asked to press a key on the keypad. The program showed 100 numbers, of which 15 constituted a relevant stimulus.

VLMT

Participants were asked to learn a list of 15 words through 5 consecutive learning trials (repeated displays of the wordlist). Interference effects were determined by then presenting participants with a distraction list of semantically and phonetically similar words before asking the participant to repeat the original list. The long-term stability of learned information was assessed by asking participants to both freely recall words from the list, and recognition from a longer list which also included distraction words.

RVDLT

The RVDLT is a measure that assesses immediate memory span, new learning, and recognition memory. As a non-verbal memory test it consists of 15 simple geometric forms, which were presented during five learning trials. Subjects were required to draw all geometric forms that they could recall, and in a second stage, they had to identify the 15 geometric forms from an array of 30 forms.

WMS-R

Digit span and block span are subtests of the WMS-R that require the forwards or backwards repetition of series of random numbers (digit span) or tapped cubes (block span) and were used to assess short term memory capacity.

MCST

This test assesses executive functions, in particular the ability to shift cognitive sets in response to changing circumstances. The MCST requires strategic planning, organized searching, utilization of environmental feedback, direction of behavior towards achieving a goal, and impulsive modulation response. The task requires the subject to sort cards by three properties – color, number and form, according to a rule that one particular organizing principle is correct. After six consecutively correct responses, the rule is changed. Percent of perseverative errors were computed.

SLP

The SLP assesses visuo-constructive capabilities. In this typical transformation problem, participants have to assemble twenty-seven small cubes to form a single large cube with a uniform outside color appearance, with each smaller cube having one possible role in the large cube. The examiner mainly rates the planning of the problem-solving strategy and the capacity to monitor the appropriateness of ones actions.

ROC-Figure

Participants were required to copy a complex two-dimensional figure, and then reproduce this from memory after an interval of 30 minutes. This exercise tested figural memory.

Data evaluation and analysis

The test battery was administered in a single session that lasted around 120 minutes. Individual performance on each of the tests was evaluated against standardized data. Test scores that fell below two standard deviations of the normative sample (Percentage range < 2.3, T-norm scores < 30) were considered to reflect impaired performance. Statistical analyses were calculated with the Statistical Package for the Social Sciences (SPSS 11.0, [14]). MS-patients and healthy participants were compared by using t-tests or Mann-Whitney U-tests for independent samples. Pearson's χ^2-tests were used to compare the observed and expected frequencies of preserved and pathological cognitive performances within the two groups (cross-over-tables). Furthermore, the test-material (verbal vs. visual), time, and group (MS vs. healthy controls) effect on memory test performance was tested by computing multivariate analysis of variance (MANOVA). Influence of verbal intelligence on neuropsychological test-performance was corrected by means of covariance analysis. Correlations between cognitive parameters and clinical parameters were calculated by means of rank correlations (Spearman) or product-moment correlations (Pearson). Multiple correlations were corrected by using the Bonferroni-method. Finally, cluster analysis served to subdivide patients according to cognitive performance (Ward method). A significance level of $\alpha = .05$ was predetermined.

Results

Mean scores of MS-patients and healthy controls in neuropsychological tests are presented in Table 2.

Attention

The reaction time differed between MS-patients and healthy controls in all subtests of the TAP (Table 2). MS-patients were generally slower than healthy controls and showed significantly weaker performances, defined as individual performance < 2 SDs or more below the mean of the calibra-

tion sample. Thirty-three percent of the MS-patients failed in Tonic alertness (χ^2 = (42, 0.05) = 6.44, p = 0.004**), 38 % in Phasic alertness (χ^2=(1,N=43)=5.06, p = 0.001**), 24% in Go/nogo (χ^2 = (42, 0.05) = 13.65, p = 0.021*), 19% in Flexibility (χ^2 = (42, 0.05) = 7.31, p = 0.048*) and 10% in Divided attention. Both groups tended to commit equal numbers of false and missed reactions in the attention subtests of the TAP (Go/nogo/number of false reactions: U-test, Z=−0.81, p=0.417; Flexibility/ number of false reactions: U-test, Z=−0.44, p=0.657; Divided attention/ number of missed reactions: U-Test, Z=−1.66, p=0.098). Overall, the results obtained from the TAP battery suggest that MS-patients can be characterized by a reduced speed of information processing.

The sample of MS-patients was subdivided into two subgroups by a cluster analysis. One subgroup performed normally on all attention tasks, whereas the other subgroup showed a generally reduced speed of information processing in all attention subtests. The patients in the latter subgroup were less likely to be employed (χ^2 (20, 0.05) = 11.38, p = 0.01*): 73% (N = 8) of the disabled subgroup were unemployed. In addition, 91% (N = 10) MS-patients from the subgroup with normal attention performance had a relapsing remitting course (χ^2 (20, 0.05) = 7.90, p = 0.048*).

Memory

Visual, but not verbal, short-term memory performance of the MS-patients fell below that of the healthy controls (Table 2). Significant group differences were also found in working memory (Table 2). Twelve percent of MS-patients showed significantly weaker performances in this test in contrast to 5% of healthy controls. Furthermore, the two groups differed similarly with respect to measures of verbal and non-verbal learning and memory (Table 2). The first multivariate analysis showed large variations between-group (F (1, 41) = 18.48, p = 0.000**) and an effect to the disadvantage of visual test-material (F (1, 41) = 129.20, p = 0.000**). Non-verbal memory performances were more strongly affected in MS-patients than verbal memory performances. The second multivariate analysis showed in addition a time effect to the disadvantage of delayed memory performances (F (1, 41) = 45.10, p = 0.000**) and interaction effects between time and group (F (1, 41) = 26.93, p = 0.000**) as well as, material and group (F (1, 41) = 7.16, p = 0.011*). Thus, MS-patients performed less well than healthy controls predominantly in visual memory and after a delay of 30 minutes (time effect). Thirty-three percent of the MS-patients showed evidence of significantly weaker visual recognition performance than healthy controls (χ^2 = (42, 0.05) = 6.48, p=0.011*). This result suggests that visual memory might be particularly affected in a subgroup of 33% of MS-patients.

Executive functions

MS-patients made more perseverative errors in the MCST (Table 2) than healthy controls. The performance on the SLP-test revealed that MS-patients are disturbed in their visuo-constructive problem-solving capabilities (Table 2). Twenty-four percent of the MS-patients showed evidence of impaired visuo-constructive problem-solving capabilities (χ^2 = (42, 0.05)=3.84, p=0.050*). This result suggests that these performances might be particularly affected in this subgroup of MS-patients.

Depressive mood

Depression scores obtained from the ADS-L-questionnaire (U-test: Z=−1.77, p=0.077) did not differ between groups (Table 2). Two MS-patients showed evidence of clinical depression in their scores. Thus, the neuropsychological performance of the MS-patients cannot be attributed to elevated levels of depression.

Intellectual ability

In order to estimate pre-morbid intellectual abilities performance on a recognition vocabulary test [62] was used. Although the MS-patients recognized fewer words than the healthy controls (Table 2), none of the MS-patients showed evidence of exceptionally poor word recognition abilities. By means of covariance analysis the influence of verbal intellectual abilities on neuropsychological test-performance was calculated. The analyses showed significant covariance between verbal intelligence and verbal memory (F (1, 40)=7.57, p=0.009**), verbal intelligence and performance on MCST (number of perseverative errors) (F (1, 40)=10.24, p=0.003**) as well as verbal intelligence and visuo-constructive problem-solving strategies (SLP) (F (1, 39)=7.19, p=0.011*). Between the remaining test indices and verbal intelligence no significant covariances were ascertained. Even allowing for verbal intellectual abilities by computing a covariance analysis, significant group differences remained in verbal memory (F (1, 40)=7.53, p=0.009**) and visuo-constructive problem-solving strategies (SLP) (F (1, 39)=9.50, p=0.004**).

Table 2 Testscores of MS-patients and healthy controls in the neuropsychological tests

Neuropsychological tests	MS-patients	Healthy controls	*p*
Attention (TAP)			
Tonic alertness	329.4 (± 153.5)	231.4 (± 30.8)	0.005**
Phasic alertness	309.1 (± 115.8)	221.6 (± 28.0)	0.002**
Go/ nogo	574.4 (± 149.6)	481.3 (± 60.6)	0.013*
Flexibility	1007.8 (± 576.1)	682.0 (± 171.4)	0.027*
Divided attention	719.6 (± 108.0)	649.9 (± 79.4)	0.013*
Working memory	606.0 (± 142.2)	511.7 (± 130.2)	0.030*
Immediate memory (WMS-R)			
Digit span (forward)	7.4 (± 1.4)	8.1 (± 1.6)	0.153
Digit span (backward)	6.9 (± 1.3)	7.9 (± 2.4)	0.232
Block span (forward)	7.5 (± 1.6)	9.6 (± 2.4)	0.003**
Block span (backward)	7.9 (± 1.9)	9.3 (± 1.9)	0.019*
Verbal learning and memory			
VLMT (learning score)	56.7 (± 8.1)	64.1 (± 7.1)	0.002**
VLMT (delayed recall)	11.1 (± 3.0)	14.1 (± 1.2)	0.000**
VLMT (loss after delay)	1.9 (± 1.8)	0.4 (± 0.8)	0.004**
VLMT (recognition)	12.6 (± 4.6)	14.9 (± 0.3)	0.001**
Visual learning and memory			
RVDLT (learning score)	37.3 (± 12.6)	52.2 (± 10.0)	0.000**
RVDLT (recognition)	12.8 (± 2.1)	14.5 (± 0.7)	0.001**
Executive functions			
MCST (perseverative errors)[1]	1.0 (0–8)	0.0 (0–2)	0.009**
SLP	15.8 (± 6.6)	24.2 (± 4.0)	0.000**
Intelligence			
WST	95 (± 10.9)	102 (± 7.5)	0.001**
Visuo spatial performance			
ROC-Figure	35 (± 7.2)	36 (± 0.9)	0.021*
Depression			
ADS-L	13.2 (± 6.9)	9.7 (± 7.8)	0.077

*p < 0.05, **p < 0.01, values are means ± SDs, MS indicates multiple sclerosis, [1]median and range

Visuo spatial ability

The visuo spatial abilities were tested using the Rey-Osterrieth-Complex Figure (ROC-Figure; [60]). Compared with healthy controls the MS-patients achieved significantly lower test-scores (Table 2) but the results were not classified below two standard deviations.

Table 3 shows the significant by Bonferoni corrected correlations between the clinical and cognitive parameters. Attention performance, visual memory and executive function as assessed by the SLP-test were correlated with length of illness and with severity of disability (EDSS) (Table 3). MS-patients with longer disease durations and higher EDSS-scores showed markedly reduced speed of information processing, poorer visual memory and more impaired visuo-constructive problem-solving than MS-patients with shorter disease durations and lower EDSS-scores. Between disease course and neuropsychological test performances significant associations were found. Patients suffering from RRMS were less frequently disabled in measures of attention (cluster analysis), working memory (χ^2 (16, 0.05) =12.32, p=0.006**) and visual memory (χ^2 (20, 0.05) =9.74, p=0.021*) than patients suffering from the progressive subtypes of the disease (PPMS and SPMS). Furthermore, disease duration was significantly associated with physical disability (EDSS) (r=.45; p=0.038*).

Discussion

Neuropsychological assessment reveals cognitive impairments of MS-patients in the early stage of their disease. Previous neuropsychological studies of MS-patients assessed cognition in more advanced stages of the disease. The results obtained here reveal discrete cognitive dysfunctions in the earliest stages of MS. The pattern of deficits in the earliest stages corresponds to the pattern that is usually obtained from MS-patients in more advanced stages of the disease. Between 10 and 38% of the MS-patients displayed significantly lengthened reaction times and deficient attention. Reduced speed of information processing may be a fundamental neuropsychological deficit in the earliest stages of the disease. Furthermore, disturbed visual memory performances were observed in 33% of the MS-patients and impaired executive functions in 24% of the MS-patients. The results are comparable with a recent study from Fischer et al. [25], who described various patterns of cognitive dysfunction in patients with MS. Nearly 33% were cognitively unimpaired, 25% showed information processing and visuo spatial deficits, 10 to 15% showed memory deficits, 10 to 15% showed dysexecutive functions, 10 to 15% showed reduced speed, memory and visuo spatial deficits and 2% showed a global cognitive decline. Achiron and Barak [1] distinguished three subgroups of patients with probable MS: 6% which performed normally in all tests, about 54% which failed in one or two tests and 40% which failed in three or more tests. In this study, 14% of the MS-patients had scores below two standard deviations in one or two neuropsychological tests, and 29% of the MS-patients showed impaired performance in more than two neuropsychological tests. Fifty-seven percent of the MS-patients did not reach test-scores below two standard deviations.

Several studies [3, 9] have found only weak relationships between cognitive impairments and disease duration or physical disability. In this study, disease durations and disability scores correlated with cognitive performance in only 5 neuropsychological test scores. As was also found in a recent study investigating differences of cognitive profiles in different disease courses [33], the progressive subtypes of the disease (PPMS and SPMS) seem to be associated with poorer attention, in particular reduced speed of information processing. In addition, RRMS-patients

Table 3 Correlations between clinical parameters and cognitive performance

Neuropsychological tests	Disease duration r	EDSS r
Attention (TAP)		
Tonic alertness	.48 p=0.036 *	.50 p=0.036 *
Phasic Alertness	.56 p=0.000**	.57 p=0.000**
Go/ nogo	.49 p=0.036 *	.41 p=0.216 ns
Learning and memory		
RVDLT (recognition)	−.63 p=0.000**	−.60 p=0.000**
Executive function		
SLP	−.58 p=0.000**	−.63 p=0.000**

ns not significant, *p<0.05, **p<0.01, Bonferroni corrected correlation coefficiences

showed less frequently working memory and visual memory deficits than MS-patients suffering from the progressive subtypes of the disease (PPMS and SPMS). Previous studies have been shown that cognitively impaired MS-patients have a higher risk of unemployment and are partially prone to social withdrawal [58]. Corresponding to this, MS-patients showing attention impairments were less likely to be employed than MS-patients without these impairment, and the severity of cognitive dysfunctions seemed to be related to the employment situation of the MS-patients. Sixty-seven percent of the cognitively unimpaired MS-patients were still employed whereas 73% of the cognitively impaired MS-patients were unemployed. One might either propose that the cognitive deficits appearing in MS-patients from the outset of the disease force patients to withdraw from employment, or that maintaining an occupation had positive effects on the mental agility of patients.

It is now recognized that axonal injury due to inflammation and neurodegenerative processes already occur in the earliest stages of MS [22, 62, 68]. Thus, neuropsychological assessment should routinely be accomplished in the earliest stages of the disease even if neurological impairment is minimal and brain imaging does not reveal extensive lesions. Any neuropsychological test battery for MS should best assess attention through measures of reaction speed, learning, memory (in particular visual memory), and executive functioning like visuo-constructive problem-solving strategies.

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