Eur Arch Psychiatry Clin Neurosci (2005) 255 : 319–326 DOI 10.1007/s00406-005-0565-y

ORIGINAL PAPER

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Attention and memory dysfunctions in mild multiple sclerosis

Received: 12 August 2004 / Accepted: 3 November 2004 / Published online: 7 January 2005

Abstract This study investigated the relationship between clinical symptoms and cognitive dysfunction in multiple sclerosis. Cognitive dysfunction and visual evoked potentials (VEPs) were studied in patients free of physical disability and mildly to moderately disabled patients with multiple sclerosis (MS). Disability-free patients (EDSS ≤ 1.5; n = 13), mildly to moderately disabled patients (EDSS ranging from 2 to 6; n = 13) and a healthy matched control group (n = 16) were examined with respect to attention, verbal and nonverbal memory and early visual processing (VEPs). Disability-free patients showed mild impairments on phasic alertness and divided attention. Deficits were more pronounced in mildly to moderately disabled patients who were additionally impaired with respect to non-verbal memory. Despite adequate visual acuity, one half of all patients showed abnormal VEP latencies for both eyes at the same time. The findings suggest that cognitive deficits are already present in multiple sclerosis even in the absence of physical disability. Even with normal visual acuity, perceptual impairments should be considered as part of the CNS affection.

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Key words multiple sclerosis · visual evoked potentials · cognitive dysfunction

Introduction

It is well known that multiple sclerosis is associated with a range of cognitive impairments [4, 13, 14, 40]. About half of all patients develop deficits in attention, memory and executive functioning [43]. The relationship between severity of MS status, assessed by physical disability, and cognitive dysfunction is, however, still unclear. Most studies investigated heterogeneous patient groups with physical disability scores ranging from 0 to 8 according to the Expanded Disability Status Scale [37]. The few studies that were concerned with cognitive changes in disability-free (EDSS ≤ 2) patients with minimal neurological signs reported impairments in learning and memory [35, 41], and it has been argued that cognitive changes may occur in mild stages of disease even before physical symptoms become evident. A recent study [46] evaluated cognitive performance of relapsing-remitting MS patients with EDSS ≤ 3.5 and found impairments in memory and abstract reasoning. A problem with interpretation is that test performance in highly disabled patients might be reduced as a result of motor dysfunction rather than cognitive changes. In a recent study, we reported deficits of visuo-constructive functions and short-term visual recognition memory in early multiple sclerosis in the absence of physical disability [30]. Further evidence suggests that psychiatric symptoms such as depression may be present in disability free stages of multiple sclerosis [18], due to changes in brain function rather than to reactive, psychological processes as a result of their physical impairment. Cognitive impairment was also present in patients with clinically isolated lesions like optic neuritis, brain stem and spinal cord lesions [7, 20]. Evidence for early cognitive changes in the absence of physical impairment is of great clinical importance because it may suggest the need of an early immune modulation and neuroprotective intervention.

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Visual evoked potentials are often used as a sensitive tool for diagnosis and assessment of the course of multiple sclerosis and the detection of subclinical lesions [23, 38]. Prolongation of VEP P100 latency indicates focal demyelination of the optic nerve [15]. Only a few studies have aimed at investigating the relation between test performance in neuropsychological tasks and VEP measurements, and the results are inconsistent [47, 49].

The aim of the present study was to further investigate the pattern of cognitive changes in early multiple sclerosis and its relation to the degree of motor impairment. Attention and memory, being major cognitive functions affecting everyday life and being frequently reported to be affected in more advanced multiple sclerosis, were studied in relapse-free multiple sclerosis patients with minimal neurological symptoms. In addition, the association of cognitive deficits with changes in visual evoked potentials (VEPs), which are frequently reported as indicators of central nervous system dysfunction in multiple sclerosis, was also investigated. We compared patients free of physical disability (EDSS ≤1.5) and mildly to moderately disabled patients (EDSS > 1.5; max: 6) with a matched healthy control group.

Materials and methods

Subjects

We investigated patients suffering from multiple sclerosis (n = 26) and one healthy control group (n = 16). One patient group (MS(–), n = 13) included patients free of physical disability (EDSS ≤1.5), the second patient group (MS(+), n = 13) included patients with mild to moderate physical disability (EDSS ranging from 2–6), five patients had an EDSS score of 4.0 and greater. All participants were female and right-handed. Patients were recruited within a six month period from the MS outpatient department of the University Hospital, Essen, Germany. In case they met the inclusion criteria (see below), patients were asked to participate in this study during their routine visit to the hospital. Demographic data and clinical variables are presented in Table 1. Subjects gave verbal consent prior to their inclusion in the study.

The study was approved by the Ethics Committee of the University of Essen.

Patients had clinically definite multiple sclerosis as defined by the Poser criteria [42]. The EDSS score had to be below 6.5 so that patients were moderately disabled and still able to walk. Patients had to be relapse-free for at least four weeks and no patient was on corticosteroids or on psychoactive drugs at the time of testing. Five patients in the MS(–) group and eight patients in the MS(+) group were treated with immunomodulating medication including interferon-beta, azathioprine and glatiramer acetate. Two MS(–) patients and five MS(+) patients were treated with interferon-beta. No patient showed signs of intoxication or adverse side effects from immunomodulating therapy. Each patient underwent a comprehensive neurological examination including VEP investigation to ensure sufficient motor and to investigate sensory abilities necessary to complete the neuropsychological assessment. All patients had normal visual acuity. VEPs were measured according to the standard technique described in detail elsewhere [10]. VEPs were assessed monocularly for whole-field and foveal presentation with a reversing checkboard pattern. Whole field triggers were provoked by checkboard screen with a visual angle exceeding 12 grades. Foveal stimulation was performed using a maximum visual angle of 3 grades. The latter has increased sensitivity in early less advanced MS, despite increased standard deviations of latencies [16]. For each subject, VEP latencies were assessed for the left and the right eye. The latency was determined as the time elapsed from stimulus onset until peak amplitude. Values that exceeded 111 ms for whole field VEP latencies and 121 ms for foveal VEP latencies were considered abnormal according to normal values determined in our laboratory.

Healthy controls were selected from a larger subject database of the Institute of Cognitive Neuroscience to match the patients on age and IQ. For general cognitive assessment, subjects completed a short version of the German Wechsler Adult Intelligence Scale (WIP) [11] including the subtests General Knowledge, Similarities and Picture Completion. Because of its high motor demand, the subtest Block Design was excluded from WIP. The three groups did not differ significantly with respect to IQ (Table 1).

Cognitive assessment

Attention

The Test Battery for Attention (TAP) [50] is a German computerized test battery designed to tap different aspects of attention. We used the subtests "alertness", "Go/Nogo" and "divided attention" to assess differences in attention performance.

"Phasic alertness" represents the ability to increase response readiness in anticipation of a stimulus. In the subtest "alertness" a stimulus (cross) is presented to the subject on a screen. In the first condition the subject has to respond as fast as possible to the stimulus by pressing a button with the dominant hand. In the second condition a warning tone is presented prior to the stimulus (phasic alertness). The subtest "Go/Nogo" is a response inhibition task. In this subtest, five different stimuli (visual patterns) are presented to the subject in random order. The subject's task is to respond to two target stimuli as accurately and as fast as possible while ignoring the three non-target stimuli (response inhibition). The subtask "divided attention" requires the ability to divide one's attention between two sensory modalities. In this task visual-spatial and auditory stimuli are presented simultaneously. In the visuo-spatial task, subjects have to detect crosses, which form a square in a visual pattern. In the auditory task, tones of two different pitches are presented. Subjects have to respond as accurately and fast as possible when they hear the same tone in a row. Both tasks have to be performed simultaneously. In all three tasks, the number of correct responses as well as reaction times (RTs) was recorded.

The subtests "elevator counting" (sustained attention) and "elevator counting with distraction" (selective attention) which are part of the "Test of Everyday Attention" (TEA) [44] were used to assess everyday attention functioning. In both tasks tone sequences are presented to the subject. The subject has to imagine an elevator with the tones symbolizing floors. In the "elevator counting" task, subjects have to

Table 1 Means (SD) of demographic data, clinical variables and intellectual functioning for MS(–) group, MS(+) group and healthy controls (HC)

	MS(–)	MS(+)	HC
n	13	13	16
Age	36.23 (7.51)	38.77 (5.1)	35.56 (7.48)
General IQ	105.62 (8.24)	101.56 (6.68)	106.01 (6.75)
Duration of disease	9.65 (2.85)	11.39 (4.58)	–
EDSS mean	0.69 (0.60)	3.42 (1.47)	–
VEP latencies			–
whole field right	116.38 (17.58)	119.63 (25.26)	–
n	13	8	
whole field left	118.77 (17.69)	114.78 (25.90)	–
n	13	9	
foveal right	126.92 (15.88)	132.88 (21.52)	–
n	12	8	
foveal left	128.77 (18.76)	128.00 (15.69)	–
n	13	8	

count the tones. In the "elevator counting with distraction" task, subjects have to count the low tones while ignoring the high ones. In both tasks, the number of correct trials served as the test score.

Memory

Performance of verbal learning was assessed using a German version of the California Verbal Learning Tests (CVLT) [32]. In this test, a 16-item word list (Monday list) is read to the subject five times. The word list consists of 4 categories with 4 items each. The subject's task is to recall as many items as possible after each presentation. An interference list (Tuesday list) with 16 items from four different categories is then presented. Again the subject has to reproduce as many words as possible. This is followed by free and cued recall of the first list. After a 20-minute delay, the subject again has to recall the first list, followed by cued recall and a recognition test. The number of correctly reproduced items of each trial (trials 1–5, interference list, short delay free and cued recall, long delay free and cued recall and recognition) was analyzed.

To investigate nonverbal memory performance, the subtest "faces" of the "Recognition Memory Test" (RMT) [48] was administered. In the study phase, 50 faces of men are presented to the subject one after another. The subject has to rate each picture as pleasant or not. Immediately after the presentation, each target face is presented together with a distractor in a pair. The subject has to indicate the face seen in the study phase. The number of correctly recognized faces was analyzed.

The "Recurring Figures Test" [34] is a visual recognition test. 120 cards with geometric and irregular nonsense figures are presented to the subject. Some figures are presented only once, some figures recur. During the presentation, the subject has to indicate the figures that recur. Three different scores were calculated: the difference of correctly recognized figures and false alarms was calculated for geometric (NETGEOM) and nonsense figures (NETNONS) separately. Overall performance (NET) was defined as the sum of NETGEOM and NETNONS.

Procedure

Each subject completed one testing session. The same order of tests was used for each subject.

Data analysis

Statistical analysis was performed using SPSS version 10. Group differences were evaluated by ANOVA or nonparametric Kruskal-Wallis-H, where appropriate. If significant group differences were found, pairwise comparisons were performed (Tukey or Mann-Whitney U Test, respectively). For analysis of MS specific data (EDSS, duration of disease and VEPs), Mann-Whitney U was appropriate. Correlations were computed bivariately (nonparametric Spearman-Rho). Significance level was $p < 0.05$.

Results

Attention

Test Battery for Attention

The means and standard deviations (SDs) for alertness, response inhibition and divided attention are presented in Table 2. With respect to "alertness", ANOVA revealed significant differences in overall RT (simple and forewarned RTs) [$F_{2,37} = 3.525$, $p = 0.04$]. MS(+) patients had significantly longer RTs compared to healthy controls ($p = 0.032$). When simple and forewarned RTs were analyzed separately, group comparisons also revealed significant differences [$H_{df=2} = 6.618$, $p = 0.037$ and $H_{df=2} = 11.765$, $p = 0.003$, respectively]. MS(+) patients responded more slowly than healthy controls in both conditions [$U = -2.419$, $p = 0.016$ and $U = -3.179$, $p = 0.001$, respectively]. MS(–) subjects had significantly longer RTs compared to healthy controls in the forewarned condition [$U = -1.959$, $p = 0.05$].

The three groups did not differ on measures of response inhibition, neither for accuracy [$H_{df=2} = 2.125$, $p = 0.346$] nor for RTs [$F_{2,39} = 2.801$, $p = 0.073$].

They did, however, differ significantly on accuracy in "divided attention" [$H_{df=2} = 11.116$, $p = 0.004$]. Both of the patients groups made more errors compared to healthy controls [$U = -2.887$, $p = 0.003$ and $U = -2.437$, $p = 0.014$, respectively]. RT analysis did not yield significant group differences [$H_{df=2} = 4.690$, $p = 0.096$].

Table 2 Means of medians (SDs) for MS(–) group, MS(+) group and healthy controls (HC) in the attention subtests of the "Test Battery for Attention" (TAP) and "Test for Everyday Attention" (TEA). RTs in ms

Test	MS(–)	MS(+)	HC	p-value
TAP				
Alertness RTs				
all	254.6 (72.5)	279.3 (67.4)	219.1 (30.84)	0.037[a]
not anticipated	235.2 (65.5)	276.2 (75.1)	222.0 (26.7)	0.037[a]
anticipated	267.0 (124.4)	280.7 (64.3)	220.3 (34.34)	0.003[a, b]
Go/Nogo RTs				
correct	23.6 (0.7)	22.5 (3.5)	23.4 (1.0)	0.346
reaction time	538.2 (75.4)	585.5 (136.7)	505.1 (45.7)	0.073
Divided attention RTs				
correct	29.7 (1.2)	24.6 (8.4)	31.1 (1.6)	0.004[a, b]
reaction time	688.3 (63.5)	787.0 (274.5)	648.0 (79.9)	0.096
TEA				
Elevator counting (no. correct)	6.9 (0.6)	6.8 (0.4)	6.9 (0.3)	0.366
Elevator counting with distraction (no. correct)	8.5 (2.5)	8.7 (1.7)	9.5 (0.9)	0.196

P-values: ANOVA group comparisons; significant ($p < 0.05$) post-hoc tests: [a] MS(+) vs. HC; [b] MS(–) vs. HC

Everyday attention

The means and SDs for the subtasks "elevator counting" and "elevator counting with distraction" as part of the "Test of Everyday Attention" (TEA) are presented in Table 2. Nonparametric group comparisons did not yield significant differences [$H_{df=2} = 2.008$, $p = 0.366$ and $H_{df=2} = 3.264$, $p = 0.196$, respectively].

After Bonferroni correction for multiple comparisons only group differences with respect to forewarned RTs and correct responses in the divided attention task remained significant ($p < 0.005$).

Memory

Verbal memory performance of the three groups is presented in Table 3. ANOVAs did not yield any significant group effects or interactions (all $p > 0.05$).

Mean scores and SDs for face recognition were 41.23 (SD = 4.68) for the MS(–) group, 38.85 (SD = 6.31) for the MS(+) group and 43.44 (SD = 3.48) for the healthy controls. ANOVA indicated a tendency towards significance [$F_{2,39} = 3.202$, $p = 0.052$], with a lower score for the MS(+) group compared to the HC group ($p = 0.040$).

Performances in the "Recurring Figures Test" are presented in Table 3. The three groups differed with respect to NETGEOM and NET; [$F_{2,39} = 4.602$, $p = 0.016$] and [$F_{2,39} = 3.559$, $p = 0.038$], respectively. Post hoc comparisons yielded significant differences between the MS(+) and HC group for both scores (both $p < 0.05$)

After Bonferroni correction for multiple comparisons, group differences failed to reach significance (all $p > 0.005$).

Table 3 Means (SDs) of correctly remembered for MS(–) group, MS(+) group and healthy controls (HC) for the "California Verbal Learning Test" (CVLT) and the "Recurring Figures Test" (RFT)

	MS(–)	MS(+)	HC	p-value
CVLT				
Monday list	15.38 (0.77)	14.23 (2.55)	14.75 (1.61)	0.567
Tuesday list	7.23 (1.96)	7.15 (2.12)	7.69 (1.85)	0.73
Short delay				
free recall	13.15 (2.12)	12.31 (3.20)	13.44 (2.66)	0.521
cued recall	14.00 (1.63)	13.15 (3.08)	13.75 (2.72)	0.689
Long delay				
free recall	13.46 (1.85)	13.00 (3.34)	13.87 (2.58)	0.584
cued recall	13.77 (1.83)	13.31 (3.64)	14.13 (2.68)	0.742
recognition	15.15 (1.46)	15.77 (0.60)	15.31 (1.08)	0.27
RFT				
NETGEOM	14.46 (3.13)	10.69 (5.28)	15.31 (4.11)	0.016[a]
NETNONS	4.23 (5.43)	2.00 (8.02)	6.37 (5.21)	0.187
NET	18.69 (7.30)	12.69 (11.84)	21.69 (7.80)	0.038[a]

P-values: ANOVA group comparisons; significant ($p < 0.05$) post-hoc tests: [a] MS(+) vs. HC

VEP measurements

Means and SDs of VEP latencies for right and left eye (whole-field and foveal) are presented in Table 1. All MS(–) patients completed the VEP measurement. Only nine MS(+) patients agreed to the VEP examination, one MS(+) patient did not complete the measurements for the right eye. For group comparisons and correlations, right and left eye measurements were summed.

Concerning whole-field VEPs, 46% (6/13) of MS(–) patients had abnormal right and 54% (7/13) had abnormal left eye latencies. In the MS(+) group, 50% (4/8) of patients had abnormal right and 44% (4/9) had abnormal left eye latencies. 46% of MS(–) and 50% of MS(+) patients had abnormal whole-field latencies in both eyes. For foveal VEPs, 50% of MS(–) and 38% of MS(+) patients had abnormal latencies in both eyes.

For further analysis, latencies for both eyes were added together in order to achieve an overall VEP score. There were no significant differences between the two patient groups concerning whole-field VEP latencies [$U = -0.109$, $p = 0.913$] or foveal VEP latencies [$U = -0.339$, $p = 0.735$].

Correlations of clinical variables with cognitive performance

Relationships between clinical variables and cognitive performance were evaluated by means of correlation analysis (see Fig. 1). We found a significant correlation between RTs in response inhibition and disease duration ($r = 0.52$; $p = 0.007$). No further significant correlations emerged between cognitive variables and disease duration. In addition, significant correlations were observed between performance on cognitive tests and EDDS score. EDSS score correlated significantly with overall and forewarned RTs in the "alertness" task ($r = 0.44$, $p = 0.025$ and $r = 0.46$, $p = 0.018$) and response inhibition RTs ($r = 0.37$; $p = 0.045$).

Correlations of VEP measurements and cognitive performance

Relationships between VEP measurements and cognitive performance were evaluated by means of correlation analysis (see Fig. 2). A number of significant ($p < 0.05$) correlations emerged between VEP data and cognitive test performance with correlation coefficients within the 0.45–0.50 range. Foveal latency correlated significantly with reaction time in the alertness task (overall, $r = 0.53$; simple, $r = 0.49$; forewarned, $r = 0.50$) and with the number of items reproduced after long delay in the CVLT ($r = -0.49$). Whole field latency correlated significantly with reaction time in the alertness task (simple, $r = 0.45$) and in the Go/Nogo task ($r = 0.46$) as well as with RMT score ($r = -0.45$) and TEA (with distraction, $r = -0.49$). The remaining correlation analysis failed to reach significance.

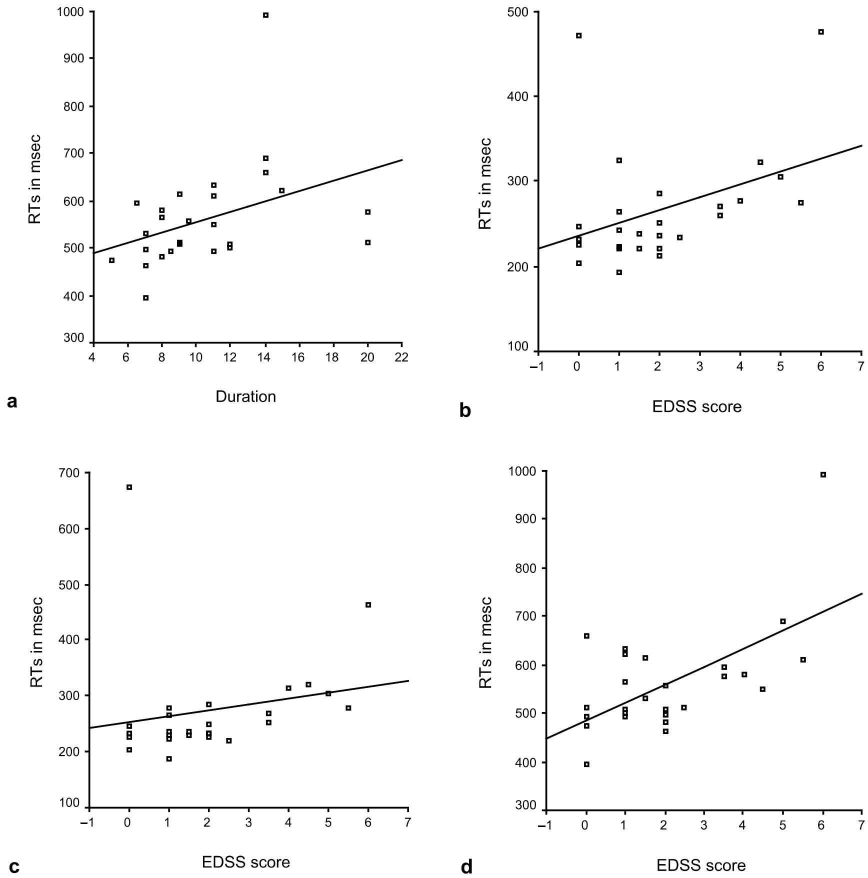

Fig. 1 Scattergram of correlation of **a** disease duration with RTs in the Go/Nogo task; **b** EDSS score with overall RTs in the alertness task; **c** EDSS score with forewarned RTs in the alertness task; **d** EDSS score with RTs in the Go/Nogo task

Concerning correlations between VEP measurements and EDSS score or duration of disease, we found a significant correlation between disease duration and whole field VEP latencies ($r = 0.56$, $p = 0.008$). The remaining correlations did not reach significance ($p > 0.20$).

No correlation was found between RFT and latencies of VEP.

Discussion

The present study aimed to investigate cognitive deficits in mild multiple sclerosis with minimal and moderate physical disability. Another aim was to explore the relationship between clinical signs as well as symptoms, VEP parameters (latencies) and cognitive dysfunctions in multiple sclerosis. We previously reported cognitive deficits in patients free of physical disability in the visual domains [30]. Even though it has been suggested that disability status assessed by EDSS may be no strong predictor for cognitive decline and may rather reflect spinal cord involvement [9], there is still a lack of consensus concerning the relationship between severity of MS and cognitive deterioration [25, 45]. The main aim of this study was to investigate patients free of physical disability with relapsing-remitting course of multiple sclerosis [27], in order to assess cognitive dysfunctions in the early clinical course of the disease, even before major physical symptoms are evident. In addition, low physical disability also reduces the contamination of cognitive test results by motor demands.

Taken together, the present study supports the conclusions of our previous study [30]. We found changes in information processing and attention, which is commonly observed in MS patients (see [6] for a review). Disability free multiple sclerosis patients showed impairments of response preparation in an alertness task and with respect to dividing attentional responses. Impairment was evident with respect to both reaction time and accuracy. Impairments were generally more severe in mildly to moderately disabled patients who showed deficits on a range of attention tests and on nonverbal memory including the Recurring Figures Test, which has been suggested to be sensitive to right temporal lobe lesions [34]. In the patient groups, cognitive dysfunction tended to correlate with both, disease duration and degree of physical symptoms. Only reaction time in the inhibition task correlated with disease duration. Correlations indicate that the attentional tasks where motor responses are required may have been already affected by clinically insignificant physical disability.

Experimental neurophysiological studies revealed a neuromodulating effect of interferon-beta on neuronal activity and excitability [31]. However, recent studies in healthy subjects suggested that interferon-beta adminis-

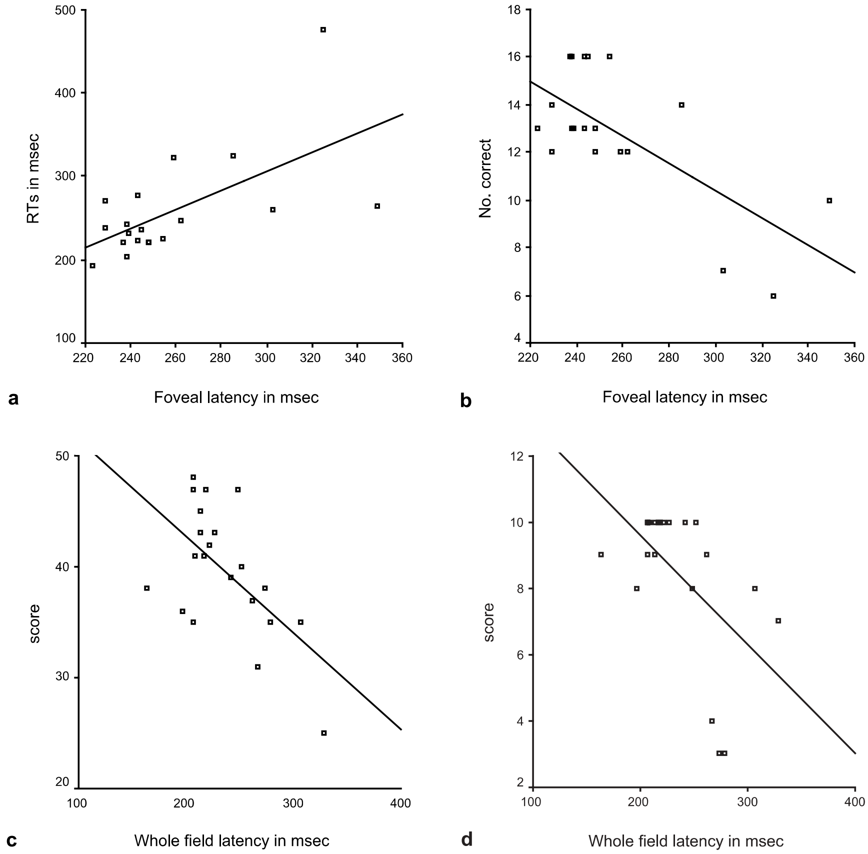

Fig. 2 Scattergram of correlation of VEP **a** foveal latencies with overall RTs in the alertness task; **b** foveal latencies with number of correctly recalled items in the California Verbal Learning Tests; **c** whole-field latencies with Recognition Memory Tests score; **d** whole-field latencies with Test of Everyday Attention (with distraction) score

tration does not have an influence on cognition following acute administration [17]. Clinical studies investigating the influence of interferon-beta on cognitive functioning found better performance in MS patients after treatment including information processing, memory, visual-spatial performance, problem solving and concentration [5, 22].

The relationship between physical disability and cognitive dysfunction is still unclear and the influence of motor impairment should be considered, particularly in cognitive tasks that involve motor responses. On the other hand, we also found impairments in reaction time with respect to response preparation and accuracy deficits in the divided attention task in the disability-free MS group with an EDSS score less than 2, suggesting independence of cognitive deficits from motor impairment. Especially in the alertness task where the emphasis exclusively lies on reaction time, deficits in performance might be attributed to motor impairment even in the MS group with clinically insignificant physical disability. This assumption is stressed by significant correlations of reaction times in the attentional tasks and EDSS score. Reduced accuracy in the divided attention task, however, cannot be explained solely by motor impairment which in turn is stressed by absent correlation of reaction times and physical disability. This might be interpreted in terms of beginning cognitive impairment in mild multiple sclerosis.

Furthermore, moderately disabled patients with EDSS less than 6 also showed impairments in visual memory tests, which cannot be explained in terms of physical disability but might be attributed to changes in the right hemisphere. Memory is the most frequently impaired cognitive function in MS patients, and it has been argued that deficits can be attributed to impairment in free recall rather than to impaired recognition (see [43] for a review). In the present study MS patients performed poorly in the RFT which is based on the recognition of pictures but they were not impaired in the verbal memory test, which requires the free recall of words. This result points out the special benefit of the RFT in the detection of early changes in visual memory.

Our results are in general agreement with previous studies addressing cognitive deficits in early multiple sclerosis [46]. In longitudinal studies [1, 24, 35, 41, 51], cognitive impairment was found in the early phase of the disease, with an increasing number of impaired patients with disease progression [2, 3, 28]. Furthermore, even in the early phase, cognitive decline was an independent predictor of impairment in everyday life [2, 3]. These results together with the results of the present study point out the importance of early neuropsychological examination.

The nature of cognitive changes in multiple sclerosis is an issue that is still controversially discussed. Suggested mechanisms are focal and total white matter lesions or changes in the normal appearing white and grey matter, which may occur early in the disease [8, 12, 26, 33, 39]. Widespread axonal damage and metabolic changes in the normal appearing white and grey matter have been found in the earliest clinical stage of multiple sclerosis with an EDSS ≤ 2 [12, 21] and ≤ 3 [8]. Especially cognitive changes in early and disability free multiple sclerosis may be attributable to changes other than macroscopic lesions. One mechanism which has been recently suggested is the activation of proinflammatory cytokines, influencing cell-to-cell communication and thus affecting higher brain functioning [19, 36]. This hypothesis clearly requires further empirical support, but may also have to be considered within the context of the discussion for early neuroprotective intervention [29].

In the present study, we assessed foveal and whole-field VEPs in the multiple sclerosis patients in addition to cognitive measures. Even though visual acuity assessed by neurological examination was considered adequate, one half of all patients in both groups showed abnormal prolongation of VEP latencies for both eyes at the same time. Prolongation of VEP latency indicates focal demyelination of the optic nerve. In accordance with one previous study [49], we found a number of correlations between VEP measurements and performance in visual as well as in non-visual neuropsychological tests. Correlations between VEP measurements and results in attention tasks with visual stimuli as well as in non-verbal memory suggest a deficit in early visual information processing which may result in decline of neuropsychological test performance. The correlation between VEP measurements and verbal memory performance or performance in auditory attention test, on the one hand, cannot be explained by means of slowness in early visual information processing, but rather in terms of a general slowness in information processing, reflected by abnormalities in neurophysiological assessment. These results raise the question of a relation between cognitive deficits and perceptual dysfunction in multiple sclerosis. Preliminary findings in this regard found significant correlations between VEP measurements and other MS pathology-related measurements like EDSS score and whole brain atrophy as well as cognitive variables [49]. Another study addressed the relationship between abnormal visual evoked potentials and deficits on visuo-perceptual tasks, but failed to find a relationship because of small sample size [47]. However, they suggested that the deficit, which underlies visuo-perceptual impairment, might be a slowness of visual information processing. Further investigation is needed to examine this relation more closely.

There are limitations to this study. First, the number of subjects is fairly small. In addition, MRI data of the multiple sclerosis patients were not available. As we found more cognitive impairments in the MS group with higher EDSS score, MRI scans would have been useful to indicate the contribution of cerebral lesions to cognitive performance.

Taken together, our results suggest that potential cognitive dysfunction in multiple sclerosis patients without physical disability should be considered.

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