Zeitschrift für Neuropsychologie, 26 (3), 2015, 171 – 178

Original Article

Perceived and Objective Attentional Deficits in Multiple Sclerosis

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Abstract: Initially we assessed self-rated cognitive deficits, depression and quality of life in MS patients and healthy controls (n = 299) by an online survey. Secondly, attention performance of MS outpatients (n = 33) was objectively assessed by the Test battery for Attention Performance and the Symbol Digit Modalities Test. Overall, MS patients rated themselves significantly worse than controls in attentional functioning. This was reflected by a weak performance in objective tests of phasic alertness and divided attention of the MS patients compared to normative data. Subscales of subjective cognitive functioning in the online survey showed significant associations with objective measures after statistical controlling for depression (r = .370 to r = .517). Results show the differences in perceived cognitive performance between MS patients and healthy controls, and self-reported instrument are able to provide relevant information on complex attention performance and hereby on everyday functioning.

Keywords: multiple sclerosis, attention, cognition, processing speed, neuropsychological assessment, self-reported outcomes, quality of life

Wahrgenommene und objektive Aufmerksamkeitsdefizite bei Multiple Sklerose

Zusammenfassung: In einer Onlineumfrage wurden wahrgenommene kognitive Beeinträchtigungen, Depression und Lebensqualität bei MS Patienten und gesunden Kontrollpersonen (n = 299) erhoben. In einem zweiten Schritt wurde die objektive Aufmerksamkeitsleistung in einer Klinikkohorte mit MS Patienten (n = 33) mit der Testbatterie zur Aufmerksamkeitsprüfung (TAP) sowie dem Symbol Digit and Modalities Test (SDMT) erhoben. MS Patienten bewerteten ihre Aufmerksamkeitsleistungen signifikant schlechter als Gesunde. Die Klinikkohorte zeigte schlechtere Leistungen in den objektiven Tests (phasische Alertness und geteilte Aufmerksamkeit) verglichen mit Normwerten. Subjektive Tests korrelierten signifikant mit objektiven Tests nachdem für Depression kontrolliert wurde (r = .370 bis r = .517). MS Patienten unterscheiden sich von Gesunden in der Wahrnehmung ihrer kognitiven Leistungsfähigkeit und Fragebögen bilden wichtige zusätzliche Informationen zum kognitiven Erleben und Funktionieren und somit zum täglichen Leben der MS Patienten ab.

Schlüsselwörter: Multiple Sklerose, Aufmerksamkeit, Kognition, Informationsverarbeitung, Informationsverarbeitungsgeschwindigkeit, neuropsychologische Begutachtung, Fragebögen/Selbstreporte, Lebensqualtität

Introduction

Multiple Sclerosis (MS) is the most common inflammatory and neurodegenerative disease of the central nervous system among young adults. In addition to an impairment of sensory and motor skills, it causes a substantial decline of neuropsychiatric functions. This results in cognitive deficits, fatigue, depression and anxiety (Feinstein, DeLuca, Baune, Filippi & Lassman, 2013).

The occurrence of cognitive impairment in early and more advanced stages of the disease is prevalent in up to 70 % of all MS patients (Chiaravalloti & DeLuca, 2008; Peyser et al., 1990). Affected domains include information processing speed, attention, working memory and declarative memory, as well as executive functioning (Chiaravalloti & DeLuca, 2008). This has serious implications for social functioning and employment (Patti et al., 2011).

Reduced processing speed has often been described as a key component of cognitive impairment in MS (Archi-

bald & Fisk, 2000; DeLuca, Chelune, Tulsky, Lengenfelder & Chiaravalloti, 2004). However, deficits in domains of higher complexity such as selective and divided attention might even be more relevant for everyday functioning. Furthermore, attention can be seen as a crucial neuropsychological domain that is required for other higher order cognitive processes such as learning and memory, information processing, executive functioning as well as communication and interaction. We therefore assume that attention may represent a fundamental cognitive aspect in MS patients.

Indeed, several studies have suggested that attention deficits may be one of the first cognitive aspects affected in MS and may contribute to the occurrence of impairments in other domains later on. In one of the first studies, Kujala, Portin, Revonsuo, and Ruutiainen (1994) compared MS patients without global cognitive impairment to healthy controls (HCs) in a domain referred to as "automatic processing", which requires effortless recognition of simple visual stimuli, merely an attention paradigm. On the other hand, working-memory-dependent "controlled processing" was not diminished. In patients with mild cognitive impairment, both, automatic and controlled processing was affected. Schulz, Kopp, Kunkel und Faiss (2006) studied MS patients with short disease duration (< 2 years) and reported deficits in alertness, selective and divided attention as well as mental flexibility when compared to HCs. However, to date, little is known about domain specific attention abilities and their relation to overall cognitive decline or their impact on patients' self-perception of cognitive function.

Self-reported cognitive deficits – as measured e. g. with the MS Neuropsychological Screening Questionnaire (MSNQ; Benedict et al., 2003) or using the Perceived Deficits Questionnaire (PDQ; Christodoulou et al., 2005) – and objective testing as obtained by trained neuropsychiatrists via a neuropsychological test battery seem to correlate to some extent. However, reported correlations between self-ratings and objective neuropsychological tests are often only modest. Several studies have indicated that self-reported cognitive complaints may be more closely associated with depressive symptoms than with cognitive status (Benedict et al., 2004; Benedict et al., 2003; Bruce & Arnett, 2004; O'Brien et al., 2007).

The current study aims to better characterize perceived and objective attention deficits in MS. We were interested in a) comparing self-perceived attention functioning in MS patients to healthy individuals and b) in correlating self-reported attention functioning to objective attention measures. In addition, we assessed the impact of attention complaints on health-related quality of life (HRQoL).

Materials and methods

We here report results from two studies. Both studies enrolled participants between the age of 18 and 69. Study 1 was an online study, where self-perceived attention deficits, cognitive functioning, depression and quality of life from MS patients and HCs were obtained likewise. For this purpose the following self-report parameters were administered: Scale for the Evaluation of Attention Deficits (SEA; Volz-Sidiropoulou et al., 2007), Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ; Benedict et al., 2003), the depression subscale of the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), and psychosocial and cognitive subscales (fatigue, thinking, mood, communication) of the Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS; Gold et al., 2001; Schäffler et al., 2013).

In study 2, a sample of consecutive MS patients was recruited from our MS outpatient centre in Hamburg. These patients completed all self-report measures mentioned above and in addition underwent objective neuropsychological testing using the Test Battery for Attention Performance (TAP; Zimmermann & Fimm, 1992; 2002) as well as the Symbol Digit Modalities Test (SDMT; Smith, 1995).

Informed consent was obtained and the work was approved by the local Ethics Committee of the Hamburg Chamber of Physicians (PVN 3745).

Subjects

Study 1

For the online study, patients were recruited by advertisements published on the website of the German Multiple Sclerosis Self-help Society (DMSG) and through the quarterly e-newsletter of our MS outpatient centre. Healthy participants were recruited from a pre-existing pool of volunteers.

A specified link was provided to connect directly to the online questionnaires. "Cookies" permitted multiple logins by the same participant. MS patients and HCs gave their informed consent online prior to participation. We used the well-established software EFS Survey® as a utility tool for implementation of electronic surveys, provided by the University of Hamburg.

Study 2

Here, MS patients were recruited consecutively from our out-patient clinic in Hamburg. All patients were diagnosed according to revised diagnostic criteria (Polman et al., 2011). Patients were excluded if they experienced an acute relapse within the last month, had an Expanded Disability Status Scale (EDSS) > 6.5, or showed evidence for severe cognitive impairment (Symbol Digit and Modalities Test (SDMT), oral version < -3.0 SD). MS patients were assessed in a single test session, which took approximately 1.5 hours. After neuropsychological assessment all patients completed the above-mentioned online survey (see below for details). To evaluate test-retest reliability, 30 out of 33

patients completed the online questionnaires again after four weeks.

Neuropsychological self report measures

To assess self-perceived deficits in attention, the Scale for the Evaluation of Attention Deficits (SEA) was applied. This scale was originally developed and validated to examine perceived attention deficits in heterogeneous patient groups with neurological diseases including multiple sclerosis, Parkinson's disease, ischaemic/haemorrhagic infarction, cranial injury, and brain tumors. The SEA covers a wide spectrum of attention deficits and has been analyzed and structured by Rasch modeling (Volz-Sidiropoulou et al., 2007).

Items ask participants to rate their perceived level of attention deficits in context of their daily lives (e.g. *I can concentrate only for a short time*; *I have to read a newspaper article several times to pick up the content).* The questionnaire consists of 36 items and uses a 5-point-Likert answer format.

To assess self-perception of overall cognitive performance, we also applied the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ), a 15-item self-report instrument. It assesses perceived cognitive problems in relation to their frequency and severity. Benedict et al. (2003) showed that the MSNQ is a reliable instrument which distinguishes between cognitively impaired and preserved patients. However, these authors also found, that the MSNQ correlates with depressive symptoms more strongly than with objective cognitive performance (Benedict et al., 2004).

Self-report measures of depression and quality of life (QoL)

We assessed depressive symptoms using the Hospital Anxiety and Depression Scale (HADS). This short self-report questionnaire consists of 14 (0–3 Likert scale) items evaluating anxiety (7 items) and depression (7 items). The published cut-off for the HADS depression score (HADS > 8) suits as a screening tool for major depression (90% sensitivity, 87% specificity) in patients with MS (Honarmand & Feinstein, 2009). In our study, we applied the 7-item subscale for depression.

Health-related quality of life was assessed using the Hamburg Quality of Life Questionnaire for MS (HAQUAMS). The HAQUAMS consists of 5 subscales (fatigue/thinking, mobility of upper and lower limbs, communication and mood). Items are scored on a scale between 1 and 5. Lower scores on the HAQUAMS indicate better quality of life. The HAQUAMS has previously been shown to be reliable and valid in MS and remains robust in patients with cognitive impairment (Gold, Schulz, Monch, Schulz & Heesen, 2003). In the current study, we only used the subscales fatigue, thinking, mood, and communication.

Neuropsychological measures

Two objective measures of cognitive function were administered in the outpatient cohort: The Symbol Digit Modalities Test (SDMT) and the Test Battery for Attentional Performance (TAP).

The SDMT assesses information processing speed and working memory while requiring directed visual-shifting and pairing of specific digits with a set of pre-specified symbols within 90s. Because of its short and easy assessment application, the SDMT has become a standard neuropsychological screening measure in MS (Sheridan et al., 2006).

The Test Battery for Attention Performance (TAP) is a computerized tool and was developed to measure different attention domains: e.g. alertness, divided attention, and selective attention. The TAP is a well-established battery to assess attention in neurological disorders and has previously been shown to be sensitive to cognitive impairment in MS (Heesen et al., 2010; Ruet, Deloire, Charrè-Morin, Hamel & Brochet, 2013; Weinges-Evers et al., 2010). In our study, we used the sub-tests 'alertness', 'divided attention' and 'Go/NoGo'. The subtest alertness is a simple reaction test that consists of a series of timed responses to a visual stimulus without cues (tonic alertness) and with cues (phasic alertness). The Go/No-go test assesses selective attention, as well as determining the choice reaction time under conditions of stimulus selection. Divided attention is a "dual-task" paradigm, and assesses the ability for simultaneous visual and auditory discrimination. Performance in the TAP subtests was measured as reaction time in milliseconds meaning that higher scores indicate poorer performance.

Statistical analysis

Normality of data distribution for all variables of interest was evaluated using the Kolmogorov–Smirnov test. In addition, we examined homogeneity of variance with Levene's test. Two-group comparisons (i.e. MS patients vs. healthy controls) were performed with t-test and in case of controlling for a variable with analyses of covariance (ANCOVAs). For categorical data (e.g. sex), Fisher's exact test was calculated. Correlative associations were assessed using the Pearson's coefficients. All analyses were carried out using SPSS version 15.0. All tests were performed two-tailed and the alpha level was set at $p \leq .05$.

Table 1
Sociodemographic and clinical data of pwMS and HCs (study 1)

	MS patients n = 162	HCs n = 137	p
Age	40.04 (9.35)	38.55 (10.46)	.201
Sex	106 female (65 %)	81 female (59 %)	.282
	56 male (35 %)	56 male (41 %)	
Years of education	12.00 years (1.50)	12.27 years (1.37)	.104
Depression (HADS) (160/136)	5.71 (4.07)	3.05 (2.31)	< **.001**
Disease course	RRMS n = 110 (69 %)	N/A	
	SPMS n = 32 (20 %)		
	PPMS n = 6 (4 %)		
	Unknown n = 12 (7 %)		
Disease duration (n = 159)	7.13 years (6.20)	N/A	

Data as mean with standard deviation (SD) or percentages in brackets as indicated. HADS = The hospital depression and anxiety scale.

Results

Study 1

A total of 596 individuals registered on the website to access the online questionnaires and 484 of them completed the survey. We included n = 331 MS patients (i. e. participants who indicated that they had a neurologist-confirmed diagnosis) and n = 153 healthy controls without any self-reported neurological or other chronic diseases. One-hundred and fifty-three participants (HCs and MS patients) were excluded due to self-reported comorbid psychiatric disease, such as major depression, borderline personality disorder or psychotic episodes in the past. Five other participants were excluded because they were outside the predefined age range (above 69 years, n = 4 or younger than 18 years, n = 1). Twenty-seven MS patients were excluded (blind to survey results) in order to achieve sample comparability regarding age, sex, and level of education. No incentive for participation was provided in this study. Patients and HCs did not differ in age, years of education and sex (see table 1). As expected, depression scores were significantly higher in the MS group, 37 of 160 MS patients (23 %) and 5 of 136 (3 %) HCs had a depression score above the published cut-off for clinical depression

Perception of attention and neuropsychological impairment in MS patients and HCs

MS patients and HCs differed significantly in their self-reported attention and neuropsychological functioning even after statistical controlling for depression (SEA and MSNQ $p < .001$). Disease duration as well as disease course were not correlated to the perception of cognitive deficits on SEA and MSNQ. Already at the early disease stage, i. e. disease duration ≤ 5 years (n = 70), MS patients rated their cognitive function significantly worse than controls (SEA and MSNQ $p < .001$).

Correlations between neuropsychological self-reports and MS specific quality of life measures

All four quality of life subscales of the HAQUAMS showed moderate to strong correlations with SEA and MSNQ, with the subscales fatigue and thinking revealing the strongest associations (see table 2). After statistically controlling for depression (measured by HADS subscale depression), the significant associations between SEA and MSNQ and the mood subscale were lost and the correlation to the communication subscale substantially reduced. However, controlling for depression did not change the associations between SEA, MSNQ, and the other two HAQUAMS subscales fatigue and thinking.

Study 2

Thirty-three MS patients were included. Mean age was 43.0 years (SD 9.42), and mean disease duration was 7.91 years (SD 6.15). The sample included 9 males and 24 females and all MS disease types (RRMS n = 28, SPMS n = 4, PPMS n = 1). Mean HADS depression score was low (4.45, SD 4.14). However, seven patients (23 %) showed a score above the cut-off for clinically meaningful depression. We found no significant correlations between HADS depression and any objective neuropsychological measures (r between .01 and .13). Thirty MS patients participated

Table 2
Correlations between HAQUAMS subscales with SEA and MSNQ (n = 160, study 1)

(n = 160)	HAQUAMS Fatigue	HAQUAMS Thinking	HAQUAMS Communication	HAQUAMS Mood
SEA	**.699*****	**.786*****	**.445*****	**.373*****
	(.621*****)**	**(.733*******)**	**(.271******)**	(.046)
MSNQ	**.621*****	**.790*****	**.433*****	**.370*****
	(.529*****)**	**(.741*******)**	**(.280*******)**	(.074)

Notes. Partial correlations controlling for depression as measured by the HADS in brackets.
*** $p < .001$, ** $p < .01$, MSNQ – Multiple Sclerosis Neuropsychological Screening Questionnaire, SEA – Scale for perceived attention deficits, HAQUAMS – Hamburg Quality of Life Questionnaire for MS.

Table 3
Correlation coefficients between SEA, MSNQ and objective measures in the MS group (n = 33, study 2)

	TAP tonic alertness	TAP phasic alertness	TAP selective attention	TAP divided attention auditive	TAP divided attention visual	SDMT
SEA	.281	.253	.223	.323	.199	**-.428***
	(.381***)**	(.325)	(.344)	**(.410*****)**	**(.354*****)**	**(-.541******)**
MSNQ	.311	.291	.215	.285	.178	**-.376***
	(.458****)**	**(.405*****)**	**(.372*****)**	**(.394*****)**	**(.370*****)**	**(-.517******)**

Notes. Partial correlations controlling for depression as measured by the HADS in brackets.
* - $p < .05$, ** - $p < .02$, TAP = Test for Attention Performance, MSNQ – Multiple Sclerosis Neuropsychological Screening Questionnaire, SEA – Scale for perceived attention deficits, SDMT = Symbol Digit and Modalities Test.

in the retest and filled in the online questionnaire again after four weeks (range 27 to 50 days). Three MS patients were excluded because of delayed retest date (> 50 days). The test-retest-reliability (Pearson's correlation coefficient) was high for both questionnaires (SEA: $r = .930$, $p < .001$; MSNQ: $r = .933$, $p < .001$).

Neuropsychological assessment of attention

To examine whether hand motor impairment influences the results of the computerized attention examination, we calculated correlations between the 9-Hole-peg-Test (9-HPT) and all sub-test results of the TAP. No significant correlations between the dominant hand and any of the TAP subtests were found. In comparison to normative data, MS patients performed worse on the dimensions phasic alertness and divided attention, but not on tonic alertness, SDMT, and selective attention (data as mean T-value and standard deviation in brackets): TAP tonic alertness, mean-T = 42 (9); TAP phasic alertness, mean-T = 40 (8); TAP selective attention, mean-T = 46 (11); TAP divided attention visual, mean-T = 49 (11); TAP divided attention auditory, mean-T = 39 (10); SDMT mean-T = 51 (1).

Correlations between self-reported neuropsychological functioning and objective measures

In the clinical cohort, MSNQ and SEA were highly correlated ($r = .906$, $p < .001$), and both showed significant correlations with HADS depression scores (MSNQ: $r = .678$, $p = < .001$, SEA: $r = .603$, $p < .001$).

Only the SDMT but not the TAP subtests showed modest significant correlations with SEA and MSNQ. After statistically controlling for depression (HADS), MSNQ correlated positively with all cognitive outcome measures (alertness, selective and divided attention) and negatively with SDMT indicating consistency between objective and subjective measures. Similarly, correlations between SEA and the objective tests increased after controlling for depression, reaching statistical significance for TAP tonic alertness, divided attention and SDMT (see Table 3).

Table 4
Correlations between HAQUAMS subscales with SEA, MSNQ, TAP and SDMT (n = 33, study 2)

	HAQUAMS Fatigue	HAQUAMS Thinking	HAQUAMS Communication	HAQUAMS Mood
SEA	**.581*****	**.891*****	**.532****	**.602*****
	(.498***)**	**(.826******)**	**(.366****)**	(.247)
MSNQ	**.542*****	**.840*****	**.389****	**.647*****
	(.447***)**	**(.726******)**	(.127)	(.233)
TAP tonic alertness	.321	.305	.171	.028
	(.356*)	**(.421*)**	(.210)	(.098)
TAP phasic alertness	.304	.293	.203	.081
	(.328)	**(.383*)**	(.233)	(.150)
TAP selective attention	**.443****	.244	.147	.018
	(.505***)**	**(.381*)**	(.208)	(.146)
TAP divided attention auditive	**.417***	.315	.122	.015
	(.447*)	**(.408*)**	(.140)	(.034)
TAP divided attention visual	**.359***	.214	.040	-.059
	(.436*)	**(.385*)**	(.114)	(.084)
SDMT	-.285	**-.380***	-.237	-.158
	(-.306)	**(-.491*****)**	(-.242)	(-.274)

Notes. Partial correlations controlling for depression (as measures by the HADS in brackets.
*** p < .001, ** p < .01, * p < .05, TAP = Test for Attention Performance, MSNQ – Multiple Sclerosis Neuropsychological Screening Questionnaire, SEA – Scale for perceived attention deficits, SDMT = Symbol Digit and Modalities Test, HAQUAMS – Hamburg Quality of Life Questionnaire for MS.

Correlations between self-reported neuropsychological functioning, objective measures and MS specific quality of life measures

All quality of life dimensions showed a moderate to strong correlation with SEA and MSNQ, with the subscales fatigue and thinking exhibiting the strongest associations (see table 4). Statistically controlling for depression (HADS) eliminated the association with the mood subscale and substantially reduced the correlation to the communication subscale. However, this had no effect on associations of subscales thinking or fatigue. All cognitive outcome measures correlated with the subscale thinking when depression was adjusted for. Even after this adjustment the subscale fatigue correlated only with tonic alertness.

Discussion

In this trial, we tried to specify perceived and objective impairments in attentional functioning in MS. Overall, MS patients rated their attention performance worse than HCs.

In line with the results of Benedict et al. (2003), disease duration and disease course did not correlate with self-reported measures of cognition. Even MS patients in early disease stage (< = 5 years) perceived their cognitive and especially attention performance significantly worse than HCs.

In our clinical cohort group (study 2), MS patients scored below normative data on alertness and divided attention, while selective attention and SDMT were not altered. Recently, Ruet et al. (2013) studied cognitive impairment patterns in MS and also included attention measures in his analysis. He could show that MS patients were more frequently and more severely affected in their attention performance than HCs, underlining the relevance of attentional functioning in MS.

It is of importance to recognize that in our cohort no attentional measure correlated with MSNQ or SEA suggesting that especially in the dimension of attention subjective and objective cognitive impairment are only weakly correlated. However, after controlling for depression, SEA and MSNQ correlated significantly with most applied attention measures.

These findings highlight that inconsistencies between self-perceived and objective cognitive performance can in part be explained by depressive mood (Benedict et al., 2004). Secondly, our results illustrate that, despite the lack of a strong association with neuropsychological test results, self-report measures such as the MSNQ may still provide useful additional information regarding the impact of cognitive deficits on patients' lifes. This is also reflected

by the higher correlation of self-reported cognitive function with quality of life compared to correlations with objective measurement by TAP and SDMT.

Interestingly, the TAP subtests for selective and divided attention only correlated with the HAQUAMS fatigue subscale. This may indicate that fatigue is more closely associated with attention measures than other deficits and supports prior studies claiming attention measures as objective fatigue read-outs (Flachenecker & Meissner, 2008; Weinges-Evers et al., 2010).

Our study has some limitations. First, in study 1, we were not able to verify all stated clinical diagnosis since all disease related information was based on self-reports, both in the HCs group as well as in the MS group. Thus, some participants in this study may have conditions that would have led to exclusion in a clinical research setting. Second, the sample size in the clinical cohort study (study 2) was small and neuropsychological assessment only focused on attention and processing speed. Therefore, we were not able to analyze associations to other cognitive domains.

Based on our results, we conclude that self-reported cognitive measures such as the SEA or MSNQ provide important and clinically relevant additional information about attentional deficits and may be useful to monitor modifications in the perception of cognitive abilities in interventional studies. As the clinical meaning of any objective test result is not necessarily established and patients may differ in the use of their cognitive skills in their daily routine, we postulate that triangulation of measurement, i.e. objective, self-perceived and physician-based assessments, is required to obtain a meaningful picture of cognitive deficits in MS. In clinical practice, where time and cost effectiveness are major issues, an instrument for self-report such as the MSNQ might be a feasible tool to estimate attentional deficits in MS patients. Nevertheless, the SEA does not seem to provide substantial additional information.

Acknowledgement

This research was supported by a grant from the Werner Otto Stiftung, Germany. (grant No 5/78). Ethics approval: Ethics Committee of the Hamburg Chamber of Physicians.

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