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Fatigue and its relation to general cognition, social cognition and social activity in multiple sclerosis and stroke

Tobias Lohaus [a], Judith Witt[a], Anne Schürmeyer[b], Oliver T. Wolf [c] and Patrizia Thoma [a]

[a]Neuropsychological Therapy Centre (NTC), Faculty of Psychology, Ruhr University Bochum, Bochum, Germany; [b]Practice for Neuropsychology and Psychotherapy, Bochum, Germany; [c]Department of Cognitive Psychology, Institute of Cognitive Neuroscience, Faculty of Psychology, Ruhr University Bochum, Bochum, Germany

ABSTRACT

Introduction: The relationship between fatigue and (socio-)cognitive deficits in neurological diseases has sparked increasing research interest in the past years. So far, findings are inconsistent. Most studies focused on general cognitive functioning in specific disorders, particularly cancer or multiple sclerosis (MS).

Methods: This study aims to examine the relationship between fatigue, social cognition and social activity, also taking into account general cognition, more closely, including a stroke patient group ($n = 57$), a MS patient group ($n = 31$) and a healthy control group ($n = 20$). The participants underwent a comprehensive (socio-)cognitive test battery and completed questionnaires on fatigue and psychopathology which, in addition to fatigue, can also affect (socio-)cognitive performance.

Results: In both MS and stroke patients high fatigue scores were observed. Irrespective of aetiology, patients with high and low fatigue did not differ with regard to general cognition and social cognition. However, high fatigue scores were associated with a reduction of social activities in both patient groups. No other significant relationships were observed between fatigue and (socio-)cognitive measures.

Conclusions: Future studies ought to further explore the potentially complex nature of fatigue symptoms and their relationship with (socio-)cognitive performance and social activity in neurological populations.

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1. Introduction

Fatigue represents a multi-causal, multi-dimensional construct (Piper et al., 1987) which is typically difficult to treat and highly individual with regard to symptom presentation and associated triggers. It comprises cognitive (e.g. detrimental effects to attentional and memory functions), emotional (emotional exhaustion) and physical (feelings of physical tiredness) aspects (Ilies et al., 2015; Smets et al., 1995). In general, fatigue is defined as an

CONTACT Tobias Lohaus tobias.lohaus@rub.de Neuropsychological Therapy Centre (NTC), Faculty of Psychology, Ruhr University Bochum, Universitätsstraße 150, Bochum D-44780, Germany

overwhelming, persistent feeling of exhaustion and decreased physical and mental performance (Piper, 1989) that typically increases during task performance (Wylie et al., 2017). Fatigue accompanies various diseases, among them cancer (Al Maqbali, 2021), multiple sclerosis (MS; Krupp et al., 2010) or stroke (Lerdal et al., 2012). In clinical practice, it may be difficult but still important to distinguish fatigue from other psychopathological syndromes, such as depression (Corfield et al., 2016; Hanken et al., 2016).

Cognitive impairments, particularly regarding attention, memory and executive function, are characteristic of most neurological disorders, including MS (for an overview see: Benedict et al., 2020) and stroke (for an overview see: Wall et al., 2015). Although intuitively obvious, evidence that fatigue exacerbates cognitive impairment is inconsistent and patients' subjective cognitive complaints are not necessarily related to results of objective assessment (e.g. Kinsinger et al., 2010). A systematic review examining the association between fatigue and cognitive impairment in MS concludes that fatigue has no effect on most of the cognitive domains assessed apart from vigilance and alertness (Hanken et al., 2015). Regarding stroke, a review paper on the relationship between fatigue and cognition after stroke demonstrated a lack of significant associations in seven out of 11 included studies (Lagogianni et al., 2018). However, previous studies have widely neglected the domain of social cognition, which comprises various subcomponents, such as emotion recognition, theory of mind (ToM) and empathy. Other subcomponents of social cognition are more behaviour-related, e.g. social problem solving ability which more overtly manifests itself in the ability to adaptively engage in (problematic) social interactions. Difficulties in social cognition can translate into difficulties in social activity and thus social participation (Sirois et al., 2017), that is, any form of goal-directed action or pursuit that involves other people and extends physical and personal maintenance routines (Lemon et al., 1972). Social cognition deficits have been associated with numerous neurological diseases, among them MS (for an overview see: Lin et al., 2021) and stroke (for an overview see: Adams et al., 2019). It seems likely that the relationship between fatigue and reduced social activity (Murphy et al., 2021) could be mediated by deficits in social cognition, although it cannot be ruled out that there also is a direct, non-mediated relationship between fatigue and social activity.

To date, few studies have examined the relationship between fatigue and social cognition and social activity, revealing mixed results. Genova et al. (2020) demonstrated in 28 MS patients that poorer performance in facial emotion recognition and ToM was associated with greater psychosocial fatigue. Moreover, investigating 61 MS patients, Berneiser et al. (2014) found a correlation between a reduced ability to recognise emotions and fatigue. Similar to Berneiser et al. (2014), Bodini et al. (2008) reported higher fatigue levels in MS patients with alexithymia (i.e., patients having difficulties in recognising and describing emotions; Lundh & Simonsson-Sarnecki, 2001). However, other studies did not find an association between social cognition and fatigue. Cecchetto et al. (2014) who included 30 MS patients did not observe any relationship between alexithymia and fatigue. Both Roca et al. (2014) and Henry et al. (2011) found that fatigue in a MS sample ($n = 18$ and $n = 64$) was not related to performance on ToM tasks.

For MS patients, evidence exists that fatigue is associated with limitations in social activity: Based on a large sample of $n = 6883$ MS patients, Salter et al. (2019) could demonstrate that MS patients suffering from fatigue show less social participation. For

stroke patients, Neff et al. (2021) revealed that fatigue was associated with lower social success ($n = 48$). With regard to stroke, to our knowledge, no study to date has examined the relationship between social cognitive measures and fatigue. None of the studies mentioned above compared clinical populations with each other and few (Berneiser et al., 2014; Cecchetto et al., 2014; Henry et al., 2011; Roca et al., 2014) included a healthy control (HC) group.

As the evidence on the relationship between fatigue and general cognition / social cognition / social activity in patients with neurological diseases so far turns out to be very ambiguous, this study aims to shed further light on this by adding the following aspects: For the first time, two clinical groups, MS patients and stroke patients, will be assessed and compared to a HC group in terms of different facets of fatigue (physical and cognitive) and general cognition, social cognition and social activity. The inclusion of both MS and stroke patients seems justified since it is known that fatigue is a frequent pathological side effect in both etiologies. While MS patients were included because the role of fatigue has already been evaluated fairly well for this patient population, the inclusion of stroke patients provides the opportunity to investigate whether a similar pattern of outcomes can be observed in association with fatigue, regardless of the underlying neurological aetiology.

In this study, a long and comprehensive test battery was used which may have the potential to evoke the underlying associations between fatigue and (socio)cognitive performance more clearly compared to shorter test batteries. Also, for the first time, a comprehensive assessment of both cognitive (attention, memory, executive function) and sociocognitive domains (empathy, ToM) as well as social activity was carried out, considering both subjective and objective measures. The following assumptions were made based on the evidence available so far:

> Hypothesis 1: Fatigue scores should be higher and (socio)cognitive performance / social activity should be impaired in both patient groups in comparison to the HC group.

Consistent with previous research, Hypothesis 1 expects increased fatigue and lower performance scores for both patient groups, since there is no evidence to expect differences between the patient groups. Hypothesis 2 next analyses the associations between fatigue and performance within the patient groups.

> Hypothesis 2: Patients with higher fatigue scores show larger deficits regarding social cognition / social activity and general cognitive outcome measures. This effect should be independent of the disease, meaning that the disease is not a moderator.

Since fatigue and depression are strongly intercorrelated, depression may be expected to partially mediate the association between fatigue and (socio)cognitive deficits in MS and stroke patients. If fatigue is indeed a relevant predictor, the relationship between fatigue and cognitive deficits should not completely be explained by depression alone. Consequently, the final aim was to investigate whether fatigue still has an effect on cognitive / sociocognitive abilities and social activity when depression is included as mediator. As a result, a third Hypothesis was stated as follows:

> Hypothesis 3: The expected positive association between higher fatigue scores and deficits in cognitive and sociocognitive abilities as well as social activity in patients is mediated by depression scores but is still substantial despite the mediation effect (partial mediation).

2. Methods

2.1. Participants

Data was collected from mid-2017 to mid-2018 and from mid-2019 to early 2020. The patients were recruited from the Neuropsychological Therapy Centre (NTC) of the Ruhr University Bochum and collaborating local neuropsychological practices (particularly involving co-author AS). Only outpatients were included to rule out any acute effects of hospitalisation. Healthy participants were recruited from the personal environment of the students administering the neuropsychological assessments and matched for age and gender as far as this was possible. A total of 108 participants were recruited based on the inclusion criteria specified below and all recruited participants were ultimately tested (31 MS patients, 57 stroke patients and 20 HC). To participate in the study, participants had to have been diagnosed with MS (1) or stroke (2) or not have any neurological or mental disorder (3). In order to make sure that no neurological or mental disorder was present, a semi-structured interview was conducted. If no neurological or mental disorder was reported in this interview, the participants were assigned to the control group. Participants were not excluded if they had comorbid diseases in addition to MS or stroke or if they were on medication, but each comorbidity and medication was well documented to be able to control for these variables post-hoc. The estimated intelligence quotient (IQ, see below for details) had to exceed 80 and the participants should not be currently pregnant, as being pregnant can often be accompanied by fatigue symptoms (Lee & Zaffke, 1999). In addition, the participants had to be between 18 and 70 years old. Since a total of four participants had to be excluded based on these exclusion criteria after initial recruitment and testing, data analysis could be carried out for 104 participants (30 MS patients, 54 stroke patients, 20 HC). The demographic and clinical data of the participants analysed in this study are summarised in Tables 1 and 2. According to Table 1, the MS patients, the stroke patients and the HC significantly differ in their sample characteristics regarding both age and intelligence. The stroke patients in this study are on average about eight years older than the MS patients. They also have a lower estimated IQ when compared to the MS patients and the control group. In addition, Table 2 indicates that the patient groups are significantly more clinically burdened than the control group (depression, anxiety, stress). With regard to illness characteristics of MS, the average year of first MS diagnosis was 2007 (data available for $n = 23$ patients). On average, the MS patients experienced 6.18 MS relapses (in this case, data were available for $n = 17$ patients). For stroke patients, the average year of the last stroke was 2016 ($n = 54$) and 23 patients had more than one stroke in the past.

Regarding comorbid mental disorders (current or within the last years), which were assessed via self-report, comorbid depression was most common (10 MS patients and 14 stroke patients). In addition, some patients reported an anxiety disorder (two MS patients and three stroke patients), attention deficit disorder (two stroke patients), anorexia (one stroke patient) or borderline personality disorder (one stroke patient). With regard to comorbid neurological disorders, there was one patient with Parkinson's disease, one with restless legs syndrome, one with epilepsy, and one with a brain tumour affecting the optic nerve (all in the stroke group). All patients except seven MS patients and two stroke patients received medication. Specifically, stroke patients took medications for hypertension or other cardiovascular medications (39 out of 57

Table 1. Demographic characteristics of the different study groups.

	Group						
Characteristics	Stroke patients ($n = 54$)	MS Patients ($n = 30$)	Controls ($n = 20$)	Overall ($n = 104$)	Statistical values	*df*	*p*-Values
Age in years, *M*(*SD*)	54.06 (7.12)	46.10 (9.24)	50.80 (9.91)	51.13 (8.95)	$F = 8.79$	2,101	<.001*
Years of education, *M*(*SD*)	10.39 (1.72)	11.27 (1.53)	11.00 (1.68)	10.76 (1.69)	$F = 2.96$	2,101	n.s.
Intelligence (IQ), *M*(*SD*)	112.87 (12.91)	120.06 (13.34)	124.30 (10.30)	117.14 (13.32)	$F = 7.15$	2,101	.001*
Gender (f/m), *n*	25/29	22/8	12/8	59/45	$\chi 2 = 5.85$	2	n.s.

Key: f = Female; m = Male; *M* = Mean; n.s. = not significant; *SD* = Standard deviation; * = significant difference between groups $p < .05$.

Table 2. Clinical characteristics of the different study groups.

	Group						
Outcomes measures	Stroke patients (n =53–54)	MS Patients (n = 30)	Controls (n = 20)	Overall (n = 103–104)	F-Values	df	p-Values
Depression (BDI-II)	16.10 (9.96)	13.93 (9.86)	2.80 (4.75)	12.88 (10.40)	15.54	2,100	<.001*
State anxiety (STAI)	43.09 (9.59)	38.27 (10.09)	26.80 (4.06)	38.57 (10.80)	24.06	2,101	<.001*
Trait anxiety (STAI)	46.15 (9.97)	45.37 (10.32)	29.60 (7.18)	42.74 (11.50)	23.19	2,101	<.001*
Stress (PSS)	30.17 (6.10)	29.47 (6.00)	21.65 (7.51)	28.33 (7.10)	13.77	2,101	<.001*

Key: BDI-II = Beck Depression Inventory; PSS = Perceived Stress Scale; STAI = The State-Trait Anxiety Inventory; * = significant difference between groups $p < .05$.

stroke patients), whereas MS patients primarily took medications for the treatment of MS (19 out of 31 MS patients). Furthermore, the use of psychotropic medication was widespread among patients, especially antidepressants (nine MS patients and 15 stroke patients). In addition, two patients (one stroke patient and one MS patient) were on a neuroleptic and one stroke patient took an ADHD psychotropic.

2.2. Procedure and assessments

The participants were assessed at the NTC, the collaborating practices or in the participants' home environment. All assessments were conducted after 1 pm in the afternoon in order to gauge fatigue effects that had possibly built up during the day. All participants gave written informed consent for study participation. Demographic and clinical information (e.g., type of illness, illness onset, current medication, diagnosis of other neurological or mental disorders) was gauged in a semistructured interview developed by the researchers. Various self-report and objective measures were then administered to evaluate fatigue, intelligence, psychopathology, social cognition / social activity and cognitive performance. For the assessment of *fatigue*, the participants completed the Multidimensional Fatigue Inventory (MFI-20; Smets et al., 1995), which includes the subscales General Fatigue, Physical Fatigue, Reduced Activity, Reduced Motivation and Mental Fatigue. Furthermore, a multiple-choice vocabulary test was administered to estimate a premorbid *IQ* (Mehrfachwahl-Wortschatz-Test, MWT-A; Lehrl et al., 1991). Symptoms of *depression and anxiety* were screened with the German versions of the Beck Depression Inventory (BDI-II, Hautzinger et al., 2006) and the State Trait Anxiety Inventory (Laux et al., 1980). Data about *perceived stress* was assessed via the German version of the Perceived Stress Scale (PSS; Klein et al., 2016). Two different instruments were used to assess distinct domains of *social cognition*: The Saarbrücken Personality Questionnaire (Saarbrücker Persönlichkeitsfragebogen, SPF; Paulus, 2007), which is the German version of the Interpersonal Reactivity Index, assessing self-reported empathy (IRI; Davis, 1983) and the German version of the Reading the Mind in the Eyes Test (RMET) by Baron-Cohen et al. (2001) measuring ToM abilities. The German version of the Social Adaptation Self-Evaluation Scale (Soziale Aktivität Selbstbeurteilungs-Skala, SASS; Duschek et al., 2003), which refers to the general social activity level, was used to assess *social activity*. For the assessment of *general cognitive functions*, the German version of the Auditory Verbal Learning Test (Verbaler Lern- und Merkfähigkeitstest, VLMT; Helmstaedter et al., 2001) was included for measuring short- and mid-term verbal learning and memory. As another measure of verbal short-term

memory, the forward digit span subtest of the Wechsler Memory Scale was used (Wechsler, 2012). The Rey–Osterrieth Complex Figure Test (ROCF; Osterrieth, 1944) was included for visuo-spatial memory and the reverse digit span subtest of the Wechsler Memory Scale (Wechsler, 2012), the Trail Making Test (TMT; versions A and B; Reitan, 1992) as well as the divided attention subtest of the testing battery for attentional performance (Testbatterie zur Aufmerksamkeitsprüfung, TAP; Zimmermann & Fimm, 1995) were administered to evaluate working memory and executive functions. The TAP was also used for measuring basic attentional performance (subtest: sustained attention). The whole assessment session lasted about 2.5–3 h. Participants were not paid any remuneration for their participation in the study. The procedure of the study was approved by the local ethics committee of the Ruhr University Bochum (approval number: 399).

2.3. Data analysis

SPSS 28 was used for data analysis. The different patient groups and the control group were compared regarding sample characteristics and performance on general cognition, social cognition and social activity calculating univariate analyses of variance. In addition, linear (moderated) regression models, taking into account the two different disease subgroups, were used to examine the relationship between fatigue and general cognition as well as between fatigue and social cognition and social activity. Furthermore, to evaluate the expected relationship between fatigue, depression, and social cognition / social activity, mediation analyses were performed, using Hayes' Process Macro within SPSS (Preacher & Hayes, 2004). Since age and intelligence in the groups differed significantly from each other (see Table 1), all calculations were additionally performed with age and intelligence as covariates – if deviations from the result pattern appeared with these covariates included, these deviations are addressed in the body of the results section.

3. Results

To investigate Hypothesis 1, univariate analyses of variance were calculated to test whether MS and stroke patients show higher fatigue scores and perform more poorly on general cognition, social cognition and social activity measures compared to HC. The results of these analyses of variance are summarised in Tables 3–5. With respect to *fatigue*, the analyses of variance consistently revealed significant group differences ($p < .001$ for each subscale; with and without controlling for age and intelligence). Post hoc tests revealed significant effects between the MS group and the control group ($p < .001$ in all cases but the Reduced Motivation subscale [$p = .033$]) and between the stroke group and the control group ($p < .001$ in each case) but not significant differences between the two clinical groups (all p-values > .515). Significant group differences were also found for one *social cognition* and the included *social activity outcome measure* (RMET, SASS), with the control group achieving higher total scores both for self-reported social activities and ToM performance relative to the stroke group only ($p = .018$ for SASS, $p < .001$ for RMET). For RMET, a significant difference between the clinical groups was also revealed with the MS group achieving higher total scores (p

= .010). No other significant group differences emerged in the post-hoc analyses (all *p*-values > .090). Regarding self-reported empathy (SPF), the groups did not differ. However, it is important to note that when controlling for age and intelligence, all group differences regarding social cognitive performance and social activity disappeared.

Regarding the *cognitive measures*, significant group differences were found in 12 out of 17 outcome measures presented in Table 5. For five measures (TMT A, TMT B, Reverse Digit Span, TAP Sustained Attention Omissions, memory interference effects [VLMT 5-6]) post-hoc tests revealed significant differences in comparison to the control group, both for the MS and the stroke group (*p*-values range from $p < .001$ to $p = .030$). In five other cases (TAP Divided Attention Visual Reaction Time, TAP Sustained Attention Reaction Time, Rey Figure recall, memory loss for delayed recall [VLMT 5–7], Forward Digit Span), the difference between the control group and the stroke group was the decisive factor for the revealed overall difference (smallest *p*-value: $p < .001$, largest *p*-value: $p = .040$). In two cases (TAP Divided Attention Auditory Reaction Time, verbal learning performance [VLMT 1–5]) and thus definitely in the minority of cases, in addition to the difference between the control group and stroke group, the difference between the MS group and stroke group also had an influence on the overall significant effect (smallest *p*-value: $p < .001$, largest *p*-value: $p = .046$). No other significant group differences emerged (all *p*-values > .057).

When controlling for age and intelligence, considerably fewer group differences with regard to general cognitive measures appeared. Significant group differences after controlling for age and intelligence were still apparent with respect to the TMT, the digit span, the sustained attention omissions outcome, the recall task from the Rey Figure, and two out of three VLMT outcomes considered (VLMT 1–5 reflecting learning performance, VLMT 5–6 reflecting interference effects). In conclusion, Hypothesis 1 can only partly be supported: In some cases, the control group performed better in the general cognition, social cognition and social activity tests and questionnaires than the patient groups (especially compared to the stroke group), but not consistently (when controlling for age and intelligence).

Regarding Hypothesis 2, a moderated regression analysis using fatigue (based on the MFI total score) as independent variable and disease group (MS vs. stroke) as moderator was calculated for each general cognition, social cognition and social activity measure.

Table 3. Descriptive results (means and standard deviations of subscale scores and total score) of the MFI-20 assessing fatigue in the different study groups.

	Group						
Outcome measures	Stroke patients ($n = 51–54$)	MS patients ($n = 30$)	Controls ($n = 20$)	Overall ($n = 101–104$)	*F*-Values	*df*	*p*-Values
General fatigue, *M*(*SD*)	13.35 (3.81)	13.27 (3.61)	7.85 (2.52)	12.27 (4.13)	19.25	2,101	<.001*
Physical fatigue	11.98 (4.04)	12.10 (4.42)	7.35 (2.21)	11.13 (4.27)	11.70	2,101	<.001*
Reduced activity	12.77 (3.75)	11.53 (4.61)	7.20 (2.91)	11.33 (4.38)	15.02	2,100	<.001*
Reduced motivation	9.98 (2.99)	9.17 (3.88)	6.85 (2.30)	9.14 (3.35)	7.16	2,101	<.001*
Mental fatigue	13.33 (4.06)	13.27 (3.28)	7.40 (2.06)	12.15 (4.22)	22.45	2,99	<.001*
Total score	61.53 (15.16)	59.33 (17.18)	36.65(9.83)	55.95 (17.68)	21.01	2,98	<.001*

Key: *M* = Mean; MFI-20 = Multidimensional Fatigue Inventory; n.s. = not significant; *SD* = Standard deviation; * = significant difference between groups $p < .05$.

Table 4. Descriptive results (means and standard deviations of total scores) of the social cognition and social activity outcomes in the different study groups.

Outcomes measures	Group			Overall (n = 104)	F-Values	df	p-Values
	Stroke patients (n = 54)	MS patients (n = 30)	Controls (n = 20)				
Social cognition							
RMET	19.67 (4.51)	22.13 (3.94)	23.65 (3.25)	21.14 (4.41)	7.96	2,101	<.001*
SPF	54.22 (7.56)	54.33 (8.00)	49.90 (5.33)	53.42 (7.46)	2.86	2,101	n.s.
Social activity							
SASS	38.96 (7.21)	41.63 (7.36)	43.30 (4.76)	40.57 (7.02)	3.42	2,101	.036*

Key: M = Mean; n.s. = not significant; RMET = Reading the Mind in the Eyes Test; SASS = Social Adaptation Self-Evaluation Scale; SPF = The Saarbrücken Personality Questionnaire; SD = Standard deviation; * = significant difference between groups $p < .05$.

With regard to *social cognition and social activity*, for one outcome measure (SASS assessing self-reported social activity) indeed a main effect emerged in the expected direction ($t[77] = -2.15$, $\beta = -.62$, $p = .035$; Figure 1). Considering the individual subscales of the MFI in a subsequent analysis involving all MFI subscales as independent variables (instead of focusing on the MFI total score), it becomes evident that this effect is in

Table 5. Descriptive results (means and standard deviations of subscale scores) of the most important neurocognitive subdomains in the different study groups.

Outcomes measures	Group			Overall (n = 92–104)	F-Values	df	p-Values
	Stroke patients (n = 46–54)	MS patients (n = 27–30)	Controls (n = 19–20)				
Executive functions							
TMT-A (sec)	44.85 (23.41)	35.26 (13.31)	23.53 (8.43)	37.91 (20.27)	9.85	2,100	<.001*
TMT-B (sec)	103.76 (61.94)	81.47 (36.69)	58.75 (21.34)	88.38 (52.14)	6.37	2,99	.003*
Reverse Digit Span	5.98 (1.92)	6.40 (1.67)	8.05 (2.33)	6.50 (2.07)	8.37	2,101	<.001*
TAP DA visual							
RT	939.16 (214.23)	852.83 (150.20)	781.79 (82.68)	883.36 (186.81)	6.04	2,97	.003*
Omissions	2.20 (2.91)	1.53 (2.10)	1.00 (1.15)	1.77 (2.46)	1.87	2,97	.159
TAP DA auditory							
RT	699.94 (163.79)	622.90 (115.73)	621.37 (74.12)	661.90 (141.40)	4.00	2,97	.022*
Omissions	1.24 (1.75)	2.07 (6.14)	0.37 (0.76)	1.32 (3.61)	1.33	2,97	.271
TAP DA mistakes	4.23 (6.73)	3.10 (5.40)	1.26 (2.26)	3.33 (5.80)	1.89	2,97	.157
Attention							
TAP SA							
RT	707.39 (156.64)	649.37 (113.18)	617.68 (81.15)	671.84 (136.00)	3.65	2,89	.030*
Omissions	16.80 (10.23)	14.56 (10.82)	7.95 (5.61)	14.32 (10.15)	5.66	2,89	.005*
Mistakes	12.35 (14.51)	8.41 (10.01)	6.26 (10.94)	9.93 (12.76)	1.83	2,89	.166
Memory							
Rey figure copy	33.85 (5.14)	34.92 (3.86)	35.75 (0.55)	34.53 (4.29)	1.62	2,101	.203
Rey figure recall	17.46 (6.90)	19.93 (6.31)	24.13 (5.88)	19.48 (6.96)	7.62	2,100	<.001*
VLMT 1–5	42.06 (12.75)	49.43 (11.76)	56.65 (8.65)	47.04 (12.99)	12.01	2,100	<.001*
VLMT 5–6	2.28 (1.63)	2.20 (1.73)	0.85 (1.23)	1.98 (1.67)	6.27	2,100	.003*
VLMT 5–7	2.02 (1.86)	1.57 (1.63)	0.90 (1.21)	1.67 (1.73)	3.25	2,99	.043*
Forward digit span	6.57 (1.82)	7.37 (2.03)	8.40 (1.76)	7.15 (1.98)	7.24	2,101	.001*

Key: DA = Divided attention; M = Mean; n.s. = not significant; RT = reaction time; SA = Sustained attention; SD = Standard deviation; TAP = Test of Attentional Performance; TMT = Trail Making Test; VLMT = German version of the Auditory Verbal Learning Test (VLMT 1–5 reflects learning performance, VLMT 5–6 reflects interference effects, VLMT 5–7 reflects retrieval performance after delay); * = significant difference between groups $p < .05$.

particular due to the pronounced significant effect on the Reduced Motivation scale (t[69] = −4.31, β = −.49, p = <.001). For the analysis involving the MFI total score as independent variable, no significant interaction between disease group and fatigue was found, meaning that the disease group did not moderate the effect of fatigue on SASS (t[77] = .34, β = .15, p = .739). In addition, there were no moderation effects for the MFI subscales.

Concerning the two social cognition measures (RMET, SPF), increased fatigue was not found to be associated with social cognitive deficits. Moderated regression analyses showed neither a main effect (RMET: t[77] = −1.43, β = −.47, p = .157; SPF: t[77] = 1.17, β = .40, p = .247), nor an interaction with disease group (RMET: t[77] = 1.78, β = .89, p = .079; SPF: t[77] = −.86, β = −.45, p = .394). When controlling for age and intelligence, the same pattern of results was revealed for all social cognition / social activity outcomes. The results did not change when the MFI subscales were used in the analyses. When patients who had comorbid neurological diseases and severe mental illness (borderline personality disorder) were excluded, the same pattern of results emerged, with the effect then being even more pronounced with regard to the SASS (t[72] = −2.42, β = −.72, p = .018).

With regard to *general cognition*, the results of the moderated regression analyses covering the main dependent variables (including reaction times / omission scores / error scores) of the assessed subdomains of attention, memory and executive function are presented in Table 6. To sum up, only in one case a significant main effect and a significant interaction effect between fatigue and disease group was found (for the outcome measure Reverse Digit Span assessing working memory). Excluding patients who had comorbid neurological diseases and severe mental illness (borderline personality disorder) did not change the pattern of results. When age and intelligence were added as covariates, one more significant main effect (but no interaction effect) with respect to another outcome appeared, assessing a memory performance decrease after an interfering word list was learned (VLMT 5-7). It should, however, be noted that a total of 17 regression analyses were performed for the evaluation of attention, memory and executive function. Therefore, a Bonferroni correction had to be applied at this point, which ultimately leads to the conclusion that there were no significant main or interaction effects at all after the correction. Moreover, the

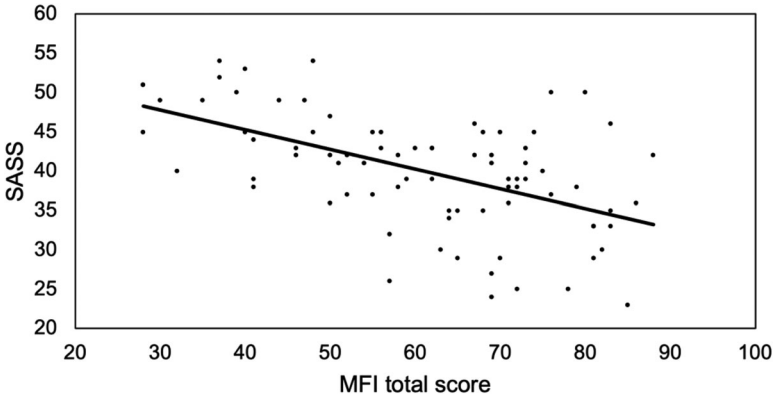

Figure 1. The prediction of social activity (SASS) by fatigue (MFI total score).

Table 6. Regression analyses with fatigue (assessed using the MFI) and group as independent variables and the main dependent variables (RTs/raw scores/omission scores/error scores) representing the assessed subdomains of attention, memory and executive function.[a]

Outcomes measures	*t*-Values	*df*	*β*	*p*-Values
Executive functions				
TMT-A	.71	77	.24	.483
TMT-B	−.52	77	−.18	.607
Reverse digit span	2.14	77	.72	.035*
TAP DA visual				
RT	−.55	74	−.19	.583
Omissions	.25	74	.09	.800
TAP DA auditory				
RT	−.53	74	−.18	.600
Omissions	1.31	74	.46	.196
TAP DA mistakes	1.03	74	.36	.306
Attention				
TAP SA				
RT	−.48	66	−.18	.635
Omissions	.36	66	.13	.723
Mistakes	.73	66	.27	.467
Memory				
Rey figure copy	−1.27	77	−.43	.209
Rey figure recall	.06	76	.02	.954
VLMT 1–5	.27	76	.09	.786
VLMT 5–6	−1.22	76	−.42	.228
VLMT 5–7	−1.77	75	−.61	.080
Forward digit span	.86	77	.29	.395

Key: DA = Divided attention; *M* = Mean; n.s. = not significant; RT = reaction time; SA = Sustained attention; *SD* = Standard deviation; TAP = Test of Attentional Performance; TMT = Trail Making Test; VLMT = German version of the Auditory Verbal Learning Test (VLMT 1–5 reflects learning performance, VLMT 5–6 reflects interference effects, VLMT 5–7 reflects retrieval performance after delay).

[a]Only the main effects of fatigue are presented in this table; * = significant difference between groups $p < .05$.

results are basically the same for the MFI subscales. Thus, it can be stated that these results are not in line with Hypothesis 2.

To sum up, Hypothesis 2 is only valid for social activity, since only for this domain increased fatigue was found to be associated with deficits. In line with Hypothesis 2, no significant interaction between disease group and fatigue was found.

To examine Hypothesis 3, two mediation analyses were performed with fatigue as the independent variable (analysis 1: MFI total, analysis 2: MFI Reduced Motivation subscale), the only measure covering a social domain that revealed significant results regarding Hypothesis 2 as the dependent variable (SASS, self-reported social activity), and the total score of the BDI (assessing depression) as the mediator. Table 7 shows the total, direct and indirect effects. Considering the confidence intervals obtained after bootstrapping, a significant mediation regarding the SASS outcome measure was revealed in both analyses, as the confidence intervals do not include 0. Moreover, in both analyses the direct effect between fatigue and SASS remained significant when the mediator depression was taken into account. The same pattern of results emerged when controlling for age and intelligence. Thus, as assumed in Hypothesis 3, a partial mediation was indeed shown with respect to SASS. However, as already noted in relation to Hypothesis 2, there was no association between fatigue and (socio)-cognitive measures, which means that the mediation analysis cannot provide any additional information in these cases.

Table 7. Total, direct and indirect effects of fatigue (MFI total and MFI Reduced Motivation subscale) on SASS with depression (assessed using the BDI) as a mediator.

			Bootstrapping 95% CI	
	Effect	SE	Lower	Upper
Independent variable: MFI total, mediator: BDI, dependent variable: SASS				
Total effect	−0.251	0.04	−0.3392	−0.1625
Direct effect	−0.106	0.05	− 0.2043	−0.0085
Indirect effect	−0.144	0.04	−0.2509	−0.0822
Independent variable: MFI Reduced Motivation subscale, mediator: BDI, dependent variable: SASS				
Total effect	−1.306	0.20	−1.6970	−0.9155
Direct effect	−0.754	0.22	−1.1908	−0.3168
Indirect effect	−0.552	0.18	−0.9921	−0.2828

Key: BDI = Beck Depression Inventory; CI = Confidence Interval; SASS = Social Adaptation Self-Evaluation Scale.

4. Discussion

Our study confirmed that MS and stroke patients show significantly increased fatigue scores and that they perform more poorly in some cognitive (but not sociocognitive after controlling for age and IQ) domains when being compared to the HC included in this study (Hypothesis 1). Moreover, higher fatigue levels in patients were found to be particularly associated with a decrease in social activity (Hypothesis 2). This effect was still evident when controlling for age and intelligence and when the mediator depression was included (Hypothesis 3). Therefore, in view of the results of this study, evidence is provided that depression and fatigue both might affect social activity. This finding also suggests that fatigue and depression are to be considered as different entities in either patient group, an aspect that should also be taken into account in therapeutic practice. In addition, an important finding of this study is that the association between fatigue and reduced social activity occurs independently of the disease (Hypothesis 2). This finding not only confirms that MS patients suffering from fatigue report more deficits in social cognition related social activities, but also suggests that fatigue also affects socially relevant domains in stroke patients.

The significant effect for social activity and not for ToM or self-rated empathy underscores the idea that fatigue is particularly associated with social activity instead of social cognition. Patients might be cognitively able to process social cues despite the presence of fatigue, but their fatigue hinders them from participating in social events. A special finding of the present study is that the fatigue-related lack of motivation seems to be the decisive factor of not participating in social interactions – physical fatigue and mental fatigue, on the other hand, do not seem to have a major influence. Assuming that fatigue should not be considered as a factor that makes social interactions inevitably impossible, therapeutic interventions in patients with fatigue should therefore particularly include motivational support.

General cognitive measures revealed nearly no significant effects at all in terms of a potential association with fatigue (Hypothesis 2) and disappeared completely when applying Bonferroni-correction. This is in line with previous findings (e.g. Hanken et al., 2015; Lagogianni et al., 2018) and suggests that fatigue and cognitive performance are indeed uncorrelated, even if, as in our study, a very extensive test battery is used.

Several factors might limit the generalisability of the findings: First, the number of participants with respect to the different groups is rather small, especially with respect to MS

and HC. Also, the number of participants is somewhat unbalanced (e.g., more than twice as many stroke patients were recruited than HC). Moreover, in contrast to our study, subsequent studies should – if possible – always include both self-assessments and objective measures for each outcome, since it is possible that discrepant findings appear for objective and subjective outcomes. Furthermore, a general problem arises from the fact that it cannot be ensured that the comprehensive battery we used to assess general cognition, social cognition and social activity actually detects deficits in these domains.

It should also be noted that the findings of this study are specific to MS and stroke patients and cannot be generalised to other patient groups. Although it can be considered a strength of this study to compare patient groups with two distinct neurological diseases with regard to the relationship between fatigue and general cognition, social cognition and social activity was included, there are a number of other neurological diseases accompanied by fatigue for which the hypotheses examined in this study also need to be investigated in the future.

As another limitation of our study it should be emphasised that although evidence was obtained about the relationship between fatigue and general cognition / social cognition / social activity, no information could be gathered about whether fatigue is more likely to lead to less engagement in social activity or, conversely, whether engaging in less social activity leads to more fatigue. In order to gain insight into the direction of this relationship, long-term studies involving several measurement time points are needed in the future. Moreover, it was not possible in this study to determine whether the variety of heterogeneous medications that the patients were taking may have affected the results. Finally, it has to be considered that the investigated patients all received outpatient neuropsychological therapy and might thus represent more high-functioning samples. Some of the pre-existing (socio)cognitive impairments might have already been ameliorated by treatment.

Overall, despite these limitations, the results of this study provide further important evidence regarding the role of fatigue with respect to deficits in general cognition, social cognition and social activity both for MS and stroke patients. Fatigue represents an enormously stressful psychological condition, which – even if it may have only little influence on basal sociocognitive outcomes – may lead to patients being restricted in their social life and thus in a central area of psychological well-being.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, TL, upon reasonable request.

Notes on contributors

Tobias Lohaus, PhD student in clinical neuropsychology, conducts research on social cognition deficits and its treatment. Most recently, he published a review article on computerized interventions for social cognition deficits: *Use of Technologies in the Therapy of Social Cognition Deficits in Neurological and Mental Diseases: A Systematic Review* (Lohaus et al., 2022).

Judith Witt, Master of Science psychologist, is working as a neuropsychologist in a neurological clinic.

Anne Schürmeyer, clinical neuropsychologist as well as licensed psychological psychotherapist, works in her own practice for Neuropsychology and Psychotherapy located in Bochum, Germany.

Oliver T. Wolf, full professor of Cognitive Psychology at Ruhr University Bochum. His research addresses the impact of acute and chronic stress on human cognition with a special focus on learning, extinction, and memory. He contributed multiple original research papers as well as reviews. Some examples are *How stress hormones shape memories of fear and anxiety* (Merz & Wolf, 2022) and *Effects of cortisol on cognition in major depressive disorder, posttraumatic stress disorder and borderline personality disorder* (Wingenfeld & Wolf, 2015).

Patrizia Thoma, adjunct professor, is a licensed psychotherapist and clinical neuropsychologist and co-head of the Neuropsychological Therapy Center in Bochum, Germany. Her main research interest is social cognition in patients with mental disorders and neurological diseases, among her recent publications is a review paper on brain cancer patients: *Sociocognitive functioning and psychosocial burden in patients with brain tumors* (Pertz et al., 2022) and a book on the Neuropsychology of schizophrenia (Thoma, 2022).

ORCID

Tobias Lohaus http://orcid.org/0000-0002-6407-4231
Oliver T. Wolf http://orcid.org/0000-0002-9320-2124
Patrizia Thoma http://orcid.org/0000-0003-4415-1719

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