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Psychological factors and brain magnetic resonance imaging metrics associated with fatigue in persons with multiple sclerosis

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ABSTRACT

Background: Besides demographics and clinical factors, psychological variables and brain-tissue changes have been associated with fatigue in persons with multiple sclerosis (pwMS). Identifying predictors of fatigue could help to improve therapeutic approaches for pwMS.
Therefore, we investigated predictors of fatigue using a multifactorial approach.
Methods: 136 pwMS and 49 normal controls (NC) underwent clinical, neuropsychological, and magnetic resonance imaging examinations. We assessed fatigue using the "Fatigue Scale for Motor and Cognitive Functions", yielding a total, motor, and cognitive fatigue score. We further analyzed global and subcortical brain volumes, white matter lesions and microstructural changes (examining fractional anisotropy; FA) along the cortico striatal thalamo cortical (CSTC) loop. Potential demographic, clinical, psychological, and magnetic resonance imaging predictors of total, motor, and cognitive fatigue were explored using multifactorial linear regression models.
Results: 53% of pwMS and 20% of NC demonstrated fatigue. Besides demographics and clinical data, total fatigue in pwMS was predicted by higher levels of depression and reduced microstructural tissue integrity in the CSTC loop (adjusted $R^2 = 0.52$, $p < 0.001$). More specifically, motor fatigue was predicted by lower education, female sex, higher physical disability, higher levels of depression, and self-efficacy (adjusted $R^2 = 0.54$, $p < 0.001$). Cognitive fatigue was also predicted by higher levels of depression and lower self-efficacy, but in addition by FA reductions in the CSTC loop (adjusted $R^2 = 0.45$, $p < 0.001$).
Conclusions: Our results indicate that depression and self-efficacy strongly predict fatigue in MS. Incremental variance in total and cognitive fatigue was explained by microstructural changes along the CSTC loop, beyond demographics, clinical, and psychological variables.

1. Introduction

Fatigue is one of the most common symptoms in persons with multiple sclerosis (pwMS), present in up to 78% [1]. MS-related fatigue is defined as a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities [2,3]. It frequently occurs already in early stages of the disease and has a major impact on patients' daily living [2]. PwMS suffering from fatigue report decreased quality of life, increased psychological impairment, and they are furthermore more likely to have problems at work or even to lose their job due to their persistent tiredness, lack of concentration, and weakness. Accordingly, the demands on

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resources and costs for the health care and social system associated with this condition are enormous [1,4].

Fatigue can be further divided into *cognitive fatigue*, denoting for instance mental exhaustion, impairment of concentration, attention, or memory and *motor fatigue*, characterized by decreased physical stamina, coordination problems, slowness, clumsiness, and increased needed effort [5].

Despite the obvious medical and socioeconomic consequences, research into predictors allowing to identify pwMS susceptible to fatigue and defining underlying factors including brain alterations is still relatively scarce [6]. Current evidence suggests multidimensional factors influencing MS-related fatigue such as female sex, older age, lower level of education, and longer disease duration [7–9]. More specifically, psychological variables (such as depression, anxiety, and self-efficacy) [2,10] and structural brain changes such as reductions in global and subcortical (striatum and thalamus) brain volumes have been associated with fatigue [6,11,12]. Furthermore, studies using more advanced neuroimaging methods (such as tractography and/or functional magnetic resonance imaging; MRI) highlighted cortical-subcortical pathways/networks to be related to fatigue in MS [12–14]. In particular, damage in the pathway between the thalamus, striatum, and frontal cortical areas seem to be involved in the pathogenesis of MS fatigue [12]. Altoghether, these studies lead to the assumption that disruptions of the cortico striato thalamo cortical (CSTC) loop play a major role in the development of fatigue [6,12].

Given the fact that fatigue represents a heterogeneous concept and multiple factors seem to be involved in the development of this complex syndrome [3], using a multidimensional approach to scrutinize factors influencing fatigue including its cognitive and motor subcomponents is essential. Therefore, we performed an exploratory investigation of potential demographic, clinical, psychological, and MRI predictors of total, motor, and cognitive fatigue in pwMS. Since 10–18% of the general population suffer from chronic fatigue without meeting the criteria of having chronic fatigue syndrome [15,16], we were also interested in how common fatigue is in a group of normal controls (NC), and whether any demographic, psychological, or MRI variable can predict fatigue in NC.

Due to the complexity of fatigue, a better understanding of the most crucial predictors might help to identify and improve targeted therapeutic approaches for pwMS in clinical routine practice.

2. Methods

2.1. Patients and normal controls

A total of 136 (86 females (63%)) pwMS underwent clinical, neuropsychological, and brain MRI assessments at the University Hospital of Graz, Austria. Their mean age was 39.5 ± 9.9 years and the mean disease duration was 9.8 ± 7.4 years. 101 (74.3%) pwMS were on disease modifying treatment (DMT). This cohort included 4 (2.9%) pwMS with a clinically isolated syndrome (CIS), 128 (94.1%) with relapsing-remitting MS (RRMS), three (2.2%) with secondary progressive MS (SPMS), and one (0.7%) with primary progressive MS (PPMS).

All participants data were assessed between June 2020 and January 2022. Time between clinical, neuropsychological, and MRI assessment was not more than eight weeks.

Exclusion criteria for pwMS were an acute relapse or steroid therapy within eight weeks prior to the neuropsychological and MRI assessments. PwMS were further excluded from this study if they had been diasgnosed with a relevant neurological disorder (other than MS) or psychiatric disease in the past.

To be able to explore MS-specific effects of fatigue, we examined 49 NC (34 females, 69%; mean age 33 ± 10 years), applying the same procedures. NC had to be free from any chronic neurologic or psychiatric diseases.

This project was approved by the Ethics Committee of the Medical University of Graz (31–432 ex 18/191264–2019). Written informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki.

2.2. Neuropsychological assessment

Fatigue was assessed using the "Fatigue Scale for Motor and Cognitive Functions" (FSMC), providing a score for motor, cognitive, and total fatigue. Participants had to answer 20 questions on a 5-point Likert scale (total fatigue maximum score: 100; motor and cognitive fatigue maximum score: 50). Fatigue severity was classified using the recommended cut-off values [17]. For total fatigue, scores ≥43 were defined as mild fatigue, ≥53 as moderate fatigue, and ≥ 63 as severe fatigue. For motor and cognitive fatigue, scores ≥22 were classiefied as mild motor/cognitive fatigue, ≥27/28 as moderate motor/cognitive fatigue, and ≥ 32/34 as severe motor/cognitive fatigue [17]. Furthermore, we assessed levels of anxiety and depression with the "Hospital Anxiety and Depression Scale" (HADS; maximum score for anxiety and depression: 21; cut-off scores for clinical relevant levels of depression/anxiety: ≥ 8; clinically significant depression/anxiety: ≥11) [18,19] and self-efficacy with the "Skala zur Allgemeinen Selbstwirksamkeitserfahrung" (SWE; maximum score: 40) [20].

2.3. Clinical assessment

An experienced neurologist assessed the clinical phenotype (CIS, RRMS, SPMS, PPMS), degree of physical impairment (Expanded Disability Status Scale, EDSS) [21], and provided information on annual relapse rate, DMT, and disease duration in the pwMS.

2.4. MRI protocol

MRI of the brain was performed on a 3 Tesla scanner (Siemens MAGNETOM 3 T Prisma Fit system) at the Department of Radiology, Medical University of Graz, Austria. To enable assessment of normalized cortical and subcortical brain volumes, high resolution 3D images were acquired by means of a T1-weighted MPRAGE sequence with 1 mm isotropic resolution (repetition time (TR) 1900 ms, echo time (TE) 2.7 ms). A T2-weighted 3D Fluid-Attenuated Inversion Recovery (FLAIR) sequence with 1 mm isotropic resolution was used for the assessment of hyperintense T2 white matter lesion load (T2-LL) in the patients (TR 5000 ms; TE 393 ms, inversion time (TI) 1800 ms). To assess abnormalities of white matter tracts, a diffusion-tensor imaging (DTI) sequence with 1.5 mm isotropic resolution (TR 3318 ms, 64 directions) was obtained.

All images were examined for morphological changes by a clinician with expertise in neuroradiology (C.E.).

2.5. Structural MRI analyses

To assess T2-LL, hyperintense white matter lesions were segmented with the Lesion Segmentation Toolbox (available online) on SPM 12, with the automated lesion prediction algorithm (LPA) [22] on FLAIR images. Afterwards, a binary lesion mask (threshold = 0.25) was generated with fslmaths (FSL, v5.9) and the T2-LL (volume in mm^3) of each patient was extracted using fslstats (FSL) [23]. Further, for lesions probability mapping, lesion masks were transformed to MNI-space to identify lesions associated with total, motor, and cogntive fatigue (generalized linear model (GLM) and fsl randomize with 5000 permutations; whole brain, corrected for age) [24]. Transformation information was first calculated by co-registering the individual FLAIR to the T1 and nonlinearly registering the T1 to MNI-space [23,25].

After lesion filling with the FSL lesion filling toolbox [26], brain volumes were assessed based on T1-weighted MPRAGE images using SIENAX [27], part of the FMRIB Software Library (FSL) [23]. All brain volumes were normalized for head size using the V-scaling factor

derived by SIENAX. Subcortical volumes (thalamus and striatum consisting of the nucleus caudate and putamen) were determined from T1-weighted images using FSL FIRST [28].

Since recent studies have highlighted the importance of the CSTC loop in the context of fatigue (as described in the introduction), we wanted to track and investigate the predictive value of the entire CSTC loop. As suggested in a review article of Arm and colleagues (2019), the CSTC loop (Fig. 1) was tracked separately for the left and right hemisphere using FSL ProbtrackX [6,29]. The CSTC loop includes tracts from the prefrontal cortex (PFC) to the striatum, the striatum to the pallidum, the pallidum to the thalamus and the thalamus to the PFC [6].

Since clinically relevant fatigue in MS was found to be strongly associated with abnormalities in the fractional anisotropy (FA) [30], we therefore only focused on FA of the CSTC loop. After DTI data preprocessing (correcting for susceptibility-induced distortions (topup) [23,31] and eddy currents [32]) and tract-bassed spatial statistics [33], mean FA was extracted for each white matter tract of the CSTC loop. Afterwards, the mean FA values of all individual tracts were merged to form the overall mean FA of the CSTC loop.

2.6. Statistical analyses

Demographic, clinical, neuropsychological, and MRI data were analyzed with the Statistical Package of Social Science (IBM SPSS Statistics 27). The level of significance was set <0.05. We applied the Shapiro-Wilk test to assess normal distribution of all variables and controlled for outliers. Outliers (>3.0 times the interquartile range of a boxplot) were excluded from the entire analyses. The false discovery rate (FDR) was used to correct for multiple comparisons.

Correlations were performed to explore associations between total, cognitive, and motor fatigue, demographics, clinical, psychological, and MRI data. Independent sample *t*-test or Mann-Whitney *U* test was used to analyze differences in demographics, neuropsychological, and MRI parameters between pwMS and NC.

To predict total, cognitive, and motor fatigue in pwMS, we performed hierarchical linear regression models (method "STEPWISE") with demographics (age, sex, years of education), clinical (disease duration, EDSS, clinical phenotype, DMT, annualized relapse rate), psychological (continuous measures of level of depression, level of anxiety, self-efficacy), and MRI parameters (T2-LL, normalized brain volume (NBV), thalamic and striatal volumes, and overall FA of CSTC loop) as predictors.

To ensure that the results of the regression models predicting total, motor, and cognitive fatigue were not mainly caused by pwMS ($N = 8$) with higher levels of depression (HADS-D scores $\geq$11) at the time of the assessment, we did the same analyses without those eight pwMS. The main results of the three models identifying the contributing predictors of fatigue remained unchanged (Suppl. 4).

To identify lesion distribution patterns associated with total, cognitive, or motor fatigue, a whole brain randomize-analysis, corrected for age, was performed using FSL ($p < 0.05$).

To predict total, cognitive, and motor fatigue in NC, we performed the same hierarchical linear regression models (method "STEPWISE") as in pwMS including the same variables except for clinical data and T2-LL.

Due to the heterogeneous findings in the literature on factors associated with fatigue in MS and the resulting large number of variables, we opted for a stepwise approach (criteria: probability of F to enter $\leq$0.05; probability of F to remove $\geq$0.10) for the linear regression models.

We checked assumptions for the linear regression models such as linearity, autocorrelation, collinearity, homoscedasticity, and normal distribution of the residuals.

3. Results

3.1. Patients' characteristics

Detailed information on demographics, clinical, psychological, and MRI parameter of pwMS are presented in Table 1.

The fatigue assessment showed that out of 136 pwMS, 72 (53%) pwMS had at least mild total fatigue, scoring above 43 points on the FSMC (14 (10%) mild, 24 (18%) moderate, 34 (25%) severe total fatigue). 76 (56%) pwMS had at least mild motor fatigue (15 (11%) mild, 16 (12%) moderate, 45 (33%) severe motor fatigue). 65 (48%) pwMS had at least mild cognitive fatigue (22 (16%) mild, 19 (14%) moderate, 24 (18%) severe cognitive fatigue). 18 pwMS (13%) had distinct motor and 7 pwMS (5%) suffered from distinct cognitive fatigue, respectively.

3.2. Total fatigue in pwMS

Results of the correlations showed assocaiations between total fatigue and demographics, clinical, psychological, and MRI parameters (Table 2). The hierarchical linear regression model (total explained variance: adjusted $R^2 = 0.52$, $p < 0.001$) to predict total fatigue explained 10% by demographics, an incremental 13% by clinical data, additional 27% by psychological data, and 2% by MRI data (Suppl. 1). Years of education ($\beta = -0.13$, 95% confidence interval (95% CI): $-1.47, -0.09$, $p = 0.028$), female sex ($\beta = 0.15$, 95% CI: 1.44, 11.48, $p = 0.012$), EDSS ($\beta = 0.28$, 95% CI: 1.72, 4.88, $p < 0.001$), level of depression ($\beta = 0.38$, 95% CI: 1.36, 3.17, $p < 0.001$), self-efficacy ($\beta = -0.19$, 95% CI: $-0.68, -0.10$, $p = 0.009$), and FA of the CSTC loop ($\beta = -0.16$, 95% CI: $-281.22, -34.98$, $p = 0.012$) were significant independent predictors of total fatigue.

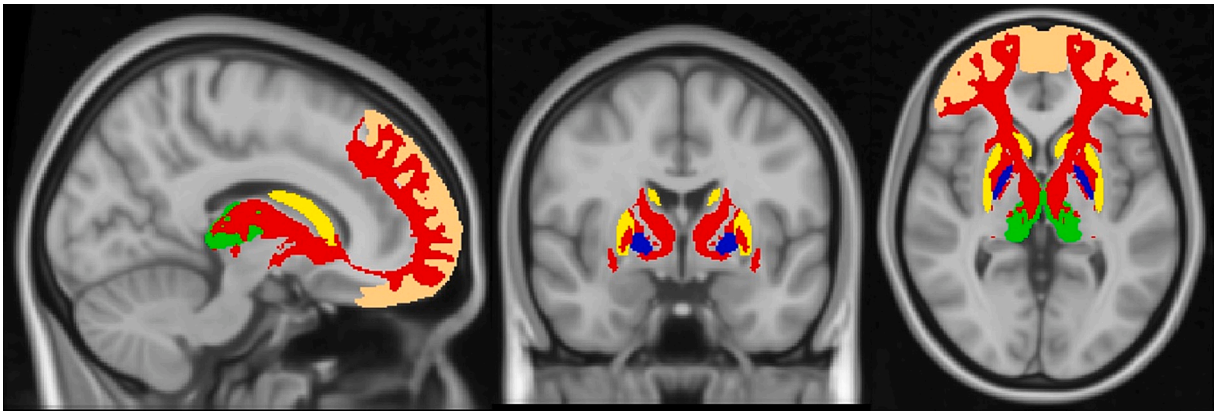

Fig. 1. Cortico striato thalamic cortical (CSTC) loop.
Schematic illustration of the cortico striato thalamic cortical (CSTC) loop; radiological orientation; orange: prefrontal cortex; green: thalamus; yellow: striatum; blue: pallidum; red: CSTC loop.

Table 1
Patients' and normal controls characteristics.

Demographics and clinical data	PwMS $N = 136$	NC $N = 49$	p
Age, mean (SD) (years)	39.5 (9.9)	33.3 (10.7)	<0.001*
Sex (female), N (%)	86 (63.2)	35 (70.0)	0.440
Education, mean (SD) (years)	13.7 (3.5)	17.1 (3.6)	<0.001*
Disease duration, mean (SD) (years)	9.8 (7.4)	NA	
EDSS, median (IQR)	1.5 (2.5)	NA	
Annual relapse rate, mean (SD)	0.5 (0.5)	NA	
DMT, N (%)	101 (74.3)	NA	
Dymethilfumarate, N (%)	39 (38.6)	NA	
Fingolimod, N (%)	12 (11.9)	NA	
Glatiramer, N (%)	8 (7.9)	NA	
Interferon, N (%)	19 (18.8)	NA	
Natalizumab, N (%)	7 (6.9)	NA	
Ocrelizumad, N (%)	6 (5.9)	NA	
Spionimod, N (%)	3 (3.0)	NA	
Teriflunomid, N (%)	7 (6.9)	NA	
Clinical phenotype, N (%)			
CIS	4 (2.9)	NA	
RRMS	128 (94.1)	NA	
SPMS	3 (2.2)	NA	
PPMS	1 (0.7)	NA	
Neuropsychological data			
Total fatigue, mean (SD)	48.7 (20.3)	36.2 (11.1)	<0.001*
Motor fatigue, mean (SD)	25.8 (11.4)	17.52 (5.6)	<0.001*
Cognitive fatigue, mean (SD)	22.9 (10.3)	18.7 (5.9)	<0.001*
HADS–A, mean (SD)	5.3 (3.8)	3.8 (2.7)	0.002*
HADS–D, mean (SD)	3.4 (3.4)	1.6 (1.8)	<0.001*
SE, mean (SD)	55.7 (10)	58.8 (8.1)	0.044*
MRI parameters			
T2-LL, median (IQR) (cm^3)	3.6 (6.1)	NA	
NBV, mean (SD) (cm^3)	1530.6 (77.7)	1573 (57.5)	<0.001*
Thalamus volume, mean (SD) (cm^3)	15.5 (1.9)	16.6 (1.6)	<0.001*
Striatum volume, mean (SD) (cm^3)	8.2 (1.0)	8.6 (0.7)	0.003*
FA CSTC loop, mean (SD)	0.48 (0.02)	0.49 (0.01)	<0.001*

PwMS: persons with MS; NC: normal controls; p: *p*-value; N: number of patients; SD: standard deviation; NA: not applicable; EDSS: Expanded Disability Status Scale; IQR: inter quartile range; DMT: disease modifying treatment; CIS: clinically isolated syndrome; RRMS: relapse remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; HADS-A: Hospital Anxiety and Depression Scale – Anxiety; HADS-D: Hospital Anxiety and Depression Scale – Depression; SE: self-efficacy; MRI: magnetic resonance imaging; T2-LL: T2-lesion load; NBV: normalized brain volume; FA: fractional anisotropy, CSTC: cortico striato thalamic cortical loop.
* Indicates $p < 0.05$.

3.3. Motor fatigue in pwMS

Correlations were found between motor fatigue and demographics, clinical, psychological, and MRI parameters (Table 2). The hierarchical linear regression model (adjusted $R^2 = 0.54$, $p < 0.001$) to predict motor fatigue explained 12% by demographics, incremental 25% by clinical data, and additional 17% by psychological data (Suppl. 2). MRI parameters did not add to the prediction. Years of education ($\beta = -0.16$, 95% CI: −0.88, −0.13, $p = 0.009$), female sex ($\beta = 0.15$, 95% CI: 0.80, 6.30, $p = 0.012$), EDSS ($\beta = 0.44$, 95% CI: 2.04, 3.77, $p < 0.001$), level of depression ($\beta = 0.33$, 95% CI: 0.61, 1.60, $p < 0.001$), and self-efficacy ($\beta = -0.15$, 95% CI: −0.33, −0.01, $p = 0.036$) were significant independent predictors of motor fatigue.

3.4. Cognitive fatigue in pwMS

For cognitive fatigue, correlations were found with demographics, clinical, psychological, and MRI parameters (Table 2). The hierarchical linear regression model (adjusted $R^2 = 0.45$, $p < 0.001$) to predict cognitive fatigue explained 40% by psychological variables and 5% by MRI parameters (total explained variance =45%; Suppl. 3). Level of depression ($\beta = 0.31$, 95% CI: 0.35, 1.50, $p = 0.002$), self-efficacy ($\beta = -0.20$, 95% CI: −0.37, −0.05, $p = 0.012$), and FA of the CSTC loop ($\beta = -0.16$, 95% CI: −152.23, −10.57, $p = 0.025$) were significant independent predictors of cognitive fatigue.

Table 2
Correlations between total, motor and cognitive fatigue and demographics, clinical, psychological and MRI variables in persons with MS.

	Total fatigue $N = 136$, r (p)	Motor fatigue N = 136, r (p)	Cognitive fatigue N = 136, r (p)
Age	0.18 (0.041*)	0.24 (0.004*)	0.10 (0.332)
Sex	0.20 (0.027*)	0.16 (0.070)	0.22 (0.015*)
Education	−0.22 (0.016*)	−0.25 (0.004*)	−0.15 (0.106)
Disease duration	0.32 (<0.001*)	0.32 (<0.001*)	0.23 (0.013*)
EDSS	0.47 (<0.001*)	0.57 (<0.001*)	0.28 (0.002*)
Annualized relapse rate	−0.01 (0.903)	−0.03 (0.766)	0.01 (0.930)
Clinical phenotype	0.11 (0.239)	0.18 (0.042*)	0.01 (0.930)
HADS-A	0.50 (<0.001*)	0.43 (<0.001*)	0.51 (<0.001*)
HADS-D	0.63 (<0.001*)	0.58 (<0.001*)	0.60 (<0.001*)
SE	−0.44 (<0.001*)	−0.39 (<0.001*)	−0.48 (<0.001*)
T2-LL	0.23 (0.013*)	0.22 (0.016*)	0.23 (0.013*)
NBV	−0.16 (0.066)	−0.21 (0.017*)	−0.09 (0.337)
Thalamus volume	−0.30 (<0.001*)	−0.25 (0.004*)	−0.29 (0.002*)
Striatum volume	−0.31 (<0.001*)	−0.26 (0.004*)	−0.28 (<0.001*)
FA CSTC loop	−0.29 (<0.001*)	−0.23 (0.007*)	−0.31 (<0.001*)

N: number of patients; r: correlation coefficient; p: *p*-value; EDSS: Expanded Disability Status Scale; HADS-A: Hospital Anxiety and Depression Scale – Anxiety; HADS-D: Hospital Anxiety and Depression Scale – Depression; SE: self-efficacy; T2-LL: T2-lesion load; NBV: normalized brain volume; FA: fractional anisotropy; CSTC: cortico striato thalamic cortical loop.
* Indicates $p < 0.05$; corrected for multiple comparison (false discovery rate; FDR).

3.5. Lesion patterns associated with fatigue in pwMS

Lesions (Fig. 2) along the left thalamus and striatum to the prefrontal cortex tract (part of the CSTC loop) correlated with cognitive fatigue ($p < 0.05$, corrected for age). Total and motor fatigue were not significantly correlated with a specific lesion pattern overlapping the CSTC loop.

3.6. Fatigue in NC

Detailed information on demographics, psychological, and MRI parameters of NC are presented in Table 1.

Out of 49 NC, 10 (20%) had at least mild total fatigue (7 (14%) mild, 2 (4%) moderate, 1 (2%) severe total fatigue). Eight (16%) NC had at least mild motor fatigue (5 (10%) mild, 3 (6%) moderate). 14 (29%) NC had at least mild cognitive fatigue (12 (25%) mild, 1 (2%) moderate, 1 (2%) severe cognitive fatigue). 1 NC had distinct motor (2%) and 7 NC (14%) suffered from distinct cognitive fatigue, respectively.

Considering that 10 persons of the NC cohort also reported at least mild total fatigue, we additionally conducted the analyses without these 10 NC. Since the results remained the same, we decided to include the entire sample of NC in the final analyses.

Total, motor, and cognitive fatigue correlated with demographics and psychological variables, but not with MRI parameters (Table 3).

A hierarchical linear regression model (adjusted $R^2 = 0.33$, $p < 0.001$) to predict total fatigue in NC explained 33% by psychological data. Level of depression ($\beta = 0.38$, 95% CI: 0.77, 3.58, $p = 0.003$) and self-efficacy ($\beta = -0.39$, 95% CI: −0.80, −0.19, $p = 0.002$) were significant independent predictors of total fatigue.

Motor fatigue (adjusted $R^2 = 0.28$, $p < 0.001$) was independently predicted by level of depression ($\beta = 0.42$, 95% CI: 0.51, 2.00, $p = 0.001$) and self-efficacy ($\beta = -0.29$, 95% CI: −0.34, −0.02, $p = 0.027$).

Cognitive fatigue (adjusted $R^2 = 0.44$, $p < 0.001$) was independently

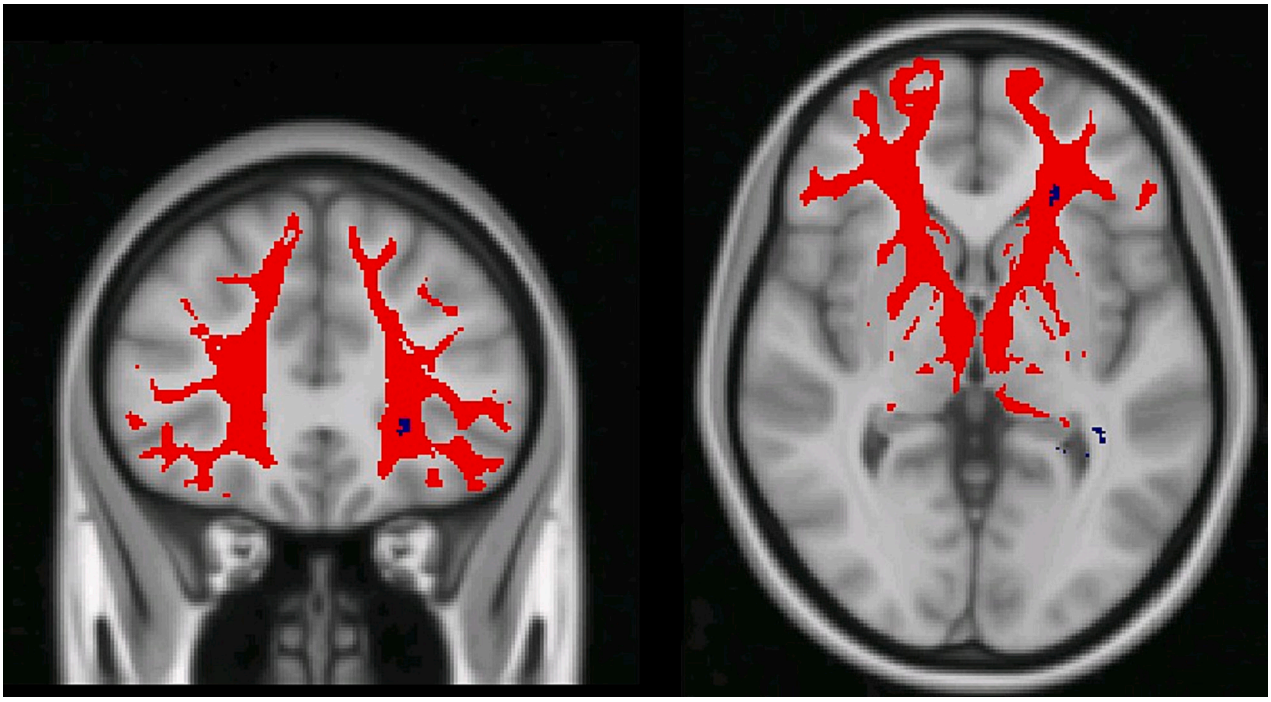

Fig. 2. Lesions associated with cognitive fatigue ($p < 0.05$; corrected for age).
Results of the lesion probability mapping showing lesions associated with cognitive fatigue; radiological orientation; blue: lesions associated with cognitive fatigue ($p < 0.05$; corrected for age); red: tract from thalamus and striatum to the prefrontal cortex, part of the CSTC loop. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Correlations between total, motor and cognitive fatigue and demographics, clinical, psychological and MRI variables in normal controls.

	Total fatigue N = 49, r (p)	Motor fatigue N = 49, r (p)	Cognitive fatigue N = 49, r (p)
Age	0.22 (0.284)	0.25 (0.211)	0.17 (0.519)
Sex	−0.28 (0.143)	−0.24 (0.211)	−0.29 (0.118)
Education	−0.03 (0.946)	−0.07 (0.830)	0.02 (0.907)
HADS – A	0.38 (0.029*)	0.32 (0.095)	0.40 (0.018*)
HADS – D	0.46 (0.006*)	0.49 (0.001*)	0.40 (0.018*)
SE	−0.48 (0.006*)	−0.38 (0.039*)	−0.53 (0.001*)
NBV	0.04 (0.946)	0.01 (0.975)	0.07 (0.873)
Thalamus volume	−0.08 (0.828)	−0.06 (0.830)	−0.09 (0.873)
Striatum volume	−0.15 (0.559)	−0.17 (0.475)	−0.12 (0.741)
FA CSTC loop	−0.19 (0.202)	−0.14 (0.332)	−0.21 (0.146)

N: number of patients; r: correlation coefficient; p: *p*-value; HADS-A: Hospital Anxiety and Depression Scale – Anxiety; HADS-D: Hospital Anxiety and Depression Scale – Depression; SE: self-efficacy; NBV: normalized brain volume; FA: fractional anisotropy; CSTC: cortico striato thalamic cortical loop.
* Indicates $p < 0.05$; corrected for multiple comparison (false discovery rate; FDR).

predicted by female sex ($\beta = -0.34$, 95% CI: −6.47, −1.37, $p = 0.003$), level of depression ($\beta = 0.30$, 95% CI: 0.24, 1.62, $p = 0.010$), and self-efficacy ($\beta = -0.49$, 95% CI: −0.48, −0.18, $p < 0.001$).

4. Discussion

Our findings show that fatigue in MS is influenced by multiple factors such as demographics, clinical, psychological, and MRI parameters, with the strongest contribution of modifiable psychological factors. Levels of depression and self-efficacy were strongly associated with MS-related total, motor, and cognitive fatigue (explaining 17–40% of the whole variance). Given the fact that fatigue is a subjectively perceived symptom, higher levels of depression and lower self-efficacy may lead to a higher perceived burden and subsequently reported fatigue severity in pwMS.

Fatigue in our patients cohort was present in 53% (at least mild total fatigue) of pwMS, whereas 56% had at least mild motor fatigue and 48% had at least mild cognitive fatigue. These numbers are within the range of the reported prevalence rates, ranging from 36% to 78% of fatigued pwMS [1].

In pwMS, total, motor, and cognitive fatigue showed the strongest correlations with psychological variables such as levels of depression, anxiety, and self-efficacy. These results are in line with current literature reporting a frequent coexistence of fatigue and depression in pwMS [34]. Furthermore, it is suggested that shared brain pathologies of both conditions may explain the common co-occurrence in pwMS [34]. However, fatigue was not only correlated with psychological variables, but also the level of depression was a significant independent predictor of all types of fatigue. This indicates that fatigue and depression may share some common features but indeed, they are distinct conditions in MS [35]. It is also noteworthy that the level of depression was the strongest predictor for total and cognitive fatigue. We assume that higher levels of depression often result in lower motivation and a stronger focus on negative effects of the disease [36] and therefore may lead to a higher perceived total and cognitive fatigue severity in pwMS. Furthermore, self-efficacy was a significant predictor of total, motor, and cognitive fatigue beyond the level of depression. Self-efficacy is defined as the individual belief in one's own capacity to mobilize resources and motivation to deal with critical situations and challenges in everyday life [37]. PwMS with lower self-efficacy might not believe that they are able to cope with their fatigue in everyday life and, therefore, might subjectively perceive fatigue, and especially cognitive fatigue stronger. These results are of critical importance and clinical relevance, since therapeutic approaches for reducing depression and improving self-efficacy (e.g., psychoeduction, cognitive behavioral therapy) [38] already exist and are well validated for clinical application [39]. In clinical practice, individual tasks of these therapeutic approaches could be combined for a specific fatigue management training for pwMS. Moreover, a patient's feeling of self-efficacy could be simply increased in

clinical routine by involving pwMS in decision-making and treatment planning by their clinicians [40].

Furthermore, incremental variance was explained by fractional anisotropy (FA) in tracts of the CSTC loop underlying total and cognitive fatigue. This finding is in line with recent work by Bertoli and Tecchio (2020) highlighting that fatigue is not sufficiently explored by focusing on single brain regions, but rather explained by changes in brain networks [41]. Due to an altered functioning of the neuronal communication in involved networks [41], tissue damage reflected by the FA in CSTC loop tracts might lead to a more strongly subjectively perceived total and cognitive fatigue in pwMS. Furthermore, lower FA in the CSTC loop may also reflect MS-related disconnections between cortical and subcortical brain regions. Disruptions in these pathways are known to increase the effort of compensatory mechanism that contribute to the pathogenesis of fatigue in MS [42]. We additionally assume that damage to the prefrontal parts of the CSTC loop could lead to less efficient top-down control, which negatively affects cognitive performance and higher perceived fatigue. Impaired top-down control (using prior knowledge, mental heuristics, goal-directed cognitive processes) and less effortful neural signalling potentially results in greater perceived cognitive fatigue [43].

It has to be mentioned, however, that we only observed small to moderate correlations between fatigue and MRI parameters such as T2-LL, normalized brain volume, thalamic volumes, striatal volumes, and FA changes of the CSTC loop. We therefore hypothesise that MS-related brain changes in brain (micro-) structure are more widespread and vary from patient to patient on MRI, as opposed to a simple sum score of a questionnaire. The diverse spatial variation of MS-related brain changes probably results in a lower statistical power of MRI parameters. Nonetheless, in the regression analyses, FA variations in the CSTC loop were the only significant MRI predictor of total and cognitive fatigue. We therefore assume that changes in structural MRI parameters are associated with MS-related fatigue, which is also described in earlier studies [6,44]. Furthermore, it appears that at least total and cognitive fatigue might result primarily from damage in neuronal networks such as the CSTC loop.

Another surprising yet interesting finding is that motor fatigue correlated with most of the MRI parameters, but in the regression analyses none of the MRI variables significantly added to the prediction of motor fatigue. Interestingly, the strongest single predictor of motor fatigue was physical impairment (as measured by the EDSS). This is in line with previous studies reporting moderate to strong correlations between EDSS and fatigue [9,45]. However, latest literature reports that fatigue is not necessarily associated with the degree of physical disability or disease stage [46]. As a consequence, we assume that pwMS with increased physical impairment may need more effort to manage their daily life and due to that, they perceive the motor aspects of fatigue more strongly.

A further noteworthy result of our study is that only lesions overlapping with the pathway from the thalamus to the prefrontal cortex tract (as part of the CSTC loop) were associated with cognitive fatigue. The thalamus and its connections to cortical areas are known to play a crucial role in the development of fatigue [42]. Lesions in thalamo-frontal connections may lead to compensatory mechanism such as rerouting of neuronal signalling via other pathways. This reorganization process may result in an additional effort to compensate for impaired structural connectivity to frontal areas involved in cognitive processes (e.g. memory, executive functions, top down control) [42,47,48], leading to greater perceived cognitive fatigue in pwMS. However, regarding total and motor fatigue, we did not observe any association with a specific lesion pattern overlapping with the tracts of the CSTC loop. It has been previously shown that white matter lesions result in a greater decrease of FA in the surrounding area [49]. Therefore, it was surprising that we only found one lesion pattern associated with cognitive fatigue overlapping with the CSTC loop. However, lesions are only the 'tip of the pathological iceberg' affecting further the microstructure of normal appearing white matter (NAWM) in the rest of the brain [49]. Since lower FA values across the entire CSTC loop were the only significant MRI parameter predicting cognitive and total fatigue, we assume that the wide spreading effect of white matter lesions on the NAWM is reflected in the FA even though we did not observe specific lesion pattern overlapping the CSTC loop.

In normal controls, 20% reported at least mild fatigue (compared to 53% in pwMS), which is in line with previous studies [50]. In contrast to pwMS, the influencing factors of fatigue were only psychological variables and demographics, but not MRI variables. This supports the assumption that the association between fatigue and brain damage is unique to MS-related fatigue.

Some limitations have to be considered when interpreting our results. First, the cross-sectional design did not allow us to describe the time-dependent association between psychological variables, MRI paramters, and fatigue. Second, as we only focused on psychological and MRI parameters influencing fatigue, it would be of great interest for future studies to also include biomarkers (e.g., inflammatory body fluid biomarkers) and sleep quality that is known to be associated with perceived fatigue in pwMS [10]. Third, due to our sample size and the current suggestions of the literature, we only focused on white matter tracts of the CSTC loop. However, different white matter tracts (e.g. particularly associative tracts connected to frontal lobes such as frontal and occipital juxtacortical fibers, the external capsule, uncinated fasciculus, forceps minor, superior longitudinal fasciculus, and cingulum [51]) may also contribute to the prediction of fatigue.

5. Conclusion

In conclusion, our results highlight the important role of malleable factors such as level of depression and self-efficacy regarding total, cognitive, and motor fatigue in pwMS. According to this, psychological interventions such as psychoeducation, cognitive behavioral therapy, or fatigue management training might help to reduce fatigue and to improve patients' quality of life. Furthermore, incremental variance of total and cognitive fatigue was explained by FA changes along the CSTC tracts. This emphasizes the importance to explore brain networks regarding fatigue.

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Ethics approval

This prospective study was approved by the ethics committee of the Medical University of Graz (permit number 31–432 ex 18/191264–2019).

Consent to participate

All participants included in the study gave written informed consent.

Consent for publication

All data was anonymized.

CRediT authorship contribution statement

Stefanie Hechenberger: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. **Birgit Helmlinger:** Formal analysis, Writing – review & editing. **Iris-Katharina Penner:** Writing – review & editing. **Lukas Pirpamer:** Writing – review & editing. **Viktoria Fruhwirth:** Writing – review & editing. **Bettina Heschl:** Writing – review & editing. **Stefan Ropele:** Data curation, Writing –

review & editing. **Sebastian Wurth:** Writing – review & editing. **Anna Damulina:** Writing – review & editing. **Sebastian Eppinger:** Writing – review & editing. **Rina Demjaha:** Writing – review & editing. **Michael Khalil:** Validation, Writing – review & editing. **Daniela Pinter:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Christian Enzinger:** Conceptualization, Methodology, Validation, Writing – review & editing, Resources, Supervision.

Declaration of Competing Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

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Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2023.120833.

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