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ORIGINAL ARTICLE

Neural distinctiveness of fatigue and low sleep quality in multiple sclerosis

Adriana L. Ruiz-Rizzo[1,2] | Peter Bublak[2] | Steffen Kluckow[2] | Kathrin Finke[1,2] | Christian Gaser[2] | Matthias Schwab[2] | Daniel Güllmar[2] | Hermann J. Müller[1] | Otto W. Witte[2] | Sven Rupprecht[2]

[1]Department of Psychology, General and Experimental Psychology Unit, LMU Munich, Munich, Germany

[2]Department of Neurology, Jena University Hospital, Jena, Germany

Correspondence
Adriana L. Ruiz-Rizzo, Department of Psychology, Ludwig-Maximilians-Universität München, Leopoldstr. 13, Munich 80802, Germany.
Email: Adriana.RuizRizzo@med.uni-jena.de

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Abstract

Background and purpose: Fatigue and low sleep quality in multiple sclerosis (MS) are closely related symptoms. Here, the associations between the brain's functional connectivity (FC) and fatigue and low sleep quality were investigated to determine the degree of neural distinctiveness of these symptoms.

Method: A hundred and four patients with relapsing–remitting MS (age 38.9 ± 10.2 years, 66 females) completed the Modified Fatigue Impact Scale and the Pittsburgh Sleep Quality Index and underwent resting-state functional magnetic resonance imaging. FC was analyzed using independent-component analysis in sensorimotor, default-mode, fronto-parietal and basal-ganglia networks. Multiple linear regression models allowed us to test the association between FC and fatigue and sleep quality whilst controlling for one another as well as for demographic, disease-related and imaging variables.

Results: Higher fatigue correlated with lower sleep quality ($r = 0.54$, $p < 0.0001$). Higher fatigue was associated with lower FC of the precentral gyrus in the sensorimotor network, the precuneus in the posterior default-mode network and the superior frontal gyrus in the left fronto-parietal network, independently of sleep quality. Lower sleep quality was associated with lower FC of the left intraparietal sulcus in the left fronto-parietal network, independently of fatigue. Specific associations were found between fatigue and the sensorimotor network's global FC and between low sleep quality and the left fronto-parietal network's global FC.

Conclusion: Despite the high correlation between fatigue and low sleep quality in the clinical picture, our findings clearly indicate that, on the neural level, fatigue and low sleep quality in MS are associated with decreased FC in distinct functional brain networks.

KEYWORDS
functional connectivity, left fronto-parietal network, multiple sclerosis, resting-state fMRI, sensorimotor network

[Correction added on 7 July 2022 after first online publication: The symbol above the Greek beta letter in the text of 'Statistical analysis' and 'Results' was corrected.]

INTRODUCTION

Fatigue represents one of the most disabling and burdening secondary symptoms in multiple sclerosis (MS) impacting the quality of life [1, 2] in the majority of patients [3, 4], with a prevalence of 36.5%–78.0% [5]. Fatigue in MS is complex and involves symptoms of energy loss, sleepiness and/or the inability to sustain mental or physical activity [6]. Due to its multidimensionality, the pathophysiological background of fatigue is incompletely understood [7, 8] and treatment approaches thus remain limited. Sleep disturbances [9] (e.g., in maintaining sleep), poor sleep quality [10–12] and alterations of sleep microstructure [12] (e.g., spontaneous arousals or periodic limb movements) are closely linked to fatigue. For example, coefficients of the relationships between fatigue and insomnia [9], sleep quality [11] or sleep latency [12] range from |0.4| to |0.5| in previous MS samples. Although sleep disorders (e.g., insomnia, sleep-related breathing disorders or restless-legs syndrome) are highly prevalent in MS [13, 14], with estimates ranging between 42% and 65% [15], they can go unnoticed if referred to as complaints of fatigue. Furthermore, sleep disorders require treatment approaches that differ from those used for fatigue [16, 17]. Thus, it is crucial to determine to what extent fatigue and low sleep quality represent two distinct phenomena, rather than two aspects of the same clinical phenomenon. Here, it is sought to determine their degree of overlap at the neural level by investigating their distinctive association with the connectivity within functional brain networks.

Studies on the correlated activity of cortical and subcortical brain regions based on the spontaneous fluctuations of the blood oxygenation level dependent signal during resting-state functional magnetic resonance imaging (fMRI), that is, functional connectivity (FC), have shed light on the level of disease disability [18] and cognitive impairments [19, 20] in MS. For example, previous studies focusing on fatigue in MS have examined the FC in the sensorimotor network (i.e., including precentral and postcentral cortices) [21], default-mode network (i.e., including medial prefrontal and parietal cortices) [22, 23] and subcortical network (i.e., including basal-ganglia and thalamus) [24–26] in particular. One of the scarce studies on sleep in MS patients showed reduced FC between the fronto-parietal and thalamic regions to be linked to an increase in sleep disturbances [27]. Reduced FC in the fronto-parietal regions (i.e., inferior parietal and left orbital middle frontal cortices) has also been associated with poor sleep quality in healthy adults [28]. Together, this evidence suggests associations between the FC of the thalamic/basal-ganglia, sensorimotor and fronto-parietal networks with fatigue and poor sleep quality in MS. Revealing distinct functional network correlates for fatigue and poor sleep quality in MS can prove beneficial for determining the degree of independence of these symptoms. In particular, identifying these functional neural correlates could provide information on candidate target regions for the analysis of potential changes in the functional organization of the brain. However, despite its relevance, the degree of distinctiveness of these associations is yet unclear.

Here, the associations of FC in sensorimotor, default-mode, basal-ganglia and fronto-parietal networks with fatigue and sleep quality were assessed in MS patients. Based on the assumption that fatigue and low sleep quality are partially independent symptoms, it was hypothesized that (i) the association between FC and fatigue would be predominantly observed in sensorimotor, default-mode and/or subcortical networks controlling for sleep quality, whereas (ii) the association between FC and sleep quality would be predominantly observed in fronto-parietal and/or subcortical networks controlling for fatigue.

MATERIALS AND METHODS

Participants

The study was approved by the Jena University Hospital Ethics Committee (3948-12/13) and registered at the German Clinical Trials Register (DRKS00005625). All patients gave written informed consent before participating in the study, in accordance with the Declaration of Helsinki. A hundred and thirteen patients with relapsing–remitting MS, drawn from the baseline measurement of a longitudinal study at the Jena University Hospital, were included in the present study. The main selection criterion was complete resting-state fMRI, fatigue and sleep quality data. Inclusion criteria for the larger study were a confirmed MS diagnosis, according to the revised McDonald criteria [29], and age between 18 and 65 years. Exclusion criteria were acute relapse (i.e., 4 weeks or less, including the need for glucocorticoid therapy), immunosuppressive treatment for reasons other than MS, pregnancy, any systemic diseases and/or related treatment influencing cognition, and severe depression or suicidal ideation. Specifically for the current study, exclusion criteria were low global cognitive status (Montreal Cognitive Assessment [MoCA] ≤ 23; $n = 6$) [30], to control for the confounding effect of marked global cognitive impairment [31]. One further patient was excluded because of extreme disease duration (>30 years, >1.5 interquartile range from the sample median) and two patients due to fMRI data issues (i.e., enlarged ventricles and ventral signal loss). The remaining 104 participants (mean age 38.9 ± 10.2 years; 66 females) had complete and valid imaging and behavioral data, no marked global cognitive decline and comparable overall functioning (Table 1). The clinical visit (including the questionnaires and physical examination) was performed within 14 days around the date of the MRI.

Clinical measures

Disability status

Disability status was determined with the Expanded Disability Status Scale (EDSS) [32], which quantifies the level of disability in MS from 0 (normal neurological examination) to 10 (death due to

TABLE 1 Demographic and clinical data of the study sample

Variable	*n* = 104, mean (SD), *N* (%)
Age (years)	38.9 (10.2)
Sex	
Male	38 (36.5%)
Female	66 (63.5%)
Education levels[a]	
Lower secondary level	3 (2.9%)
Upper secondary level A	57 (54.8%)
Upper secondary level B	44 (42.3%)
Disease duration (years)	10.3 (6.1)
Current medication for MS (yes)[b]	92 (88.5%)
Number of relapses (last year)	
0	74 (71.2%)
1	20 (20.4%)
≥2	10 (10.2%)
Disability status (EDSS)	
<3	61 (58.7%)
3–7	43 (41.3%)
Total lesion volume (FLAIR) (ml)	10.7 (9.6)
Functional impairment (MSFC)[c]	0.4 (0.5)
Auditory information processing speed (PASAT)[d]	0.2 (0.8)
Global cognitive status (MoCA)	28.8 (1.3)
Depression/anxiety (HADS-D)	11.1 (7.6)
Subjective fatigue (MFIS)	35.8 (20.5)
Sleep quality (PSQI)	6.5 (3.5)

Abbreviations: EDSS, Expanded Disability Status Scale; FLAIR, fluid-attenuated inversion recovery; HADS-D, Hospital Anxiety and Depression Scale, German version (sum of scales); MFIS, Modified Fatigue Impact Scale (total score); MoCA, Montreal Cognitive Assessment (total score); MS. Multiple sclerosis; MSFC, MS Functional Composite (total score); PASAT, Paced Auditory Serial Addition Test; PSQI, Pittsburgh Sleep Quality Index (global score).

[a]German education system (the three levels correspond to Hauptschule, Realschule and Gymnasium, respectively).

[b]Specific medication types are listed in Appendix S1.

[c]Two missing observations.

[d]Three missing observations.

MS), with incremental units of 0.5. The EDSS score was used to control for the covariance of disability with fatigue and/or sleep quality.

Functional status

Disease status was assessed with the MS Functional Composite (MSFC) [33], which captures major clinical dimensions (i.e., arm, leg and cognitive function). The MSFC total score, computed as the average of the *z*-scores (i.e., standardized across the entire baseline cohort) in each of the MSFC measures (i.e., lower extremity function and ambulation, upper extremity function, and cognitive function: speed of auditory information processing and calculation, assessed with the Paced Auditory Serial Addition Test, PASAT) was obtained.

Global cognitive status

The MoCA [30] was used to characterize the patients' global cognitive status and rule out possible marked global cognitive impairment. According to recent suggestions [34], a cutoff of 23 (maximum 30) was used as an indicator of marked global cognitive impairment.

Psychiatric comorbidities

Symptoms of anxiety and depression were assessed using the German version of the Hospital Anxiety and Depression Scale (HADS-D) [35], a self-administered 14-item questionnaire with a 4-point response category (0 to 3) that allows symptoms of anxiety (seven questions) and depression (seven questions) to be measured. To avoid collinearity whilst including both variables in the linear regression models (e.g., given their known high correlation, also observed in these data: $r = 0.63$, $p < 0.0001$), an overall score was computed reflecting the degree of psychological burden, ranging from 0 to 42, by adding up all questions' scores. This aggregate score was used as a control covariate in the regression models.

Measures of fatigue and sleep quality

Fatigue

To measure fatigue, a German version of the Modified Fatigue Impact Scale (MFIS) [36] was used to assess how frequently fatigue has impacted patients' daily living during the past 4 weeks on a 0–4 Likert scale ("never" to "almost always"). The MFIS consists of 21 items (nine "physical", 10 "cognitive" and two "psychosocial"); the maximum possible total score is 84 (higher scores indicate a greater impact of fatigue). The established cutoff score of 38 was used to define low versus high fatigue.

Sleep quality

To measure sleep quality, the Pittsburgh Sleep Quality Index (PSQI) [37], a self-rated questionnaire that provides estimates of sleep duration and latency and of the frequency and severity of sleep disturbances over the past month, was used. The PSQI consists of 19 questions, grouped into seven components (i.e., subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep

disturbances, use of sleep medication and daytime dysfunction), each weighted on a 0–3 point scale. The PSQI global score thus ranges between 0 and 21 (higher scores indicate worse sleep quality). The established cutoff of 5 was used to define high versus low sleep quality.

Magnetic resonance imaging data acquisition

Magnetic resonance imaging data were acquired on a Siemens Prisma Fit 3 T (Siemens Healthineers) MRI scanner using a 64-channel head coil. A high-resolution, T1-weighted whole-brain volume was acquired for each participant using a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (with generalized autocalibrating partially parallel acquisition [GRAPPA] acceleration factor of 2) in sagittal image orientation. The following imaging parameters were used: repetition time (TR) 2300 ms; echo time (TE) 3.03 ms; flip angle 9°; inversion time (TI) 900 ms; field of view (FOV) 256 mm; matrix size 256 × 256; voxel size 1 mm^3; no interslice gap; 192 slices; no fat suppression; phase-encoding direction A→P; and total acquisition time (TA) 5 min 21 s. Additionally, whole-brain volumes of blood oxygenation level dependent fMRI were acquired whilst patients were resting with their eyes closed. Forty-five (ascending) interleaved axial slices were acquired for each brain volume with a T2*-weighted echo-planar imaging sequence (with GRAPPA acceleration factor 2) and the following parameters: TR = 2540 ms; TE = 30 ms; flip angle 90°; FOV = 252 mm; matrix size 84 × 84; voxel size 3 mm isotropic; slice thickness 3 mm, no interslice gap; phase-encoding direction A→P; 203 volumes; and TA = 8 min 43 s.

Total white matter lesion volume (TLV)

White matter lesions were segmented based on the T1-weighted and the fluid-attenuated inversion recovery image in order to compute the degree of damage in the white matter for each patient (see Appendix S1). TLV was included in the statistical analyses of FC as a general measure of the impact of MS on white matter.

Resting-state fMRI data preprocessing

Resting-state fMRI data preprocessing included discarding the first three volumes, slice-timing correction, co-registration of the functional and structural images, normalization to Montreal Neurological Institute space, nuisance covariate regression, temporal filtering (0.01–0.1 Hz), smoothing (6 mm full-width at half-maximum Gaussian kernel), linear detrending, despiking and removal of non-neural physiological (i.e., cardiac and respiratory) signals and between-slice motion (see Appendix S1).

Functional connectivity analysis

Independent-component analysis (ICA) and dual regression

Functional connectivity was estimated by a spatial group ICA of the preprocessed resting-state fMRI data (30 components), yielding 30 group-level spatial maps with associated time courses. Next, individual-level spatial maps and associated time courses were obtained, which were then used for group statistical analyses (see Appendix S1 for details).

Network selection

To identify networks of interest, our 30 ICA spatial maps were cross-correlated with the 28 resting-state network maps reported by Allen et al. [38] (available at https://trendscenter.org/data/). The spatial maps exhibiting the highest correlation coefficients and including, by visual inspection, the brain regions expected for that network were selected as networks of interest on which the group statistical analyses were conducted (see Appendix S1).

Statistical analyses

To test whether and on which networks the association between FC and fatigue and sleep quality would be observed, two complementary types of multiple linear regression models were used, namely voxelwise (within each network, to obtain anatomical specificity) and global (including all networks, to control for the FC of all networks; see Appendix S1 for details). In the voxelwise regressions, both fatigue and sleep quality were included as predictors (to control for the effect of each other) of FC across all voxels of each of the networks of interest. In the global regressions, all networks' average or global FC—obtained by calculating the mean across all voxels belonging to a given network (i.e., z-value > 0)—were included as predictors (to control for the effect of each other) of fatigue and sleep quality. Both model types included the HADS-D, TLV, EDSS, age, sex, education and mean frame-wise displacement (head motion) as covariates of no interest because these variables may relate to functional abnormalities within large-scale networks in MS [23–40] and to ensure the specificity of observed associations. The threshold-free cluster enhancement approach (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise/UserGuide) was used to assess significance in the voxelwise regressions, which did not require a minimum cluster size to be specified, and with family-wise error correction across space ($\alpha = 0.05$). Significant results were further corrected for the false discovery rate ($q < 0.05$) to account for the multiple networks for which the associations with fatigue and sleep quality were tested. Pearson's product–moment correlations were used to test the zero-order

correlation between the behavioral variables. Welch's two-sample *t* tests were used to test differences between two levels of a categorical variable. All hypothesis-testing results were considered significant at an $\alpha = 0.05$, and standard errors, 95% confidence intervals and partial eta squared (η_p^2) for the estimated unstandardized betas ($\hat{\beta}$) are reported where appropriate. Analysis scripts used to generate the present results can be accessed at https://osf.io/y865u/.

RESULTS

Fatigue and sleep quality

The proportion of participants with high/low fatigue and high/low sleep quality, as defined by the respective cutoffs, is shown in Table 2. Higher fatigue was correlated with lower sleep quality ($r_{104} = 0.54$, $p < 0.0001$). Both higher fatigue and lower sleep quality correlated with advancing age (fatigue $r_{104} = 0.35$, $p = 0.0003$; sleep quality $r_{104} = 0.27$, $p = 0.005$) and with higher depression/anxiety scores (fatigue $r_{104} = 0.66$, $p < 0.0001$; sleep quality $r_{104} = 0.54$, $p < 0.0001$) but not with poorer global cognitive status (MoCA, both *p* values > 0.409). Only fatigue correlated with auditory processing speed (PASAT) ($r_{101} = -0.26$, $p = 0.007$) and education level ($r_{104} = -0.24$, $p = 0.013$), whilst sleep quality did not (all *p* values >0.10). Finally, neither fatigue nor sleep quality correlated with TLV ($r_{104} = 0.11$ and $r_{104} = -0.03$, respectively; both *p* values > 0.272) or head motion ($r_{104} = -0.10$ in both cases; both *p* values > 0.299).

Fatigue, sleep quality and voxelwise within-network FC

Seven brain networks were identified and selected (Figure 1): namely two sensorimotor (lateral and central, Figure 1a); one basal-ganglia (Figure 1a); two default-mode (anterior and posterior, Figure 1b); and two lateralized fronto-parietal (left and right, Figure 1c). To obtain within-network anatomical information, the association of fatigue and sleep quality with FC was assessed in each of these networks. Higher fatigue was significantly associated with lower FC in the precentral gyrus within the sensorimotor networks, in the precuneus/posterior cingulate cortex within the posterior default-mode network and in the superior frontal gyrus within the left fronto-parietal network (Table 3 and Figure 2a). Moreover, lower sleep quality was associated with lower FC in the left intraparietal sulcus within the left fronto-parietal network (Table 3 and Figure 2b; all *p* values <0.05, family-wise-error-corrected at the cluster level; all of these results further survived false-discovery-rate correction, $q < 0.05$). No significant results were observed in the basal-ganglia, anterior default-mode or right fronto-parietal networks, and no opposite associations (i.e., higher fatigue or lower sleep quality related to higher FC) for any of the networks.

TABLE 2 Frequency of high fatigue and low sleep quality

	Sleep quality		
Fatigue	**High**	**Low**	**Total**
High	9 (9%)	42 (40%)	51 (49%)
Low	26 (25%)	27 (26%)	53 (51%)
Total	35 (34%)	69 (66%)	104 (100%)

Note: Cell percentages are based on the total sample.

Fatigue, sleep quality and global within-network functional connectivity

In line with the voxelwise results, the global FC of the central sensorimotor network was associated with fatigue (Table 4 and Figure 3a; $\hat{\beta} = -4.03$, SE = 1.80, $p = 0.027$, $\eta_p^2 = 0.05$). Additionally, sleep quality ($\hat{\beta} = 1.07$, SE = 0.51, $p = 0.041$, $\eta_p^2 = 0.05$) and depression/anxiety ($\hat{\beta} = 1.33$, SE = 0.23, $p < 0.0001$, $\eta_p^2 = 0.28$) were positively associated with fatigue, as expected from the literature. No other predictor variable was significantly associated with fatigue.

As with the voxelwise results, the left fronto-parietal network's global FC ($\hat{\beta} = -0.80$, SE = 0.40, $p = 0.048$, $\eta_p^2 = 0.04$) was associated with sleep quality (Table 5 and Figure 3b). From the clinical variables, only fatigue ($\hat{\beta} = 0.04$, SE = 0.02, $p = 0.041$, $\eta_p^2 = 0.05$; as already shown in the fatigue model for the sleep quality predictor) and depression/anxiety ($\hat{\beta} = 0.14$, SE = 0.05, $p = 0.010$, $\eta_p^2 = 0.07$) were associated with sleep quality as expected from the literature. No other predictor variable was significantly associated with sleep quality. Notably, the effect size of the depression/anxiety predictor was lower compared to its effect size in the fatigue model (i.e., 7% here vs. 25% there).

DISCUSSION

Although fatigue and poor sleep quality in relapsing–remitting MS are clinically interrelated, our results indicate that they exhibit distinct separate neural correlates in functional brain networks. More specifically, higher fatigue was associated with lower FC in frontal and medial parietal regions within three functional brain networks (sensorimotor, posterior default-mode and left fronto-parietal network), independently of sleep quality, depression/anxiety, disability status, age, sex and head motion. In contrast, lower sleep quality was associated with lower FC of the left intraparietal sulcus within the left fronto-parietal network, independently of fatigue, depression/anxiety, disability status, age, sex and head motion. Global FC analyses across networks revealed connectivity in the central sensorimotor network to be specifically associated with fatigue, whereas connectivity in the left fronto-parietal network was specifically associated with sleep quality over and above the associations between fatigue and sleep quality or of these two with depression/anxiety.

In the present study, higher fatigue was associated with lower FC in (i) the left precentral gyrus/premotor cortex (sensorimotor

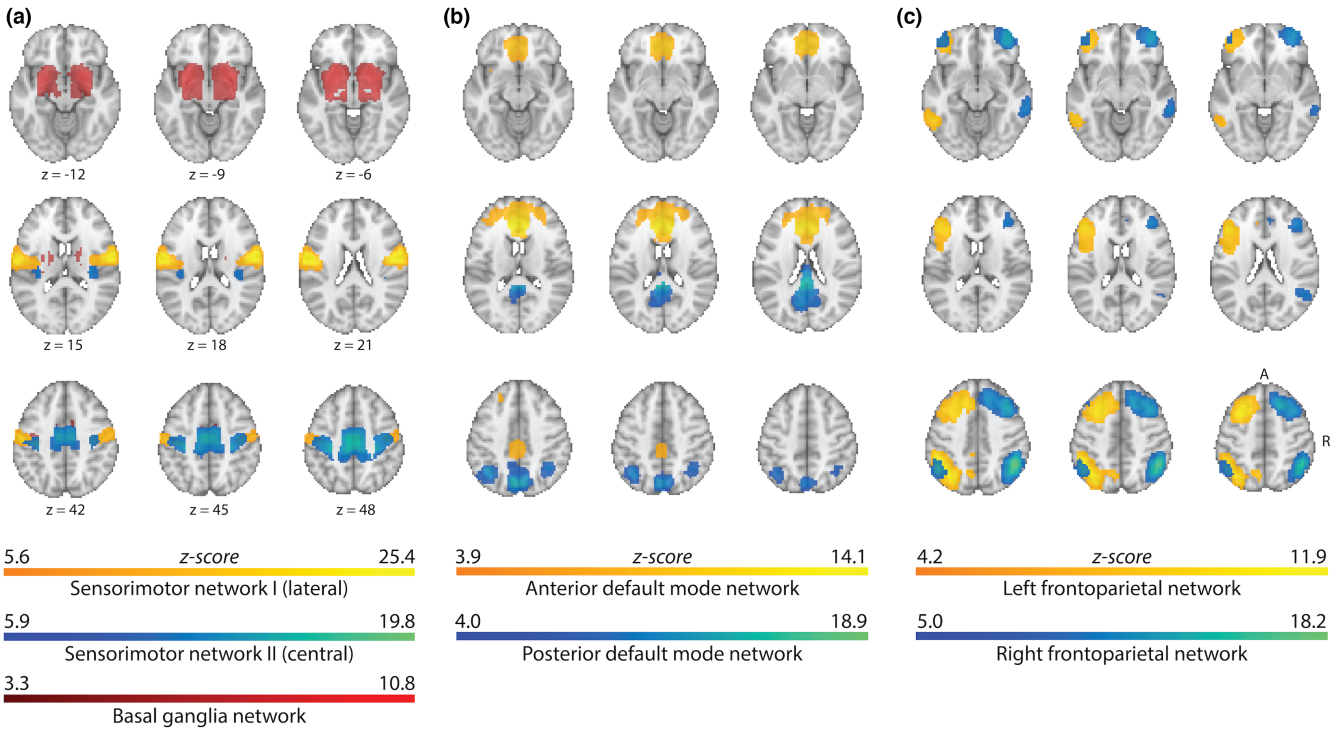

FIGURE 1 Independent components representing the networks of interest. Group spatial maps representing the networks of interest for fatigue and sleep quality in multiple sclerosis: (a) sensorimotor (lateral in yellow and central in blue) and basal ganglia (in red), (b) default mode (anterior in yellow and posterior in blue) and (c) fronto-parietal (left in yellow and right in blue). Color bars represent the components' *z*-scores (thresholded using as a cutoff $\bar{x} + 4\bar{\sigma}$) (following Allen et al. [38]). All spatial maps are overlaid on the same axial slices of a T1-weighted Montreal Neurological Institute template. A, anterior; R, right [Correction added on 7 July 2022 after first online publication: The symbol above the "x" and the Greek letter sigma was corrected.]

TABLE 3 Significant clusters of the voxelwise within-network FC analysis

Network	Anatomical location	Cluster size (*k*)	MNI *x*–*y*–*z* coordinates of the peak voxel (mm)	Peak voxel's *t*-statistic (*p* value)
Association with fatigue				
Sensorimotor I (lateral)	L precentral gyrus	15	−57 −6 24	4.04 (0.020)
	L postcentral gyrus	1	−51 −18 33	3.57 (0.050)
Sensorimotor II (central)	L precentral gyrus	55	−27 −18 63	4.11 (0.012)
	L premotor cortex	27	0 −12 63	3.96 (0.021)
	R precentral gyrus	16	24 −30 63	3.19 (0.043)
		13	33 −24 57	3.44 (0.034)
Posterior default mode	R precuneus	11	15 −51 27	4.96 (0.009)
	L posterior cingulate gyrus	8	−9 −54 27	3.69 (0.037)
	L precuneus	1	−15 −54 36	3.79 (0.044)
Left fronto-parietal	L superior frontal gyrus	6	−24 18 42	4.35 (0.031)
Association with sleep quality				
Left fronto-parietal	L intraparietal sulcus	26	−45 −39 36	3.86 (0.020)

Abbreviations: FC, functional connectivity; L, left; MNI, Montreal Neurological Institute; R, right.

FIGURE 2 Relationship between fatigue/sleep quality and within-network functional connectivity (FC). (a) Higher fatigue (i.e., higher MFIS score) is associated with lower FC in the left precentral gyrus (or primary motor cortex) within the sensorimotor network (SMN I and II, first and second row, respectively), as well as in the right precuneus/posterior cingulate cortex within the posterior default-mode network (PDMN, third row) and the left superior frontal gyrus within the left fronto-parietal network (LFPN, fourth row). (b) Lower sleep quality (i.e., higher PSQI score) is associated with lower FC in the left intraparietal sulcus within the LFPN. Significant voxels are shown at two levels of significance: $p < 0.05$ (in red) and $p < 0.025$ (in yellow). MFIS, Modified Fatigue Impact Scale; PSQI, Pittsburgh Sleep Quality Index

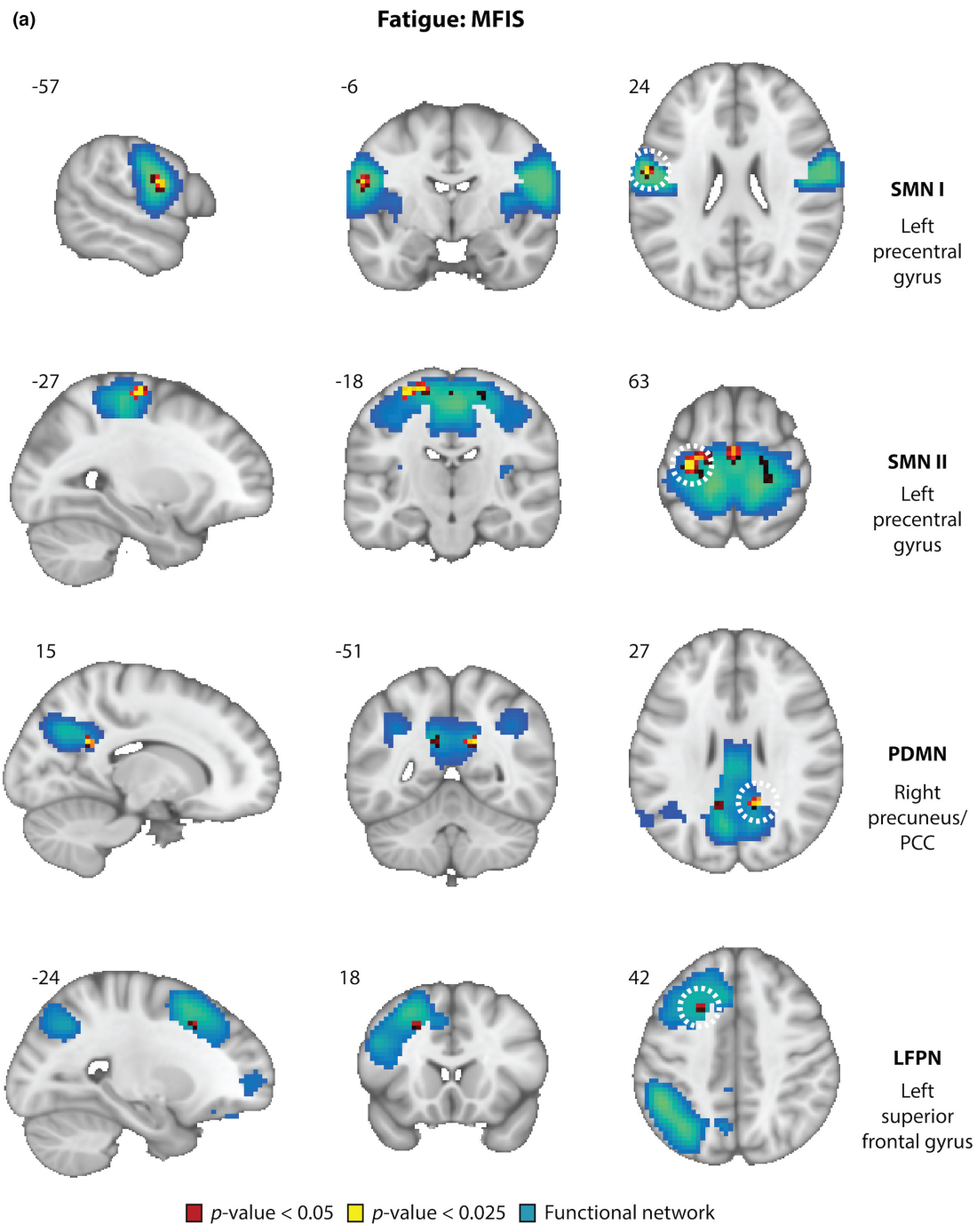
(a)
Fatigue: MFIS
-57
-6
24
SMN I
Left precentral gyrus
-27
-18
63
SMN II
Left precentral gyrus
15
-51
27
PDMN
Right precuneus/ PCC
-24
18
42
LFPN
Left superior frontal gyrus
p-value < 0.05
p-value < 0.025
Functional network
(b)
Sleep Quality: PSQI
-45
-39
36
L
LFPN
Left intraparietal sulcus

TABLE 4 Summary table of the regression model for fatigue

Predictor variable	Beta	SE	95% CI	*p* value
Network variables				
FC BGN	0.24	2.32	−4.4, 4.8	>0.9
FC SMN-I	−1.20	1.47	−4.1, 1.7	0.4
FC SMN-II	−4.03	1.80	−7.6, −0.46	**0.027**
FC ADMN	2.21	2.21	−2.2, 6.6	0.3
FC PDMN	−1.54	2.09	−5.7, 2.6	0.5
FC LFPN	−2.95	2.00	−6.9, 1.0	0.14
FC RFPN	2.35	2.42	−2.5, 7.2	0.3
Clinical variables				
Sleep quality	1.07	0.515	0.05, 2.1	**0.041**
Depression/anxiety	1.33	0.229	0.88, 1.8	**<0.001**
Total lesion volume	−0.06	0.163	−0.38, 0.26	0.7
Disability status	2.15	1.20	−0.24, 4.5	0.078
Demographic variables				
Age	0.16	0.181	−0.20, 0.52	0.4
Sex				
Male	—	—	—	
Female	−3.10	3.10	−9.3, 3.1	0.3
Education level	−3.85	2.65	−9.1, 1.4	0.15
Imaging variable				
Head motion	32.92	408	−778, 843	>0.9

Note: Significant *p* values are in boldface.

Abbreviations: ADMN, anterior default-mode network; BGN, basal-ganglia network; CI, confidence interval; FC, functional connectivity; LFPN, left fronto-parietal network; PDMN, posterior default-mode network; RFPN, right fronto-parietal network; SMN, sensorimotor network (-I, lateral; -II, central).

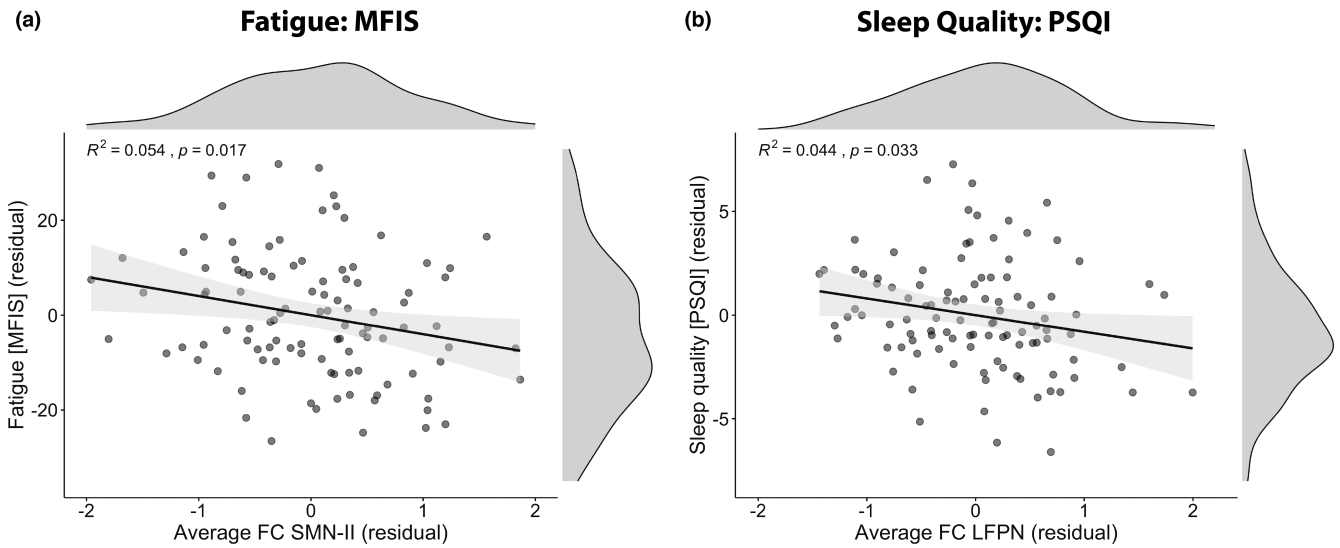

FIGURE 3 Fatigue, sleep quality and global network FC. The two networks with significant results in the regression models for fatigue and sleep quality (i.e., SMN-II and LFPN, respectively) are depicted as scatter plots in (a) and (b), respectively. The density plots parallel to the scatter plot axes show the data distribution for each variable. The shaded area around the regression line marks the 95% confidence interval. FC, functional connectivity; LFPN, left fronto-parietal network; MFIS, Modified Fatigue Impact Scale; PSQI, Pittsburgh Sleep Quality Index; SMN-II, central sensorimotor network

TABLE 5 Summary table of the regression model for sleep quality

Predictor variable	Beta	SE	95% CI	*p* value
Network variables				
FC BGN	0.37	0.467	−0.56, 1.3	0.4
FC SMN-I	0.33	0.297	−0.26, 0.92	0.3
FC SMN-II	0.09	0.373	−0.65, 0.84	0.8
FC ADMN	0.14	0.448	−0.75, 1.0	0.8
FC PDMN	0.05	0.424	−0.79, 0.90	0.9
FC LFPN	−0.80	0.400	−1.6, −0.01	**0.048**
FC RFPN	−0.57	0.488	−1.5, 0.40	0.2
Clinical variables				
Fatigue	0.04	0.021	0.00, 0.09	**0.041**
Depression/anxiety	0.14	0.052	0.03, 0.24	**0.010**
Total lesion volume	−0.05	0.033	−0.11, 0.02	0.2
Disability status	0.23	0.247	−0.26, 0.72	0.4
Demographic variables				
Age	0.07	0.036	0.00, 0.14	0.059
Sex				
Male	—	—	—	
Female	1.10	0.620	−0.13, 2.3	0.078
Education level	0.02	0.542	−1.1, 1.1	>0.9
Imaging variable				
Head motion	−82.62	82.0	−246, 80	0.3

Note: Significant *p* values are in boldface.

Abbreviations: ADMN, anterior default-mode network; BGN, basal-ganglia network; CI, confidence interval; FC, functional connectivity; LFPN, left fronto-parietal network; PDMN, posterior default-mode network; RFPN, right fronto-parietal network; SMN, sensorimotor network (-I, lateral; -II, central).

networks), (ii) the right precuneus/posterior cingulate cortex (posterior default-mode network) and (iii) the left superior frontal gyrus (left fronto-parietal network). These results are in line with previous findings of decreased FC in sensorimotor [21, 24], left dorsal prefrontal and medial parietal [25] and default-mode network [22, 23] regions in MS patients with higher versus lower fatigue. Our findings, however, go beyond this by indicating that the association between fatigue and FC in sensorimotor, parietal and frontal brain regions is independent of the potential effects of low sleep quality or depression/anxiety on fatigue [11]—a fundamental question that had not been directly addressed in the past. The associations of fatigue with brain regions in both "higher-order"/cognitive (i.e., default-mode and fronto-parietal) and "lower-order" (i.e., sensorimotor) networks reflect the inherent complexity of the fatigue experience, which spans both mental and physical spheres. Fatigue has been related to behavioral interoceptive disturbances (i.e., in the processing of signals from the internal milieu) in MS [41]. FC involving the brain regions associated with fatigue in the present study has been found to converge as part of the wider "allostatic-interoceptive system" [42], a domain-general brain system that matches the body's physiology with behavior [43]. Taken together, the present and previous evidence thus suggest that the decreased FC in these brain regions might reflect interoceptive disturbances. This suggestion should be directly tested in future studies.

Lower sleep quality was associated with lower FC in the left intraparietal sulcus within the left fronto-parietal network. This finding aligns well with a previous report on decreased FC between the thalamus and frontal and parietal areas in patients with MS with insomnia, compared to those without [27]. Overall, left fronto-parietal cortices are brain regions relevant for conscious awareness and sleep/wake drive [44] and have been linked to insomnia, the most prevalent sleep disorder in MS [13, 14]. In this context, our study sets the ground for future studies to investigate how more fine-grained sleep disturbances (e.g., sleepiness, insomnia) impact FC in MS. It is worth noting that a frontal cluster within this same network was associated with fatigue (fourth row of Figure 2a). This (partial) overlap of fatigue and sleep quality in the left fronto-parietal network is congruent with their close link at the clinical level. However, despite this commonality, our overall results demonstrate that fatigue is related to several other brain networks outside the left fronto-parietal network.

Also supporting the neural distinctiveness of fatigue and low sleep quality is the finding of differential associations of fatigue and

sleep quality with global FC over and above the global FC in the other relevant networks and depression/anxiety—namely, in the central sensorimotor network and the left fronto-parietal network, respectively. This is remarkable because fatigue and low sleep quality are closely associated with one another as well as with anxiety/depression [9–12]. This phenomenological closeness often renders fatigue treatment decisions complicated. There are different potential treatment options available, in principle, for improving sleep quality on the one hand (e.g., via cognitive-behavioral therapy [45]) and fatigue on the other (e.g., pharmacological treatment with modafinil [46]). Our finding of a neural distinctiveness of these two symptoms thus implies that it makes sense to address them in separate treatments.

The correlation between the PASAT score and fatigue is not surprising, given the demand on vigilance and sustained attention of the PASAT, which reflects cognitive fatigue. In contrast, the lack of correlation between the PASAT score and sleep quality is another dimension of the distinctiveness of fatigue and low sleep quality. Fatigue has been considered a key factor amplifying cognitive impairment in multiple sclerosis even in the early stages of the disease [47]. With respect to intrinsic brain network changes, however, cognitive impairment in MS has been associated with reduced FC of the left inferior parietal lobule [20], a region lying just below the left intraparietal sulcus, which was found to relate to sleep quality in the current study. Accordingly, sleep quality might also be relevant for the course of the cognitive decline that goes beyond the fatigue/vigilance-related factors that are measured in the PASAT. Longitudinal studies will thus help us determine whether the brain network changes associated with low sleep quality and/or fatigue lead to cognitive impairment in MS.

Our study has some limitations. First, our main aim was to identify the degree of distinctiveness of functional network correlates of fatigue and sleep quality in MS. Therefore, the associations of fatigue and sleep quality with FC observed in the current study might not generalize to other fatigue syndromes, diseases or progressive forms of MS. Secondly, despite our large sample size and careful covariate control, previously reported findings could not be replicated in the basal-ganglia network [24, 26], possibly because cortico-subcortical FC may require other analysis approaches (e.g., dynamic or seed-based FC).

In sum, in patients with relapsing–remitting MS, higher fatigue was mainly associated with lower FC in the sensorimotor network, whereas lower sleep quality was mainly associated with lower FC in the left fronto-parietal network, despite the high correlation between fatigue and low sleep quality at the clinical level. This finding of a neural distinctiveness of fatigue and low sleep quality thus underscores the relevance of assessing and treating sleep quality, separately from fatigue, in MS.

AUTHOR CONTRIBUTIONS

Adriana L. Ruiz-Rizzo: Conceptualization (equal); data curation (equal); formal analysis (lead); methodology (equal); software (lead); visualization (lead); writing – original draft (lead); writing – review and editing (equal). **Peter Bublak:** Conceptualization (equal); investigation (equal); writing – review and editing (equal). **Steffen Kluckow:** Investigation (equal). **Kathrin Finke:** Conceptualization (equal); writing – review and editing (equal). **Christian Gaser:** Investigation (equal); writing – review and editing (supporting). **Daniel Güllmar:** Data curation (equal); project administration (equal); writing – review and editing (supporting). **Matthias Schwab:** Funding acquisition (equal); project administration (equal); writing – review and editing (equal). **Hermann J. Müller:** Resources (equal); writing – review and editing (equal). **Otto W. Witte:** Funding acquisition (equal); supervision (equal). **Sven Rupprecht:** Conceptualization (lead); investigation (equal); methodology (equal); resources (equal); validation (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors report no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the last author. They are not publicly available because of restrictions on patient information that could compromise the privacy of research participants. Unthresholded statistical maps of functional networks are openly available at https://identifiers.org/neurovault.collection:11342 and the group functional brain networks resulting from the ICA and dual regression are openly available at https://osf.io/uknmq/.

ORCID

Adriana L. Ruiz-Rizzo https://orcid.org/0000-0003-1467-0745
Sven Rupprecht https://orcid.org/0000-0002-6291-2721

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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