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Original Research Paper

Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue

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Abstract

Background: Fatigue is one of the most frequent and disabling symptoms in multiple sclerosis, but its pathophysiological mechanisms are poorly understood. It is in particular unclear whether and how fatigue relates to structural and functional brain changes.

Objective: We aimed to analyse the association of fatigue severity with basal ganglia functional connectivity, basal ganglia volumes, white matter integrity and grey matter density.

Methods: In 44 patients with relapsing–remitting multiple sclerosis and 20 age- and gender-matched healthy controls, resting-state fMRI, diffusion tensor imaging and voxel-based morphometry was performed.

Results: In comparison with healthy controls, patients showed alteration of grey matter density, white matter integrity, basal ganglia volumes and basal ganglia functional connectivity. No association of fatigue severity with grey matter density, white matter integrity and basal ganglia volumes was observed within patients. In contrast, fatigue severity was negatively correlated with functional connectivity of basal ganglia nuclei with medial prefrontal cortex, precuneus and posterior cingulate cortex in patients. Furthermore, fatigue severity was positively correlated with functional connectivity between caudate nucleus and motor cortex.

Conclusion: Fatigue is associated with distinct alterations of basal ganglia functional connectivity independent of overall disability. The pattern of connectivity changes suggests that disruption of motor and non-motor basal ganglia functions, including motivation and reward processing, contributes to fatigue pathophysiology in multiple sclerosis.

Keywords: Multiple sclerosis, fatigue, basal ganglia, reward system, functional neuroimaging, diffusion tensor imaging, voxel-based morphometry

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Introduction

Fatigue is one of the most common and disabling symptoms in multiple sclerosis (MS) and is characterized by an overwhelming sense of tiredness, lack of energy or feeling of exhaustion.[1–3] Despite recent studies greatly contributing to the understanding of fatigue, the exact pathophysiological mechanisms of fatigue are still not fully understood.[4,5]

Conventional neuroimaging studies have yielded divergent results regarding a correlation between fatigue severity and magnetic resonance imaging (MRI) lesion load or number and volume of gadolinium-enhancing lesions.[6–8] Structural and functional imaging studies have shown an association between brain atrophy and fatigue and altered activity of brain regions involved in motor planning and control.[4,5,9–11] Recently, it has been hypothesized that failure of non-motor basal ganglia functions and disruption of striatocortical pathways may be key elements in the generation of fatigue.[12,13] These hypotheses date back to early lesion studies showing that structural damage to the basal ganglia is associated with profound fatigue and reduced internal drive.[12] Contemporary investigations revealed that fatigue is a central symptom following ischemic infarctions of the basal ganglia and in patients with

Table 1. Demographic and clinical characteristics.

		Patients (44)	**Healthy controls** (20)	***p*-value**
Gender	Male (%)	18 (41%)	9 (45%)	0.69*
	Female (%)	26 (59%)	11 (55%)	
Age (years)	Mean ± s.e.m.	45.9 ± 1.5	43.1 ± 2.6	0.37**
	(Range)	(26-67)	(23-67)	
FSS score	Mean ± s.e.m.	3.94 ± 0.26	2.16 ± 0.19	<0.001**
	(Range)	(1.00-7.00)	(2.16-4.67)	
Normalized brain volume (ml)	Mean ± s.e.m.	1464 ± 95	1461 ± 121	0.91
	(Range)	(1302–1759)	(1175–1709)	
T2 lesion volume (ml)	Mean ± s.e.m.	6.30 ± 0.90		
	(Range)	(0.45–25.82)		
EDSS	Mean ± s.e.m.	2.3 ± 0.22		
	(Range)	(0-6)		
MSSS	Mean ± s.e.m.	5.1 ± 0.40		
	(Range)	(0.45-9.35)		
Time since diagnosis (months)	Mean ± s.e.m.	125 ± 13		
	(Range)	(6–340)		

FSS: fatigue severity scale; s.e.m,: standard error of the mean.
*Pearson's Chi square ** Mann–Whitney *U* test.

post-encephalitic and idiopathic Parkinson's disease.[13] In MS, involvement of the basal ganglia in fatigue pathophysiology has been substantiated by neuroimaging studies showing structural and functional changes of basal ganglia in fatigued MS patients, including atrophy, reduced perfusion, reduced glucose metabolism, and increased activation during the performance of motor tasks.[9,14–16] However, other studies observed no such correlation and it is therefore currently unclear whether the basal ganglia are indeed involved in fatigue pathophysiology.[10,17] This controversy may in part be due to the fact that not only local dysfunction, but also changes in the cortico-basal ganglia networks need to be taken into account to further our understanding of fatigue, especially given the abundant connectivity of the basal ganglia.[18] We therefore investigated the correlation of fatigue severity with basal ganglia volumes, whole-brain grey matter density, white matter integrity and basal ganglia functional connectivity in a well-characterized cohort of patients with MS and healthy controls.

Methods

Subjects

Forty-four patients with MS fulfilling the 2010 revisions to the McDonald criteria[19] (mean age 45.9 years; range, 26–67 years) and 20 age- and gender-matched healthy controls were included. Patients were prospectively recruited from the outpatient clinic of the Clinical and Experimental Multiple Sclerosis Research Center at the Charité-University Medicine Berlin. Only patients without concurrent neurological or psychiatric diseases were included. Healthy controls without neurological or psychiatric diseases were recruited via the Charité intranet (Table 1). Patients had a stable immunomodulatory therapy for >3 months (interferon beta, glatiramer acetate, fingolimod, or natalizumab), no acute relapse and no systemic steroid treatment within 30 days prior to enrolment. All patients underwent a complete neurological examination by a board-certified neurologist and were evaluated with the multiple sclerosis functional composite (MSFC). The MS Severity Score (MSSS) was calculated for all patients. Fatigue was assessed with the fatigue severity sale (FSS).[20] The FSS was chosen over other potential scores since it assesses impact of fatigue on daily living rather than primary symptoms, which reduces potential confounding of results by primary motor or cognitive symptoms. The revised Beck depression inventory (BDI-IA) was used to measure depression. Patients with a BDI score ≥17 indicating moderate or severe depression were not included (leading to exclusion of four out of 48 initially recruited patients). Cognitive performance was assessed in all subjects using the three-second version of the Paced Auditory Serial Addition Test (PASAT), a measure of processing speed, calculation and working memory, and the Symbol Digit Modalities Test (SDMT), which tests processing speed and attention. The study was approved by the ethics committee of the Charité-University Medicine

Berlin and was conducted in accordance with the Declaration of Helsinki. All patients and healthy controls gave written informed consent.

MRI data acquisition

A detailed description of the MRI protocol is available in the supplementary material. The following sequences were acquired on a Siemens Tim Trio 3T scanner at the Berlin Center of Advanced Neuroimaging at the Charité: (1) 3D 1 mm isotropic magnetization prepared rapid acquisition gradient echo; (2) echo-planar imaging sequence for the acquisition of resting-state data (voxel size = 3.4 × 3.4 × 3.4 mm^3, 260 volumes); (3) single-shot echo-planar imaging sequence for the acquisition of DTI data (voxel size = 2.5 × 2.5 × 2.3 mm^3, 64 diffusion directions); (4) 3D T2-weighted sequence; and (5) 3D 1mm isotropic T2-weighted fluid-attenuated inversion recovery sequence.

MRI data analysis

All analyses were performed using FSL[21] (FMRIB Software Library, www.fmrib.ox.ac.uk) and AFNI[22] (Analysis of Functional NeuroImages, afni.nimh.nih.gov/afni) software. MRI analyses were performed as described previously; a detailed decryption is provided in the supplementary material.[23] Voxel-based morphometry was performed using FSL-VBM after masking of white matter lesions. Voxel-wise statistics were performed using non-parametric permutation testing (5000 permutations) with TFCE implemented in the FSL tool randomize ($p<0.05$, corrected). Basal ganglia were segmented using FSL FIRST and basal ganglia volumes were corrected for subject head size using the v-scaling factor derived from FSL SIENAX. Diffusion tensor imaging data were analysed using FSL tools with derivation of fractional anisotropy (FA), mean diffusivity (MD), parallel diffusivity (PD) and radial diffusivity (RD). FSL TBSS was used for whole-brain voxel-based analysis and cross-subject statistics were performed using FSL randomize ($p<0.05$, TFCE-corrected). Resting-state functional connectivity preprocessing included discarding the first four volumes to obtain steady-state magnetization, slice-time correction, 3D motion correction, spatial smoothing with a 6 mm full-width-at-half-maximum (FWHM) Gaussian kernel, mean-based intensity normalization, removal of linear and quadratic trends and temporal band-pass filtering (0.01–0.1 Hz). Several sources of spurious variance were removed using linear regression including six motion parameters, white matter signal and cerebrospinal fluid signal. Basal ganglia functional connectivity was assessed with a seed-based analysis using FSL FEAT. Seed regions included left and right caudate nucleus, putamen and pallidum and masks were generated using the probabilistic Harvard–Oxford subcortical structural atlas in FSL with a threshold of 50%. The average time series from each seed region was extracted and correlated with the time series of every voxel in the brain. The resultant individual whole-brain correlation maps were normalized using Fisher's r-to-z transformation for subsequent group-level analyses. Group-level analyses were carried out separately for each seed region using a repeated-measures mixed-effects model as implemented in FSL FLAME. Corrections for multiple comparisons were carried out at the cluster level using Gaussian random field theory (initial cluster-forming threshold $z>2.3$, corrected cluster significance threshold $p<0.05$).

Two main analyses were performed for all imaging modalities. First, MS-associated alterations of grey matter, white matter and resting-state functional connectivity were assessed with a between-group analysis comparing patients with healthy controls. Second, structural and functional alterations related to fatigue were analysed in MS patients using correlation analyses with individual FSS scores as covariate of interest and age, gender and MSSS scores as nuisance covariates. MSSS was chosen instead of Expanded Disability Status Scale (EDSS), since MSSS allows comparisons of relative disease severity at all EDSS levels for a given disease duration.[24]

Results

Comparison of MS patients with healthy controls

Cognitive performance was not significantly different between patients and controls in the PASAT (51.3 ± 1.3 vs. 50.9 ± 1.1; $p=0.87$) and SDMT (54.5 ± 1.8 vs. 61.5 ± 2.6; $p=0.08$). Voxel-based morphometry identified significantly reduced grey matter volume in MS patients in bilateral pre- and postcentral gyrus, supplementary motor area, caudate nucleus, putamen, thalamus, paracingulate gyrus, precuneus and insula (Figure 1(a)). Basal ganglia volumes were significantly smaller in patients relative to healthy controls (Table 2). Diffusion tensor imaging showed widespread FA reduction in MS patients throughout the white matter, most pronounced in central corpus callosum, optic radiation, forceps major and minor (Figure 1(b)). FA decreases were paralleled by increases in MD, PD and RD (Figure S1, supplementary material). Given that FA decreases can be the result of RD increases or PD decreases, FA decreases were thus mainly driven by RD increases (outweighing PD increases), Significantly decreased functional

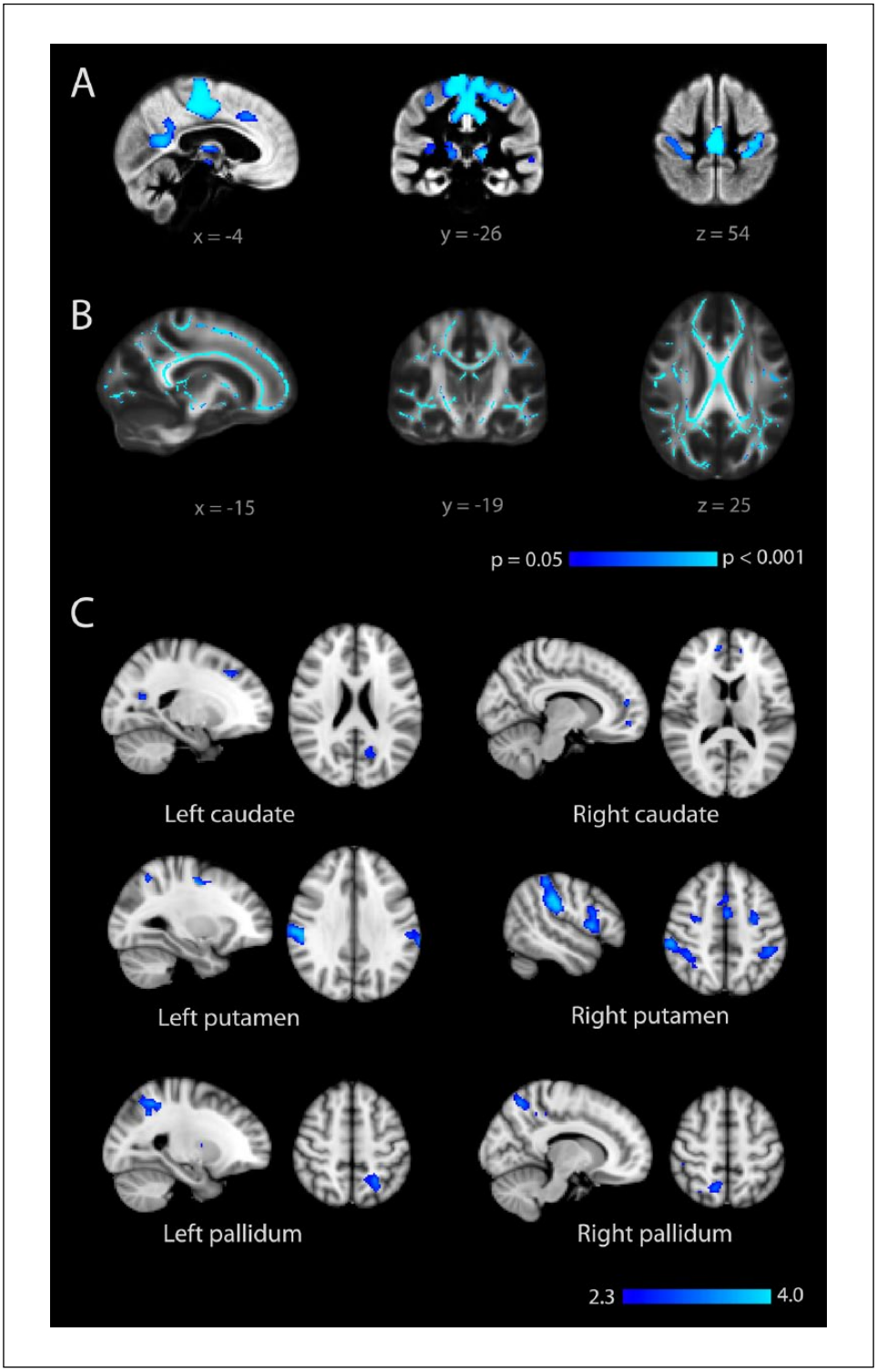

Figure 1. Comparison between MS patients and healthy controls.
(A) Regions with significant grey matter density reduction in MS patients (p<0.05, corrected), involving the bilateral pre- and postcentral gyrus, supplementary motor area, caudate nucleus, putamen, thalamus, paracingulate gyrus, precuneus and insula.
(B) Widespread significantly reduced fractional anisotropy in MS patients (p<0.05, corrected), most pronounced in the central corpus callosum, optic radiation, forceps major and minor.
(C) Reduced functional connectivity of the caudate nucleus (Cd), the putamen (Pt) and the pallidum (Pd) with the superior (Cd, Pt), middle (Cd) and inferior frontal gyrus (Pt, Pd), medial prefrontal cortex (Cd), orbitofrontal cortex (Pt, Pd), precentral gyrus (Pt, Pd), supplementary motor area (Pt), supramarginal gyrus (Pt, Pd), paracingulate gyrus (Cd), insula (Pd), precuneus (Cd) and superior parietal lobule (Pt, Pd) in MS patients (z>2.3, p<0.05, corrected).

Table 2. Basal ganglia volumes (mm^3).

	Patients	Healthy controls	*p*-value
	Mean ± s.e.m.	Mean ± s.e.m.	
Left caudate	4164 ± 76	4503 ± 116	0.016
Right caudate	4441 ± 82	4740 ± 128	0.049
Left pallidum	2223 ± 54	2394 ± 35	0.045
Right pallidum	2234 ± 53	2454 ± 42	0.011
Left putamen	5875 ± 126	6367 ± 122	0.019
Right putamen	6115 ± 121	6531 ± 135	0.043

connectivity was observed in patients between basal ganglia seeds (caudate nucleus, putamen and pallidum) and superior, middle and inferior frontal gyrus, medial prefrontal cortex, orbitofrontal cortex, precentral gyrus, supplementary motor area, supramarginal gyrus, paracingulate gyrus, insula, precuneus and superior parietal lobule (Figure 1(c); for details see supplementary Table 1). While for pallidum and caudate nucleus reduced functional connectivity to ipsilateral cortex regions was observed, putamen functional connectivity was reduced to homologous brain regions in both hemispheres. No increase of grey matter volume, FA and functional connectivity was observed in MS patients in comparison with healthy controls.

Correlation with fatigue severity in MS patients

PASAT and SDMT performance of patients did not correlate with fatigue severity (Pearson's r=0.032/−0.10; p=0.84/0.51) while disease severity (MSSS) was significantly correlated with fatigue severity (FSS; Pearson's r=0.416; p=0.005). We therefore included MSSS as covariate of no interest in all analyses to correct for the effect of disease severity. No significant correlation of fatigue severity with grey matter density, basal ganglia volumes and diffusion tensor imaging parameters (FA, MD, PD and RD) was observed in MS patients when controlling for age, gender and MSSS. In contrast, fatigue severity correlated with alterations of the functional connectivity between basal ganglia and frontal and parietal cortex (controlled for age, gender and MSSS; Figure 2; Table 3; Table S2). Specifically, fatigue severity was negatively correlated with functional connectivity of left and right putamen with dorsal and ventral medial prefrontal cortex, precuneus and posterior cingulate cortex. Likewise, functional connectivity of left and right pallidum with dorsal and ventral medial prefrontal cortex and functional connectivity of right pallidum with precuneus and posterior cingulate cortex was negatively correlated with fatigue severity. A different pattern emerged for left and right caudate nucleus. Here, functional connectivity with more caudal parts of medial prefrontal cortex that included anterior cingulate cortex was negatively correlated with fatigue severity. Furthermore, fatigue severity was positively correlated with functional connectivity of left and right caudate nucleus with motor cortex. For all investigated seed regions, we observed bilateral connectivity changes with similar location and extent. Right and left-sided seeds of all analysed basal ganglia nuclei showed similar functional connectivity changes.

In healthy controls, no significant correlations between fatigue severity and grey matter density, basal ganglia volumes, diffusion tensor imaging measures and basal ganglia functional connectivity were observed.

Discussion

The main focus of our study was to investigate structural and functional brain correlates of MS-related fatigue. Previous research has implicated basal ganglia dysfunction in fatigue pathophysiology and has revealed local basal ganglia pathology in MS patients with fatigue.[9,14,15] However, given the complex clinical nature of fatigue, it was recently proposed that fatigue is a network disorder associated with alterations of striatocortical connectivity.[12,13] Here, using resting-state fMRI we show that functional connectivity of the basal ganglia is correlated with individual fatigue severity independent of overall disability in MS patients. Higher fatigue scores were negatively correlated with functional connectivity of the caudate nucleus, the putamen and the pallidum with the medial prefrontal cortex, the precuneus and the anterior and posterior cingulate cortex, but also positively correlated with functional connectivity between the caudate nucleus and the motor cortex bilaterally. In contrast, we observed no correlation of fatigue severity with grey matter density, white matter

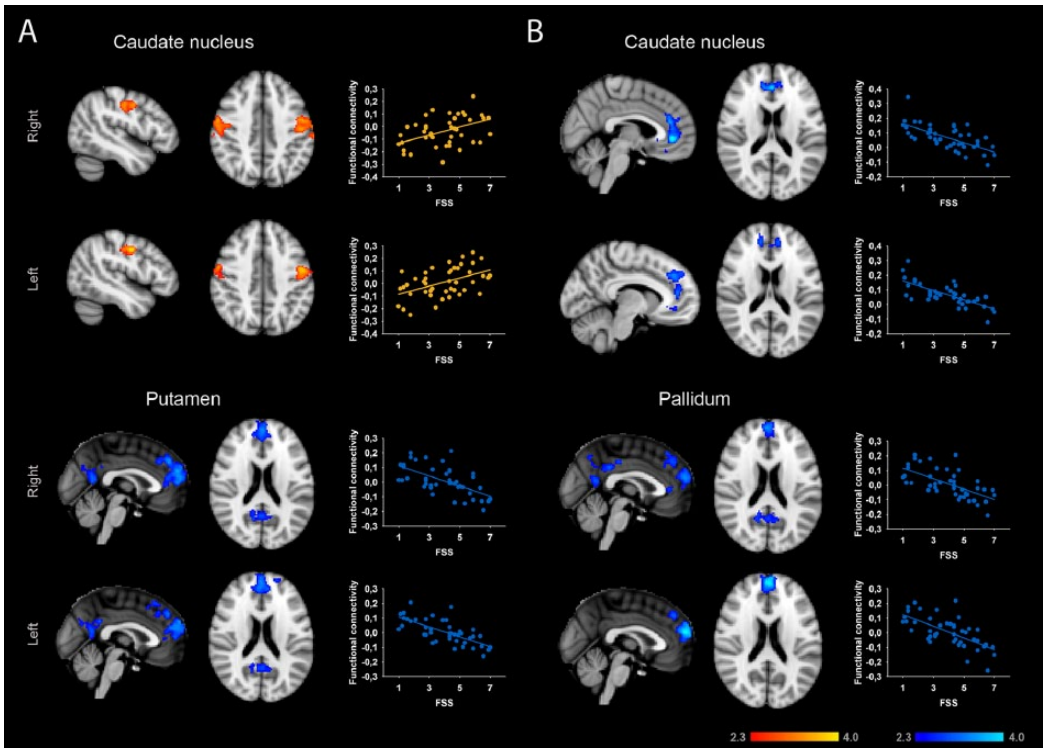

Figure 2. Correlation of basal ganglia functional connectivity with fatigue severity in MS patients.
Fatigue severity correlated with an increased functional connectivity of the bilateral caudate nucleus with the motor cortex (A) and a decreased functional connectivity of the bilateral caudate nucleus with the medial prefrontal/anterior cingulate cortex (B). Furthermore, fatigue severity was associated with a reduced functional connectivity of the bilateral putamen and pallidum with the medial prefrontal cortex, the precuneus and the posterior cingulate cortex (C, D). For illustrative purposes, scatterplots depicting the correlation between individual FSS scores and functional connectivity changes are shown for all analyses.

integrity and basal ganglia volumes. In comparison with healthy controls, patients with MS showed widespread alterations of white matter integrity and grey matter density, reduced basal ganglia volumes and reduced functional connectivity of the basal ganglia with frontal and parietal cortical regions.[25,26]

The basal ganglia have strong interconnections with the cerebral cortex, organized in structurally and functionally segregated cortico-basal ganglia circuits.[28] These circuits support a wide range of functions that include not only motor control, but also learning, memory, motivation and reward-guided behaviour.[29] Lesions of the basal ganglia can produce profound fatigue, and fatigue is observed in ischemic basal ganglia infarcts and neurodegenerative diseases affecting the basal ganglia including post-encephalitic and idiopathic parkinsonism.[12,13] Neuroimaging studies revealed atrophy,[14] reduced cerebral blood flow[16] and metabolic changes[30] in the basal ganglia of MS patients with fatigue. Recent fMRI studies observed an increased activation of the basal ganglia in fatigued MS patients during performance of cognitively demanding tasks that was interpreted as compensatory mechanism or increased effort to maintain normal function.[9,31] These studies provided clear evidence for local structural, functional and metabolic alterations of the basal ganglia, but also hypothesized possible implications for the functional integrity of the cortico-basal ganglia circuits.[15]

Using resting-state fMRI, we were able to delineate changes in the functional connectivity of the basal ganglia underlying fatigue in MS. For all investigated basal ganglia nuclei (caudate nucleus, putamen and pallidum), a negative correlation between fatigue severity and functional connectivity with the medial prefrontal cortex was observed. The medial prefrontal cortex is strongly interconnected with the basal ganglia[28] and has repeatedly been implicated in the pathophysiology of fatigue.[9,15,31] Interestingly, Roelcke et al. observed a concurrent reduction of glucose metabolism in the basal ganglia and the medial prefrontal cortex in MS patients with fatigue.[15]

Table 3. Correlation of basal ganglia functional connectivity with fatigue severity in MS patients ($z>2.3$, $p<0.05$, cluster corrected).

Region	Side	Local maximum			Local maximum
		MNI coordinates (mm)			T value
		x	y	z	
Negative correlation with FSS					
Left pallidum					
Medial prefrontal cortex	L	−2	58	22	3.91
	R	2	58	20	3.95
Right pallidum					
Medial prefrontal cortex	L	−4	54	24	3.19
	R	2	58	18	3.34
Precuneus/	L	−4	−38	34	3.01
Posterior cingulate cortex	R	12	−62	24	3.15
Left putamen					
Medial prefrontal cortex	L	−4	44	40	3.52
	R	4	56	16	3.18
Middle frontal gyrus	L	−40	4	48	4.35
Precuneus	L	−10	−66	42	3.52
	R	12	−36	46	3.31
Right putamen					
Medial prefrontal cortex	L	−2	54	26	3.17
	R	2	58	18	3.09
Paracingulate gyrus	L	−8	24	38	3.53
Superior frontal gyrus	R	22	44	24	3.84
Precuneus	L	−10	−64	42	3.14
	R	12	−56	28	3.08
Left caudate					
Medial prefrontal cortex /					
Anterior cingulate cortex	L	−10	44	14	3.17
	R	12	46	22	3.04
Right caudate					
Medial prefrontal cortex /					
Anterior cingulate cortex	L	−6	44	8	3.14
	R	4	40	−2	4.07
Positive correlation with FSS					
Left caudate					
Precentral gyrus	L	−48	−6	40	3.74
	R	56	−2	42	3.22
Right caudate					
Precentral gyrus	L	−56	−8	46	3.69
	R	56	−6	42	3.22

The medial prefrontal cortex is involved in processing of motivational context information, and both the basal ganglia and the medial prefrontal cortex are part of the human reward system.[32] Recently, an effort-reward imbalance, i.e. a (biased) perception of high performance costs and low benefits, based on dysfunction of the cortico-striatal network, has been proposed as the central feature of fatigue.[12,33] The negative relationship of cortico-basal ganglia functional connectivity with individual fatigue severity observed in the present study might hence represent the neural substrate of this imbalance.

Caudate nucleus functional connectivity with the anterior cingulate cortex was likewise negatively

correlated with fatigue severity. Connections between the two structures form the anterior cingulate circuit, one of the major basal ganglia loops.[18] The anterior cingulate cortex plays a key role for several higher cognitive functions, including motivation and performance monitoring.[34] Lesions of the anterior cingulate lead to reduced effort and lethargy, and it has been proposed that fatigue is associated with decreased levels of dopaminergic transmission in the anterior cingulate and the basal ganglia.[33] Given the roles of the basal ganglia and the anterior cingulate for reward and performance monitoring, reduced functional connectivity between these structures may likewise contribute to the proposed imbalance between internal effort and reward signals.[32,33]

Furthermore, putamen and pallidum functional connectivity with the precuneus and the posterior cingulate cortex was negatively correlated with fatigue severity. Precuneus and posterior cingulate cortex both have dense connections with the medial prefrontal cortex, and together they form the midline hubs of the default mode network, a network that is preferentially activated during internally focused tasks. Previous research has found both increased and decreased activation of the precuneus in MS patients with fatigue.[4,9] The precuneus and the posterior cingulate cortex are involved with higher cognitive functions including internally directed cognition and memory retrieval, but posterior cingulate cortex activity is also modulate by arousal state.[35] Since low arousal levels have been linked to fatigue pathophysiology, lower posterior cingulate functional connectivity might reflect reduced arousal levels in highly fatigued MS patients.[13]

Functional connectivity of the caudate nucleus with the motor cortex was positively correlated with fatigue severity. This is in line with recent resting-state fMRI studies that observed increased functional connectivity of the sensorimotor network in patients with clinically isolated syndrome and in patients with early MS in comparison with healthy controls.[36] Moreover, Dogonowski et al. found a stronger functional integration of the basal ganglia into the motor network in patients with MS.[37] However, the functional connectivity increase in the motor system seems to disappear during later disease stages.[27,36] Here, we show that motor network connectivity scales with fatigue severity also independently of disease severity. It has been suggested that functional connectivity increases represent a compensatory mechanism or an increased effort to limit the consequences of disease-related cerebral damage and to maintain normal function.[27,36] However, such a compensatory increase of activity may be subject to exhaustion and might therefore come at the cost of an increased fatigability. Alternatively, increases of functional connectivity may reflect a maladaptive reorganization and contribute directly to fatigue pathophysiology.

Of interest, we did not observe a correlation of fatigue severity with structural brain measures as assessed with diffusion tensor imaging, voxel-based morphometry and basal ganglia volumetry, although widespread alterations of white matter integrity and grey matter volume were present in the MS cohort. This observation highlights that not all symptoms in MS are attributable to structural lesions, but instead may be related to distinct functional connectivity changes. This is in keeping with similar results obtained in autoimmune encephalitis and emphasizes the contribution of multimodal imaging protocols to the understanding of complex disease mechanisms.[23] Previous research has yielded divergent results regarding an association of structural brain changes and fatigue severity in studies using conventional MRI analyses,[7,10] voxel-based morphometry[11,17,31] and diffusion tensor imaging.[31] While some previous studies did not include disease severity as covariate, or analysed only selected regions of interest and considerable heterogeneity of included MS patients exists, a full comprehension of the differences between studies would clearly be facilitated by multimodal imaging approaches that include structural and functional analyses. Furthermore, we did not observe a significant correlation between fatigue severity and structural or functional brain measures in healthy controls. While this result could point to a specific fatigue mechanism present in MS patients, it should be interpreted with caution given the smaller group size and the lower variability of FSS scores in healthy controls.

As in previous studies, fatigue correlated with BDI scores in our study as well. When looking at BDI and FSS questionnaires, a high resemblance in many questions is apparent. For example, BDI also measures exhaustion, tiredness, and lack of drive; all symptoms also traditionally attributed to fatigue. A correlation between BDI and FSS scores is therefore an imperative. Consequently, describing fatigue and depression as presumably distinct syndromes with a certain symptom overlap is appropriate.[15,38] As a result, we did not correct against BDI in our models, since doing so would have most certainly removed important fatigue effects from our data. Instead, we excluded all patients above the established BDI cutoff in MS for fulfilling a clinical diagnosis of depression prior to all analyses.

Our study points to possible future avenues of research. While we observed similar fatigue-related functional connectivity alterations of putamen, pallidum and caudate nucleus, the latter structure additionally exhibited a positive relationship between fatigue severity and functional connectivity with motor cortex. When comparing patients with healthy controls, differences of functional connectivity patterns were even more pronounced and also included lateralization effects. Disentangling these different connectivity profiles, possibly in combination with substructure analyses, may further enhance the understanding of MS pathophysiology. Moreover, analysis of the functional connectivity of the thalamus with basal ganglia and cortical regions appears as promising strategy for future studies.

In conclusion, our results suggest that fatigue is more closely correlated with functional than with structural brain changes, although widespread grey and white matter alterations were present in our cohort of MS patients. We observed functional connectivity changes in correlation with fatigue severity that affected both motor and non-motor basal ganglia functions independent of overall disease severity. First, functional connectivity of the basal ganglia with the medial prefrontal cortex and the anterior cingulate cortex was negatively correlated with fatigue severity and might therefore reflect an effort–reward imbalance that was proposed as a key feature of fatigue. Second, the positive correlation of fatigue severity with connectivity of the caudate nucleus and the motor cortex may constitute a compensatory mechanism that can help to maintain function. Together, our results suggest that alterations of cortico-basal ganglia networks contribute to the pathophysiology of fatigue. The observed distinct connectivity changes may moreover serve as biomarker and treatment target for future studies.[39]

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Conflict of interest

None declared.

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