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GRAY MATTER STRUCTURAL CORRELATES OF FATIGUE IN MULTIPLE SCLEROSIS

by

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GRAY MATTER STRUCTURAL CORRELATES OF FATIGUE

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ABSTRACT

We aimed to assess whether frontal cortex-striatum-thalamus (FCST) pathway or other grey matter (GM) structures are associated with longitudinal patterns of fatigue, namely reversible (RF) versus sustained fatigue (SF).

MS patients enrolled in our prospective cohort were grouped based on their longitudinal Modified Fatigue Impact Scale (MFIS) scores: 1. SF: MFIS≥38 at the two most recent yearly assessments; 2. RF: MFIS<38 at last assessment, but presence of at least one previous MFIS≥38; 3. Never Fatigued (NF): at least five MFIS<38. Accordingly, we selected 98 patients (30 SF, 31 RF, 37 NF; age-range:29-66, female/male:76/22, Extended Disability Status Scale (EDSS)≤6; 13 patients with secondary progressive (SP) MS and 85 with relapsing remitting (RR) MS in remission). Disability and depression were assessed using the EDSS and CES-D, respectively. 3T T1-weighted MRI was used for voxel based morphometry (VBM) to survey for GM atrophy associated with fatigue, controlling for age, sex and EDSS. Group-wise volumetric comparison was performed on deep GM structures identified by VBM, controlling for age, sex, EDSS and CES-D score.

VBM showed significant inverse relation between the MFIS cognitive subscale score and areas within the bilateral fronto-medial and fronto-orbital cortices, anterior striata, thalami, temporal poles, insulae and left lateral occipital cortex (peak FWE-*p* value of 0.021), and

between the MFIS physical subscale and areas within the bilateral frontal poles, and frontal medial cortices (peak FWE-*p* value of 0.043). Volumetric analysis showed significant atrophy in the putamen (RF < NF $p<0.0004$; SF < NF $p<0.0085$) and thalamus (RF < NF $p<0.00048$).

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LIST OF ABBREVIATIONS

BWH ..... Brigham and Women's Hospital

CES-D ..... Center for Epidemiologic Studies Depression Scale

CLIMB ..... Comprehensive Longitudinal Investigation of Multiple Sclerosis at BWH

DARTEL ..... Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra

EDSS ..... Extended Disability Status Scale

FCST ..... Frontal Cortex-Striatum-Thalamus

FLAIR ..... Fluid-Attenuated Inversion Recovery

FWE ..... Family-Wise Error

GM ..... Gray Matter

MFIS ..... Modified Fatigue Impact Scale

MRI ..... Magnetic Resonance Imaging

MS ..... Multiple Sclerosis

LGA ..... Lesion Growth Algorithm

LST ..... Lesion Segmentation Tool

NF ..... Never Fatigue

PP ..... Primary Progressive

RF ..... Reversible Fatigue

RR ..... Relapsing Remitting

SF ..... Sustained Fatigue

SP ..... Secondary Progressive

SPM ..... Statistical Parametric Mapping

T ..... Tesla

TR ..... Repetition Time

TE ..... Echo Time

VBM ..... Voxel-Based Morphometry

INTRODUCTION TO MULTIPLE SCLEROSIS

Epidemiology

Multiple Sclerosis (MS) is the most common demyelinating disease that solely affects the central nervous system (CNS) (Calabresi, 2004; Heesen et al., 2006). MS is one of the leading causes of disability in young adults (Ramagopalan & Sadovnick, 2011). MS is more prevalent in women, and some studies have suggested that the female to male ratio falls between 1.4:1-2.3:1(Alonso & Hernan, 2008). While the incidence of MS is increasing between females, the reason behind the increase in female to male ratio in MS remains elusive (Dunn & Steinman, 2013). The average age of onset for MS is between 28-31 years of age (Goodin, 2014). The prevalence of MS is estimated to be about 0.1 percent in the United Sates (Langer-Gould, Brara, Beaber, & Zhang, 2013).

Risk Factors

Several enviornmental risk factors have been suggested for MS. However, a history of infectious mononucleosis, anti-Epstein–Barr virus nuclear antigen (EBNA) IgG seropositivity, and smoking are well-established risk factors for MS (Belbasis, Bellou, Evangelou, Ioannidis, & Tzoulaki, 2015). In addition, the prevalence of MS increases in higher latitudes (Alonso & Hernan, 2008). Several studies have suggested that these findings can be explained by lower sun exposure and serum vitamin D levels in these regions (Orton et al., 2011; Salzer et al., 2012).

The risk of developing MS for non-twin siblings is similar to dizygotic twins (3 to 5 percent). However, this risk increases to 20-39 percent in monozygotic co-twins of patients with MS (Sadovnick et al., 1993). This suggests that genetic background plays a singnificant role in the pathogenesis of MS. In fact, more than a hundred genetic polymorphisms that contribute to the risk of MS have been identified in distinct loci across the human genome (Beecham et al., 2013). Among these variants, HLA-DRB1*1501 has shown the strongest association with MS (Lincoln et al., 2005).

Signs and Symptoms

Since MS lesions are multifocal and the temporal sequence of their appearance is not stereotypical, there is significant heterogeneity in the presentation of the disease and the symptoms between patients, depending on the regions that has been affected by MS in each of them. Although there is no symptom that can be considered specific for MS, there are signs and symptoms that can be suggestive of MS. These symptoms include: a) unilateral optic neuritis, which is typically characterized by subacute visual loss (Balcer, 2006); b) fatigue that affects 53.7% (95%CI 47–61%) of patients with MS (Wood et al., 2013); c) Uhthoff phenomenon, which is characterized by an exacerbation of the symptoms due to the increase in body temperature (Selhorst & Saul, 1995); d) bilateral internuclear ophthalmoplegia, which is a disorder of conjugate lateral gaze; e) Lhermitte sign, which is characterized by electric shock feeling associated with bending the neck down (Richards, Sampson, Beard, & Tappenden, 2002). Other symptoms include but are not limited to

muscular weakness or paralysis, paresthesia, vertigo, pain, bowel dysfunction, urinary dysfunction, sexual dysfunction, cognitive dysfunction, and ataxia (Richards et al., 2002).

Clinical Course

The clinical course of MS is subcategorized into four clinical subtypes. a) clinically isolated syndrome (CIS): is defined as an attack that has a clinical feature of MS, but does not fully meet the McDonald diagnostic criteria; these patients have a high risk for developing MS in the future (Lublin et al., 2014); b) relapsing remitting (RR): this course is characterized by MS attacks (also referred to as clinical relapses) with subsequent recovery or some residual sequelae. Of note, the progression of the disease between clinical attacks is minimal; c) secondary progressive (SP): this course follows a typical relapsing-remitting course, but at some point gradual clinical worsening of the patient occurs irrespective of the presence of attacks. Typically it takes 10 to 20 years before RRMS converts to SPMS (Eriksson, Andersen, & Runmarker, 2003); d) primary progressive (PP): is characterized by progressive worsening from the beginning with sporadic plateaus. Notably, PPMS usually presents as a spinal cord syndrome. Older age of onset is frequent, as well as a poor prognosis relative to RRMS (Lublin et al., 2014; Rice, Cottrell, Wilkins, & Scolding, 2013).

Diagnosis

The McDonald criteria for RRMS are as follows (Polman et al., 2011): (i) dissemination in space, which requires either the visualization of white matter lesions occuring in more than two typical regions for MS [periventricular, juxtacortical,

infratentorial, or spinal cord] or the symptoms that can be attributed to two distinct regions); (ii) dissemination in time, which either requires more than one attack, simultaneous presence of gadolinium-enhancing and non-enhancing lesions on the same MRI, or a new lesion on a T_2 weighted image.

Pathology

The pathological hallmarks of MS are inflammatory demyelination and neurodegeneration. Demyelination can occur in both gray matter and white matter (Geurts & Barkhof, 2008). T-cells, B-cells, activated microglia, and demyelination are prominent features of demyelinating white matter plaques visible in conventional MR imaging of MS patients (Figure 1). In addition to focal white matter plaques, white matter not affected by focal lesions (sometimes referred to as normal appearing white matter (NAWM)) also shows abnormal features such as microglial activation, gliosis, mild demyelination, and axonal loss(Moll et al., 2011). These pathologies exist in both RRMS and SPMS, but neurodegeneration severity and chronic demyelination with impaired remyelination tend to increase with the progressive phase of the disease (Lassmann et al., 2012). Neurodegeneration manifests itself as gray matter atrophy in various brain areas (i.e, cortical and subcortical structures). The principal mechanisms that underly MS-related neurodegeneration are largely unknown. However,

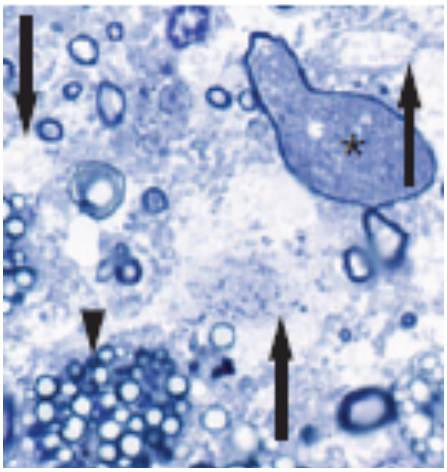


Figure 1. *demyelinated axons (arrows), macrophages containing myelin debris (arrowheads) and dystrophic axons (asterisk) have been shown.(Lassmann, van Horssen, & Mahad, 2012)*

various mechanisms have been implicated in MS-induced neurodegeneration. These include: axonal injury, energy failure and mitochondrial damage secondary to chronic demyelination, iron accumulation and chronic oxidative injury (Mahad, Trapp, & Lassmann, 2015).

Magnetic Resonance Imaging

Currently, MRI is the imaging modality of choice for MS diagnosis and monitoring of disease activity (Sahraian & Eshaghi, 2010). With respect to healthy white matter, lesions appear hyperintense on T_2-weighted or proton density images and hypointense on T_1-weighted images. MS plaques usually have ovoid shape. White matter lesions can be best identified with a fluid attenuated inversion recovery (FLAIR) sequence that eliminates the hyper-intense signal of CSF and therefore improves the sensitivity for detecting periventricular lesions (Figure 2).(Klawiter, 2013)

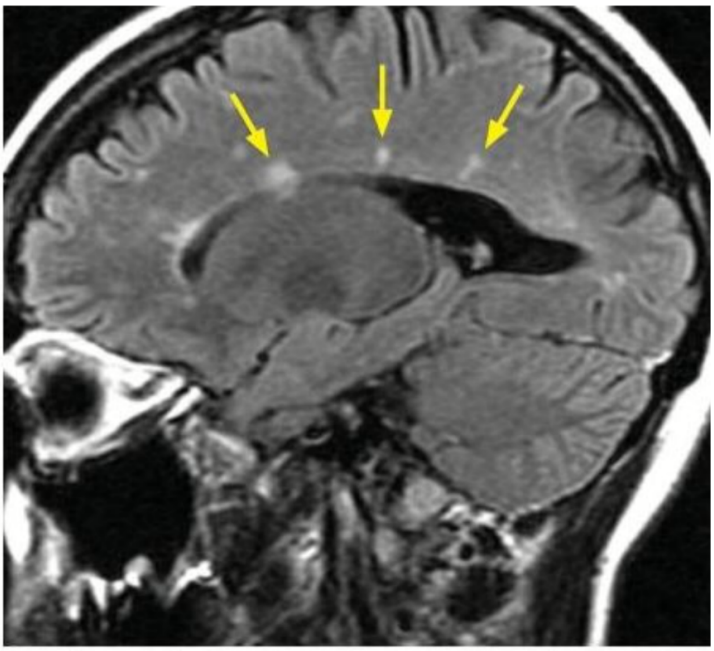


Figure 2. *Hyperintense periventricular lesions (also known as Dawson fingers) on a sagittal fluid attenuated inversion recovery (FLAIR) image (Mandell, 2013).*

The border of the acute lesions is not as sharp as that of chronic lesions. The appearance of enhancing lesions upon I.V. administration of MRI contrast agent is considered as a measure of disease activity.(Morgen et al., 2001) Using Magnetization Transfer Imaging (MTI) or increasing the dosage of the intravenous Gadolinium will enhance the sensitivity of the MRI for detecting the enhancing lesions.(Silver et al., 1997; Wolansky et al., 1994)

Most lesions appear isointense on T1 weighted images, but if they appear hypointense (compared to GM) they are called black holes; the MRI signal tends to normalize due to the resolution of the acute inflammation and the associated edema, as well as due to remyelination and astrocytosis.(Bitsch et al., 2001)

It has been argued that the persistence of black holes on T1-weighted images may be attributable to axonal injury and loss. The black holes have the potential to be used as a measure of MS progression.(Paolillo et al., 2000) The main imaging features that have a direct relation with disease severity are the lesion load and the atrophy in either grey or white matter.(Klawiter, 2013) It has been suggested that the lesion load in the first five years of the disease can predict the disability level in the long run.(Brex et al., 2002)

Fatigue in MS

Fatigue affects 53.7% (95%CI 47–61%) of patients with MS (Wood et al., 2013). In general, fatigue can be referred to as an excessive sense of tiredness or exhaustion (Comi, Leocani, Rossi, & Colombo, 2001). Multiple mechanisms are believed to contribute to fatigue in MS:

A) *Neurogenic:* various lines of evidence support that MS-related fatigue results from structural and functional abnormalities in the brain (e.g., neurovascular coupling impairment, abnormal brain metabolism, and neurodegenerative process). Filippi et al. have shown an inverse correlation between the fatigue severity score and the blood oxygen level dependent (BOLD) signal of the contralateral intraparietal sulcus, ipsilateral rolandic operculum, and thalamus during fMRI during finger tapping and 9 hole peg test (Filippi et al., 2002) Researchers have also used positron emission tomography (PET) to demonstrate that glucose metabolism is decreased in the frontal cortex and the deep gray matter structures in MS patients with fatigue. In another study, atrophy in the striatum, thalamus, and frontoparietal cortex has been shown to be correlated with fatigue in patients with MS (Calabrese et al., 2010). It has also been suggested that regional atrophy in the right nucleus accumbens (Nacc), and left superior frontal gyrus, right inferior temporal gyrus and the forceps major is more pronounced in MS patients with fatigue as opposed to those without fatigue and healthy controls (Rocca et al., 2014). Finally, using magnetic resonance spectroscopy (MRS) it has been shown that axonal damage is associated with fatigue severity (Tartaglia et al., 2004).

B) *Neurotransmitter Imbalance:* there is emerging evidence regarding the role of the dopaminergic and glutamatergic pathways in fatigue pathophysiology. Firstly, the glutamatergic innervation of the striatum from the frontal cortex, secondly, the

commonly used antifatigue drug target dopaminergic neurotransmission.(Bamford et al., 2004; Dani & Zhou, 2004; Ledinek, Sajko, & Rot, 2013)

C) *Endocrinological factors:* dysregulation of the hypothalamic-pituitary-adrenal axis has been associated with fatigue symptoms in MS (Gottschalk et al., 2005).

D) *Cytokines:* interferon-γ (IFN-γ) and tumor necrosis factor -α(TNF-α) levels are higher in MS patients with fatigue (P. Flachenecker et al., 2004; Heesen et al., 2006).

Fatigue and Depression

Fatigue is prevalent in both MS and depression, fatigue and depression have a tendency to co-occur in MS. (Wood et al., 2013) The severity of fatigue has been decreased when subjects were treated for depression.(Mohr, Boudewyn, Goodkin, Bostrom, & Epstein, 2001) It has been suggested that these two are correlated and depression and be used as fatigue predictor in patients with MS.(Kroencke, Lynch, & Denney, 2000) It has been argued that the severity of fatigue is higher in patients with depression and certain symptoms such as sleep problems, and avolition co-occur in both depression and fatigue.(Krupp, Serafin, & Christodoulou, 2010; Mills, Young, Pallant, & Tennant, 2010) Hence, It seems that the relationship between fatigue and depression is complex.

Objective and Aim

As discussed earlier, multiple studies have pointed to the potential role of the frontal cortex-striatum- thalamus (FCST) pathway(Calabrese et al., 2010; Filippi et al., 2002;

Rocca et al., 2014; Tartaglia et al., 2004) in fatigue development associated with MS. However, these findings were not always reproducible. We aimed to assess whether FCST and other grey matter (GM) structures are associated with longitudinal patterns of fatigue, namely reversible (RF) versus sustained fatigue (SF). We hypothesized that patients in the SF group would demonstrate more severe atrophy within the FCST, unnder the assumption that fatigue is not reversible when determined by irreversible brain structural changes. We also hypothesized that fatigue severity in MS is associated with cortical and deep gray matter atrophy

MATERIALS AND METHODS

Participants

We selected 98 patients from a larger pool of over 403 patients undergoing a sub-study of quality of life (QOL) in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital (http://www.climbstudy.org/).

All patients met the McDonald criteria for relapse-onset MS (2010 revision) (Polman et al., 2011) and underwent MRI with the same scanner (see below). The selected patients did not meet the exclusion criteria: (i) less than 12 weeks from the last relapse at the time of the clinical and quality of life assessment and the MRI scans, and no history of relapse between the MRI scan and the MFIS score assessment; (ii) a prior history of significant head trauma or any other neurological disease; (iii) a prior history of psychotic disorders; (iv) ongoing history of substance abuse; (v) EDSS > 6, (vi) a history of major medical illness such as malignancy; (vii) Age > 65; (viii) image acquisition with other scanner

than the 3 Tesla Skyra Siemens at BWH-221 Longwood. The age-range of the selected patients was 29-66. Thirteen patients were SPMS while the rest of the participants were RRMS.

In the CLIMB study, participants are followed every six months with clinical interviews and examination. The patients have completed QOL questionnaires every other year, and undergone MRI scan annually. Fatigue and disability were assessed using the Modified Fatigue Impact Scale (MFIS)(Guidelines, 1998; Krupp, Alvarez, LaRocca, & Scheinberg, 1988) and Expanded Disability Status Scale (EDSS)(Kurtzke, 1983) scores, respectively. The severity of depression was evaluated using the Center for Epidemiological Studies Depression Scale (CES-D)(Radloff, 1977). We used 38 as the cut-off point for MFIS score for being fatigued(P Flachenecker et al., 2002).

We grouped the patients into 3 distinct categories based on the longitudinal course of the MFIS score: (i) *sustained fatigue* (SF): last two consecutive MFIS score ≥ 38, (ii) *reversible fatigue* (RF): most recent MFIS score was less than 38 while their previous MFIS score ≥ 38; (iii) *never fatigue* (NF): had no prior history of MFIS score ≥ 38. We identified 30 MS patients who met the criterion for the SF group, 31 patients for the RF group, and 37 patients for the NF group. These groups were matched by age, sex, disease duration, and EDSS.

Magnetic Resonance Imaging

Brain images were acquired at a single site at the Brigham and Women's Hospital (BWH) using a 3 Tesla Siemens Skyra scanner. The following parameters were used for the T1-weghted images: repetition time= 2300 ms, echo time= 2.96ms, voxel dimension of 1 X 1 X 1 mm^3. The following parameters were used for the FLAIR images: repetition time= 5000 ms, echo time= 389 ms, voxel dimension of 1 X 1 X 1 mm^3.

Lesion Segmentation

To segment lesions on FLAIR images we used the lesion growth algorithm module (LGA) of the lesion segmentation toolbox (LST v2.0.15) implemented in Statistical Parametric Mapping [SPM] Toolbox)(Schmidt et al., 2012). As per the LST manual, the optimal threshold was determined after running the LGA multiple times with different thresholds. We selected 0.1 as the threshold for lesion segmentation. White matter areas falsely classified as lesion were manual excluded from the lesion mask using 3DSlicer (www.slicer.org). Finally, the lesions were filled on T_1-weighted images using the lesion filling module of the LST.

Voxel Based Morphometry

Voxel-based morphometry (VBM) was performed to detect regional gray matter volume differences between groups and gray matter atrophy associated with fatigue

severity (J. Ashburner & Friston, 2000). Lesion-filled T_1-weighted images were preprocessed using the Statistical Parametrical Mapping 12 (SPM 12) VBM toolbox (John Ashburner, 2012). We used diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) (J. Ashburner, 2007) to create a study-specific template and register structural images to the Montreal Neurological Institute (MNI) space. VBM image analysis steps are summarized as follows: (i) tissue segmentation; (ii) creating DARTEL template; (iii) normalization to the MNI space. The preprocessed images were merged using *fslmerge* and then smoothed with a Gaussian kernel (σ=4 mm) using *fslmaths*.

We used nonparametric permutation analysis implemented in FSL-Randomise for (fsl.fmribox.ac.uk/fsl/fslwiki/Randomise) voxel-wise statistical analysis to survey the whole brain for potential gray matter atrophy associated with fatigue severity and patient groups defined by temporal patterns of fatigue (Nichols & Holmes, 2002). Threshold-free cluster enhancement was used to adjust for family-wise error (FWE) correction for multiple comparisons (S. M. Smith & Nichols, 2009). Voxels with an FWE-corrected $p< 0.05$ were considered significant. Effects of temporal course and severity of fatigue subscores on local gray matter volume were assessed while controlling for age, sex, and EDSS score.

Volumetric Analysis

For volumetric analysis, subcortical gray matter stuctures were segmented using FIRST (a model-based segmentation and registration tool implemented in FSL)(Patenaude, Smith, Kennedy, & Jenkinson, 2011). Figure 3 shows a sample subcortical segmentation result. Subcortical volumes were calculated using *fslstats*. We averaged the volume of the bilateral putamina, thalami and caudate nuclei in each patient.

Statistical Analysis

We used general linear models to assess the following effects on the subcortical volumes: (i) effects of group membership (SF, RF, and NF) while controlling for age, sex, EDSS, and CES-D scores (Bonferroni corrected p-value <0.0166); (ii) effect of fatigue severity (MFIS score) while controlling for age, sex, EDSS, and CES-D scores Unless

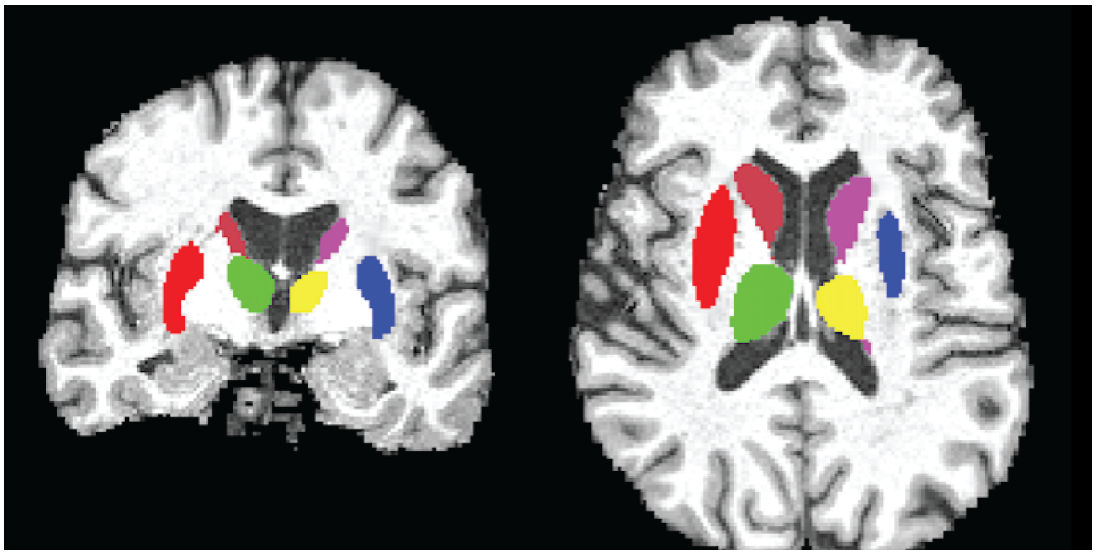


Figure 3. *Automated subcortical segmentation using FIRST.*

noted otherwise, all statistical tests were perfomed using the R statistical package v3.1.3 (http://cran.r-project.org/).

RESULTS

Demographic and Clinical Characteristics of Fatigue Groups

Demographic and clinical characteristics of the study participants are summarized in Table 1. In our sample, there were no significant differences in age, sex, disease duration, and EDSS among the fatigue groups (SF, RF, and NF). In contrast, MFIS total score as well as all subscores of MFIS (i.e., cognitive, physical, and psychosocial) were significantly higher in SF patients than in both the RF and NF groups at their last visit ($p \leq 1 \times 10^{-7}$; Figure 4). MS patients with RF also showed greater fatigue severity than patients in the NF group (MFIS-Total: p=0.007; MFIS-cognitive subscore: p=0.04; MFIS-physical subscore: p=0.03; MFIS-psychosocial subscore: p=0.10).

Table 1. Demographic and clinical characteristics of the study participants.

Diagnosis	All (n=98)	SF (n=30)	RF (n=31)	NF (n=37)
Age, y, mean (SD) [range]	49.3 (8.4) [29-66]	48.9 (8.9) [34-66]	49.5 (9.8) [29-64]	49.4 (6.7) [34-66]
Sex, Female/Male	76/22	24/6	23/8	29/8
Disease duration, y, mean (SD)	17.2 (7.5)	17.7 (6.6)	16.9 (8.0)	17.0 (8.1)
EDSS, mean (SD)	2.0 (1.5)	2.3 (1.5)	2.0 (1.8)	1.8 (1.0)
MFIS-total, mean (SD)	28.9 (17.5)	50.3 (7.6)	23.2 (9.8)	16.2 (10.6)
MFIS-cog, mean (SD)	13.9 (9.0)	24.1 (5.5)	11.0 (5.9)	8.0 (5.9)
MFIS-phys, mean (SD)	13.0 (8.4)	22.3 (4.4)	10.7 (6.0)	7.4 (6.0)
MFIS-psych, mean (SD)	2.1 (1.8)	3.9 (1.7)	1.5 (1.2)	1.1 (1.2)

Abbreviations: EDSS: expanded disability status scale; MFIS: Modified Fatigue Impact Scale; MFIS-cog: cognitive subscore of MFIS; MFIS-phys: physical subscore of MFIS; MFIS-psych:

psychosocial functioning subscore of MFIS; NF: never fatigue; RF: reversible fatigue; SF: sustained fatigue.

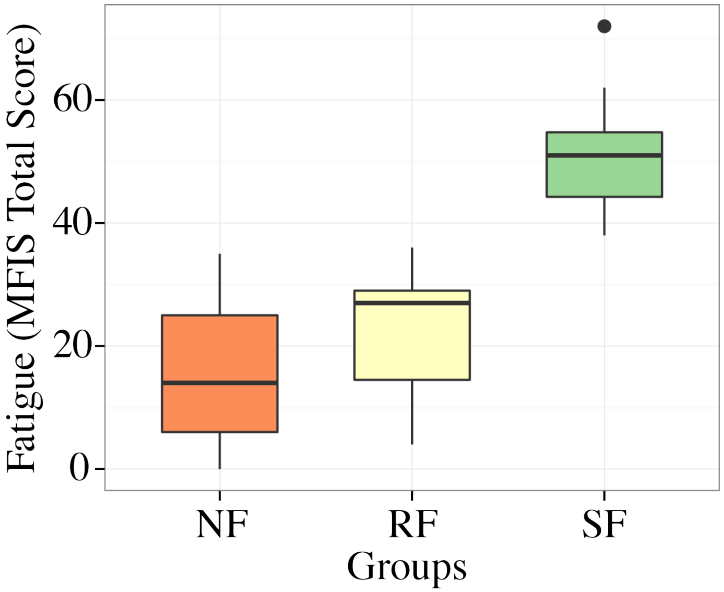


Figure 4. *MFIS Total Score differences among the fatigue groups (never fatigue, reversible fatigue, and sustained fatigue).*

Association between Fatigue Severity and Clinical Disability

Across all participants, higher EDSS was associated with higher MFIS total score (β=+0.22; p=0.048), MFIS-physical subscore (β=+0.33; p=0.003) and MFIS-psychosocial subscore (β=+0.22; p=0.047) while controlling for effects of age and sex. In contrast, no significant association was observed between MFIS-cognitive subscore and EDSS (p=0.6).

Voxel-based Morphometry

VBM did not show a significant difference in gray matter regional volume among the temporal patterns of fatigue (i.e., SF, RF, and NF groups). Greater MFIS-cognitive

subscore severity was significantly associated with lower regional gray matter volume in various cortical regions encompassing all four lobes and insula along with subcortical structures (i.e., putamen, thalamus, and caudate) in both hemispheres (peak FWE-p=0.021 in right insula; Table 2; Figure 5).

Figure 5. *VBM results showing brain regions demonstrating significant atrophy with more severe cognitive fatigue (MFIS-cognitive subscore; FWE-p<0.05).*

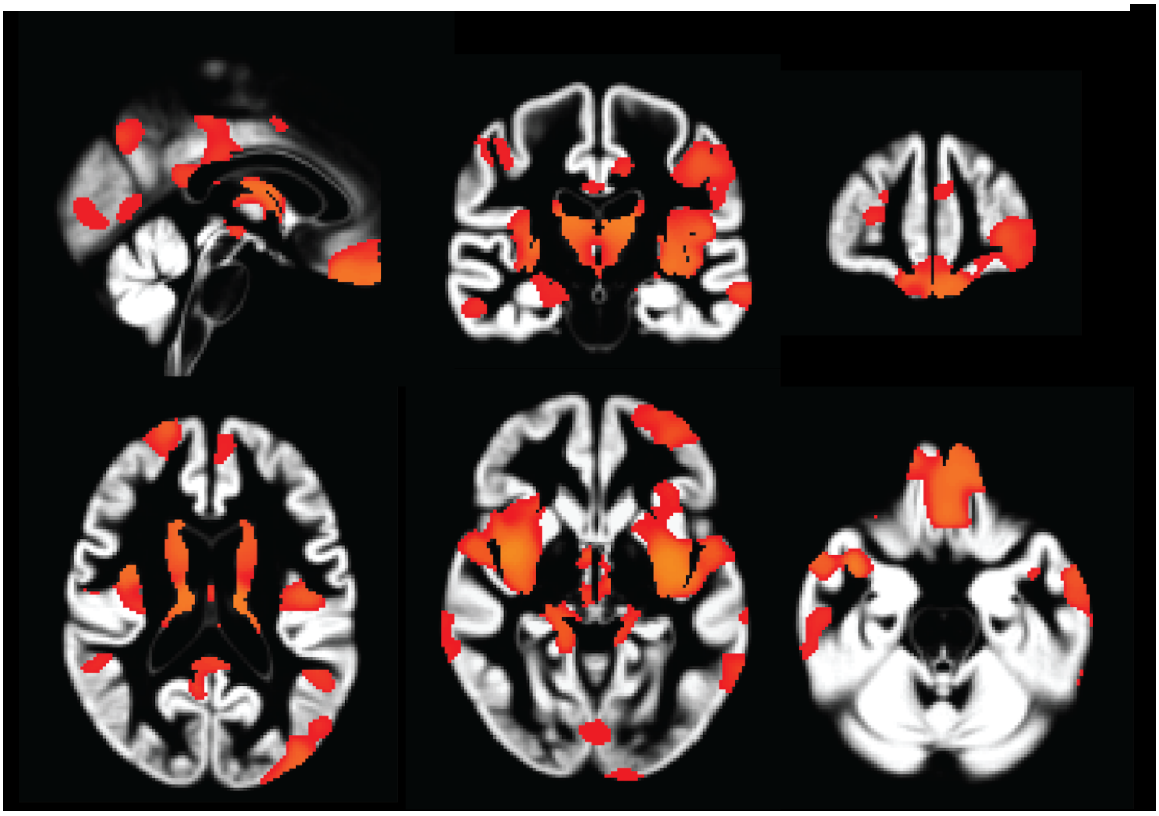
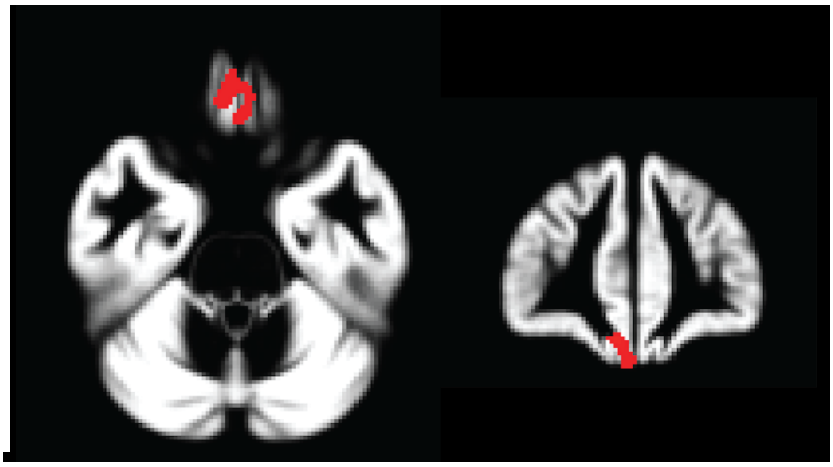


Table 2. MNI coordinates and volumes of clusters (P_{FWE}<0.05) from voxel-based morphometry demonstrating significantly lower gray matter volume with more severe cognitive fatigue among participants with multiple sclerosis.

Cluster	Volume (mm^3)	Peak P Value	MNI Coordinate			Gray Matter Regions
			X	Y	Z	
1	32,943	0.021	39	6	-16.5	Bilateral insulae, caudate nuclei, putamina, thalami, planum polare, parahippocampal gyri, cingulate gyri, right temporal pole, hippocampus left inferior temporal gyrus, and precentral gyrus
2	6,715	0.027	-3	45	-28.5	Bilateral fronto-medial cortices and frontal poles
3	5,354	0.03	-63	-45	-16.5	Left inferior temporal gyrus, middle temporal gyrus, and left angular gyrus
4	4,177	0.041	48	-28.5	52.5	Right posterior central and right inferior temporal
5	3,447	0.031	-39	-90	16.5	Left lateral occipital cortex
6	1,055	0.032	21	64.5	18	Right frontal pole
7	710	0.038	0	-72	36	Bilateral precuneus cortices
8	474	0.049	-1.5	-82.5	-4.5	Bilateral intra-calcarine cortices
9	396	0.046	-4.5	54	19.5	Left paracingulate gyrus
10	300	0.048	-12	-105	-3	Left occipital pole
11	254	0.046	61.5	3	33	Right precentral gyrus
12	106	0.048	36	-60	49.5	Right lateral occipital cortex
13	17	0.05	-15	34.5	42	Left superior frontal gyrus

Figure 6. *VBM results showing brain regions demonstrating significant atrophy with more severe physical fatigue (MFIS-physical subscore; family-wise error corrected-p<0.05).*



VBM showed significant inverse relationship between the physical subscale of MFIS with the volume of the bilateral frontal poles, and frontal medial cortices (peak FWE-*p* value of 0.043)

Subcortical Volumetric Analysis

Subcortical volumetric analysis revealed that the average volume of the bilateral thalami and putamina are significantly different between the three groups while controlling for EDSS, age, gender, and CESD scores (p=0.0078 and p=0.0024 respectively) but the average bilateral caudate nuclei volumes were not significantly different (p=0.084). Further subgroup analysis revealed that there are no differences between the SF and RF group with respect to the average thalami and putamina volumes while controlling for the EDSS, age, gender, and CESD score (p=0.96 and p=0.81 respectively), but the average thalami and putamina volumes were significantly larger in the NF group vs RF group (p<0.00048, p<0.0005 respectively), and the average putamina volumes were significantly larger in NF group vs SF group (p<0.0085)

DISCUSSION

Fatigue is one of the most prevalent symptoms amongst patients with MS and has been considered one of the most troubling symptoms of MS by patients. (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994) Fatigue has serious social implications for the patients; it has been reported that it is one of the main reasons of unemployment in MS patients.(M. M. Smith & Arnett, 2005) It's worth to mention that fatigue is one of the main factors that determines the quality of life in MS.(Ziemssen, 2009) Fatigue in general is a difficult to define symptom as it has different components such as physical and cognitive which are different in nature although they are both referred to as fatigue. These components are not totally independent and are actually correlated. It has been suggested that fatigue and depression usually cluster. One simple explanation for this phenomenon is the existence of common risk factors for the emergence of these two, and a shared pathophysiological pathway for their development. One study reported a significant relationship between fatigue and depression even after correcting for EDSS.(Bakshi, Shaikh, et al., 2000) Treatment of depression is associated with decrease in fatigue.(Mohr, Hart, & Goldberg, 2003) Atrophy in the frontal lobe and lesions in frontal, temporal, and parietal lobes were associated with depression in MS.(Bakshi, Czarnecki, et al., 2000) Hence we decided to

control for depression score while assessing the association of fatigue and deep gray matter atrophy; to meticulously evaluate the relationship of fatigue and gray matter atrophy while limiting the effect of other contributing factors.

To better define fatigue more detailed questionnaires might be needed. On the other hand, fatigue development as discussed in the introduction is multifactorial and can not be only attributed to neurogenic origins.

We used voxel-wise and volumetric region-of-interest analyses to characterize gray matter neural correlates of fatigue severity and groups of patients with different temporal course of fatigue. Our study did not show a significant difference between MS patients who had sustained fatigue, reversible fatigue, or were free of significant fatigue in their follow up. Across all participants included in this study, voxel-wise analysis (using VBM) showed that more severe cognitive fatigue was associated with greater atrophy mainly in basal nuclei and thalamus along with insular, temporal, and prefrontal cortices. In addition, greater physical fatigue was associated with greater medial frontal lobe atrophy. Post-hoc region-of-interest volumetric analysis showed significant differences in volume when comparing the average size of the bilateral thalami and putamina between the NF and RF group. The average volume of the bilateral putamina was also significantly larger in the NF vs RF group while there were no significant differences between these structures when comparing the SF vs RF group. Contrary to our initial

hypothesis, it appears that different temporal patterns of self-reported fatigue are not associated with regional atrophy in the grey matter of patients with MS. Grey matter atrophy in distinct anatomical regions was however associated with the severity of fatigue subscales.

We were able to reproduce the previously reported results that linked regional gray matter atrophy in the fronto-temporal lobes, insulae, occipital cortex, caudate nuclei, putamina and thalami to the cognitive subscale of fatigue in MS(Andreasen et al., 2010; Batista et al., 2012; Sepulcre et al., 2009; Wilting et al., 2016) In contrast to our study, none of these studies have corrected their results based on the EDSS scores; hence, we were able to compare patients with wider range of EDSS and estimate the effect of gray matter atrophy on fatigue development, specifically the cognitive component, while controlling for the EDSS score. Our VBM analysis could not differentiate between the three groups(NF, SF, and RF) that were classified based on the temporal course of their MFIS scores. This result might be partly explained by the fact that the groups were classified based on their total MFIS score over time, rather than by the cognitive subscale of fatigue. When pooling all patients, fronto-medial atrophy was correlated with the physical component of fatigue.

We acknowledge that our study had certain limitations: (i) The design of our study was cross-sectional, a longitudinal design will help us to better understand the relationship of gray matter atrophy with respect to fatigue development; (ii) We did not assess the damage to white matter connectivity on fatigue development, either

independently or through gray matter atrophy; (iii) Only 57 subjects had their MRI scan within a month of MFIS score assesment; The average and standard deviation between the MRI scan and the MFIS score assesment were 4.02 months and 5.39 months, respectively; (iv) The number of subjects selected for the SF and RF groups were less than those in the NF group.

CONCLUSION

In addition to the role of the frontal cortex-striatum-thalamus the insula and occipital cortex may also be involved in the pathogenesis of fatigue. Cognitive and physical MFIS were associated with different gray matter atrophy patterns. Moreover, gray matter atrophy was associated with fatigue severity, independently from its temporal course.

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