Thalamic shape abnormalities in patients with multiple sclerosis-related fatigue

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Abstract

Thalamus plays an important role in the pathogenesis of multiple sclerosis-related fatigue (MSrF). However, the thalamus is a heterogeneous structure and the specific thalamic subregions that are involved in this condition are unclear. Here, we used thalamic shape analysis for detailed localization of thalamic abnormalities in MSrF. Using Modified Fatigue Impact Scale, we measured fatigue in 42 patients with relapsing-remitting multiple sclerosis (MS). Thalamic shape was extracted from T1w images using an automated pipeline. We investigated the association of thalamic surface deviations with the severity of global fatigue, and its cognitive, physical, and psychosocial subdomains. Cognitive fatigue was correlated with an inward deformity of the left anteromedial thalamic surface, but no other localized shape deviation was observed in correlation with global, physical or psychosocial fatigue. Our findings indicate that the left anteromedial thalamic subregions are implicated in cognitive fatigue, possibly through their role in reward processing and cognitive and executive functions.

Keywords: Multiple Sclerosis; Fatigue; Thalamus; Magnetic Resonance Imaging; Shape Analysis.

1 Introduction

Multiple sclerosis-related fatigue (MSrF) affects up to 95% of the patients with multiple sclerosis [1], and is commonly defined as a subjective feeling of reduced energy and an inability to initiate and sustain tasks that require attention or physical activity, such that it interferes with daily activities [2]. The mechanisms underlying MSrF are poorly understood, and its treatment options are limited and not sufficiently effective [3]. Recently, the role of the thalamus and its aberrant connectivity with the cerebral cortex and/or basal ganglia has been highlighted in the pathology of MSrF (reviewed by Capone et al. [4]). Thalamus has also been associated with fatigue in other neurologic disorders, such as Parkinson's disease [5], or traumatic brain injury [6].

However, thalamus is a complex and heterogeneous structure, consisting of several nuclei with distinct connections and functions [4]. Therefore, it is important to understand which thalamic subnuclei are specifically associated with MSrF. Shape analysis of subcortical structures is a novel approach of studying their structural abnormalities which enables their investigation in more detail, and can indirectly hint at their microstructural alterations. Using this automated approach, we here aimed to investigate the association of MSrF and its dimensions with localized abnormalities in thalamic shape, for better understanding the microanatomy of thalamus in this disorder.

2 Methods

2.1 Patients

Forty-three patients (32 females and 11 males) with relapsing-remitting MS were recruited in this study, as described previously [7]. The patients were diagnosed based on the 2010 McDonald criteria [8]. All cases were

in the age range of 18-59 years and had an Expanded Disability Status Scale (EDSS) score 6 [9]. We excluded patients with recent relapse or corticosteroid therapy within the last 3 months, in addition to patients with clinically significant depressive symptoms (Beck Depression Inventory-Fast Screen score 10), or a history of head trauma, loss of consciousness, other neurologic disorders, psychotic disorders, substance abuse, chronic systemic disorders, uncontrolled thyroid dysfunction, or malignancy. The local Ethics Committee approved the study protocol, and written informed consent was obtained from all subjects prior to their participation.

2.2 Behavioral assessment

We measured fatigue severity using Modified Fatigue Impact Scale (MFIS) [10]. It consists of 21 items and evaluates how fatigue has impaired the physical, cognitive, and psychosocial functioning of the patient over the last month. Each item is scored from zero to four, and the global MFIS score is calculated as the sum of scores from all 21 items (range: 0-84), with higher scores indicating more severe fatigue. The subscale score for the physical (range: 0-36), cognitive (range: 0-40), and psychosocial (range: 0-8) domains were calculated similarly as the sum of scores from their corresponding items. In addition, cognitive function was assessed using Symbol Digit Modalities Test (SDMT) (see Text, Supplemental Digital Content 1, which describes the details of cognitive assessment).

2.3 Scan acquisition

T1-weighted brain images were acquired using a 1.5 Tesla Siemens Magnetom Avanto scanner using the three-dimensional magnetization-prepared rapid acquisition with gradient echo (3D-MPRAGE) protocol with the following parameters: repetition time = 2730 ms, echo time = 2.81 ms, inversion time = 1000 ms, flip-angle = 7°, matrix size = 256×256×176, voxel-size = 1×1×1 mm.

2.4 Image processing

We used FMRIB Software Library (FSL) version 6.0.3 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) to perform thalamic segmentation and shape reconstruction. T1-w images were first skull-stripped using FSL's Brain Extraction Toolbox (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET), and underwent bias field correction using FMRIB's Automated Segmentation Tool (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FAST). We then used FMRIB's Integrated Registration and Segmentation Tool (FIRST;

https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST) to automatically segment the bilateral thalami and reconstruct them as surface mesh models [11]. Briefly, the FIRST initially registers the structural images to the MNI152 reference space with a two-stage registration method that is optimized for subcortical structures. Next, pretrained 3D deformable mesh models of each thalamus, which represent their surfaces, are fitted to the preprocessed and registered images. Each mesh model is a tessellated surface consisting of a fixed number of vertices connected by edges. The locations of these vertices are standardized and can be compared across individuals. We controlled the quality of thalamus segmentation for each subject by visually inspecting the mask for bilateral thalami overlaid on the whole-brain images, and excluded one patient due to failed segmentation. In the next step, the thalamic surface models for the patients are averaged to generate a native thalamic shape template. The surface model for individual subjects are then projected onto this native template, creating a 4D Nifti image (one volume per subject), in which the voxel values represent the perpendicular distances of the corresponding vertices from the average native template, with positive/negative values showing outward/inward shape alterations at that location relative to the average shape across the whole sample. In addition, the thalamic volume for each subject was calculated using fslstats, as the sum of the volume of all voxels within each thalamic mask. Similarly, the total intracranial volume (TIV) was calculated as the sum volume of all voxels in the brain-extracted image.

2.5 Statistical analysis

We used mass-univariate general linear model analysis to investigate the correlation of the left and right thalamus shape deviations with the global, physical, cognitive, and psychosocial fatigue, as well as the SDMT performance. FSL's first_utils and randomise commands were used to perform these analyses on the vertex-wise distance of each subject's thalamic surface from the average template. In all analyses, we included age, sex, handedness, EDSS score, and TIV as nuisance covariates of no interest. TIV was included in the models to control for its known association with brain volumetric measures [12]. All variables in the model were demeaned. To assess the collinearity of the design matrix, we calculated the variance inflation factor of the variables included in the general linear models and observed that it was lower than 2 for all variables, indicating no considerable collinearity. Finally, we tested for the statistical significance of shape aberrations using a nonparametric permutation-based test with 5000 iterations, while cor-

recting for multiple comparisons using threshold-free cluster enhancement at a family-wise error rate of < 0.05. In addition, we used the Python programming language (v. 3.7) with the pandas (v. 0.25) and pingouin (v. 0.3) packages to investigate the partial correlation of the thalamic volumes with global fatigue and its subscales, as well as the SDMT performance, , with age, sex, handedness, EDSS, and TIV as the nuisance variables.

3 Results

The patients were on average 30.2 ± 7.1 (range: 21-57) years old, and had an EDSS score of 2.9 ± 1.3 (range: 0-6). The physical subscale of Modified Fatigue Impact Scale (MFIS) was significantly associated with the EDSS score (r = 0.41), but no other significant association was observed between the global MFIS and its subscales or SDMT performance with age, sex, EDSS score, or TIV.

We observed no significant localized correlation of global MFIS with the shapes of the left or right thalamus. The severity of cognitive fatigue was significantly correlated with an inward deformation in 18.7% of the left thalamic surface in its superior anterior and medial anterior areas (Figure 1). However, right thalamic shape deviation was not significantly correlated with cognitive fatigue. Likewise, we observed no significant correlation between thalamic shape abnormalities and physical or psychosocial fatigue. Moreover, thalamic volumes were not significantly correlated with the global, cognitive, physical or psychosocial fatigue (Table 1). SDMT performance was significantly correlated with the volume of the bilateral thalami, and widespread shape deviations that were more prominent in the anterior superior and posterior regions of the left thalamus (see Text and Figure, Supplemental Digital Content 2, which report the thalamic changes associated with cognitive performance).

4 Discussions

Thalamus is thought to have an integral role in the pathogenesis of MSrF [4], but considering its complex structure, it is unclear which thalamic subregions or subnuclei are more involved in this condition. Here, we used thalamic shape analysis as an indirect measure for localizing these subregions and showed an inward deformity of the left anteromedial thalamic surface in patients with higher cognitive fatigue, suggesting selective atrophy of the subnuclei underneath it, i.e., the anterior nucleus (ATN), laterodorsal nucleus (LD), mediodorsal nucleus (MD), and the midline nuclei (ML). We also observed that lower cognitive processing speed in patients

with MS was associated with a widespread inward deformity of bilateral thalamic surfaces, most prominently on the left side and in the anterior superior and posterior thalamic regions.

It has been suggested that MSrF results from a decreased sensitivity to rewards, i.e., the benefits of the outcomes resulting from actions, along with overestimating the effort required for them [13,14]. Below we have discussed the role of anteromedial thalamus in reward sensitivity and overestimation of effort.

Reward expectation is probably why healthy individuals without clinically significant fatigue can exert effort regardless of feeling physically or mentally fatigued (e.g., after repeatedly performing a difficult task) [15]. Patients with MSrF, particularly those with higher cognitive fatigue, are less responsive to rewards, and interestingly, lower reward responsiveness in these patients predicts a higher therapeutic response to bupropion [16], a medication that enhances the brain reward function [17]. Animal studies have shown that MD nucleus is crucial for the representation of outcome value to guide behavior [18]. This nucleus serves a similar function in humans, as a coordinate-based meta-analysis aggregating the findings of all functional imaging studies on reward processing has shown convergent activation in MD [19]. MD is structurally connected to the dorsolateral prefrontal cortex (dlPFC) [20], which is a key region in reward processing and its integration with cognitive information to guide behavior [21]. The connectivity of medial thalamic nuclei to dlPFC is reduced in patients with MSrF [22], and dlPFC is atrophied in these patients [23]. These findings suggest that abnormalities in the MD nucleus, as a component of the cortico-striatal-thalamic loop [24], may be involved in MSrF through an impairment in reward sensitivity [13].

Overestimation of effort in MSrF patients results from a metacognitive process in which there is a mismatch between perceptions/reality and expectations about the internal bodily states, sensorimotor functions, or task performance, causing the brain to infer that it is not fully capable of controlling the body, and therefore its actions are futile/non-efficient and require more effort than predicted. In this context, fatigue can result from maladaptive perceptions, expectations, or actions that would lead to this prediction error, which can be due to impairments in the allostatic-interoceptive system, sensorimotor system, executive and cognitive functions, or metacognition [14]. ATN and LD nuclei of the thalamus have widespread connections to the frontal cortex, cingulate cortex, and hippocampal formation, and are involved in cognitive functions [25]. Lesions in the ATN nucleus can cause anterograde amnesia in humans [26] and animal models [27]. In addition, the MD nucleus is a component of the cortico-striatal-thalamic loop, which

MFIS	Left thalamus volume		Right thalamus volume	
	r (CI95%)	p-value	r (CI95%)	p-value
Global	-0.19 (-0.47, 0.11)	0.211	-0.05 (-0.35, 0.25)	0.733
Physical	-0.02 (-0.32, 0.28)	0.884	0.12 (-0.19, 0.41)	0.437
Cognitive	-0.30 (-0.56, 0)	0.051	-0.21 (-0.49, 0.10)	0.174
Psychosocial	-0.19 (-0.47, 0.11)	0.209	0 (-0.31, 0.30)	0.951

Table 1: The correlation of left and right thalamus volumes with the global, physical, cognitive and psychosocial fatigue. Age, sex, handedness, Expanded Disability Status Scale score and total intracranial volume were included as nuisance covariates. MFIS: Modified Fatigue Impact Scale; r: partial correlation coefficient; CI95%: 95% confidence interval.
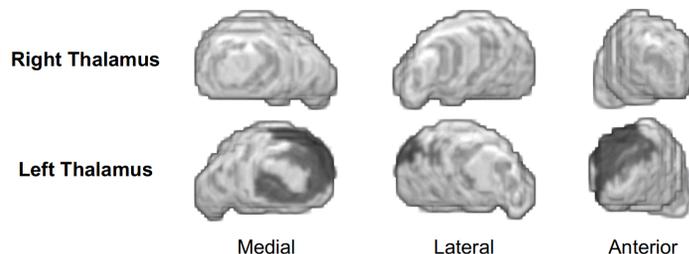
Figure 1: Inward thalamic shape deformation (dark grey) in patients with higher cognitive fatigue.

has an important role in executive functions [24]. Cognitive and executive dysfunctions have been consistently observed in patients with MS, correlating with fatigue severity [28,29]. Interestingly, as was shown in ours as well as previous studies [30,31], cognitive and executive dysfunction in patients with MS is associated with the atrophy of thalamus, mostly in its anterior superior, medial, and posterior regions. Therefore, based on the metacognitive hypothesis of MSrF, cognitive fatigue may partly arise from an impaired performance in cognitive and executive functions beyond patients' expectations, leading to a mismatch between the actual and expected performance, which will result in the belief that succeeding in these tasks requires extra effort [14].

Of note, by using shape analysis, it is difficult to pinpoint the atrophy of specific thalamic nuclei particularly in the inner regions distant from the surface, and these regions may as well be involved in the neurobiology of MSrF. Importantly, impairments in the level of vigilance and arousal has been suggested as a contributing mechanism in MSrF [32,33], and intralaminar nuclei (ILN), as key hubs in the ascending reticular activating system (ARAS) [34], may be involved in MSrF through their role in arousal and alertness. Although there is no direct evidence for the atrophy/dysfunction of ILN in fatigue, previous studies on these patients have reported deficits in the ARAS white matter connecting the brainstem to the thalamus or more specifically ILN [35,36].

Our study was not without limitations. First, our moderate sample size in addition to using a stringent multiple comparisons correction method has limited the power of our study for detecting small effects. Second, the close interrelation of fatigue with depression is a challenge for studying MSrF. Fatigue or loss of energy is one of the criteria for the diagnosis of depression, and fatigue questionnaires such as MFIS often include items that could indicate depressive symptoms. For these reasons, here we removed subjects with clinically significant depression from our analyses, but, nevertheless, we cannot exclude the possibility that our findings might partly represent thalamic correlates of depressive symptoms. Third, although we investigated the thalamic shape differences associated with cognitive processing speed using SDMT, we had limited/no data on the other aspects of cognitive and executive functions, as well as reward sensitivity, and thus were unable to further explore the potential effects of thalamic abnormalities on cognitive MSrF through impairments in task performance and reward processing. Fourth, as we did not have a healthy control group, we cannot be certain whether the observed effects are specific to MSrF, or is associated with fatigue or one of its subcomponents in general, and not just limited to patients with MS. Finally, we deduced the localized atrophy of anteromedial thalamus indirectly and using shape analysis, and therefore, future studies should utilize MRI sequences optimized for the thalamus, and directly measure the volume of each thalamic subnuclei using tools such as FreeSurfer Thalamic Segmentation (http://freesurfer.net/fswiki/ThalamicNuclei). It

is also important to note that considering the association of brain volumetric measures with TIV [12] we have regressed out TIV to remove thalamic shape/volume differences associated with the changes in global brain volume. However, by using this approach we may have underestimated some of the thalamic shape abnormalities associated with MSrF, as brain size or thalamic shape abnormalities that covary with it may also be relevant in the neurobiology of fatigue, although we observed no correlation between MFIS and its subscales with TIV.

4.1   Conclusions

Overall, we showed that the atrophy of the left antero-medial thalamic regions may contribute to cognitive MSrF, perhaps through their involvement in reward processing and task performance. Future research should focus on directly localizing structural and functional abnormalities of thalamus in MSrF, as well as using longitudinal and interventional/lesion data to investigate the causality of deficits in these thalamic subregions for MSrF.

Acknowledgements

Conflict of Interest

There are no conflicts of interest.

References

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Supplemental Digital Content 1

Symbol Digit Modalities Test (SDMT) was performed as a component of Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) - Farsi translation [1]. SDMT consists of nine abstract symbols paired with a number from 1 to 9. On top of the page, a key to the symbol/number pairings is provided, and below, a series of pseudo-randomized symbols is given and the participant is asked to say out load the numbers associated with each symbol as quickly as possible and within 90 seconds. The number of correct answers is recorded as the measure of task performance. SDMT performance measures visuospatial processing speed, sustained attention, concentration, and working memory [2].

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Supplemental Digital Content 2

Poorer SDMT performance was significantly correlated with inward deviation of 80.2% of the left thalamic surface, which was most prominent in the anterior superior, and posterior regions. On the right side, inward deviation of 66.2% of thalamic surface was significantly correlated with poorer SDMT performance, which similar to the left thalamus, was more prominent in the anterior superior and posterior regions (Supplementary Fig. 1). SDMT performance was also significantly correlated with the left (r = 0.48; CI95% = 0.21-0.69; p = 0.001) and right (r = 0.36; CI95% = 0.06-0.60; p = 0.018) thalamic volumes.
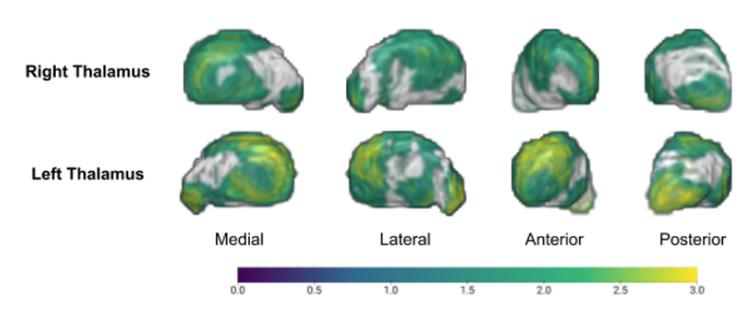
Supplementary Fig. 1: Inward thalamic shape deformation in patients with higher cognitive fatigue. The colored surface shows regions with significant inward deformity. Brighter colors represent higher correlation.