

# Brain morphometry changes with fatigue severity in fibromyalgia

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## Abstract

### Objective

*This study investigated brain morphometry changes associated with fatigue severity in fibromyalgia (FM).*

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### Methods

*Clinical profiles and brain-MRI data were collected in patients with FM. Patients were divided into three groups based on their fatigue severity. Using voxel-based morphometry analysis and trend analysis, neural substrates showing volumetric changes associated with fatigue severity across the three groups were identified. Their seed-to-voxel structural covariance (SC) networks with the whole brain were studied in distribution and strength.*

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### Results

*Among the 138 enrolled patients with FM, 23, 57, and 58 were categorised into the mild, moderate, and severe fatigue groups, respectively. The number of musculoskeletal pain regions and intensity of pain were not associated with fatigue severity, but somatic symptoms and psychiatric distress, including waking unrefreshed, depression, and anxiety, were associated with fatigue severity. After adjusting for anxiety and depression, decreased bilateral thalamic volumes were associated with higher fatigue severity. The SC distributions of the thalamic seed were more widespread to the frontal, parietal, subcortical, and limbic regions in patients with higher fatigue severity. In addition, increased right inferior temporal cortex volumes were associated with higher fatigue severity. The SC distributions of the right inferior temporal seed were more over the temporal cortex and the SC strengths of the seed were higher with the bilateral occipital cortex in patients with higher fatigue severity.*

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### Conclusion

*The thalamus and the right inferior temporal cortex are implicated in the manifestation of fatigue severity in FM. Future therapeutic strategies targeting these regions are worthy of investigation.*

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### Key words

fibromyalgia, fatigue, magnetic resonance imaging, thalamus, right inferior temporal cortex

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Data availability. Unthresholded  
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## Introduction

Fibromyalgia (FM) is a nociplastic pain disorder that manifests as widespread chronic pain and involves multiple somatic symptoms. Neuroplasticity may participate in the pathogenesis of FM and give rise to its symptoms. Fatigue, an overwhelming sense of lacking physical or mental energy, is highly prevalent in patients with FM and substantially reduces their function, performance, and quality of life (1). The biological mechanism for fatigue remains inconclusive (2–6), and the efficacy of the available treatments for FM-related fatigue is not satisfactory (7). Given the advancement of neuroimaging, studies in FM have addressed brain morphometric changes corresponding to many fibromyalgia symptoms, including widespread pain, psychological distress, or sleep quality (8, 9). However, the changes associated with fatigue are unclear. Studying how the brain structures change with the symptom of fatigue in FM may help decipher the elusive pathogenesis of this symptom and assist in developing relevant solutions.

This study aimed to investigate brain morphometry changes associated with fatigue severity in FM. We hypothesised that patients with FM with different fatigue severities would present different brain morphometry, including neural substrates volumes and neural structural interactions. We also hypothesised that these volumetric and interactional changes would be proportional to the severity of fatigue. To prove our hypothesis, we pragmatically categorised patients with FM into three groups (no and mild/moderate/severe fatigue) according to their fatigue severity scores on the modified 2010 American College of Rheumatology criteria for FM (10). We investigated the neural structures that showed a linear trend of volumetric changes across the three groups. Then, using the identified regions as the candidate seeds of interest, we further explored their structural covariance networks (SCNs) with the whole brain and studied the distribution and strength of the SCNs that showed a linear trend of changes across the three groups. Our goal is to demonstrate neural signatures associated with fatigue severity in patients with FM.

## Methods

### Participants

We consecutively recruited patients aged 20–60 years, with newly-diagnosed FM between May 2013 and August 2019 at Taipei Veterans General Hospital. The diagnosis of FM followed the modified 2010 American College of Rheumatology criteria for FM (10). The following 3 conditions should be met: (1) a Widespread Pain Index (WPI)  $\geq 7$  and a Symptom Severity Score (SSS)  $\geq 5$ , or a WPI of 3–6 and a SSS  $\geq 9$ , (2) symptoms have been present at a similar level for at least 3 months, and (3) the patient does not have a disorder that would otherwise explain the pain. Patients comorbid with major systemic diseases, neurological diseases and psychiatric diseases, or women that were pregnant or breastfeeding were excluded. Participants receiving any daily medication or hormone therapy were also excluded. All of the recruited participants were right-handed, presented with normal neurologic findings, and had no major neurological diseases.

### Protocol approval and patient consent

All information that would potentially expose individual patient identities has been encrypted. Informed consent forms were completed by all the participants after a thorough explanation. The whole study protocol was approved by the Institutional Review Board of Taipei VGH. All methods were carried out in accordance with relevant guidelines and regulations.

### Study design

A semi-structured questionnaire was conducted to all of the participants at their first visit to obtain the information on demographics, symptoms related to FM, and psychiatric comorbidity. The number of body pain areas was assessed using the WPI (10), which records regions in which the patient has had pain over the past week, scoring between 0 and 19. We used the SSS to assess the severity of somatic symptoms (10), including fatigue, waking unrefreshed, and cognitive dysfunction during the past week, scoring from 0–3 of each symptom domain. The SSS was

also used to assess the presence (score 1) of headache, pain and/or cramps in the lower abdomen, and depression, respectively in the past 6 months. The Revised Fibromyalgia Impact Questionnaire (FIQR) was used to evaluate the function, overall impact, and severity of symptoms in patients with FM (11). The psychiatric comorbidity was evaluated using the Hospital Anxiety and Depression scale (HADS) (12). All of the patients underwent a scheduled MRI within 1 month of their first visit after recruitments.

Patients' severity of fatigue was categorised as no or mild fatigue (jointly characterised as mild fatigue in this study), moderate fatigue, and severe fatigue based on the answers corresponding to the fatigue subitem in the SSS. Notably, only one patient with FM reported experiencing no fatigue.

#### *MRI data acquisition*

The physicians who enrolled patients were blinded to the MRI data acquisition. Structural MRI scans were obtained using a standard eight-channel phase array head coil on a 3.0 Tesla GE Discovery MR750 scanner (General Electric Healthcare, Milwaukee, WI, USA) at the Taipei Veterans General Hospital. Individual whole brain three-dimensional axial T1-weighted anatomical scans were acquired using the inversion recovery-prepared fast spoiled gradient recalled sequence with the following imaging parameters: repetition time = 9.4 ms, echo time = 4.0 ms, inversion time = 450 ms, flip angle = 12°, slice thickness = 1 mm, image matrix = 256 x 256, field of view = 256 x 256 mm, and 172 slices without an inter-slice gap.

#### *Estimation of the voxel-wise grey matter volume maps*

For estimating the voxel-wise grey matter volume map of each individual, we applied the enhanced voxel-based morphometry (VBM) pipeline with Statistical Parametric Mapping 12 (SPM12, version 7487, Wellcome Institute of Neurology, University College London, UK) in a MATLAB environment (v. R2015b; Mathworks, Natick, MA). All the preprocessing steps have been documented in our previous study (13),

which were summarised as follows. First, all the individual T1-weighted images were corrected for intensity nonuniformities and segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) tissue compartments using the unified segmentation algorithm with enhanced tissue probability maps (14). These segmented tissue compartments were then rigidly aligned to the Montreal Neurological Institute (MNI) space. For achieving a higher spatial correspondence among the participants, the study-specific GM and WM tissue templates were generated from all the participants using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox (15). Then, the individual rigidly-aligned tissue segments were warped to match the constructed study-specific templates and resized to 1.5 mm cubic resolution. Finally, these individual MNI-space GM tissue segments were modulated with the corresponding DARTEL flow field and smoothed with an isotropic Gaussian filter (8 mm full width at half maximum). For adjusting the effect of global brain size in the following statistical analyses, the individual global tissue volume and total intracranial volume (TIV = GM + WM + CSF volumes) were also calculated in the native T1 space for each individual.

#### *Analyses of demographic and clinical data*

The descriptive data in the demographic and clinical profiles are presented as mean  $\pm$  standard deviation or numbers and percentages. We used the chi-square test to assess differences in categorical data. For normally-distributed continuous variables, we used one-way analysis of variance (ANOVA) to compare their means and used the Tukey test for post-hoc analyses. For variables that were not distributed normally, including the intensity of body pain (Numeric Rating Scale 0–10) and scores of WPI, SSS, cognitive symptom and unrefreshed symptom, we used Kruskal-Wallis test to compare and used Mann-Whitney U test for *post-hoc* analysis. The statistical analyses were done using SPSS version 21.0 for Windows (SPSS, Chicago, Il-

linois, USA) and a *p*-value lower than 0.05 was regarded as significant.

#### *Statistical criteria of voxel-wise imaging-based analyses*

Using SPM12, we constructed several appropriate general linear models with the corresponding statistical contrasts to perform voxel-wise statistical analyses, including regional GM volumes (GMV) and global SCNs analyses. To adjust for multiple comparisons in the voxel-wise statistical analyses, a thresholding approach based on cluster-extent was conducted using the updated version of related command-line tools (3dFWHMx and 3dClustSim; available in the Analysis of Functional Neuroimages software, version 20.1.06; 10,000 Monte Carlo simulations with explicit GM mask). For all the voxel-wise statistical analyses, the significance level was set at a cluster-level family-wise error (FWE) rate-corrected *p*-value <0.05, which was equivalent to a combination threshold of an initial voxel-level *p*-value <0.001 with a minimum cluster size of 129 voxels. In addition, following the previous VBM study with a more liberal initial voxel-level *p*-value (16), we also evaluate the GMV alterations with a statistical criteria which was set at an initial voxel-level *p*-value <0.005 with a minimum cluster size of 255 voxels (also equivalent to cluster-wise FWE corrected *p*-value <0.05). The detailed settings of each statistical model have been listed in the following subsection.

#### *Identifying the neural substrates with a linear trend of GMV alterations across the 3 fatigue groups*

We applied a whole-brain voxel-wise analysis of covariance (ANCOVA) model to identify the clusters showing a linear trend of GMV changes across the 3 fatigue groups. Participants' age, sex, HADS, and TIV were entered into the statistical model as nuisance variables. After model estimation, the following two statistical contrasts were used to investigate trends of GMV changes: ascending linear contrast (increasing GMV among 3 fatigue groups) defined as [-1 0 +1], and descending linear contrast (decreasing

**Table I.** Demographics, clinical profiles, and imaging data of three fatigue groups.

		All patients with FM fatigue		
		Mild* (%)	Moderate (%)	Severe (%)
Number of patients	138	23	57	58
Age (years)	43.0 ± 10.5	44.3 ± 11.8	43.1 ± 9.3	42.4 ± 11.1
Sex (F/M)	117/21	22/1	50/7	45/13
Tender points	13.7 ± 4.1	14.2 ± 4.2	12.6 ± 4.3	14.5 ± 3.6
Intensity of body pain (NRS 0–10)	4.8 ± 2.3	4.9 ± 2.6	4.4 ± 2.3	5.1 ± 2.2
WPI (0–19)	11.0 ± 4.0	11.1 ± 3.2	10.2 ± 3.4	11.7 ± 4.7
SSS (0–12) <sup>abc</sup>	8.3 ± 2.0	6.7 ± 1.6	7.6 ± 1.6	9.6 ± 1.7
Cognitive symptoms (0–4)	1.7 ± 0.8	1.6 ± 0.8	1.6 ± 0.8	1.9 ± 0.9
Waking unrefreshed <sup>ab</sup> (0–4)	2.1 ± 0.8	1.7 ± 0.9	2.0 ± 0.7	2.5 ± 0.7
Headache	130	22 (95.7%)	54 (94.7%)	54 (93.1%)
Abdomen pain	79	14 (60.9%)	31 (54.4%)	34 (58.6%)
Depression	85	17 (73.9%)	29 (50.9%)	39 (67.2%)
FIQR <sup>b</sup>	49.1 ± 18.3	47.4 ± 19.8	45.3 ± 15.9	53.7 ± 19.3
HADS <sup>b</sup>	21.4 ± 7.8	19.6 ± 7.2	19.8 ± 7.6	23.7 ± 7.8
TIV (liter)	1.408 ± 0.119	1.366 ± 0.076	1.407 ± 0.130	1.426 ± 0.118
GMV (liter)	0.706 ± 0.064	0.687 ± 0.043	0.708 ± 0.072	0.713 ± 0.063
WMV (liter)	0.402 ± 0.043	0.385 ± 0.031	0.403 ± 0.044	0.409 ± 0.045
CSFV (liter)	0.299 ± 0.056	0.295 ± 0.034	0.297 ± 0.059	0.303 ± 0.610

CSFV: cerebrospinal fluid volume; FM: fibromyalgia; FIQR: Revised Fibromyalgia Impact Questionnaire; GMV: grey matter volume; HADS: Hospital Anxiety and Depression Scale; NRS: numeric rating scale; SSS: symptom severity scale; TIV: total intracranial volume; WMV: white matter volume; WPI: widespread pain index.

\*The mild fatigue group includes patients reporting no or mild severity of fatigue.

<sup>a</sup>denotes the difference between patients with mild and severe fatigue, <sup>b</sup>denotes the difference between patients with moderate and severe fatigue, and <sup>c</sup>denotes the difference between patients with mild and moderate fatigue.

GMV among 3 fatigue groups) defined as [+1 0 -1]. The identified brain regions with statistically significant linear trend of GMV alterations were further defined as the candidate seeds of interest for subsequent whole brain voxel-wise SCNs analyses.

#### Identifying the regions with a linear trend of changes in SC distribution across 3 fatigue groups

Using the similarity of morphometrical features between different brain regions across participants as a surrogate index, structural covariance (SC) analysis provides an alternative way to study large-scale brain network organisation (17). Recent neuroimaging studies also demonstrate the spatial distribution of the SCN is not only highly concordant with gene expression pattern but also similar with intrinsic functional connectivity network, which continues to be reshaped during the lifespan by a variety of trophic influences (17–20). To map spatial distribution of the corresponding SCNs in each fatigue group, we first extracted the mean GMV

value of the candidate seed of interest which identified from the above VBM analysis for each individual. Then we entered these values into multiple linear regression models, with the nuisance variables identical to the VBM analysis, to identify morphometrical coupling patterns between the seed regions and other voxels of the whole brain. The voxels showing significant positive correlations with the seed regions were indicated as the spatial coverage of the morphometric network of the candidate seed of interest. However, the difference of sample size may change the results of the SCNs maps. Notably, the sample sizes across the fatigue groups differed in our study. To overcome this potential bias, and to confirm the reliability of the SCNs maps and further explore the difference in spatial distribution of SCNs across fatigue groups, we performed an additional resampling analysis with a matched sample size. To be specific, the corresponding SCNs maps of the fatigue groups were estimated with a 20–100 bootstrapping resampling

scheme at an interval of 10, in which 20 subjects were randomly extracted for each resampling. Furthermore, to quantify the spatial distribution of these SCNs maps, the whole-brain was parcellated into 7 regions using the WFU PickAtlas (21), including the bilateral frontal, parietal, limbic, sub-cortical, temporal, and occipital lobes, as well as the cerebellum. The voxels that demonstrated SC to the seed of interest were calculated for each sub-region. We then conducted an ANOVA model with a linear trend contrast to determine if the voxel numbers in each sub-region showed a significant linear trend change across 3 patient groups. The same analytical approach was adopted in our recent work that studied neural signatures associated with pain widespreadness in FM (8).

#### Identifying regions with a linear trend of changes in SC strength across the 3 fatigue groups

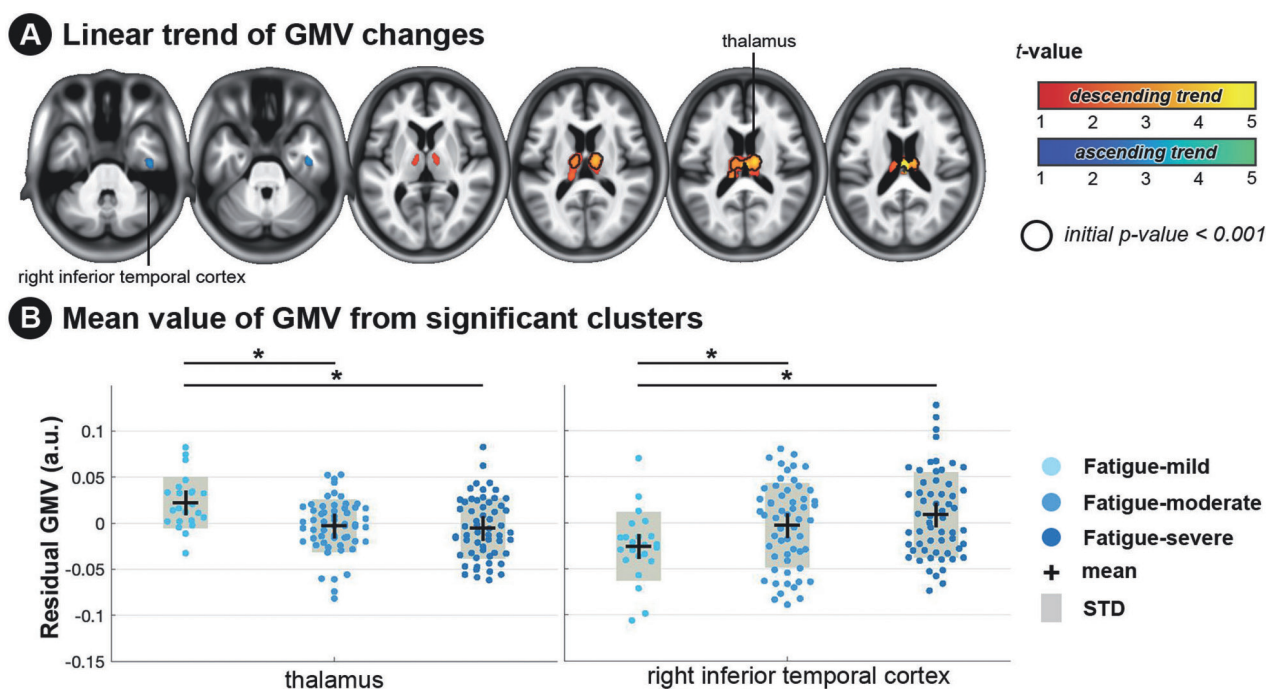
To explore the potential changes in strength of the corresponding SCNs across patient groups, we used two distinct general linear models that contained a main effect term of the group (mild, moderate, and severe fatigue), a main effect term of GMV of the corresponding candidate seed of interest, and an interaction term of group X seed GMV, with nuisance variables identical as the above VBM analyses. We tested the significance of the interaction term with ascending- and descending linear contrast at each voxel to identify SC strength that showed trends of changes among 3 fatigue groups.

## Results

### Demographics and clinical profiles of participants

A total of 145 patients with FM were enrolled, and 7 of them were excluded because of poor MRI-data quality. The data of the remaining 138 patients with FM (age 43.0±10.5 years; 117 female) were included in the final analysis. Among them, 23, 57 and 58 were categorised into the mild, moderate and severe fatigue groups, respectively. Among the 3 fatigue groups, there were no differences in their age, sex, the WPI scores, number of tender points,





**Fig. 1.** GMV changes in brain regions associated with the severity of fatigue.

**A:** Brain regions with GMV showing linear trend of changes across 3 groups of patients. Warm/cold colour indicated descending/ascending trend alteration in volume. Findings corrected for multiple corrections with initial voxel-level  $p$ -value < 0.005 showed on solid colour and initial voxel-level  $p$ -value < 0.001 are outlined in black. The bilateral thalamus showed decreasing volumes with increasing fatigue severity, while the right inferior temporal cortex showed increasing volume with increasing fatigue severity.

**B:** Difference of the GMV of identified significant clusters among the 3 groups of patients. The asterisk denotes a  $p$ -value < 0.05.

intensity of body pain, or severity of cognitive dysfunction. However, the severity of waking unrefreshed and the SSS, FIQR, and HADS scores differed among the 3 groups (Table I).

#### GMV differences among the mild, moderate and severe fatigue groups

The GMV of the bilateral thalamus consistently appeared to be inversely proportional to the severity of fatigue with two different statistical thresholds (FWE corrected  $p$ -value < 0.05, initial voxel-level  $p$ -value < 0.001 and < 0.005) (Fig. 1A). The GMV of the bilateral thalamus was larger in patients with mild fatigue than in patients with moderate or severe fatigue (Fig. 1B).

With a liberal statistical threshold of initial voxel-level  $p$ -value (< 0.005), we found another cluster over the right inferior temporal cortex showing increased volume proportional to the severity of fatigue (FWE corrected  $p$ -value < 0.05) (Fig. 1A). FM patients with mild fatigue symptom had smaller GMV of the right inferior temporal cortex compared to FM patients with moderate or severe fatigue (Fig. 1B).

#### SC distribution and strength in patients with mild, moderate and severe fatigue: thalamic seed

The thalamic seed showed a more widespread SC distribution to cortical and subcortical regions with increasing fatigue severity (Fig. 2A). Using resampling analysis with different resampling times, we consistently observed that there were more neural substrates located at the frontal, parietal, subcortical, and limbic regions showing SC to the thalamic seed with increasing fatigue severity (Bonferroni corrected  $p$ -value < 0.05) (Fig. 2B). We did not find changes in terms of SC strength across the 3 patient groups.

#### SC distribution and strength in patients with mild, moderate and severe fatigue: the right inferior temporal cortex seed

The right inferior temporal cortex seed showed SC distributions over the bilateral temporal regions in moderate and severe fatigue groups (Fig. 3A). With resampling analysis, there were more neural substrates in the temporal cortex but not in the other brain areas showing

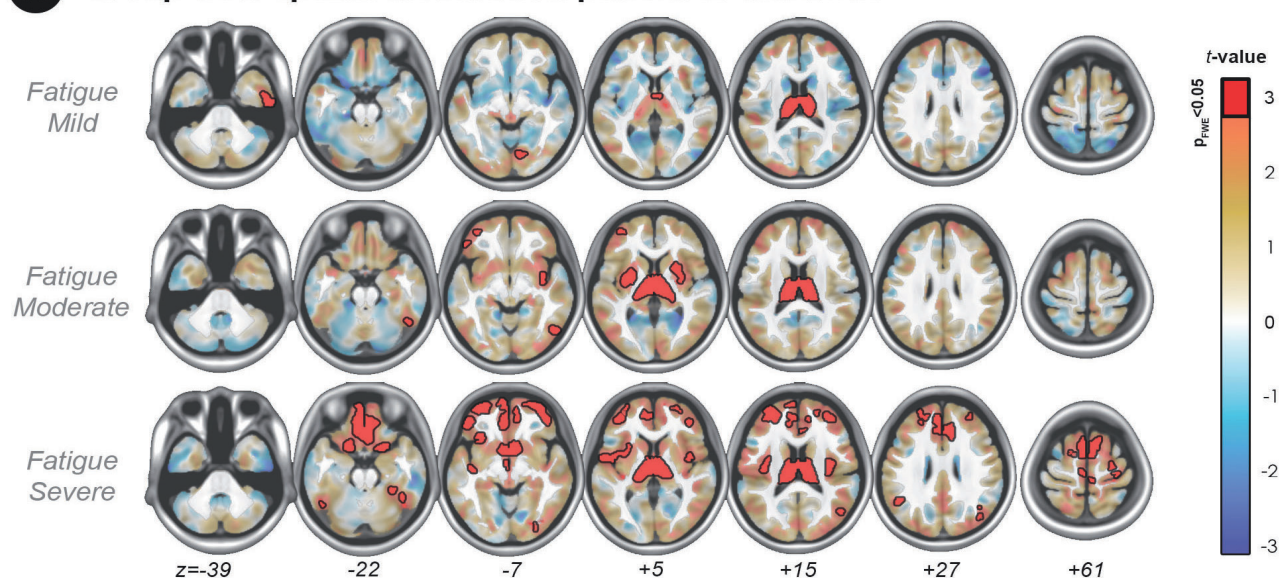
SC to the right temporal seed in patients with more severe fatigue (Bonferroni corrected  $p$ -value < 0.05) (Fig. 3B). As for SC strength, there were increased SC strength between the right temporal seed and the right occipital pole and the left occipital fusiform gyrus with increasing severity of fatigue (FWE corrected  $p$ -value < 0.05) (Fig. 3C).

#### Discussion

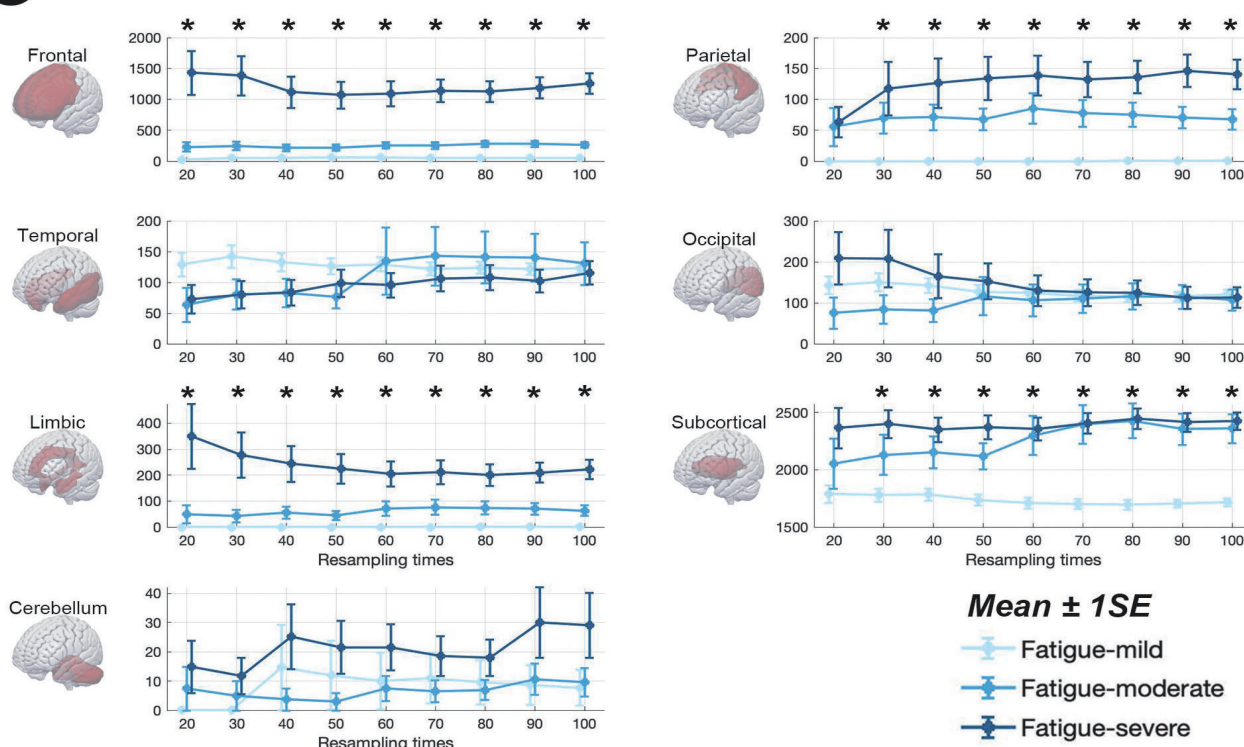
Our study showed that the thalamus and the right inferior temporal cortex are intimately implicated in the manifestation of fatigue severity in FM. Volumetric changes as well as altered SC distributions or strengths of these two regions were associated with the severity of the fatigue experienced by patients with FM.

Our study showed that patients with different severities of fatigue had similar number of regions of musculoskeletal pain and pain intensity, suggesting that fatigue is not directly derived from widespread pain in patients with FM, and may comprise different neural signatures from widespread pain. In contrast, patients with more severe fatigue

## A Group SCN spatial distribution pattern of thalamus



## B SCN involved voxel number in each brain region with different sampling times



**Fig. 2.** Distribution and strength of the thalamic SCNs among the fatigue groups.

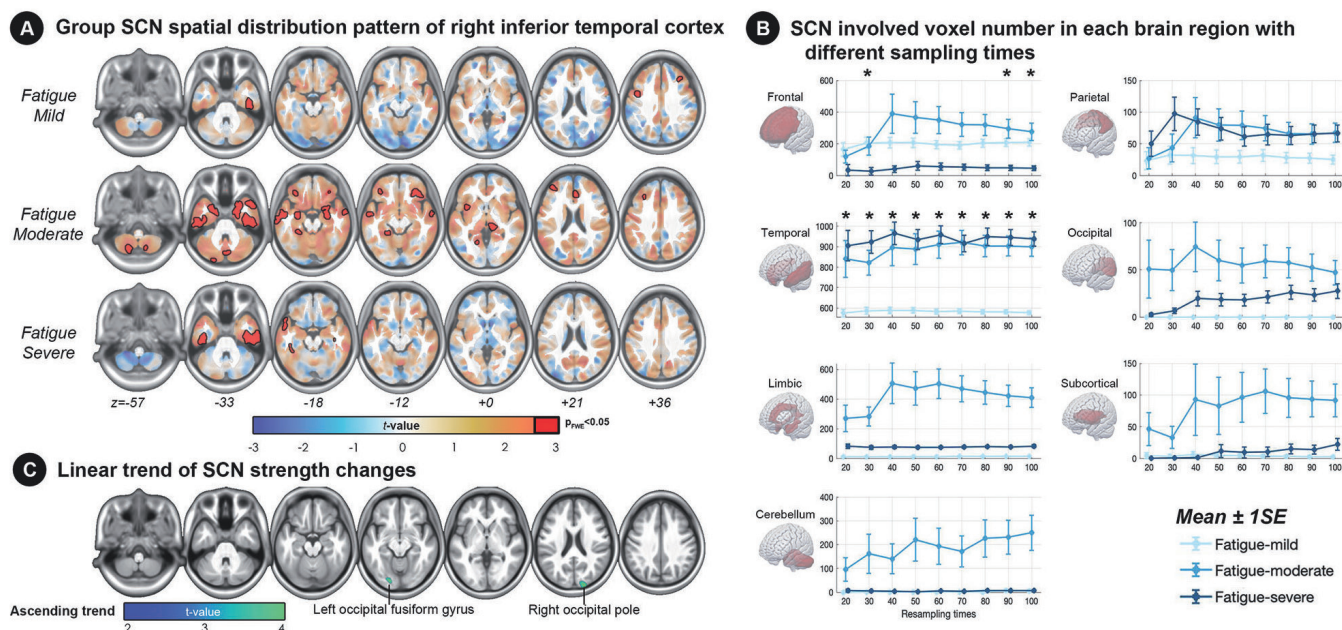
**A:** The regions marked in red denote the distributions of neural substrates showing SC with the thalamic seed in patients with different fatigue severities. **B:** Voxel number in each brain regions showing SC to the thalamic seed with 20–100 times resampling. The number of voxels in the frontal, parietal, limbic, and subcortical regions increased with higher fatigue severity (The asterisk denotes  $p$ -value  $< 0.05$  after Bonferroni correction for multiple comparisons across 7 brain regions).

had a greater degree of somatic symptoms and experienced a higher degree of psychiatric distress, suggesting that fatigue and these symptoms may share an overlapping pathogenesis. Much less research attention has been

paid on fatigue than on pain in FM, and neuroimaging studies focusing on fatigue in FM are scarce. However, studies have been conducted in patients with chronic fatigue syndrome, a disorder characterised by extreme

fatigue and is considered as a central sensitivity syndrome similar to FM. In these patients, increased activation and additional recruitment of brain regions were demonstrated on fMRI during a challenge task (22, 23). Our study





**Fig. 3.** Distribution and strength of the right inferior temporal seed SCNs among the fatigue groups.

**A:** The regions marked in red denote the distributions of neural substrates showing SC with the right inferior temporal cortex seed in patients with different fatigue severities. **B:** Voxel number in each brain regions showing SC to the right inferior temporal seed with 20–100 times resampling. The number of voxels in the temporal regions increased with higher fatigue severity (The asterisk denotes  $p$ -value < 0.05 after Bonferroni correction for multiple comparisons across 7 brain regions). **C:** Clusters that showed increased SC strength across the patient groups with increasing fatigue severity.

showed that wider thalamic SC distributions over cortical and subcortical regions are linked to fatigue severity in patients with FM. The thalamus actively integrates information between remote brain areas, which enables rapid coordination of spatially segregated cortical computations and constructs task-relevant functional networks (24, 25). The wider thalamic coordinative distribution shown in our study echoes the findings of increase in brain-region recruitment during tasks in chronic fatigue syndrome. Increased activation of multiple brain regions may lead to increased demand for neural resources, which may in turn cause fatigue. The thalamus is the structure that sensory information relayed to the cerebrum and filters out unnecessary information, acting as the sensory gating of the brain (26). Therefore, dysfunction of the thalamus may impair its ability to filter input information and efficiently modulate information processing, with excessive information overloading the brain and leading to fatigue. Notably, decreased thalamic volume and altered connectivity of the fronto-thalamic circuit were also found in patients with multiple sclerosis and with mild traumatic brain injury with symptoms

of fatigue (27–29). This suggests that fatigue, despite being a subjective impression, may be similarly experienced across patients with different diseases. Another cluster at the right inferior temporal cortex and its altered connections with the occipital cortex were shown to be related to fatigue in our study. A diffusion tensor image study of chronic fatigue syndrome also showed increased cortical thickness of the right temporal cortex and increased connectivity of the right inferior longitudinal fasciculus connecting the temporal and occipital regions in their patients (30). Our results suggest that neuroplasticity associated with fatigue in FM is beyond somatosensory domain. Altered SCNs between visual and temporal cortex in FM may be associated with altered functional interactions between visual areas and emotional and memory associated areas, the processes of memory and learning of visual information and visual repetition suppression formed (31–34). Further studies using electrophysiological measures or fMRI may help elucidate if fatigue in FM is associated with visually specific memory and emotional dysfunction. A strength of this study is that we could include a relatively large number of

patients with FM, which allowed us to categorise the patients based on the severity of our target symptom. It should be noted that the majority of patients in this study were female. Reported symptoms of FM were different between males and females (35), and male FM patients reported less fatigue than female patients, suggesting that different pathophysiologies may underlie the manifestations of FM in different sexes. Therefore, brain morphometry features reflecting the severity of fatigue may also differ between males and females. Hence, the results of the current study should not be generalised to male patients with FM. Other caveats and limitations must be considered to interpret this study better. First, symptoms in FM are intertwined with and influence one another. We attempted to specify the symptom of fatigue and properly control for covariates (*e.g.* HADS scores), but some potential confounders may have influenced the GMV of the identified structures. Second, as this was a cross-sectional study, we could not clarify the causes and consequences of the symptoms and associated changes in the neural structures. Last, the number of patients with mild fatigue was relatively smaller than that of patients with

moderate or severe fatigue. It is possible that the number of patients could have affected the results with respect to the significance of SC. However, we used a bootstrapping resampling scheme to compensate for this limitation.

## Conclusion

The thalamus and the right inferior temporal cortex as well as their interactions with cortical and subcortical regions are responsible for the manifestations of fatigue severity in FM. This study provides evidence for future invention of treatments and therapeutic strategies that aim to improve fatigue in this patient population.

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