Structural brain magnetic resonance imaging correlates of fatigue in patients with multiple sclerosis

PhD thesis

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Budapest
2021

1. INTRODUCTION

The etiology of fatigue in multiple sclerosis (MS) is multifactorial. The neural basis of fatigue has been investigated by several magnetic resonance imaging (MRI) studies. The replicability of these studies was limited due, at least in part, to the criteria applied to classify patients. Previous neuroimaging studies allocated MS patients into "fatigued" or "non-fatigued" groups using a single time-point assessment of fatigue, which may not be adequate to summarize the fluctuating dynamics of fatigue.

Our overarching hypothesis of our studies described in this PhD thesis is that persistent fatigue is more likely to be caused by irreversible neurodegeneration, whereas fluctuating fatigue may reflect reversible pathobiological changes (e.g. inflammatory cytokine and hormone levels) not directly affecting brain morphology. Under this hypothesis, we proposed a novel classification that reflects temporal patterns from longitudinal fatigue

impact assessments: Sustained Fatigue (SF: experienced clinically significant fatigue over the most recent two years), Reversible Fatigue (RF: did not report clinically significant fatigue at the most recent clinical visit, but did in the past), and Never Fatigued (NF).

2. OBJECTIVES

Specific Aim 1: To investigate whether a novel group allocation that reflects temporal dynamics of fatigue improves our ability to detect fatigue-associated global structural brain abnormalities.

Specific Aim 2: To investigate the association of fatigue with regional structural brain damage, using the patient stratification strategy defined under Specific Aim 1.

3. METHODS

Study Participants

Study participants were selected from the "Quality of Life" (QOL) subset (n>800) of the CLIMB study (Comprehensive Longitudinal Investigations of MS at the Brigham and Women`s Hospital (BWH), Boston, MA, USA) (n>2400), a large-scale, long-term study of patients with MS. The patients underwent annual 3 Tesla brain MRI and neurological examination, including disability assessment using the Expanded Disability Status Scale (EDSS). Fatigue and depression were assessed using the Modified Fatigue Impact Scale (MFIS) and the Center for Epidemiological Studies – Depression scale, respectively.

Fatigue group definitions

Patients were allocated to the following three groups based on biennial MFIS assessments: Sustained Fatigue (SF) – last two consecutive

MFIS≥38; Reversible Fatigue (RF) – most recent MFIS<38 and at least one prior MFIS≥38; Never Fatigued (NF) – no MFIS≥38 (minimum 5 assessments needed). Our novel group allocation was compared to a more traditional (fatigued versus non-fatigued) allocation based only on the latest MFIS assessment. A fourth group of patients (1 time-point Fatigue group, 1F), with most recent MFIS≥38 and penultimate MFIS<38, and may or may not reported fatigue at previous assessments, was also included in the analysis to better represent the entirety of the traditional fatigued spectrum when combined with the SF group. 29 SF, 15 1F, 31 RF and 54 NF patients were included in the volumetric brain MRI analyses. 26 SF, 25 RF and 42 NF patients were included in the voxel-based brain MRI analyses. We analyzed the closest MRI time-point to the latest MFIS assessment available in the CLIMB database.

Volumetric brain MRI analyses

We used an automated MRI analysis workflow that has been developed and validated within the CLIMB study to measure total T2 brain lesion volume (T2LV) and brain parenchymal fraction (BPF, i.e., brain parenchymal volume normalized by the total intracranial volume) for each patient using T1-weighted, T2-weighted, and fluid attenuated inversion recovery (FLAIR) images.

Voxel-based brain MRI analyses

For each patient, fractional anisotropy (FA) maps were calculated based on their diffusion-weighted brain MRI. Affine followed by non-linear co-registration were used to bring each subject`s FA map into MNI (1-mm isotropic) space. Diffusion maps were smoothed using a Gaussian kernel of 3 mm full width at half maximum. Voxel-wise analysis of the smoothed diffusion maps was performed using SPM8.

Statistical analysis

Differences in demographic and clinical variables between the fatigue groups were assessed using one-way ANOVA or Kruskal-Wallis test for continuous variables (depending on the distribution of the data), and Chi-square or Fisher exact test (when n<5) for categorical variables.

General linear models (GLMs) were used (1) to compare global volumetric brain MRI metrics (i.e., BPF and T2LV: outcome variables), and (2) to investigate the voxel-wise difference in FA values (i.e., outcome variable) between the groups (i.e., predictors). The following co-variates were included in the GLMs: age, sex, disease duration, EDSS, T2LV, CES-D. The global volumetric brain MRI analyses were corrected also for the presence/absence of anti-fatigue, antidepressant and/or anxiolytic treatment. Cohen`s d effect size was calculated for BPF and T2LV comparisons. In the voxel-based FA analyses, family-wise error

(FWE) correction was used to correct for multiple comparisons. Threshold for statistical significance was set at $p<0.05$.

4. RESULTS

4.1. Demographic and clinical characteristics

Demographic and clinical variables did not show significant differences among the fatigue groups, except for EDSS, which was significantly higher in 1F patients compared to the other three groups ($p<0.05$), as well as MFIS ($p<0.05$) and CES-D scores ($p<0.05$), which were significantly higher in SF patients.

4.2. Volumetric brain MRI analyses

The four-group (ie, SF, 1F, RF, NF) comparisons showed that T2LV of the SF ($p=0.005$) and RF ($p=0.043$) groups was significantly higher compared to the NF group, but there was no significant difference in the other contrasts. The

two-group comparison showed significantly higher T2LV in fatigued versus non-fatigued patients (p=0.040). Neither the four-group, nor the two-group analysis showed significant difference in BPF

Cohen`s d effect size was larger for T2LV and BPF in the SF versus NF, and 1F versus NF contrasts, as well as for BPF in the RF versus NF contrast compared to the fatigued versus non-fatigued contrast.

Correction for medication (i.e., anti-fatigue, antidepressant, anxiolytic treatment) and CES-D had no considerable effect on the above-mentioned results.

4.3. Voxel-based brain MRI analyses

When controlling for age, sex, disease duration, and EDSS, significantly lower FA was observed in several bilateral brain regions, including cortical and white matter (WM) areas of the frontal, temporal, parietal and occipital lobes, and subcortical

structures, such as the striatum, thalamus, amygdala, hippocampus, in the following contrasts: SF versus NF, RF versus NF, SF versus RF ($p<0.001$).

When controlling also for T2LV (in addition to age, sex, disease duration, and EDSS), the number of voxels with significantly lower FA decreased by a factor of 20 in the SF versus NF contrast ($p<0.001$), but there was no difference in SF versus RF or RF versus NF patients. The observed signal (i.e., significantly lower FA) was mainly localized in the cingulo-postcommissural-striato-thalamic regions in the SF versus NF contrast.

When controlling also for CES-D (in addition to age, sex, disease duration, EDSS, T2LV), FA in the ventromedial prefronto-precommissuro-striatal and temporo-insular areas remained significantly lower in the SF versus NF contrast. No significant difference was observed between RF versus NF or SF versus RF patients.

5. CONCLUSIONS

We developed and tested a novel classification of multiple sclerosis-related fatigue based on retrospective longitudinal Modified Fatigue Impact Scale scores. Our most salient findings are the following:

(1) Discriminating patients by their longitudinal Modified Fatigue Impact Scale pattern improves the power to detect pathological MRI correlates of fatigue. Specifically, when confirming Sustained Fatigue or Never Fatigued status through more than one observation, we noted a significant increase in discriminating power.

(2) Both Sustained Fatigue and Reversible Fatigue are associated with diffuse structural brain damage.

(3) Sustained Fatigue patients have more widespread structural damage compared to Reversible Fatigue.

(4) Damage to the cingulo-postcommissural-striato-thalamic network are implicated in the

development of both fatigue and depression, whereas damage to the ventromedial prefronto-precommissuro-striatal network and temporo-insular network are associated with fatigue independent of depression.

8. BIBLIOGRAPHY OF MY PUBLICATIONS RELATED TO THIS DISSERTATION

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