Neural correlates of fatigue in granulomatosis with polyangiitis: a functional magnetic resonance imaging study

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Abstract

Objective. The aim of this study was to investigate the neurophysiological effects of fatigue among patients with granulomatosis with polyangiitis (GPA).

Methods. A case–control functional MRI (fMRI) study was conducted. Stable GPA subjects were recruited according to fatigue status, with those reporting fatigue defined as cases and those not defined as controls. In addition, a control group of general population subjects with idiopathic fatigue were studied. During fMRI, all participants performed a fatigue-inducing cognitive task. Functional data were acquired with a 3 T MRI scanner during periods of task activity and rest. Analyses of the differences in blood oxygen level dependent (BOLD) signal were then performed using SPM8 software and comparisons were made between case and control groups.

Results. GPA cases (n = 12) were demographically matched to GPA controls (n = 14) and were clinically similar apart from the higher reporting of fatigue, by design, and depressive symptoms (P = 0.0007). After adjusting for depressive symptoms, comparison of BOLD signals revealed significantly greater activation in the right thalamus, left paracentral lobule, left medial frontal gyrus and right medial globus pallidus among GPA cases. When compared with the similarly fatigued population control group (n = 13), GPA cases shared many overlapping areas of activation. However, in addition, the population control group revealed significantly greater activation elsewhere, principally the left precentral gyrus, right superior frontal gyrus and right cingulate gyrus.

Conclusion. fMRI has identified specific differences in the neurophysiology of fatigued GPA subjects. Future application of this promising biomarker may inform the precise mechanisms of this clinically important symptom.

Key words: granulomatosis with polyangiitis, vasculitis, fatigue, functional MRI.

Introduction

Fatigue is a common burdensome problem among patients with rheumatic autoimmune disease. Studies across conditions have consistently reported prevalence rates between 60% and 90% [1–4] and have regularly identified this issue as a key determinant of poor quality of life [5–8]. Despite its clear importance, there are no effective and well-tested fatigue interventions available to patients. Current barriers to the development and study of future therapies include a poor understanding of the symptom’s underlying mechanisms and an absence of biological markers to aid in its assessment.

Although never tested, it has been hypothesized that fatigue related to rheumatic autoimmune diseases may reflect subtle changes in the CNS [9]. In other disciplines, evidence is building to support an important mechanistic role for the brain in fatigue. Specifically, functional magnetic resonance imaging (fMRI) techniques have identified neurophysiological differences among subjects with...
idiopathic chronic fatigue and multiple sclerosis (MS) when challenged with a fatigue-inducing task [10, 11].

fMRI provides a measure of neural blood flow by quantifying changes in local oxygenated and deoxygenated haemoglobin ratios and their related paramagnetic strengths—also known as the blood oxygen level dependent (BOLD) signal. Since neural activity is associated with changes in blood flow, the BOLD signal offers a surrogate measure of brain activation. The resultant physiological signatures allow for neural correlation with regions of the brain that may be crucial to the pathogenesis of the symptom under investigation. In other fields, such data are being employed to develop specific CNS drug treatments [12] and have exhibited potential as biological markers for clinical trials [13].

Using fMRI, we sought to examine the neural correlates of a fatiguing task in a rheumatic autoimmune disease, granulomatosis with polyangiitis (GPA). First, we aimed to determine the presence of physiological differences between the brains of fatigued and non-fatigued GPA subjects. Second, we looked for differences between similarly fatigued GPA and general population subjects.

Patients and methods

A single-centre case–control study was performed. Ethical approval for the study was obtained from the North of Scotland Research Ethics Committee (ref: 09/S0801/83) and all participants gave informed written consent according to the Declaration of Helsinki.

Participants

Three groups were examined: (i) cases—GPA subjects with fatigue, (ii) disease controls—GPA subjects without fatigue and (iii) population controls—general population subjects with idiopathic fatigue.

GPA was classified according to the European Medicines Agency’s classification algorithm [14] and fatigue was defined as anyone reporting problems with fatigue for >3 months and scoring >3 on the Chalder Fatigue Scale (CFS), a validated generic measure of fatigue (scored 0–11 using the bimodal scale, with higher scores reflecting greater levels of fatigue and substantial fatigue established as a score >3 [15]). Idiopathic fatigue was further defined as subjects without a clear explanation for their symptoms as evaluated by national guidance [16].

Potential subjects were consecutively approached from a parallel questionnaire study of a series of clinic-attending GPA patients and an age- and gender-matched sample of general population members [17]. Recruitment was restricted to the Grampian region of Scotland and limited to 14 subjects per group.

All invitees were screened by telephone. In order to improve population homogeneity, only right-hand dominant and, of those with GPA, clinically inactive (as defined by BVAS = 0 [18]) subjects were selected. Furthermore, subjects with certain co-morbidities (symptomatic cardiorespiratory disease, major psychiatric illness, cancer within 5 years, untreated thyroid disease, significant anaemia, other systemic autoimmune diseases, pregnancy) and/or those receiving beta-blockers were excluded due to their association with fatigue. With regard to safety, subjects with claustrophobia and those with MRI incompatible implants (e.g. pacemakers, artificial heart valves, artificial joints, nerve stimulators, artificial eyes, intrauterine devices) were not selected.

Selected invitees then attended the MRI research facility where they underwent a clinical assessment. First, all participants completed a questionnaire in order to reaffirm their fatigue status (CFS) and to characterize their mental health [Hospital Anxiety and Depression Scale (HADS) [19]], a recognized independent confounder of the fatigue-inducing task [20]. Second, a full clinical examination was undertaken to (i) clinically characterize and confirm disease inactivity among GPA subjects and (ii) confirm the idiopathic nature of fatigue among population controls. Third, putative biological confounders of fatigue (haemoglobin, creatinine) were collected.

Fatiguing task

Prior to scanning, subjects practised the fatigue-inducing task for 1 min. The paced auditory serial additional test (PASAT), when applied within the scanner, has been validated to induce transient fatigue and is known to result in distinct fMRI BOLD signals among patients with chronic fatigue syndrome [10]. Participants listened to a series of numbers ranging from 1 to 9 presented for 1.5 s and separated by 0.5 s. They were required to sum consecutive numbers (i.e. the first and the second, the second and the third, etc.) and to record, via a button press, every occasion on which two consecutive numbers summed to the number 10. Concurrently they were asked to focus on a computer screen displaying three boxes containing random, rapidly changing (every 0.5 s) single-digit numbers. They were instructed not to process the visual numbers in any way, its purpose being simply to distract the participants from the auditory task with a view to increasing its difficulty and consequent fatiguing capacity. Those unable to understand and successfully execute the task were excluded from the study.

Image acquisition

MRI data were collected using a 3.0 T scanner (Achieva X-series, Philips Medical, Best, The Netherlands). An eight-channel phased-array head coil was used to obtain high-resolution gradient echo three-dimensional (3D) volumetric images and a set of functional images using BOLD contrast. The high-resolution images were collected using a T1-weighted sequence with the following parameters: field of view (FOV), 24 cm; repetition time (TR)/echo time (TE), 20/6; flip angle, 35°; slices, 124; slice thickness, 1.0 mm; matrix, 256 × 256. Functional MR images were acquired in the axial plane with a T2*-weighted single-shot, gradient-echo, echo-planar pulse sequence with the following parameters: FOV, 24 cm; TR/TE, 2500/30 ms; flip angle, 78°; slices, 30; slice thickness, 5 mm; matrix, 96 × 96. The head was firmly stabilized in the head coil with foam pads.
The PASAT was undertaken during 3 × 3 min on periods and interspersed by 4 × 30 s rest or off periods. The 3D T1-weighted structural data were acquired for subsequent registration of fMRI data. Presentation software (Neurobehavioural Systems, Albany, CA, USA) computed the PASAT intervention. The auditory stimulus was delivered by MRI-compatible headphones and the visual stimulus was projected onto a screen visible by a mirror on the head coil. Also, in order to quantify the level of current fatigue, participants were asked to complete a fatigue numeric response scale (0–10) on the screen immediately before and after each on period. All participant responses were captured via a fibre-optic button box and foam pads were used to restrict head motion within the coil.

Data analysis and image processing

The clinical characteristics of cases and controls were expressed using simple descriptive statistics. Comparisons were made using Fisher’s exact tests for categorical variables, t-tests for parametrically distributed variables and Mann–Whitney tests for non-parametrically distributed variables. These statistical analyses were performed using STATA version 12.0 (StataCorp, College Station, TX, USA).

Functional MRI data were analysed using MATLAB software with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8). After discarding the first four volumes to allow the magnetization to reach equilibrium, the remaining 222 functional images were realigned to the first image. The structural scans were then co-registered to a mean generated from the functional scans, after which they were segmented. The scans were normalized to the standard SPM MNI grey prior probability map via the individuals segmented grey matter image and then the functional scans were smoothed with an 8-mm FWHM Gaussian kernel. The observed time series for each 3D MRI voxel was compared with a boxcar model for each condition, either off or on, convolved with a standard haemodynamic response function using a general linear model (GLM). The movement data from the realignment step were included as a regressor. The fatigue assessment was excluded from the GLM. Two-sample t-tests produced on-greater-than-off BOLD contrast, revealing which voxels showed more activity in the on task compared with the off task. For all analyses, regions are reported as significant at a whole brain \( P < 0.05 \) cluster level. This was achieved by a simultaneous requirement for a voxel threshold of \( P < 0.001 \) plus a minimum cluster size of 38 continuous voxels. Cluster size was identified using standard Monte Carlo simulations [21] with code available at http://www2.bc.edu/~slotnics/script.html.

Assuming a voxel type I error, this method estimates a probability for each cluster extent (number of contiguous voxels). In this way the desired family-wise error correction for multiple comparisons can be enforced by using the corresponding cluster extent as a threshold.

Coordinates are quoted in standard Talairach and Tournouix space following application of a conversion factor (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) from the Montreal Neurological Institute space employed by SPM. Regional designation of the activation location was determined by the Talairach Daemon [22, 23] and confirmed by comparison of local anatomy with a standard atlas [24] that further allowed regional mapping according to Brodmann areas [25].

Head movement was assessed for each participant with thresholds of 3.6 mm and 5°. A participant was excluded if their head movement at any one time point, compared with the first time point, was greater than the defined threshold.

Results

Subject characteristics

In total, 49 GPA subjects were approached and sufficient functional MRI data were retrieved from 26: 12 fatigued (cases) and 14 non-fatigued (disease controls). Of the non-participants, 12 were not interested, 3 were precluded due to MRI-incompatible implants, 3 were claustrophobic, 2 were left-handed and 1 was experiencing active disease. A further two underwent scanning, but one was unable to conduct the fatiguing task due to previously undetected hearing problems and another as a consequence of large artificial data related to excessive head motion during the procedure. No significant group differences were observed for most subject characteristics (Table 1) apart from greater fatigue, which was by design, and depressive symptoms \( (P=0.0007) \) among cases. More specifically, among GPA participants, no significant differences in disease duration, damage, creatinine, CRP or prevalence of anaemia (adjusted for gender) were recorded. All patients were maintained on immunosuppressants (AZA, MTX or mycophenolate) and most on low-dose prednisolone (Table 1), but again no significant differences were observed between cases and controls. No participants had a history of GPA-related CNS disease.

Of the 38 general population subjects approached, 13 were not interested, 4 were claustrophobic, 3 failed the study’s criteria for chronic fatigue, 2 were excluded due to MRI-incompatible implants, 2 had medical explanations for their fatigue and 1 was scanned but his data were rejected because of excessive head movement. Thus 13 population controls were analysed and were not significantly different from cases in terms of comparable subject characteristics (Table 1).

Effect of fatiguing task

As expected, all subjects reported greater overall fatigue levels following the PASAT intervention, as measured by an increase in the fatigue numerical response scale (pre-intervention: 2 [interquartile range (IQR) 1–5]; post-intervention: 5 (IQR 3–6); \( P=0.0005 \)). Several brain structures appeared to be significantly involved during the intervention, primarily the bilateral superior temporal, right inferior frontal and superior frontal gyri (Fig. 1).
Neural correlates of fatigue in GPA

Table 1 Baseline characteristics of fatigued and non-fatigued granulomatosis with polyangiitis subjects

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 12)</th>
<th>Disease controls (n = 14)</th>
<th>Population controls (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>58.5 (15.9)</td>
<td>51.6 (13.8)</td>
<td>52.2 (10.5)</td>
</tr>
<tr>
<td>Sex (male), %</td>
<td></td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Median depression&lt;sup&gt;a&lt;/sup&gt; (IQR)</td>
<td>4 (2–8)</td>
<td>1 (0–1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (1–4)</td>
</tr>
<tr>
<td>Median anxiety (IQR)</td>
<td>5.5 (2–9)</td>
<td>2.5 (1–4)</td>
<td>3 (3–6)</td>
</tr>
<tr>
<td>Median fatigue (IQR)</td>
<td>9 (8.5–11)</td>
<td>1 (0–3)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8 (6–9)</td>
</tr>
<tr>
<td>Chronic widespread pain, n</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Haemoglobin, mean (s.d.), g/l</td>
<td>132.7 (12.2)</td>
<td>132.6 (14.7)</td>
<td>138.8 (14.0)</td>
</tr>
<tr>
<td>Creatinine, median (IQR), μmol/l</td>
<td>82.5 (70–92.5)</td>
<td>92.5 (79–105)</td>
<td>73 (69–80)</td>
</tr>
<tr>
<td>Disease duration, median (IQR), months</td>
<td>35 (25–89)</td>
<td>83.5 (48–110)</td>
<td>N/A</td>
</tr>
<tr>
<td>VDI, median (IQR)</td>
<td>1.5 (1–2)</td>
<td>1 (0–1)</td>
<td>N/A</td>
</tr>
<tr>
<td>Current prednisolone dose, median (IQR), mg</td>
<td>7.5 (5–10)</td>
<td>5 (5–7.5)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<sup>a</sup>Hospital anxiety and depression scale. <sup>b</sup>Disease controls vs cases; P = 0.0007 (Mann-Whitney test). <sup>c</sup>Disease controls vs cases; P < 0.0001 (Mann-Whitney test). IQR: interquartile range; VDI: vasculitis damage index.

Fig. 1 Principal areas of brain activity during PASAT

[Image of brain activity during PASAT]

Principal areas of brain activity during PASAT shown in orange/yellow. Pane +3: bilateral superior temporal gyrus (green circle), bilateral middle temporal gyrus (blue circle) and bilateral inferior frontal gyrus/insula (yellow circle). Pane +58: superior frontal gyrus (red circle). Colour scale measures t-score [a quantification of the difference in mean brain activity (blood oxygen level dependent response to PASAT task) between groups], marking regions of significance. PASAT: paced auditory serial additional test.

Comparison of GPA subjects with and without fatigue

Initial analysis revealed greater activity in the right superior parietal lobule and left middle frontal gyrus of disease controls compared with cases. However, following correction for depressive symptoms, their statistical significance was eliminated. Instead, the adjustment for HADS depression scores revealed four regions of statistically greater activation in cases compared with disease controls—the right thalamus, left paracentral lobule, left medial frontal gyrus and right medial globus pallidus (MGP) (Table 2 and Fig. 2)—and no regions of greater activity among disease controls.

Comparison of fatigued GPA and general population subjects

A direct comparison of activation patterns between cases and population controls identified regions of similar activation, but also differences. As Fig. 3 illustrates, the BOLD signals of population controls largely overlap with those of the cases, but additionally involve other areas of the brain. Statistical comparison identified the left precentral gyrus, right superior frontal gyrus, right inferior frontal gyrus and right cingulate gyrus as locations where the activation levels of population controls significantly exceeded those of cases (Table 2). Conversely, greater activation was not observed among cases compared with population controls. Since the two groups were similar in terms of other baseline characteristics, no statistical adjustments were deemed necessary.

Discussion

This study, the first to apply fMRI to elucidate the neural correlates of fatigue in a rheumatic autoimmune population, has identified significant physiological differences between fatigued and non-fatigued GPA subjects. Furthermore, fatigued GPA subjects activated common regions to similarly fatigued but otherwise healthy general population controls, although overall these controls displayed more extensive neural activity.

Unsurprisingly for a complex cognitive task, the PASAT resulted in the neural activation of several structures, reproducing the patterns observed by the researchers who originally developed the modified paradigm [10]. Between-group comparisons of these activation patterns permitted the selection of putative regions of importance in the neuroprocessing of fatigue. With regard to GPA-related fatigue, the subcortical thalamus and MGP as well as the cortical medial frontal gyrus and paracentral lobule regions were identified and all may be theoretically implicated with the reporting of fatigue. The thalamus is known to play a key role in the regulation of sleep [26], the principal association of fatigue among this patient population [27]. The MGP, a component of the basal ganglia, is intimately connected to the thalamus and is thought to be prominent in the reward neural circuit, a key mediator of motivation [28, 29]. Indeed, patients with specific damage to the MGP often suffer from apathy, an overlapping...
It is also interesting to note that up to 70% of patients with Parkinson’s disease, the most common disease of the basal ganglia, report significant fatigue [31] and, moreover, poor motivation is a recognized predictor of Parkinson’s-related fatigue [32].

Both the paracentral lobule and the adjacent medial frontal gyrus accommodate the supplemental motor area, which is thought to command motor planning as well as elements of executive function such as decision making, computation and reasoning [33]. It seems likely that disruptions of such functions may present as cognitive slowing, a common manifestation of fatigue [34].

Although, to our knowledge, this is the first fMRI study of fatigue to evaluate patients with an autoimmune rheumatic disease, chronic fatigue syndrome and MS populations have previously been examined. Cook et al.’s [10] original modified PASAT experiments compared cases with chronic fatigue syndrome (n = 9) with healthy controls (n = 11). Cases demonstrated significantly greater activation of several structures, including the thalamus and frontal cortex, as noted here, but additionally the cerebellum, cingulum gyrus and temporal cortex. In contrast, controls exhibited significantly higher BOLD signals in the parieto-occipital cortical regions. Comparability with this study is clearly limited as a result of the distinct population characteristics, but they also employed a different analytical approach. By only testing preselected regions of interest, they were able to reduce the number of undertaken statistical comparisons and consequently maintain a relatively high threshold for statistical significance. In comparison, the current study employed an automated whole brain general search approach that provided a comprehensive assessment without introducing the user bias inherent to region of interest analysis. A whole brain search approach was adopted by Tartaglia et al. [11] to examine the impact of PASAT on the BOLD signals of fatigued MS patients (n = 10) and healthy controls (n = 7). They also identified greater areas of activity in the frontal cortex in MS patients, specifically the supplementary motor area and

**Table 2** Anatomical regions of greater brain activity (BOLD signal) among cases vs controls (adjusted for depression)

<table>
<thead>
<tr>
<th>Neuroanatomical coordinates (x, y, z)</th>
<th>Hemisphere</th>
<th>Region</th>
<th>BA</th>
<th>T</th>
<th>Extent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigued vs non-fatigued GPA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22/C0 17 19</td>
<td>Right</td>
<td>Thalamus</td>
<td>N/A</td>
<td>4.5</td>
<td>53</td>
</tr>
<tr>
<td>-2/28 64</td>
<td>Left</td>
<td>Paracentral Lobule</td>
<td>6</td>
<td>4.26</td>
<td>96</td>
</tr>
<tr>
<td>-4/18 60</td>
<td>Left</td>
<td>Medial frontal gyrus</td>
<td>6</td>
<td>3.82</td>
<td></td>
</tr>
<tr>
<td>18/-8/3</td>
<td>Right</td>
<td>Lentiform nucleus</td>
<td>MGP</td>
<td>4.2</td>
<td>86</td>
</tr>
<tr>
<td>Fatigued GPA vs fatigued general population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-34/-7/54</td>
<td>Left</td>
<td>Precentral gyrus</td>
<td>6</td>
<td>4.59</td>
<td>59</td>
</tr>
<tr>
<td>18/26 45</td>
<td>Right</td>
<td>Superior frontal gyrus</td>
<td>8</td>
<td>4.50</td>
<td>43</td>
</tr>
<tr>
<td>48/43 9</td>
<td>Right</td>
<td>Inferior frontal gyrus</td>
<td>46</td>
<td>4.29</td>
<td>38</td>
</tr>
<tr>
<td>2/29 34</td>
<td>Right</td>
<td>Cingulate gyrus</td>
<td>32</td>
<td>4.11</td>
<td>49</td>
</tr>
</tbody>
</table>

*aQuantification of the size of the brain region observed to be more active, i.e. showing a statistically significant difference between groups. Bold text indicates adjacency to preceding structure in the table. BOLD: blood oxygen level dependent; BA: Brodmann area (defined mapping system of the brain); MGP: medial globus pallidus; T: t-score [quantification of the difference in mean brain activity (BOLD response) between groups].

**Fig. 2** Regions of greater BOLD among fatigued GPA vs non-fatigued GPA subjects (adjusted for depression)

Regions of significantly greater brain activity (BOLD response to PASAT task) among fatigued GPA compared with non-fatigued GPA participants (adjusted for depression). Pane –4: right lentiform nucleus; pane +20: right thalamus; pain +68: left paracentral lobule and medial frontal gyrus. Colour scale measures t-score [a quantification of the difference in mean brain activity (BOLD response to PASAT task) between groups], marking regions of significance. BOLD: blood oxygen level dependent; PASAT: paced auditory serial additional test; GPA: granulomatosis with polyangiitis.
the cingulate gyrus, but no regions of greater activity were observed among controls. It should be noted, however, that MS is a primary disease of the brain that is more likely to cause direct interference with blood flow, thus comparisons are difficult to make.

Currently the Chaudhuri and Behan [35] model is the most widely accepted hypothetical neuro-anatomical model of fatigue genesis. Based principally on their observations of high fatigue among diseases of the basal ganglia, they proposed the dysfunction of the striato-thalamo-cortical network as an important determinant of brain-related fatigue. Specifically, the connections between these brain regions are thought to be disorganized [35]. Findings from this and other studies appear to be consistent with this hypothesis and areas of hyperactivity potentially reflect a compensatory mechanism to circumvent the disruption of the involved neural circuits [36]. The precise physiological processes are as yet unknown. In other fatigued populations, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis—a conduit between neural and endocrine pathways—is commonly postulated as a putative mechanism. In patients with chronic fatigue syndrome, HPA axis hypofunction is common, reflected by a blunted endocrine response [37].

Similar patterns are also observed in rheumatic autoimmune diseases [38, 39], where patients experience higher levels of stress stimulating the HPA axis in the short term and, due to the negative feedback homeostatic mechanisms inherent in this pathway, depressing the axis in the long term [40]. Furthermore, treatment with synthetic corticosteroids is prevalent among these conditions, another depressant of the HPA axis [38, 39]. An inflammatory mechanism has also been postulated and is clearly of relevance among autoimmune rheumatic diseases. Cytokines such as IL-1 and IL-6 are known to directly influence neurons and neurotransmitters as well as effecting HPA function [41, 42] and it would be interesting to measure these in future studies.

No previous studies have made comparison between distinct clinical populations of fatigued subjects. The overlapping neural activation patterns observed in this study imply both shared and population-specific neural mechanisms. Very few other forms of study have examined the concept of disease-specific fatigue. Using a multidimensional assessment questionnaire tool, Jan et al. [43] found many similarities between chronic fatigue syndrome and fatigued MS patients, although those with chronic fatigue syndrome were more likely to report physical-related fatigue. Even between the closely related rheumatic autoimmune conditions of SLE and SS, some differences in fatigue experience have been recorded [44]. Thus the observed differences in activation patterns between fatigued GPA and general population subjects may reflect the greater heterogeneity of the latter population in terms of fatigue experience and/or underlying aetiological mechanisms. Moreover, the significant overlap between these populations could suggest that the CNS mechanisms causing fatigue may be similar independently of the pathways causing fatigue.

There are a number of study limitations to consider in the interpretation of these findings. First, by measuring relative blood oxygenation, fMRI provides only an indirect measure of neural activity. The process by which neural activity is believed to influence blood flow is referred to as neurovascular coupling. Although this is a largely accepted causal process, its function is known to vary between individuals and is especially altered in those with recognized vascular co-morbidity [45]. Although the impact of vasculitis on the BOLD signal is unknown, it is reasonable to suppose that such a condition may also confound the true neural activity due to abnormal neurovascular physiology. While this is unlikely to impact upon the GPA fatigue vs GPA non-fatigue comparison due to the sharing of any neurovascular coupling dysfunction, greater caution is warranted when considering the comparison of GPA fatigue and general population fatigue groups. Second, to be precise, the results reflect response to the PASAT, which is only a surrogate for fatigue and may distinguish other cognitive conditions such as depression. Although the potential for confounding has been reduced by the closely matched nature of the groups and the additional adjustment for depressive symptoms, other putative confounders may remain.
For example, the PASAT has been employed to distinguish subjects with reduced cognitive capacity [46]. While only those subjects able to successfully execute the test were included, variation in cognitive abilities such as short-term memory remains likely and it would have been interesting to quantify this with a formal intelligence test. That said, there is no good evidence to suppose that fatigued subjects should differ in background intelligence from non-fatigued. Third, the PASAT is a mental challenge, so it is conceivable that our results are biased towards mental rather than physical aspects of fatigue. Future studies may consider selecting subjects according to the specific domain of mental fatigue to explore this possibility further. Finally, although at first glance the sample size appears small, this study represents one of the largest fMRI studies to examine fatigue. Because of fMRI’s capacity to detect very small effect sizes, samples as small as \( n = 12 \) can assess brain activation with good power [47]. That said, this study is only sufficiently powered to offer very limited covariate analysis. In order to distinguish the true neurophysiology of fatigue from putative cognitive confounders, much larger sample sizes will be required to allow multivariable analysis.

In summary, fatigue in GPA patients appears to involve the striato-thalamo-frontal structures of the brain. If replicated in larger, longitudinal and appropriately adjusted studies, the localization of such fatigue-specific processing structures may inform the development of future targeted therapies. More immediately, the technology could emerge as a welcome biomarker in a research field currently constrained by its dependence upon subjective questionnaire tools of varying validity. Furthermore, our data suggest some population specificity in neural activation that may reflect differing aetiology and/or dimensions of fatigue, so application within other patient groups such as SS and SLE will further our understanding of this important but heterogeneous problem.

**References**


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