NeuroImage: Clinical 20 (2018) 102–109

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Hyperintense sensorimotor T1 spin echo MRI is associated with brainstem abnormality in chronic fatigue syndrome

Leighton R. Barnden[a,*], Zack Y. Shan[a], Donald R. Staines[a], Sonya Marshall-Gradisnik[a], Kevin Finegan[b], Timothy Ireland[b], Sandeep Bhuta[b]

[a] National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute Queensland, Griffith University, Southport, QLD 4222, Australia
[b] Medical Imaging Department, Gold Coast University Hospital, Parklands, QLD 4215, Australia

ARTICLE INFO

Keywords:
Chronic Fatigue Syndrome
Brainstem
Motor
Sensorimotor
T1wSE
Myelin
Upregulation

ABSTRACT

We recruited 43 Chronic Fatigue Syndrome (CFS) subjects who met Fukuda criteria and 27 healthy controls and performed 3T MRI T1 and T2 weighted spin-echo (T1wSE and T2wSE) scans. T1wSE signal follows T1 relaxation rate (1/T1 relaxation time) and responds to myelin and iron (ferritin) concentrations. We performed MRI signal level group comparisons with SPM12. Spatial normalization after segmentation was performed using T2wSE scans and applied to the coregistered T1wSE scans. After global signal-level normalization of individual scans, the T1wSE group comparison detected *decreased* signal-levels in CFS in a brainstem region (cluster-based inference controlled for family wise error rate, $P_{FWE} = 0.002$), and *increased* signal-levels in large bilateral clusters in sensorimotor cortex white matter (cluster $P_{FWE} < 0.0001$). Moreover, the brainstem T1wSE values were negatively correlated with the sensorimotor values for both CFS ($R^2 = 0.31$, $P = 0.00007$) and healthy controls ($R^2 = 0.34$, $P = 0.0009$), and the regressions were co-linear. This relationship, previously unreported in either healthy controls or CFS, in view of known thalamic projection-fibre plasticity, suggests brainstem conduction deficits in CFS may stimulate the upregulation of myelin in the sensorimotor cortex to maintain brainstem – sensorimotor connectivity. VBM did not find group differences in regional grey matter or white matter volumes. We argued that increased T1wSE observed in sensorimotor WM in CFS indicates increased myelination which is a regulatory response to deficits in the brainstem although the causality cannot be tested in this study. Altered brainstem myelin may have broad consequences for cerebral function and should be a focus of future research.

1. Introduction

The chronic fatigue syndrome or myalgic encephalomyelitis (CFS) is a common, debilitating, multisystem disorder of uncertain pathogenesis, for which there exists evidence of dysregulation of the central nervous system, immune system and cellular energy metabolism (Carruthers et al., 2011). Numerous fMRI and connectivity studies in CFS have suggested abnormal WM function (Boissoneault et al., 2016a; Boissoneault et al., 2016b; Caseras et al., 2008; Cook et al., 2007; de Lange et al., 2004; Gay et al., 2016; Kim et al., 2015; Lange et al., 2005; Mizuno et al., 2016; Mizuno et al., 2015; Tanaka et al., 2006; Wortinger et al., 2016; Wortinger et al., 2017; Shan et al., 2018a; Shan et al., 2018b) although they do not inform regarding its biological origin. Here we examine structural scan signal levels that respond to both myelin and iron levels to offer novel insights into WM status in CFS.

Early MRI utilised spin-echo (SE) sequences which yielded T1 and T2 weighted (T1wSE and T2wSE) scans with good signal to noise ratio (SNR) that showed little spatial distortion. Indeed, T1wSE and T2wSE scans still have an important clinical role. The 'weighted' or 'w' here refers to the fact that although T1w levels are primarily determined by local T1 relaxation rate, they are also weakly affected by local T2 relaxation rate. The price paid for the high quality of SE scans is a long

Abbreviations: BA, Brodmann Area; CFS, chronic fatigue syndrome; GM, grey matter; HC, healthy controls; M1, primary motor cortex; P_{FWE}, family-wise error corrected cluster P statistic; PD, Parkinson's Disease; ROI, region of interest; S1, primary somatosensory cortex; SNR, signal to noise ratio; T1wSE, T1 weighted spin echo; TE, echo time; TIV, total intracranial volume; TR, repetition time; VBIS, voxel based iterative sensitivity; VBM, voxel based morphometry; VTA, ventral tegmental area; WM, white matter

* Corresponding author at: National Centre for Neuroimmunology and Emerging Diseases, Menzies Health Institute Queensland, Griffith University, Southport, QLD 4222, Australia.

E-mail addresses: l.barnden@griffith.edu.au (L.R. Barnden), z.shan@griffith.edu.au (Z.Y. Shan), d.staines@griffith.edu.au (D.R. Staines), s.marshall-gradisnik@griffith.edu.au (S. Marshall-Gradisnik), Kevin.Finegan@health.qld.gov.au (K. Finegan), Timothy.Ireland@health.qld.gov.au (T. Ireland).

https://doi.org/10.1016/j.nicl.2018.07.011
Received 4 May 2018; Received in revised form 29 June 2018; Accepted 10 July 2018
Available online 11 July 2018
2213-1582/ © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).

acquisition time (up to 10 minutes) and limited axial spatial resolution (early axial voxel sizes were 5 mm). In research, T1wSE scans have almost exclusively been replaced by T1w gradient recalled echo (GRE) scans which typically have acquisition times of a few minutes and isotropic voxel sizes of 1 mm or less. Although T1wGRE scans also show better GM to WM contrast, their SNR is poorer than T1wSE and they suffer from significant spatial distortion. T1wSE scans are therefore expected to be more sensitive than T1wGRE for quantitative cross-sectional studies of T1 relaxation effects. Similarly, it is now common to use 'optimised 3D fast-spin-echo' for T2w scans. A selected variable flip-angle profile yields a T2w spin-echo echo signal that is stable for long enough to facilitate 3D (single slab) imaging in shorter scan times (Mugler JP 3rd, 2014). Although the resultant scan has T2 contrast, signal levels also have some T1 dependence (Mugler JP 3rd, 2014). Because of our interest in the brainstem, we chose them for their spin-echo advantages to perform segmentation and spatial normalization, instead of the distortion-prone 3D T1w gradient echo scans. It is not clear whether T2wSE scans from the variable flip angle method have the same contrast dependence on [myelin] and [Fe] as conventional (flip angle 90°) T2wSE scans.

T1w and T2w scans are regarded as 'structural' and quantitative studies based on their signal levels are few. This is mainly because their average signal levels vary considerably from subject to subject due to variable head size and positioning in the scanner. Abbott et al. (2009) have specifically addressed the problem of adjusting for inter-subject variation in global T2wSE in the context of cross-sectional voxel-based studies. Based on a preliminary voxel-based comparison of patient and control groups, they identified a subset of voxels with low inter-subject residual variance, and used its mean voxel value to adjust for inter-subject global variation. They called this method voxel based iterative sensitivity (VBIS) and validated it for T2wSE in a group of patients using T2 relaxometry (Abbott et al., 2009). We demonstrated that VBIS yielded useful clinical information when applied to both T1wSE and T2wSE in a study of CFS (Barnden et al., 2015; Barnden et al., 2011; Barnden et al., 2016). Of particular interest was our T1wSE observation indicating that in CFS, myelination increased with severity in the internal capsule (Barnden et al., 2015).

This motivated us to acquire T1wSE scans here with optimal SNR by choosing not to accelerate them (no turbo). Moreover, the 64 channel head-neck coil of the 3T MRI system used here yielded very high signal to noise ratio (SNR) in cortical GM and shallow WM. A similar 64 channel head-only coil showed that SNR at the brain centre was comparable with a body receive coil (Maubon et al., 1999), increased by a factor of 2 near 30 mm below the cortex and by a factor of 4 in the cortex (Keil et al., 2013). This CFS study therefore offered unprecedented sensitivity to variability in the near-surface gyral myelin that influences T1wSE signals and was optimal for a cross-sectional study to explore relative white matter myelination. The trade-off was an acquisition time of nearly 9 minutes and an axial voxel size of 3 mm.

We detected extended increases in T1wSE in sensorimotor WM in CFS. Decreases in the brainstem in the same scans prompted ROI analysis of relative brainstem and sensorimotor T1wSE levels which revealed an inverse correlation between them that was seen in both healthy controls and CFS.

2. Methods

2.1. Subjects

This study was approved by the Human Research Ethics Committees of the Griffith University and the Gold Coast University Hospital where scanning was performed. Patients and healthy controls were recruited over a 1-year period. Signed informed consent was obtained from all participants. The Fukuda diagnostic criteria (Fukuda et al., 1994) were used to determine the existence of CFS. The MRI scans from 83 subjects were acquired. Seven of these were excluded because they were taking medication other than paracetamol or oral contraceptive. Also excluded were four subjects with some symptoms of CFS but who did not meet the full Fukuda selection criteria, and two subjects whose body mass index (BMI) was higher than 35. The total number of subjects analysed in this study was 70, comprised of 43 CFS patients and 27 healthy controls.

2.2. MRI scans

MRI scans were acquired on a Siemens 3T Skyra with a 64 channel receive head-neck coil. We acquired T1-weighted spin echo (T1wSE) with TR/TE/flip angle = 600 ms/6.4 ms/90° and Siemens T2 'SPACE' optimized 3D fast spin-echo (T2wSE) 3200/563/variable flip angle scans. Acquisition times (min:sec) were 8:52 and 5:44. The T2wSE scans employed an optimized variable flip angle sequence (Siemens SPACE) to yield a 'true 3D' acquisition in a shortened time. Their 'contrast equivalent' TE compares with standard T2wSE TE (Busse et al., 2006), although the signal is also influenced by T1 relaxation (Mugler III, 2014), possibly more than usual.

T2wSE images were sagittal with pixel size 0.88 × 0.88 x 0.9 mm. The T1wSE were axial with voxel size 0.86 × 0.86 × 3.0 mm. A resting state fMRI and a task fMRI, each of 15 minutes duration, were also acquired and have been reported elsewhere (Shan et al., 2018a; Shan et al., 2018b). The T2wSE was acquired before the two fMRI scans and the T1wSE was acquired after them. Because the increased blood volume associated with a task stimulus lasts only a few seconds (Shan et al., 2014) the task fMRI should not influence the subsequent T1wSE signal levels.

2.3. Image processing

SPM12 (www.fil.ion.ucl.ac.uk/spm) was used to perform all voxel-based pre-processing and statistical analysis. First, the T2wSE brain images were segmented into grey matter, white matter and cerebrospinal fluid (CSF). Non-linear spatial normalization of the grey and white partitions was then optimized using DARTEL on the WM partition. An additional affine transformation of the final DARTEL grey matter template to the standard MNI grey matter template was computed and applied to the spatially normalized partitions for each subject. T1wSE images of each subject were coregistered to their raw T2wSE images and then subjected to the same deformations to MNI space. Finally, the normalised T1wSE, T2wSE and GM and WM volume images were smoothed using a 5x5x5 mm FWHM Gaussian kernel. The GM and WM partitions were further processed for voxel-based morphometry (VBM). For each subject, total GM, total WM and total intracranial volume (TIV) were computed. TIV was included as the global covariate in the VBM statistical designs.

2.4. Global normalization of MRI signal levels

T1wSE and T2wSE signal levels were normalised using the voxel-based iterative sensitivity (VBIS) method of Abbott et al (Abbott et al., 2009). VBIS requires an initial CFS group comparison with healthy controls for T1wSE (or T2wSE) images scaled using their whole-brain means (SPM's 'proportional scaling'). A mask was then defined containing those voxels with residual inter-subject variance less than the whole-brain median. A Matlab (The Mathworks Inc, Natick, MA) script was written for this purpose. The mean in this VBIS mask was then computed for each image and used as a nuisance covariate in subsequent SPM statistical designs, effectively normalising each image to a common global value. To exclude possible bias in individual analyses, a second iteration of VBIS omitted voxels from the mask where CFS vs healthy control differences (positive and negative) with uncorrected voxel $P < 0.05$ were detected. We used a 0.05 voxel threshold instead of the cluster-forming 0.001 to exclude more voxels and better minimise the bias. We only applied the second iteration to a group design

Download English Version:

https://daneshyari.com/en/article/8687508

Download Persian Version:

https://daneshyari.com/article/8687508

Daneshyari.com