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Prefrontal Structure Varies as a Function of Pain Symptoms in Chronic Fatigue Syndrome

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ABSTRACT

BACKGROUND: Chronic fatigue syndrome (CFS) is characterized by severe fatigue persisting for ≥6 months and leading to considerable impairment in daily functioning. Neuroimaging studies of patients with CFS have revealed alterations in prefrontal brain morphology. However, it remains to be determined whether these alterations are specific for fatigue or whether they relate to other common CFS symptoms (e.g., chronic pain, lower psychomotor speed, and reduced physical activity).

METHODS: We used magnetic resonance imaging to quantify gray matter volume (GMV) and the *N*-acetylaspartate and *N*-acetylaspartylglutamate/creatine ratio (NAA/Cr) in a group of 89 women with CFS. Building on previous reports, we tested whether GMV and NAA/Cr in the dorsolateral prefrontal cortex are associated with fatigue severity, pain, psychomotor speed, and physical activity, while controlling for depressive symptoms. We also considered GMV and NAA/Cr differences between patients with CFS and 26 sex-, age-, and education-matched healthy controls.

RESULTS: The presence of pain symptoms was the main predictor of both GMV and NAA/Cr in the left dorsolateral prefrontal cortex of patients with CFS. More pain was associated with reduced GMVs and NAA/Cr, over and above the effects of fatigue, depressive symptoms, physical activity, and psychomotor speed. In contrast to previous reports and despite a large representative sample, global GMV did not differ between the CFS and healthy control groups.

CONCLUSIONS: CFS, as diagnosed by Centers for Disease Control and Prevention criteria, is not a clinical entity reliably associated with reduced GMV. Individual variation in the presence of pain, rather than fatigue, is associated with neuronal alterations in the dorsolateral prefrontal cortex of patients with CFS.

Keywords: Chronic fatigue syndrome, Dorsolateral prefrontal cortex, Gray matter volume, Magnetic resonance spectroscopy, *N*-acetylaspartate, Voxel-based morphometry

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Chronic fatigue syndrome (CFS) is characterized by severe fatigue that persists for ≥6 months and leads to considerable impairment in daily functioning. Other criteria include reporting at least four of eight additional symptoms, including pain symptoms and cognitive dysfunction (1,2). The etiology of CFS is unknown; symptoms are not explained by a known medical condition and are not alleviated by rest (3). Our group and others have previously reported reduced gray matter volume (GMV) in patients with CFS compared to healthy controls (HCs) (4–6), an indication that central brain mechanisms might be involved in CFS. However, the clinical and neuronal specificity of cerebral changes in patients with CFS remains unclear.

The cerebral changes observed in patients with CFS might be related to fatigue, but this association has not been shown before. More precisely, it remains to be determined whether reduced GMV is specific to fatigue or whether it relates to other factors that coexist in CFS. Chronic pain, reduced physical activity, and lower psychomotor speed are three factors that are often present in CFS patients and are also known to influence GMV. For instance, chronic pain symptoms in patients with CFS can account for up to one third of impairments in daily functioning (7,8), and CFS is often comorbid with fibromyalgia (9), a condition characterized by chronic widespread pain. Chronic pain conditions, including fibromyalgia, have repeatedly been associated with GMV reductions, especially in prefrontal brain regions (10,11). Physical activity and psychomotor speed are also consistently reported to be reduced in subgroups of patients with CFS (12,13), and both factors have been associated with GMV changes in patients with CFS (4,5). However, physical activity has also repeatedly been associated with (prefrontal) GMV alterations in healthy nonfatigued humans (14,15) and animals (16–18). In sum, fatigue, pain, physical activity, and psychomotor speed contribute to the clinical presentation of CFS, but it is currently unknown whether these factors explain GMV alterations. In addition, despite a clear clinical dissociation between CFS and major depression (19,20), CFS is often associated with increased levels of depressive symptoms (3), which in turn have been associated with reduced GMV, even at subclinical level (21). This study assesses how neuronal structure in patients with CFS is influenced by those five factors.

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We used voxel-based morphometry (VBM) (22) to directly link this study to a number of reports showing CFS-related changes in GMV in the dorsolateral prefrontal cortex (DLPFC) (5,6). VBM has reliably been used to quantify regional GMV alterations in aging (23), neurodegenerative disorders, and various pain disorders (10). However, it remains unclear whether VBM measurements reflect variations in neuronal structure and density, number of glial cells, or variations in vascularization, water content, or interstitial space (17,24). Accordingly, we tested whether GMV changes in DLPFC, as measured with VBM, are driven by neuronal factors, quantifying the metabolite profile of the neurons in that region with magnetic resonance spectroscopy (MRS). We focused on *N*-acetylaspartate (NAA), a metabolite that is found predominantly in neuronal cell bodies and that has shown to be sensitive to neuronal injury (25). As such, NAA has been suggested to provide an in vivo MRS marker for neuronal viability and co-occurrence of GMV and NAA changes in patients with CFS would therefore suggest a neuronal correlate of this disorder.

We collected data from 89 women with CFS and from 26 age-, sex-, and education-matched HCs as part of a randomized controlled trial (26). We tested whether variations in DLPFC GMV and neuronal viability are associated with the defining clinical feature of CFS (i.e., fatigue), or with co-occurring factors (e.g., pain, psychomotor speed, and physical activity) while taking into account the presence of depressive symptoms.

METHODS AND MATERIALS

Participants

Inclusion criteria for all participants were as follows: female, between 18 and 65 years of age,[1] no use of psychotropic medications 6 months before testing (i.e., antidepressants, antianxiety medications, or stimulants), no current psychiatric disorder, except for specific phobias, as assessed with the Mini-International Neuropsychiatric Interview (27), no severe obesity (body mass index $\leq$40 kg/m^2), no contraindication for magnetic resonance examinations, normal hearing and (corrected) vision, and sufficient command of the Dutch language. Additional inclusion criteria for CFS patients were as follows: meeting U.S. Centers for Disease Control and Prevention (CDC) criteria for CFS, including severe fatigue lasting $\geq$6 months and with $\geq$4 additional symptoms (1,2), a score $\geq$40 on the subscale fatigue severity of the checklist individual strength (CIS-fatigue), and a score $\geq$700 on the Sickness Impact Profile 8 (SIP8 total), assessing the level of functional disability.

Consultants of the department of internal medicine evaluated the medical records of referred patients. When the consultants determined that the patients had not been sufficiently examined, they were seen for anamnesis, a full physical examination, a case history evaluation, and laboratory tests following the national CFS guideline, as used at the department of internal medicine, in accordance with the guidelines of the CDC (2,28). Additional inclusion criteria for HCs were a score $<$35 on the CIS-fatigue subscale and no chronic medical condition, including no chronic pain (26). All subjects included in the study provided written informed consent. The study was approved by the local medical research ethics committee (registration number NL43606.091.13) and was conducted according to the principles of the Declaration of Helsinki.

Clinical Assessments

Fatigue severity was measured using the CIS-fatigue subscale, on which scores range from 8 to 56 (29). Physical activity was objectively assessed as the mean activity level during waking hours over a period of 12 days preceding the test sessions using a motion-sensitive actometer worn at the ankle (12). Pain was assessed using diary scores during the 12 days of actometer measurements. Participants were asked to indicate the presence (yes or no) of pain on four time points of the day. Presence of pain was calculated as the percentage of all 48 time points with pain. Following the main additional symptoms of the CDC criteria and previous reports (8), pain was reported for the three most common pain symptoms: muscle pain, joint pain, and headaches. Psychomotor speed was assessed with the digit symbol substitution test of the Dutch Wechsler Adult Intelligence Scale (WAIS-dst) (30). The WAIS-dst was chosen because this measure revealed the strongest correlation with GMV at baseline in our previous study (5). Depressive symptoms were assessed with the Beck Depression Inventory primary care version (BDI-PC) (31). We also report functional disability, as measured with the SIP8 total score (range, 0–5799) (32), physical functioning as assessed with the subscale physical functioning of the Short Form 36 (33), and disease duration in years.

Anatomical Magnetic Resonance Imaging: Image Acquisition and Preprocessing

Magnetic resonance images were obtained on a 3T Siemens Magnetom Skyra magnetic resonance imaging scanner and a 32-channel head coil (Siemens Healthcare, Erlangen, Germany). High-resolution anatomical images were obtained using a T1-weighted magnetization-prepared rapid gradient-echo sequence (repetition time = 2300 ms, echo time = 3.03 ms, flip angle = 8°, 192 sagittal slices, field of view 256 $\times$ 256 mm, voxel size = 1 mm^3, and slice thickness = 1.00 mm). Participants were scanned within a standard time of the day (magnetic resonance imaging scans always began between 10 AM and noon), minimizing the effects of diurnal variations in brain volumes (34).

Images were preprocessed and analyzed using the VBM12 toolbox implemented in the software program Statistical Parametric Mapping (available at www.fil.ion.ucl.ac.uk/spm). VBM is a fully automated technique for computational analysis of differences in global and regional GMVs. Images were first segmented into gray matter, white matter, and cerebrospinal fluid and normalized into standardized anatomical space using the improved Montreal Neurological Institute tissue probability templates provided by SPM12. Images were modulated using global scaling and nonlinear warping to preserve the total amount of GMV. Images were smoothed with a Gaussian kernel of 12 mm full width at half maximum. Global GMV and global white matter volume (WMV) were extracted from native

[1]The initial maximal age of 55 years reported by van der Schaaf *et al.* (26) was extended to 65 years because of the low number of eligible patients.