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Fibromyalgia is characterized by altered frontal and cerebellar structural covariance brain networks

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ABSTRACT

Altered brain morphometry has been widely acknowledged in chronic pain, and recent studies have implicated altered network dynamics, as opposed to properties of individual brain regions, in supporting persistent pain. Structural covariance analysis determines the inter-regional association in morphological metrics, such as gray matter volume, and such structural associations may be altered in chronic pain. In this study, voxel-based morphometry structural covariance networks were compared between fibromyalgia patients ($N = 42$) and age- and sex-matched pain-free adults ($N = 63$). We investigated network topology using spectral partitioning, which can delineate local network submodules with consistent structural covariance. We also explored white matter connectivity between regions comprising these submodules and evaluated the association between probabilistic white matter tractography and pain-relevant clinical metrics. Our structural covariance network analysis noted more connections within the cerebellum for fibromyalgia patients, and more connections in the frontal lobe for healthy controls. For fibromyalgia patients, spectral partitioning identified a distinct submodule with cerebellar connections to medial prefrontal and temporal and right inferior parietal lobes, whose gray matter volume was associated with the severity of depression in these patients. Volume for a submodule encompassing lateral orbitofrontal, inferior frontal, postcentral, lateral temporal, and insular cortices was correlated with evoked pain sensitivity. Additionally, the number of white matter fibers between specific submodule regions was also associated with measures of evoked pain sensitivity and clinical pain interference. Hence, altered gray and white matter morphometry in cerebellar and frontal cortical regions may contribute to, or result from, pain-relevant dysfunction in chronic pain patients.

1. Introduction

Advances in non-invasive structural neuroimaging, including voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and surface-based cortical thickness analyses, have been used to investigate altered brain structure associated with multiple clinical disorders. Anatomical brain changes in chronic pain patients have now been reported by multiple studies, and a recent voxel based morphometry meta-analysis including 23 publications and close to 500 chronic pain patients found reduced gray matter volume in the basal ganglia, thalamus, anterior and posterior insula, anterior cingulate and both medial and lateral prefrontal cortices (Smallwood et al., 2013). Increased gray matter volume was also noted in the striatum and cerebellum (Schmidt-Wilcke et al., 2007).

Network analysis to evaluate inter-regional connectivity in the human brain has been performed with both functional and structural neuroimaging data (Bullmore and Sporns, 2009). Structural covariance analysis determines the inter-regional association in morphological metrics, such as gray matter volume. Specifically, this form

Abbreviations: AAL, automated anatomical labeling; BDI, Beck depression inventory; BPI, brief pain inventory; DTI, diffusion tensor imaging; FM, fibromyalgia; fMRI, functional MRI; FSL, FMRIB software library; HC, healthy controls; MCP, middle cerebellar peduncle; MNI, Montreal neurological institute; MRI, magnetic resonance imaging; ROI, region of interest; SCP, superior cerebellar peduncle; SPM, statistical parametric mapping; P40, the pressure level (mm Hg) for a pain intensity rating of 40/100; VBM, voxel-based morphometry.

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of network-based analysis determines how gray-matter volume in a given brain region covaries with that of other brain regions, across large multi-subject datasets (Evans, 2013). In healthy adults, the covariance network has been found to exhibit small world properties (i.e. nodes have more local connections than that of a random network) (He et al., 2007), similar to functional connectivity network topology (Bullmore and Sporns, 2009), and strong covariance has been found for homotopic regions across hemispheres (Mechelli et al., 2005). Such covariance likely arises from a combination of genetic influences during development and aging, as well as environmental/behavioral factors known to produce experience-based neuroplasticity. As such, chronic pain perception may also play an important role in shaping structural covariance in the human brain.

Brain structural covariance analysis has been performed for several pain disorders such as migraine (Liu et al., 2012) chronic back pain, knee osteoarthritis, and complex regional pain syndrome (Baliki et al., 2011), but not fibromyalgia (FM). Moreover, prior structural covariance analyses did not investigate if alterations in gray matter volume covariance were accompanied by altered white matter connectivity. Chronic pain, widely distributed throughout the body, is a key symptom of patients suffering from FM (Clauw, 2014). This functional pain disorder is characterized by altered resting functional connectivity (Napadow et al., 2010), which is associated with spontaneous pain intensity, and which can be normalized following longitudinal therapy (Harris et al., 2013; Napadow et al., 2012). FM also exhibits decreased gray matter volume in the medial frontal gyri (Kuchinad et al., 2007) and increased gray matter volume in cerebellum (Schmidt-Wilcke et al., 2007), as evidenced by VBM. Altered white matter microstructure in FM has been noted with DTI in the thalamus and postcentral gyrus (Lutz et al., 2008). Hence, we hypothesized that this centralized, functional pain syndrome may also demonstrate altered structural network topology, and white matter connectivity, specifically associated with clinically-relevant pain outcome measures.

In this study, fibromyalgia patients and age- and sex-matched, pain-free adults were enrolled in a structural covariance analysis. The aim of this study was three-fold. First, we compared structural covariance networks, including cerebral and cerebellar structures, in FM patients with those in healthy controls. Second, we investigated network topology using spectral partitioning, which can delineate local network submodules specific to FM. Third, we explored white matter connectivity within these submodules, using DTI, and evaluated the association between pain severity and the strength of structural connectivity using probabilistic tractography. Our study provides a detailed analysis of brain structural connectomics in FM patients suffering from chronic pain.

2. Materials and methods

2.1. Participants

We recruited 43 patients with fibromyalgia and 63 healthy controls (HC). Each subject provided written, informed consent in accordance with the Human Research Committee of Partners Health Care and Massachusetts General Hospital. The diagnosis of fibromyalgia was confirmed by physician and medical records, and patients also met the recently-proposed Wolfe et al. criteria (Wolfe et al., 2010), which require the presence of widespread pain as well as the endorsement of a number of somatic and cognitive symptoms. All participants underwent medical evaluations to exclude current or previous disorders that could affect brain structure. The exclusion criteria for FM subjects were as follows: (1) concurrent autoimmune or inflammatory disease that causes pain, such as rheumatoid arthritis, systemic lupus erythematosus, or inflammatory bowel disease; (2) a history of significant neurologic disorders, cardiovascular disorders, psychotic disorders, or cognitive impairment preventing completion of study procedures; (3) a history of drug abuse; (4) a history of head trauma requiring medical attention; and (5) brains with significant structural abnormality, which were referred to neuroradiological review. For healthy controls, subjects met the exclusion criteria above and were devoid of pain.

2.2. Clinical and behavioral measures for FM

Evoked pain sensitivity was measured in FM using cuff pain algometry applied to the left lower leg, over the gastrocnemius muscle belly. This mode of pressure pain algometry was used as it preferentially stimulates deep tissue nociceptors (Polianskis et al., 2002). As most clinical pain originates in deep tissue rather than cutaneous receptors, the investigation of brain responses to deep tissue pain may be more clinically relevant than brain responses to evoked cutaneous (e.g. heat) pain (Kim et al., 2015; Loggia et al., 2014; Polianskis et al., 2002). Briefly, pain stimuli were delivered with a velcro-adjusted pressure cuff connected to a rapid cuff inflator, which inflated the cuff to a constant pressure level (Hokanson Inc., Bellevenue, WA, USA). Quantitative sensory testing began by inflating the cuff to 60 mm Hg of pressure, and the level of pressure was adjusted in 10 mm Hg increments or decrements until a pain intensity rating of 40/100 was obtained. This pressure level, in mm Hg, was referred to as P40, and has been shown to be lower in FM patients than controls, reflecting the global hyperalgesia that characterizes this condition (Loggia et al., 2014). This procedure has also been described in more detail elsewhere (Kim et al., 2013; Loggia et al., 2014).

Patients completed the brief pain inventory (BPI) (Cleeland, 1991) and Beck depression inventory (BDI) (Beck et al., 1961) to evaluate their clinical pain and psychosocial functioning.

2.3. MRI acquisition

Structural MRI scans were obtained on a 3.0 T Siemens Trio (Siemens Medical, Erlangen, Germany) equipped with 32-channel head coil at the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital. T1-weighted sagittal volumes were obtained using a three-dimensional (3D) MPRAGE pulse sequence with the following parameters: 1.64 ms echo time (TE), 2530 ms repetition time (TR), 7° flip angle (FA), 1200 ms inversion time (TI), and $1 \times 1 \times 1$ mm^3 spatial resolution. Diffusion-weighted images were also obtained using spin-echo echo-planar imaging (EPI) sequence with the following parameters: 84 ms echo time (TE), 8040 ms repetition time (TR), 2 mm slice thickness, and 2 mm in-plane resolution. The diffusion-sensitizing gradients with a b-value of 700 s/mm^2 were applied to the 60 non-collinear directions, and 10 volumes with no diffusion weighting were also acquired.

One patient was excluded due to the presence of motion artifact on the T1-weighted image volume. Thus, 105 images were used for structural covariance analysis. For tractography analysis, diffusion-weighted image volumes of 39 healthy controls and 30 patients were available.

2.4. Segmentation and registration

Brain gray matter segmentation and alignment were performed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm) as implemented in SPM8 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/) (Ashburner and Friston, 2005), which included the field inhomogeneity correction, skull stripping, probabilistic tissue classification of gray matter, white matter, and cerebrospinal fluid, nonlinear registration to standard space using DARTEL (Ashburner, 2007), and intensity modulation by the Jacobian determinant. DARTEL uses a non-linear algorithm to yield excellent co-registration results, in terms of overlap and distance measures, for VBM analysis (Klein et al., 2009). The intracranial volume was calculated by summing the volumes of the segmented gray matter, white matter, and cerebrospinal fluid compartments, which was used as nuisance variable in the following correlational analyses.