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Brain white matter structural properties predict transition to chronic pain

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ABSTRACT

Neural mechanisms mediating the transition from acute to chronic pain remain largely unknown. In a longitudinal brain imaging study, we followed up patients with a single sub-acute back pain (SBP) episode for more than 1 year as their pain recovered (SBPr), or persisted (SBPp) representing a transition to chronic pain. We discovered brain white matter structural abnormalities (n = 24 SBP patients; SBPp = 12 and SBPr = 12), as measured by diffusion tensor imaging (DTI), at entry into the study in SBPp in comparison to SBPr. These white matter fractional anisotropy (FA) differences accurately predicted pain persistence over the next year, which was validated in a second cohort (n = 22 SBP patients; SBPp = 11 and SBPr = 11), and showed no further alterations over a 1-year period. Tractography analysis indicated that abnormal regional FA was linked to differential structural connectivity to medial vs lateral prefrontal cortex. Local FA was correlated with functional connectivity between medial prefrontal cortex and nucleus accumbens in SBPr. As we have earlier shown that the latter functional connectivity accurately predicts transition to chronic pain, we can conclude that brain structural differences, most likely existing before the back pain–inciting event and independent of the back pain, predispose subjects to pain chronification.

1. Introduction

Chronic pain imparts a large socioeconomic burden [2] dramatically degrading the quality of life for a large sector of society. Extensive human and animal evidence shows that chronic pain is associated with peripheral and central nervous system reorganization, with a large list of neuronal and glial changes associated with pain persistence [11]. Moreover, human brain imaging studies indicate that different chronic pain conditions exhibit distinct brain activity and morphological alterations (reviewed elsewhere [2–4]), and show partial reversal of brain morphology with treatments that reduce the burden of chronic pain [31,32]. Still, the causal relationship between brain abnormalities and transition to chronic pain remains largely unknown. The critical issue that has remained unresolved is the common clinical observation that, of patients with similar injuries inciting a painful episode, only a minority will proceed to develop chronic pain, which in many cases may persist for a lifetime. The potential respective roles of peripheral afferents and/or central nervous system circuits in pain chronification have been debated for decades [17,18]. We recently identified the first definitive evidence for a causal biomarker, indicating a causal role of brain functional connectivity in pain chronification [10].

In a longitudinal brain imaging study, we followed, over a 1-year period, subjects with a single episode of sub-acute back pain (SBP; no back pain for at least 1 year prior) as their pain either recovered (SBPr) or persisted into chronicity (SBPp). We observe that although brain gray matter density decreases and closely reflects the persistent pain of SBPp, corticostriatal functional connectivity (functional connectivity between medial prefrontal cortex, mPFC, and nucleus accumbens, NAc, mPFC-NAc) remains constant over the year, and its strength at a brain scan within weeks after onset of SBP symptoms predicts transition to chronic pain 1 year later, with high accuracy [10]. The functional connectivity was derived from fMRI scans while participants rated the spontaneous fluctuations of their ongoing back pain. Moreover, the number of functional connections between NAc and the cortex were correlated to the affective dimension of back pain in SBPp. Therefore, the mPFC-NAc functional connectivity is a physiological state

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reflecting the brain's response to back pain, and although it is causally related to pain chronification, it remains unclear whether this is an exaggerated response to the inciting injury, or whether the SBPp brain already possesses properties predisposing it to this enhanced functional connectivity. Here we address this issue by examining brain white matter properties within the same longitudinal study. We use diffusion tensor imaging (DTI) scans collected at multiple time points over a 1-year period, to contrast white matter structural integrity and connectivity between SBPp and SBPr, and to compare in healthy controls and chronic back pain patients (CBP). Our results indicate that white matter properties examined soon after initial pain onset robustly predict pain chronification 1 year later.

2. Methods

2.1. Subjects

The data presented here are part of an ongoing study in which we examine longitudinal changes in brain structure and function in SBP patients. Participants were recruited throughout the Chicago city area through advertisements in newspapers and on the Internet. We recruited into the study 120 SBP patients (duration at presentation of at least 4 but no more than 16 weeks), 31 healthy controls, and 31 CBP patients (back pain persisting for >5 years).

Brain scans (T1, diffusion tensor imaging [DTI], functional magnetic resonance imaging [fMRI]) were conducted in each subject at study entry (baseline, or visit 1, scans done as soon as possible from entry into study; on average at about 12 weeks from onset of back pain; when mean (±SEM) pain was 55.5 ± 2.72, on a visual analogue scale of 0–100, and we followed their pain and their brain markers over 4 visits for 1 year. All participants were right-handed and were diagnosed with back pain by a clinician. An additional list of criteria was imposed, including pain intensity greater than 40/100 on the visual analogue scale and duration of less than 16 weeks. Subjects were excluded if they reported other chronic painful conditions, systemic disease, history of head injury, psychiatric disease, or more than mild depression (score >19, as defined by the Beck Depression Inventory). Of the subjects recruited, 34 SBP and 7 healthy subjects dropped out or were removed by visit 2; 22 SBP and 1 healthy subject by visit 3; and 10 SBP patients by visit 4. Some SBP patients who completed the study were removed from the analysis because of missing data. The Institutional Review Board of Northwestern University approved the study.

After checking for the aforementioned criteria and image quality at all scans, the pool of remaining subjects included 46 patients with sub-acute back pain (22 females, 24 males; average age: mean = 42.7 years, SEM = 1.5 years; average education = 14.6 years, SEM = 0.4), 24 patients with chronic back pain (11 females, 13 males; average age: mean = 46.0 years, SEM = 1.6 - years; average education = 14.4 years, SEM = 0.4), and 28 healthy controls (12 females, 16 males; average age: mean = 37.7 years, SEM = 2.3 years; average education = 15.1 years, SEM = 2.3). Further demographics and pain characteristics at visits 1 and 4 and their comparisons are summarized in Table 1.

2.1.1. Discovery and validation groups, and white matter regional hypothesis testing

The first 24 SBP patients with complete DTI data were grouped separately and used to perform a whole-brain, white matter, skeleton-based, voxel-wise search, to identify regional white matter abnormalities (discovery group). The next 22 SBP patients' DTI scans were used for validation. In the validation group, only white matter regions identified in the discovery group were examined. This grouping was done a priori, and group memberships were kept strictly segregated. We also refrained from performing whole-brain contrasts in CBP and healthy controls, and instead we tested only the white matter regional hypothesis derived from the discovery group.

2.2. Scan acquisitions

For all participants and visits, MPRAGE type T1-anatomical brain images were acquired with a 3T Siemens Trio whole-body scanner with echo-planar imaging capability using the standard radio-frequency head coil with the following parameters: voxel size = $1 \times 1 \times 1$ mm, repetition time = 2,500 ms, echo time = 3.36 ms, flip angle = 9°, in-plane matrix resolution = 256×256; 160 slices, field of view = 256 mm. DTI images were acquired on the same day using echo planar imaging ($72 \times$ 2-mm-thick axial slices; matrix size = 128×128; field of view = 256×256 mm^2, resulting in a voxel size of $2 \times 2 \times 2$ mm). Images had an isotropic distribution along 60 directions using a b value of 1000 s · mm^{-2}. For each set of diffusion-weighted data, 8 volumes with no diffusion weighting were acquired at equidistant points throughout the acquisition. The total scan time for the diffusion-weighted imaging protocol was approximately 11 min. A subset of the participants also underwent fMRI scans with the following parameters: multi-slice T2$*$-weighted echo-planar images with repetition time = 2.5 s, echo time = 30 ms, flip angle = 90°, number of volumes = 244, slice thickness = 3 mm, in-plane resolution = 64×64. The 36 slices covered the whole brain from the cerebellum to the vertex.

2.3. Image preprocessing

Analysis was performed using tools from the FMRIB Software Library (FSL) (www.fmrib.ox.ac.uk/fsl) and in-house software. DTI data were manually checked volume by volume for obvious artifacts. Afterward, by using FMRIB's Diffusion Toolbox (FDT), eddy current and simple head motion correction was performed using affine registration to a reference volume (the first no-diffusion weighted volume of each subject). Eddy currents in the gradient coils may cause stretches and shears in the diffusion-weighted images, hence the correction. Data were then skull extracted [33], and a diffusion tensor model was fit at each voxel determining voxel-wise fractional anisotropy (FA) [1], which reflects the degree of diffusion anisotropy within a voxel (range 0–1, where larger values indicate directional dependence of Brownian motion due to white matter tracts and smaller values indicate more isotropic diffusion and less coherence) [12].

2.4. Analysis

Voxel-wise statistical analysis of FA data was carried out using the tract-based spatial statistics (TBSS) part of FSL [34]. All SBP subjects' FA data were non-linearly re-aligned into a high-resolution common space (MNI standard 1-mm brain). The mean FA image was then created and thinned to create a mean FA skeleton representing the centers of all tracts common to the group. Each subject's aligned FA data were then projected back onto this skeleton. The significance of the contrast between patients and healthy controls was determined using permutation methods (also known as randomization methods) used for inference on statistical maps when the null distribution is not known (n = 5000 permutations, $P < .05$, corrected for multiple comparisons). An unpaired t test model was used, with age as a covariate of no interest. For the area in which patients showed a significant difference from control, we extracted individual average FA and compared them between the different groups.