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Smaller Amygdala Volumes in Patients With Chronic Low Back Pain Compared With Healthy Control Individuals

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Abstract: Although preclinical and clinical data strongly support an association between the amygdala and chronic pain by the presence of mood and cognitive disturbances in affected individuals, little attention has been paid to morphometric measurement of the structure in patients with chronic low back pain (CLBP). In the present study, magnetic resonance volumetric and surface analysis, using FMRIB's integrated registration and segmentation tool (FIRST), were performed to compare structural magnetic resonance imaging data obtained from 33 patients with CLBP with those obtained from 33 demographically similar healthy control individuals. Our results indicated that the normalized volumes of the left and right amygdala were significantly smaller in the CLBP group than in the control group. Detailed surface analyses further localized these differences. The degree of volume reduction was different between the left and right amygdala, with a greater involvement of the left side. Both groups exhibited similar significant hemispheric asymmetry for the amygdala (left > right). Similar asymmetry was suggested in the subgroup of 24 unmedicated patients. No significant correlations were found between amygdala volumes and pain characteristics or depressive symptoms. Our study provides in vivo imaging evidence of abnormal morphology of the amygdala in patients with CLBP using a fully automated segmentation method.

***Perspective:** Our study found that patients with CLBP had statistically significantly smaller normalized volumes of the bilateral amygdala, compared with healthy control individuals, with a greater involvement of the left side. These results may help to characterize the impaired affective-cognitive dimension in patients with chronic pain.*

***Key words:** Chronic low back pain, amygdala, morphology, FSL-FIRST.*

The amygdala, a complex, small almond-shaped brain structure located bilaterally in the medial temporal lobe, plays a key role in emotion, memory, and affective disorders, including anxiety[21] and depression.[52] As a central component of the limbic system, the amygdala has efferent and afferent neural connections and receives projections from most cortical fields.[50,51,66] Preclinical and clinical data mainly from neuroimaging strongly support an association between the amygdala and chronic pain in the presence of mood and cognitive disturbances in affected individuals.[6,25,33,38,40,55]

As a crucial part of the so-called pain matrix (including the prefrontal cortex, anterior cingulated cortex, thalamus, insular cortex, amygdala, etc.), the amygdala has been shown to be a neural substrate for the interactions between persistent pain modulation and its affective dimension in an increasing number of studies.[48,58,65] Chronic low back pain (CLBP) is a highly prevalent pain condition that can cause disability.[63] In earlier studies,[1,2,41] most attention was paid to the plasticity of the pain matrix in such chronic pain states. Parallel lines of research suggest that CLBP is associated with aberrant cortical gray matter (GM) volumes/densities[2,28,54,56,64] and functional neuronal plasticity.[5,37,47] As a multidimensional experience,[22,23] the importance of the emotion-cognitive dimensions of pain is less understood than its nociceptive and nocifensive components. Recent evidence[58,65] has linked the amygdala to chronic pain and its affective disorders. Evidence from neuroimaging[58] indicates that peak activation is often

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located in the basolateral region of the amygdala during chronic pain, which corresponds to the neural site of cognitive-affective interaction in individuals with chronic pain. Although functional abnormality of the amygdala has been examined thoroughly, little attention has been paid to morphometric measurement of the structure in patients with CLBP.

Measurement of the GM volume/density of the amygdala or other subcortical structures has mainly, but not exclusively, been examined using voxel-based morphometry (VBM). For example, Burgmer et al[8] found decreased GM volume in the left amygdala in patients with fibromyalgia. Regarding methodology, it has been widely speculated that although VBM is a sensitive method to explore GM volumetric changes of cortical structures, it has limitations in terms of precisely localizing atypical brain regions, such as the subcortical structures, because of poor and variable intensity contrast.[42] Studies of morphometry of the amygdala in patients with CLBP measured using a fully automated segmentation method are scarce.

FIRST (FMRIB's Image Registration and Segmentation Tool),[49] which is part of FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/, Oxford Centre for Functional MRI of the Brain, Oxford, UK),[30] was used in the present study to measure the volume and surface morphology of the amygdala in patients with CLBP compared with healthy control individuals. FIRST[49] uses a Bayesian appearance model to perform both volumetric segmentation and vertex analysis. In particular, the vertex analysis method in FIRST uses the joint shape and appearance model to robustly determine the structural boundary, then provides a local and direct measure of the geometric change that does not rely on tissue classification or the arbitrary smoothing extent.

In this study, FIRST was used to measure the morphometry of the amygdala in patients with CLBP and demographically similar healthy control individuals. Our a priori hypothesis was that volumes would differ across the 2 groups.

Methods

Participants

A total of 33 individuals with CLBP (15 males, 18 females; mean age = 51.2 ± 9.1 years) and 33 demographically similar healthy control individuals (15 males, 18 females;, mean age = 51.2 ± 8.7 years) were included in the study. The 33 healthy volunteers were recruited by advertisements. All participants were right-handed and provided informed consent. Patients with CLBP were recruited from the Outpatient Clinic at our hospital's Department of Pain. All patients met the criteria of the International Association for the Study of Pain for the diagnosis of CLBP.[44] The diagnosis of CLBP was performed by 2 experienced clinicians (Y.X.L. and L.X.) based on health history and general physical examination. The disease duration was measured in years. The inclusion and exclusion criteria of patients with CLBP were as follows.

Inclusion criteria: 1) ≥18 years of age; 2) pain was primarily localized to the lumbosacral region, with or without pain radiating to the buttocks, thighs, and legs; 3) persistent pain for more than 1 year; 4) with average pain intensity ≥3 on a visual analog scale (VAS). The source of CLBP was not distinguished. Various causes (eg, muscle pain, discopathy, myofascitis, osteoarthritis) could be included only if the main source of pain was lumbosacral.

Exclusion criteria: 1) concomitant neurologic or psychiatric disorders and other diseases, such as hypertension, diabetes, coronary artery disease; 2) contraindications that excluded magnetic resonance (MR) examination (ie, pacemaker, metal implants, or severe claustrophobia); and 3) dentures that might lead to artifacts. This study was conducted in accordance with the principles in the Declaration of Helsinki and approved by the research ethics committee of the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.

Questionnaires

The intensity of pain was assessed using the short-form McGill pain questionnaire (SF-MPQ),[43] in which participants rated the intensity of pain on a VAS from 0 to 10 (0 = no pain, 10 = maximum imaginable pain) on the day of the scan. The Hamilton Depression (HAMD) scale[20] was used to evaluate the affective state in all groups.

Treatment Regimens

The treatment regimens were recorded for all patients with CLBP. Eight patients were untreated and 7 patients used physical therapy (massage or traction). Five patients underwent operations (radiofrequency ablation of the lumbar intervertebral disk or peripheral nerve block). Three patients were treated with Chinese herbal medicine only and 1 patient was treated with both traction and acupuncture. One patient used opiates (oxycodone) and 8 patients used nonsteroidal antiinflammatory drugs (NSAIDs) (aceclofenac, ibuprofen, or flupirtine maleate). None of the patients used antidepressants.

Image Acquisition

We performed MR imaging brain scans using a 3-T scanner (GE Signa HDX, Milwaukee, TN) equipped with an 8-channel head coil. Anatomic T1-weighted images were acquired using a three-dimensional (3D) T1-weighted fast spoiled gradient echo sequence with the following parameters: repetition time = 10.8 milliseconds, echo time = 4.8 milliseconds, matrix size = 256 × 256, field of view = 256 × 256 × 140 mm, slice thickness = 1 mm, space between slices = 0, 140 axial slices, and voxel size = 1 × 1 × 1 mm^3. MR imaging was performed when the participants were not experiencing pain.

Imaging Analysis

Image analysis was performed using tools from FSL (version 5.0.0, http://www.fmrib.ox.ac.uk/fsl/; Oxford University, Oxford, UK).[30]