American Pain Society
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ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 17, No 1 (January), 2016: pp 111-118
Available online at www.jpain.org and www.sciencedirect.com

Chronic Back Pain Is Associated With Decreased Prefrontal and Anterior Insular Gray Matter: Results From a Population-Based Cohort Study

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Abstract: Chronic back pain (CBP) is associated with circumscribed atrophy in gray matter (GM) predominantly localized in areas of the so-called pain matrix and the prefrontal cortex (PFC). Previous studies applying voxel-based morphometry (VBM) for identifying structural brain alterations related to CBP have reported inconsistent results, were limited to small sample sizes, and often did not control for medication. We therefore used VBM for high-resolution magnetic resonance images to investigate the association of CBP and regional GM volume in 111 individuals with CBP and 432 pain-free controls derived from the representative Study of Health in Pomerania, controlling for effects of medication. CBP was associated with decreased regional GM in the ventrolateral PFC and dorsolateral PFC, both the ventral and dorsal medial PFC, and the anterior insula. Pain intensity showed a weak negative correlation with GM volume in the left dorsolateral PFC, ventrolateral PFC, and anterior cingulate cortex. The CBP sample showed alterations in regions commonly associated with pain processing and emotional demands. To our knowledge, this is the first VBM study reporting decreased regional GM volume in the medial PFC in a CBP sample. We were unable to confirm alterations in regions other than the dorsolateral PFC and the insula.

***Perspective:** Previous studies reported inconsistent results for brain areas altered in chronic pain conditions, which may be in part attributable to small sample sizes, medication use, or emotional comorbidities. This study in a large and representative cohort helps to clarify these issues.*

***Key words:** Voxel-based morphometry, gray matter volume, chronic back pain.*

Received July 1, 2015; Revised September 16, 2015; Accepted October 6, 2015.

SHIP is part of the Community Medicine Research net of the University Medicine of Greifswald, Germany, which has been funded by the Federal Ministry of Education and Research (grant no. 03ZIK012), the Ministry of Cultural Affairs as well as the Social Ministry of the Federal State of Mecklenburg-West Pomerania. Whole-body MR imaging was supported by a joint grant from Siemens Healthcare, Erlangen, Germany and the Federal State of Mecklenburg-Vorpommern. The University Medicine of Greifswald is a member of the Center of Knowledge Interchange program of Siemens AG.

The authors declare that there are no conflicts of interest.

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1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2015.10.003

Back pain is a common health condition, with a point prevalence of around 20% and a lifetime prevalence of around 40%.[26] For most people, pain intensity reduces rapidly over a few weeks[17] and the episode is completely resolved by 3 months,[25] although symptoms can recur.[44] For many people with back pain, the prognosis is not so favorable and they develop chronic back pain (CBP).[27] For this group, recovery is slower[15] and symptoms can last for many years. CBP is usually associated with significant disability[47] and with changes to the individual emotional state, most notably depression.[1]

Recent studies have investigated the structural reorganization of the brain in CBP using voxel-based morphometry (VBM),[4] a widely used noninvasive technique for

group-wise comparisons of regional gray matter (GM) density and volume with preprocessed structural magnetic resonance (MR) imaging. Apkarian and colleagues[3] found relatively reduced GM volume in the dorsolateral prefrontal cortex (DLPFC) as well as in the thalamus in patients with CBP compared with age-matched, sex-matched, and scanner sequence-matched healthy individuals. Some subsequent VBM studies in patients with CBP have been able to replicate Apkarian et al's[3] findings of decreased GM in the DLPFC[29,41] and the thalamus,[29] whereas other studies have failed to do so, instead reporting reduced GM in other regions such as the primary and secondary somatosensory cortex and the temporal lobe.[9,29,41] In addition, Baliki and colleagues[9] found decreased GM volume in the insula, the hippocampus, and other regions, and Ivo et al[29] found decreased GM volume in the midcingulate cortex (MCC). Increased regional GM volume in patients with CBP was reported in the putamen and the bilateral thalamus solely by Schmidt-Wilcke et al.[41] In contrast to other studies, Dolman et al[18] reported that regional GM volume is not significantly different between patients with CBP and healthy controls when participants did not take opioids or benzodiazepines and were not depressed or anxious. To our knowledge, changes in regional white matter volumes in CBP have been reported in the MCC for older individuals.[14] Although several studies have reported differences in GM volume between patients with CBP and healthy controls, there is inconsistency in their findings. There is a major discrepancy with regard to the evidence for differences in GM volume in the PFC and the thalamus. There is also inconsistent evidence for differences in GM volume in regions of the insula and the cingulate. Differences in GM have also been reported in other brain regions, although less frequently.

There are likely to be several reasons for differences in the reported findings, for example, studies may have used different methodological approaches such as data preprocessing and thresholding, which potentially lead to variability in the analyses. There may be inadequate or no control of known confounding factors such as gender, age, medication, and depression. Several studies included small, highly selected samples of patients with CBP, potentially reducing statistical power and generalizability. That these factors may have contributed to the inconsistent results emphasizes the need for a study in a large representative sample.

We performed a standardized VBM analysis on MR images obtained from the Study of Health in Pomerania (SHIP)[46] with high-quality standards and careful selection of participants to determine structural differences between patients with CBP and healthy controls. We first hypothesized structural differences between patients with CBP and healthy controls in the PFC and the thalamus. We also hypothesized structural differences in regions of the insula and the anterior cingulate cortex (ACC). We then attempted to identify any other structural differences between patients with CBP and healthy controls.

Methods

Participants

Participants were identified from SHIP-Trend-0, a population-based study conducted between 2008 and 2012 in the counties of Nordvorpommern and Ostvorpommern and the 2 cities of Greifswald and Stralsund in northeastern Germany. For SHIP-Trend-0, a stratified sample of 10,000 was recruited from the central population registry. A total of 4,420 (2,275 women) individuals participated and were invited for an MR imaging examination; an appointment could not be made with 192 of these individuals. SHIP-Trend-0 included 2,154 whole-body MR imaging scans.

All MR imaging head scans were visually inspected with regard to artifacts or medical findings (K.W.). We first excluded participants with a history of stroke, multiple sclerosis, epilepsy, Parkinson disease, dementia, cerebral tumor, intracranial cyst, or hydrocephalus (n = 141) or participants with more than slight motion artifacts or intensive magnetic field strength inhomogeneities (n = 399).

Pain ratings were measured for several body regions using verbal ratings in which 0 indicated no pain and 10 the worst imaginable pain. Individuals with CBP were defined as those who experienced continuous back pain for a time span of at least 3 months of radiating character who had not recovered (no pain) at the time of MR imaging (n = 148). One individual was removed because of incomplete information concerning pain intensity. Pain-free controls were selected if they reported no pain in any body region other than a rare headache during the pervious year (n = 457).

In addition, individuals were excluded for the use of opioids[50] and benzodiazepines (n = 16) or if they matched the criteria for depression as assessed with the Patient Health Questionnaire (PHQ9; score > 10; n = 28). We excluded 4 individuals with CBP and 13 controls with a missing PHQ9. Our groups consisted of 111 individuals with CBP and 432 pain-free controls.

The study protocol was approved by the Ethics Committee of the University Medicine of Greifswald and written informed consent was obtained from each participant.

Image Acquisition

MR images were obtained using a 1.5-T Siemens MR imaging scanner (Magnetom Avanto; Siemens Medical Systems, Erlangen, Germany) using a T1-weighted magnetization prepared rapid acquisition gradient echo sequence and the following parameters: orientation = axial, matrix = 256 × 176 pixel, voxel size = 1.0 mm isotropic, slice thickness = 1.0 mm, repetition time = 1900 milliseconds, echo time = 3.37 milliseconds, flip angle =15°. The protocol and resulting findings are described in more detail elsewhere.[23,24]

Preprocessing

Statistical Parametric Mapping 8 (SPM8; Wellcome Department of Cognitive Neurology, University of London, London, UK) and the VBM8 toolbox (Christian