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Visceral sensitivity correlates with decreased regional gray matter volume in healthy volunteers: A voxel-based morphometry study

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ABSTRACT

Regional changes in brain structure have been reported in patients with altered visceral sensitivity and chronic abdominal pain, such as in irritable bowel syndrome. It remains unknown whether structural brain changes are associated with visceral sensitivity. Therefore, we present the first study in healthy individuals to address whether interindividual variations in gray matter volume (GMV) in pain-relevant regions correlate with visceral sensitivity. In 92 healthy young adults (52 female), we assessed rectal sensory and pain thresholds and performed voxel-based morphometry (VBM) to compute linear regression models with visceral sensory and pain thresholds, respectively, as independent variable and GMV in a priori-defined regions of interest (ROIs) as dependent variable. All results were familywise error (FWE) corrected at a level of $P_{FWE} < .05$ and covaried for age. The mean (±SEM) rectal thresholds were 14.78 ± 0.46 mm Hg for first sensation and 33.97 ± 1.13 mm Hg for pain, without evidence of sex differences. Lower rectal sensory threshold (ie, increased sensitivity) correlated significantly with reduced GMV in the thalamus, insula, posterior cingulate cortex, ventrolateral and orbitofrontal prefrontal cortices, amygdala, and basal ganglia (all $P_{FWE} < .05$). Lower rectal pain threshold was associated with reduced GMV in the right thalamus ($P_{FWE} = .051$). These are the first data supporting that increased visceral sensitivity correlates with decreased gray matter volume in pain-relevant brain regions. These findings support that alterations in brain morphology not only occur in clinical pain conditions but also occur according to normal interindividual variations in visceral sensitivity.

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1. Introduction

An improved understanding of interindividual differences in the response to painful stimuli is crucial for the pathophysiology and treatment of chronic pain conditions. Brain correlates of visceral processing have been studied using magnetic resonance imaging (MRI) techniques, both in healthy volunteers as well as in patients with chronic pain [19], including pain originating from the gastrointestinal tract such as in irritable bowel syndrome (IBS). In light of significant differences between visceral and somatic pain processing [7,9,17,22,38], studies on the central mechanisms mediating visceral pain are warranted to complement and extend knowledge from the somatic pain field. Although functional brain responses to visceral stimuli have been systematically studied in both healthy individuals and patients [7,12–14,23,24,34,35,38,39,51,53], morphological brain changes, as quantified by voxel-based morphometry (VBM), remain understudied. Thus far, altered gray matter density (GMD) or gray matter volume (GMV) has been reported in IBS [16,20,49], chronic pelvic pain or vulvodynia [4,48], and Crohn's disease [2]. One study also reported white matter abnormalities in patients with IBS [18].

The etiology and significance of these morphological brain alterations in normal interindividual variations in pain sensitivity as well as in the pathophysiology of chronic pain remain unclear. Two previous studies in nonclinical samples support that brain morphology is indeed associated with subclinical ongoing pain (of various origins) in the general population [45] and with somatic pain and temperature sensitivity [25]. Neither of these studies considered visceral pain. Herein, we present the first study conducted in healthy volunteers assessing correlations between interindividual variations in visceral sensitivity and regional GMV. The rationale

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for focusing on visceral sensitivity, quantified as rectal sensory and pain threshold, lies in the role of increased visceral sensitivity and disturbed central pain processing in the pathophysiology of IBS [8,13,14,24,34,35,37,39,51,53]. We aimed to test the hypothesis that increased rectal sensitivity (ie, a lower threshold for first perception and/or for pain) is associated with reduced GMV in brain regions known to primarily mediate sensory-discriminatory (ie, thalamus, somatosensory cortices) as well as affective-motivational (cingulate cortex, insula) pain components and descending inhibition and cognitive-evaluative pain aspects (periaqueductal gray, prefrontal cortex).

2. Methods

2.1. Study design and procedures

For the purpose of this analysis, data from healthy volunteers who participated in 1 of 2 functional brain imaging study protocols addressing various aspects of visceral pain processing were pooled. Both study protocols had identical procedures, described in detail later, with respect to the screening process, inclusion and exclusion criteria, assessment of rectal sensory and pain thresholds, and structural MRI (which always preceded the fMRI studies). All subjects were measured in the same MRI scanner with the identical head coil and settings from August 2011 to October 2012 at the Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Germany. The fMRI data have either been reported in detail elsewhere [31,47] or are unpublished as of yet. All questionnaires were completed before the study during the initial screening visit to our laboratory. On the study day, rectal perceptual and pain thresholds were initially determined using established methodology (see later). After a rest period of 10 minutes, a structural MRI scan was completed (with the rectal balloon inserted to facilitate subsequent fMRI). Note that the time of day was not standardized due to irregular availability of scanner time. The study protocols were approved by the local ethics committee (University Hospital Essen, University of Duisburg-Essen, Germany) and follow the rules stated in the Declaration of Helsinki. All participants gave written informed consent and were paid for their participation.

2.2. Inclusion and exclusion criteria

Healthy male and female subjects were recruited by local advertisement. Exclusion criteria included age <18 years and >32 years; body mass index <18 or >30; any concurrent medical condition, including neurological, psychiatric, cardiovascular, immunological, and endocrine conditions; evidence of structural brain abnormality; and the usual MRI-specific exclusion criteria (ie, phobic anxiety, claustrophobia, ferromagnetic implantations). Any chronic medication use also was exclusionary, except hormonal contraceptives, thyroid medications, or occasional use of over-the-counter allergy or pain medications for benign headaches, menstrual cramps, etc. All participants were evaluated digitally for anal tissue damage (eg, painful hemorrhoids) that may have interfered with rectal balloon placement. A history of psychological conditions (based on self-report) or presently increased scores on the Hospital Anxiety and Depression Scale (HADS) [28] also were exclusionary. Frequency and severity of gastrointestinal complaints suggestive of any functional or organic gastrointestinal condition were assessed with a standardized in-house questionnaire assessing a variety of typical upper and lower gastrointestinal symptoms [47]. In female subjects, pregnancy was excluded by a commercially available urinary test on the day of the study. Information on menstrual cycle phase and hormonal contraceptive use were assessed based on self-report.

2.3. Rectal sensory and pain thresholds

Subjects were instructed to self-apply a commercially available clyster (Clyssie, 120 mL, Braun, Melsungen, Germany) 2 hours before arriving at the laboratory. The clyster was provided to volunteers together with written instructions during the initial appointment. Upon arrival to the laboratory, an infinitely compliant balloon was inserted into the rectum 5 cm from the anal verge. This balloon is a catheter-affixed polyethylene bag of cylindrical shape and 10 cm in length. Fully inflated, it has a diameter of 8 cm and a maximum volume of 500 mL. After balloon placement, a resting period of 10 minutes was accomplished. Rectal distensions were then carried out with a pressure-controlled barostat system (modified ISOBAR 3 device, G & J Electronics, Ontario, Canada), as previously described, see for example [11,12,23,47]. Sensory and pain thresholds were determined using a double-random staircase distension protocol with random pressure increments of 2 to 10 mm Hg. Each pressure was maintained for 30 seconds, after which the subject was prompted to rate the sensation on a 6-point scale as follows: 1 = no perception; 2 = doubtful perception; 3 = sure perception; 4 = little discomfort; 5 = severe discomfort, still tolerable; 6 = pain, not tolerable. Between individual distensions, the balloon was deflated to a pressure of 0 mm Hg. The sensory threshold was defined as the pressure when the rating changed from 2 to $\geqslant 3$; the pain threshold as the pressure at which the rating changed from 5 to 6. The maximal distension pressure was set at a pressure level of 50 mm Hg per our ethics committee. For statistical analyses, in case that the pain threshold was not reached at 50 mm Hg (this was the case for N = 4 individuals), the pain threshold was coded as 51 mm Hg to reduce artificial skewing of the distribution/ceiling effects.

2.4. MR imaging and VBM analysis

All MR images were acquired using a 3-T MRI scanner (Skyra, Siemens Healthcare, Erlangen, Germany). Sixteen elements of the standard 20-channel head/neck DirectConnect coil were used. For high-resolution structural images, a 3-dimensional T1-weighted magnetization-prepared rapid gradient echo was acquired in a sagittal orientation (TR 1900 ms, TE 2.13 ms, bandwidth 230 Hertz/pixel, TI 900 ms, flip angle 9°, 100% phase field of view $239 \times 239\ mm^2$, 192 slices, slice thickness 0.9 mm, voxel size $0.9 \times 0.9 \times 0.9\ mm^3$, matrix $256 \times 256\ mm^2$, parallel MRI (pMRI) GRAPPA r = 2, TA 4.23 minutes). For VBM analysis, SPM8 software (Wellcome Department of Cognitive Neurology, London, UK) was used. The basic principles of VBM as described by Ashburner and Friston [6] were applied as follows. Tissues were first classified as gray matter (GM), white matter (WM), or cerebrospinal fluid (CSF). Magnetization-prepared rapid gradient echo images were segmented into GM, WM, and CSF images by a unified tissue-segmentation procedure after image-intensity nonuniformity correction. These segmented gray matter images were then spatially normalized to the customized template in the standardized anatomic space using the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL, Wellcome Department of Imaging Neuroscience) [5]. The customized template for DARTEL was created from the sample of N = 92 healthy participants. At each iteration, deformations were calculated using the DARTEL registration method and were applied to GM and WM, with an increasingly good alignment of participant morphology to produce templates [1]. To preserve gray matter volume within each voxel, the images were modulated by the Jacobean determinants derived from the spatial normalization by DARTEL [5] and then smoothed by using a 10-mm Full Width at Half Maximum Gaussian kernel.

To analyze linear relationships between regional GMV and visceral sensitivity, we used linear regression models with rectal

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