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Pain sensitivity is inversely related to regional grey matter density in the brain

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ABSTRACT

Pain is a highly personal experience that varies substantially among individuals. In search of an anatomical correlate of pain sensitivity, we used voxel-based morphometry to investigate the relationship between grey matter density across the whole brain and interindividual differences in pain sensitivity in 116 healthy volunteers (62 women, 54 men). Structural magnetic resonance imaging (MRI) and psychophysical data from 10 previous functional MRI studies were used. Age, sex, unpleasantness ratings, scanner sequence, and sensory testing location were added to the model as covariates. Regression analysis of grey matter density across the whole brain and thermal pain intensity ratings at 49 °C revealed a significant inverse relationship between pain sensitivity and grey matter density in bilateral regions of the posterior cingulate cortex, precuneus, intraparietal sulcus, and inferior parietal lobule. Unilateral regions of the left primary somatosensory cortex also exhibited this inverse relationship. No regions showed a positive relationship to pain sensitivity. These structural variations occurred in areas associated with the default mode network, attentional direction and shifting, as well as somatosensory processing. These findings underscore the potential importance of processes related to default mode thought and attention in shaping individual differences in pain sensitivity and indicate that pain sensitivity can potentially be predicted on the basis of brain structure.

1. Introduction

Pain is a multidimensional sensory experience involving interactions between sensory, cognitive, affective, and genetic factors [9,36,45,53]. The multifactorial nature of pain produces wide-ranging variability in pain sensitivity and responsiveness to treatment [10,36]. Functional neuroimaging has revealed pain intensity-related brain activations in the thalamus, anterior cingulate cortex (ACC), insula, and primary (SI) and secondary somatosensory (SII) cortices [11,12,16,48]. Several of these regions show activity that is positively associated with subjective pain ratings across individuals [11]. Other regions within the posterior parietal cortex, such as the intraparietal sulcus (IPS) and inferior parietal lobule (IPL), also may contribute to individual differences in pain sensitivity by directing attention to painful stimuli [37,47]. In addition, experimental pain causes deactivations in the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and precuneus (PCu) [12,34,59], whereas individuals with chronic pain show reduced deactivation in these locations [5]. These areas constitute part of the default mode network (DMN) [52], an area of increasing importance in pain research.

Structural studies suggest that pain can cause short-term and long-term morphologic changes in the brain. Using voxel-based morphometry (VBM), Teutsch et al. [67] determined that 8 consecutive days of experimentally induced noxious stimulation significantly increased grey matter volume in regions involved in processing of nociceptive information, such as the midcingulate and somatosensory cortex [67]. One year later, these differences were no longer detectable, suggesting that pain-related structural

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changes can be reversed under the absence of noxious stimulation. Additionally, chronic pain causes grey matter changes in pain-associated brain areas. The locations and direction of changes varies widely across differing chronic pain conditions [3,20,27,43,55,58,70].

Differences in grey matter may be reflective of neural processes contributing to the construction and modulation of pain in healthy individuals. A recent study by Erpelding et al. found a correlation between cold pain thresholds and cortical thickness in SI, and heat pain thresholds and cortical thickness in SI, posterior midcingulate cortex, and orbitofrontal cortex [19]. These findings highlight an important relationship between pain thresholds and cortical thickness. However, the relationship between suprathreshold differences in pain sensitivity and regional grey matter remains unknown. Elucidation of this relationship may provide novel insights into brain mechanisms contributing to individual differences in pain sensitivity. In order to address this question, we executed a VBM analysis to determine whether grey matter density (GMD) is associated with individual differences in pain sensitivity, as defined by pain intensity ratings to suprathreshold stimuli. Importantly, because pain-related differences in brain morphology vary in direction and across regions, we examined both positive and negative relationships between grey matter density and individual differences in pain sensitivity across the entire brain, in a fashion unconstrained by a priori hypotheses.

2. Materials and methods

2.1. Subjects

Structural data were collected from 10 previous functional magnetic resonance imaging pain studies [11,28,37,38,40,46,51,64,71,72]. All of these studies involved noxious heat stimuli with maximum temperatures of 49 °C. If a subject participated in more than one study, data from only their earliest study was used. Psychophysical data and structural brain images from 116 healthy volunteers (62 women, 54 men) ranging in age from 20 to 75 years with a mean age of 30 ± 11 years were used (Table 1). The distribution of ethnicities includes 7 African Americans, 8 Asians, 94 Caucasians, 3 Hispanics, 1 Indian, and 3 multiethnic subjects. Exclusion criteria included (1) existing chronic pain conditions, (2) current opioid use, (3) psychiatric disorders, (4) current psychiatric drug use, and (5) pregnancy. In all studies, subjects gave written informed consent stating (1) that they understood that they would experience painful heat stimulation, (2) that the experimental procedures were clearly explained, and (3) that they could withdraw at any time without prejudice. The Wake Forest University School of Medicine Institutional Review Board approved all study procedures.

2.2. Psychophysical data collection

Psychophysical assessment and magnetic resonance imaging (MRI) scanning sessions occurred during 2 independent experimental sessions (Table 1). Heat stimuli (35 °C, 43 °C, 44 °C, 45 °C, 46 °C, 47 °C, 48 °C, 49 °C) were applied to the ventral forearm (n = 57) or posterior aspect of the lower leg (n = 59) using a 16 × 16-mm TSA II thermal stimulator (Medoc, Ramat Yishai, Israel), with 35 °C serving as baseline. Due to the retrospective nature of the study, data on the side of stimulation are unavailable. Stimulus temperatures were delivered with rise and fall rates of 6 °C/s with a plateau duration of 5 seconds and a minimum interval of 30 seconds between stimuli. Stimulus temperatures were applied in 4 blocks, with each block consisting of all 8-stimulus temperatures (32 total). The thermal probe was moved to a different location after termination of each stimulus to prevent effects of sensitization or habituation. Subjects rated pain intensity and pain unpleasantness on a scale of 0 to 10 (where 0 is no pain or not at all unpleasant and 10 is most intense pain imaginable or most unpleasant imaginable) using a 15-cm plastic visual analogue scale (VAS; Paresian Novelty, Chicago, IL) [49,50]. Subjects were instructed to only provide a rating for painful stimuli; therefore, if the stimulus was not perceived as painful, subjects provided a zero for both pain intensity and unpleasantness. The average of pain intensity responses to the four 49 °C stimuli was used as an index of each subject's pain sensitivity.

2.3. MRI acquisition

Structural images were obtained on a GE Healthcare 1.5-T MRI scanner using similar high-resolution T1-weighted anatomical sequences shown in Table 2. Importantly, MRI scans were acquired in a different session than collection of psychophysical data (Table 1). All structural scans except those from Zeidan et al. [72] (n = 10) were obtained prior to the functional MRI (fMRI) testing paradigm. These 10 scans were obtained after 1 fMRI series that included noxious heat stimulation and 1 fMRI series that involved neutral stimulation.

2.4. Image processing and statistical analysis

2.4.1. VBM methods

Structural data were analyzed with FSL-VBM version 1.1 (http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html; Oxford University, Oxford, UK), a voxel-based morphometry analysis tool [4,23,61]. First, structural brain images were extracted from surrounding tissue using brain extraction tool (BET) [60]. Next, tissue type segmentation of grey matter, white matter, and cerebrospinal fluid was

Table 1
Subject demographics and statistics across all studies.

	Original study	Data collection year	Subjects used	Gender	Ethnicity	Age (y) mean ± SD	training/testing interval (d) mean ± SD
1	Coghill et al. (2003) [11]	2000	17	F/7 M/10	C/17	26 ± 5	2 ± 1
2	Hadsel et al. (2006) [28]	2005	8	F/3 M/6	C/4 AA/1 A/1 H/2	25 ± 2	8 ± 5
3	Martucci et al. (2006) [40]	2006	17	F/11 M/6	C/14 AA/2 A/1	27 ± 3	8 ± 12
4	Starr et al. (2011) [64]	2007	13	F/6 M/7	C/13	59 ± 10	–
5	Lobanov et al. (2013) [37]	2009	16	F/8 M/8	C/13 AA/1 A/1 H/1	26 ± 4	4 ± 2
6	Zeidan et al. (2011) [72]	2010	10	F/6 M/4	C/8 A/1 M/1	27 ± 3	3 ± 2
7	Quevedo and Coghill (in preparation) [51]	2010	3	F/2 M/1	C/3	27 ± 3	22 ± 1
8	Nahman-Averbuch et al. (2012) [46]	2011	9	F/6 M/3	C/6 AA/2 A/1	25 ± 3	10 ± 5
9	Zeidan et al. (2012) [71]	2011	10	F/5 M/5	C/9 A/1	27 ± 4	2 ± 2
10	Lobanov et al. (2013) [38]	2011	13	F/8 M/5	C/7 AA/1 A/2 M/2 I/1	26 ± 2	4 ± 3
	Total	N/A	116	F/62 M/54	C/94 AA/7 A/8 H/3 M/3 I/1	30 ± 11	5.44 ± 6.81

SD = standard deviation; F = female; M = male; C = Caucasian; AA = African American; A = Asian; H = Hispanic; M = multiethnic; I = Indian.