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 (VBM) to investigate the relationship between grey matter density across the whole brain and inter-individual differences in pain sensitivity in 116 healthy volunteers (62 females, 54 males). Structural MRI and psychophysical data from 10 previous fMRI 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 exhibited 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.

Introduction

Pain is a multidimensional sensory experience involving interactions between sensory, cognitive, affective, and genetic factors [9; 36; 45; 53]. The multi-factorial nature of pain produces wide-ranging variability in pain sensitivity and responsiveness to treatment [10;

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36]. Functional neuroimaging has revealed pain-intensity related brain activations in the thalamus, anterior cingulate cortex (ACC), insula, primary (SI), and secondary somatosensory (SII) cortices [11; 12; 16; 48]. Several of these regions exhibit 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) may also 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 and long-term morphologic changes in the brain. Employing voxel-based morphometry (VBM), Teutsch and colleagues (2008) determined that eight consecutive days of experimentally-induced noxious stimulation significantly increased grey matter volume in regions involved in processing of nociceptive information, such as the mid-cingulate and somatosensory cortex [67]. One year later these differences were no longer detectable, suggesting that pain-related structural 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 and colleagues 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.

Materials and Methods

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 females, 54 males) ranging in age from 20–75 with a mean age of 30 ± 11 were used (See Table 1). The distribution of ethnicities includes 7 African Americans, 8 Asians, 94 Caucasians, 3 Hispanics, 1 Indian, and 3 multi-ethnic. 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) 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. Wake Forest University School of Medicine Institutional Review Board approved all study procedures.

Psychophysical Data Collection

Psychophysical assessment and MRI scanning sessions occurred during 2 independent experimental sessions (Table 1). Heat stimuli (35, 43, 44, 45, 46, 47, 48, 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 is 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 following termination of each stimulus to prevent effects of sensitization or habituation. Subjects rated pain intensity and pain unpleasantness on a scale of 0–10 (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 (Paresian Novelty) [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.

MRI Acquisition

Structural images were obtained on a GE Healthcare 1.5 Tesla 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 and colleagues 2011 (n=10) were obtained prior to the 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.

Image processing and statistical analysis

VBM methods—Structural data were analyzed with FSL-VBM v1.1 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 BET [60]. Next, tissue type segmentation of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) was completed with FAST4 [73]. The segmented grey matter images were aligned to Montreal Neurological Institute (MNI) 152 standard space using a 12 parameter affine transformation accomplished with FLIRT [32; 33]. The post registration images were averaged to create a study specific template for subsequent non-linear registration of GM images using FNIRT [1; 2]. The GM images were concatenated into a 4D image and corrected for local expansion and contraction by dividing by the Jacobian of the warp field. The modulated images were smoothed with an isotropic Gaussian kernel with a sigma of 4mm (full width at half-maximum = 9mm).

A regression analysis was performed using a general linear model (GLM) to examine the relationship between grey matter differences across the whole brain and pain sensitivity (VAS intensity ratings of 49°C). Age, sex, unpleasantness ratings, scanner sequence, and sensory testing location were added as covariates. Permutation-based non-parametric testing (10,000 permutations) was used to evaluate this relationship in a voxel-wise fashion. Threshold free cluster enhancement (TFCE) was utilized to define significant clusters [62]. A family wise error (FWE) corrected p-value of $p < 0.05$ was applied to correct for multiple

comparisons and identify clusters exhibiting a significant relationship between GMD and pain sensitivity.

Psychophysical statistics—GMD can differ substantially as a function of sex, age, and ethnicity [8; 22; 23]. Accordingly, the relationships between pain sensitivity and sex, age, and ethnicity were examined. Psychophysical data and age relationships were assessed via regression analysis. Pain sensitivity between sexes was assessed using a Student's t-test. One-way ANOVA's were used to test for differences in pain sensitivity that were related to ethnicity and the study from which the data were derived. In addition, Student's t-tests were performed to ensure that pain sensitivity was not differentially distributed between the two broad types of scanning sequences (BRAVO vs. SPGR) or the two sensory testing locations (arm vs. leg).

Secondary analyses to assess potential carryover effects of sensory testing on GMD—A VBM-based Student's t-test was completed to determine grey matter differences between individuals based on sensory testing location (arm vs leg). To examine possible grey matter differences related to carry over effects from the sensory testing session, a VBM-based regression analysis of grey matter density and the number of days between sensory testing and structural acquisition was preformed.

Results

Psychophysical Responses

Across all subjects, mean intensity and unpleasantness ratings at 49°C were 3.13 ± 2.10 and 2.79 ± 2.12 (mean rating $\pm$ SD) respectively and were significantly related to each other ($R^2 = 0.66$, $F(1, 115) = 219.04$, $p < 0.001$). Accordingly, pain intensity ratings were used for all subsequent analyses. No relationship was found between intensity ratings and age, ($R^2 = 0.00$, $F(1, 114) = 0.00$, $p = 0.98$), ethnicity ($F(5,110) = 1.66$, $p = 0.15$), or sex ($t(1,114) = 0.830$, $p = 0.40$). In addition, there were no significant differences between intensity ratings and scanning sequence ($t(1,114) = 0.362$, $p = 0.72$), sensory testing location ($t(1,114) = 1.362$, $p = 0.18$), or the study from which the subjects were derived ($F(9,106) = 1.25$, $p = 0.27$) (Figure 1).

Relationship between pain sensitivity and GMD

A multiple regression based VBM analysis using a whole brain search unconstrained by regions of interest determined that pain intensity ratings at 49°C were negatively related to grey matter density in bilateral PCu, ($p = 0.006$, corrected), bilateral PCC ($p = 0.006$, corrected), bilateral anterior IPS ($p = 0.012$, corrected), bilateral IPL ($p = 0.021$, corrected) and left SI ($p = 0.012$, corrected). Figure 2 shows significant clusters in PCu (voxels (L) = 335, (R) = 289), PCC (voxels (L) = 199, (R) = 184), IPS (voxels (L) = 408, (R) = 87), IPL (voxels (L) = 100, (R) = 51), and left SI (voxels = 417). Subjects with lower intensity ratings were found to have larger grey matter densities in these areas relative to subjects with higher intensity ratings (Figure 3). Conversely, no positive relationship was found between pain sensitivity and GMD.

GMD exhibited no carryover effects from the sensory testing session

Sensory testing was completed on the arm or leg and occurred an average of 5.44 days prior to structural MRI acquisition. A between groups VBM analysis of grey matter density across the whole brain and sensory testing location (arm vs. leg) revealed no significant differences. A regression analysis of GMD across the whole brain and the number of days between sensory testing and structural scanning identified no significant relationship between GMD and time between testing and scanning.

Discussion

Using a whole brain VBM analysis, we identified an inverse relationship between pain sensitivity and GMD in the PCC, PCu, IPS, IPL, and SI. This relationship is striking since these differences in brain structure were identified an average of 5.44 days after psychophysical assessment. Accordingly, this relationship between brain structure and pain sensitivity may reflect relatively stable processes that contribute substantially to individual differences in pain sensitivity. Surprisingly, some of the regions exhibiting this relationship are deactivated during acute nociceptive stimulation and may be related to default mode processes. Others are related to top down direction of attention, as well as somatosensory processing.

DMN and Pain

The DMN consists of a collection of brain regions that are associated with self-awareness and consciousness and include the mPFC, PCC, and the PCu [52]. These regions are intrinsically active during times of rest [52], introspection [26], daydreaming [41], information gathering [25], and retrieval of episodic memories [7] and are deactivated with cognitive load [52], task performance [42], hypnosis [54], and meditation [24; 29; 72].

Our results indicate an inverse relationship between pain sensitivity and grey matter density in areas of the DMN, such that individuals who are highly sensitive to pain have less grey matter in PCC and PCu, and individuals who are least sensitive to pain have more grey matter in these areas. Areas of the DMN including the PCC and PCu have been shown to deactivate during experimental pain [12; 34; 59]. It is unclear whether structural differences in the DMN reflect a cause or a consequence of individual differences in pain sensitivity. Inter-individual differences in neural activation may result in grey matter differences, as experience is known to cause grey matter changes [17; 55; 67]. Individuals who have entrenched introspective thought patterns may have increased grey matter density in default mode areas. These introspective thought patterns may function as competitors to processes that contribute to the construction of an experience of pain, thereby resulting in relatively low pain sensitivity. For example, a recent brain imaging study by Kucyi and Colleagues found that mind wandering away from pain increased functional activations in the DMN and that structural and functional connectivity between the DMN and periaqueductal gray were associated with mind wandering away from pain [35]. Consistent with this notion, rumination about non-pain related issues may function as a competitor to the instantiation of pain. Healthy, pain-free individuals with mild sub-clinical anxiety have lower pain intensity ratings than non-anxious individuals [63].

Conversely, individuals who are easily disengaged from self-referential thought processes may have less DMN activation and decreased grey matter in default mode areas. In this case, default mode activity may not compete as efficiently with the processes generating an experience of pain. Thus, these individuals may have relatively high sensitivity to pain. Although speculative, this interpretation is consistent with findings derived from studies examining the relationship between cortical thickness and dimensions of attention including executive control, alerting, and orienting. Grey matter thickness of the PCC and PCu as well as the IPS was inversely related to the alerting response. This negative relationship was viewed as being related to reduced task motivation or a reduced ability to maintain tonic vigilance prior to presentation of warning cues [68]. Such reductions in alerting responses are consistent with a reduced ability to switch from default mode thought patterns in order to direct attention to processing external stimuli.

Posterior Parietal Cortex and Pain

Similar to the PCC and PCu, grey matter density in the posterior parietal cortex was inversely related to pain sensitivity. These changes were evident in two regions of the posterior parietal cortex: the IPS and the IPL. The IPS and IPL are involved in attentional processes related to spatial and intensity features of visual, auditory, and somatosensory modalities, including pain [14; 21; 31; 37; 39; 47; 57; 69]. Individuals with increased grey matter in IPS and IPL may be more likely to maintain top-down directed attention and not be as sensitive to the bottom up attentional demands of noxious stimuli. Consistent with this notion, intentional direction of attention away from pain has been shown to reduce pain perception [6; 15; 18]. Conversely, individuals with decreased grey matter density in IPS and IPL may be less able to regulate top-down attentional processes and therefore be more susceptible to stimuli with strong bottom-up attentional demands [68].

SI and Pain

In functional brain imaging studies, SI is frequently activated during pain and is related to perceived pain intensity, individual differences in pain sensitivity, as well as stimulus intensity [11–13]. The present investigation revealed an inverse relationship between GMD in SI and pain sensitivity to suprathreshold noxious stimuli. When pain sensitivity was determined according to heat pain thresholds, a positive relationship between cortical thickness and threshold-based sensitivity was identified in SI [19]. Thresholds and suprathreshold ratings are vastly different measures and are relatively poorly correlated within individuals [63]. Thus, differences in results from these 2 measures of pain sensitivity are not surprising. However, our findings of increased GMD in relatively insensitive individuals are consistent with the observation that repetitive exposure to suprathreshold noxious stimuli reduces pain sensitivity concomitantly with increasing grey matter volume in SI [67]. Grey matter contains both excitatory and inhibitory neurons, so a decrease in grey matter could be the result of decreased inhibitory processes. Indeed, individuals with chronic neuropathic pain show decreased grey matter volume of the somatosensory thalamus (as measured by VBM), decreased cerebral blood flow in thalamus and SI, and significantly lower thalamic GABA levels than controls [30]. Interestingly, the decreased cerebral blood flow in the thalamus was negatively correlated to pain intensity.

Limitations

Since this is a retrospective analysis of multiple data sets acquired over more than a decade, many factors could elevate variability and reduce sensitivity to more subtle changes in GMD. Although some sources of variability such as scanner sequence were incorporated into the statistical analysis, other remaining sources of variability could still somewhat diminish sensitivity. Given the variations in experimental protocols and data acquisition techniques, the identification of regional GMD differences reflecting pain sensitivity is even more striking.

Our results indicate that structural differences in areas of the DMN, IPS, IPL, and SI, are inversely related to pain sensitivity. However, more research is needed to determine the directionality of this relationship and the sources behind the grey matter differences. Although the underlying mechanism of grey matter variation is not known, there are many factors that may contribute. These include differences in blood flow, glia, neuronal cell bodies, and neuropil [17]. It is also unclear whether these differences are genetic or experience based, although it is likely both [17; 44]. Previous studies have shown that repetitive noxious heat stimulation delivered over the course of 8 daily sessions can induce changes in grey matter in healthy individuals [67]. Accordingly, we examined the possibility of carryover effects and found no relationship between grey matter density and the number of days between sensory testing and structural acquisition. Moreover, we found no effect of

stimulus location (arm vs. leg) on GMD. Therefore, it is unlikely that these intensity-related grey matter differences were driven by the stimuli delivered in the psychophysical session. In addition, although data on the side of stimulation is unavailable, the absence of carryover effects indicates that the grey matter differences seen in left SI are not the result of prior stimulation.

Future research should examine whether these findings apply to other sensory modalities. A limiting factor of this study is that only thermal pain was used to test pain sensitivity. Examination of responses to other pain modalities could provide insight as to the generalizibility of the relationship between pain sensitivity and grey matter differences found here. An additional limitation of this study is that we did not assess personality traits or pain related psychological factors, such as anxiety and neuroticism, which may influence brain structure. Incorporation of such factors could further elucidate the relationship between brain anatomy and pain sensitivity.

Summary

Pain is a subjective experience with tremendous inter-individual variation. Using a global search unconstrained by a priori biases, we determined that GMD in areas associated with default mode processes, attention, as well as somatosensory processing was significantly inversely related to individual differences in pain sensitivity. Sensitivity can fluctuate over different time scales with substantial variation from one week to the next or can be influenced by developmental factors and remain altered over the course of a lifetime [56; 65; 66]. In the present investigation, the relationship between GMD and pain sensitivity was evident over a period of more than 5 days on average, and suggesting a relatively stable phenomenon. Accordingly, these kinds of morphologic differences can serve as novel predictors of pain sensitivity and provide a foundation for the development of biomarkers for diagnosis, classification, prevention, and treatment of pain.

Acknowledgments

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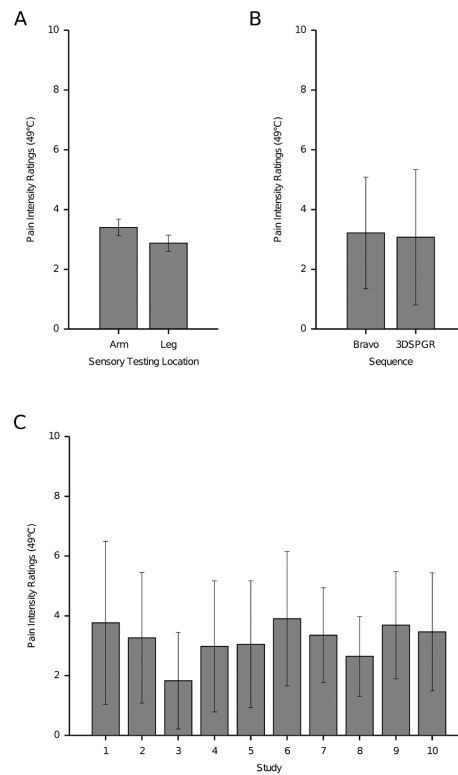
Figure 1.
Pain sensitivity differences by sensory testing location, scanning sequence, and study (mean ± SD). **A**, Subjects were tested for thermal heat pain sensitivity on the arm (n = 57) or leg (n = 59). Mean intensity ratings between locations did not differ significantly (p = 0.18). **B**, Structural images from 10 previous studies (*n=116*) were acquired using BRAVO (n = 48) and SPGR (n = 68) scanning sequences. Mean pain sensitivity between subjects of BRAVO and SPGR sequences did not differ significantly (p = 0.72). **C**, Mean intensity ratings across studies are listed according to Table 1 and did not differ significantly (p = 0.27).
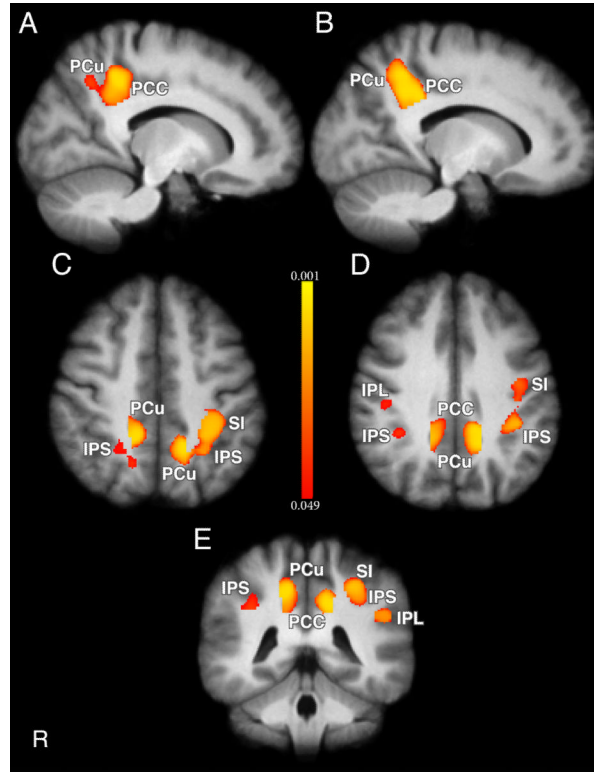
Figure 2.
Differences in regional grey matter density are inversely related to pain sensitivity in healthy subjects (*n=116*). VBM regression analysis revealed increased grey matter in subjects reporting low VAS pain ratings at 49°C. Subjects reporting high VAS pain ratings at 49°C exhibited less grey matter. **A**, **B**, Sagittal slices showing grey matter differences in right (Coordinates: 14, −44, 42) and left (Coordinates: −14, −48, 40) PCu (voxels (R) = 289, (L) = 335; p = 0.006) and right (Coordinates: 14, −42, 36) and left (Coordinates: −14, −44, 36) PCC (voxels (R) = 184, (L) = 199; p = 0.006). **C**, Horizontal slice showing grey matter differences in IPS (voxels (R) = 87, Coordinates: 24, −52, 46; voxels (L) = 408, Coordinates: −34, − 42, 46; p = 0.012), PCu, and SI (voxels = 417, Coordinates: −32, −36, 46; p = 0.012). **D**, Horizontal slice showing grey matter differences in right IPL (voxels = 51, Coordinates: 46, −24, 34, p < 0.05), IPS, PCC, PCu, and SI. **E**, Coronal slice showing grey matter differences in left IPL (voxels = 100, Coordinates: −50, −42, 28, p = 0.021), IPS, PCu, PCC, and SI. Color bar values correspond to p values. IPL = inferior parietal lobule, IPS = intraparietal sulcus, PCC = posterior cingulate cortex, PCu = precuneus, SI = primary somatosensory cortex.
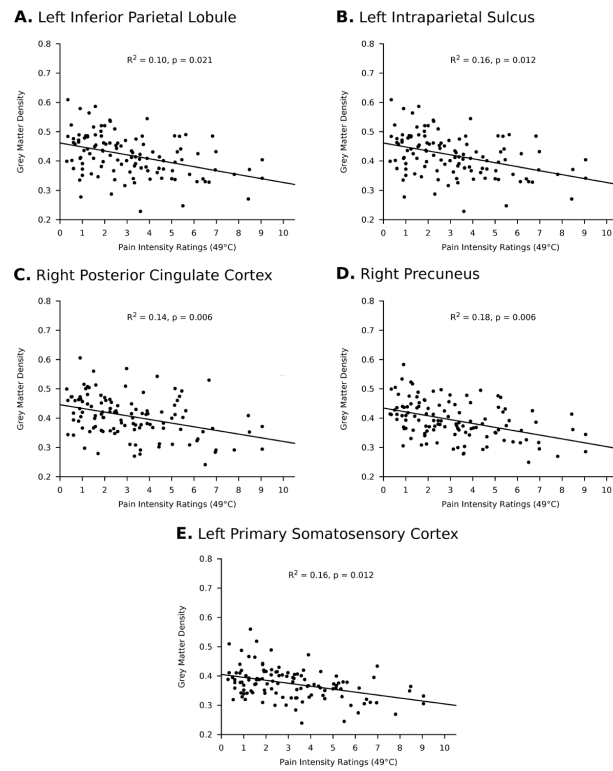
Figure 3.
Relationships between pain sensitivity and grey matter density in selected regions. Pain intensity ratings at 49°C are inversely related to grey matter density.

Table 1

Subject demographics and statistics across all studies

	Original Study	Data Collection Year	Subjects Used	Gender	Ethnicity	Age (yrs) Mean ± SD	Training/ Testing Interval (days) Mean ± SD
1	Coghill et al., 2003	2000	17	F/7 M/10	C/17	26 ± 5	2 ± 1
2	Hadsel et al., 2006	2005	8	F/3 M/6	C/4 AA/1 A/1 H/2	25 ± 2	8 ± 5
3	Martucci et al., 2006	2006	17	F/11 M/6	C/14 AA/2 A/1	27 ± 3	8 ± 12
4	Starr et al., 2011	2007	13	F/6 M/7	C/13	59 ± 10	-
5	Lobanov et al., 2013	2009	16	F/8 M/8	C/13 AA/1 A/1 H/1	26 ± 4	4 ± 2
6	Zeidan et al., 2011	2010	10	F/6 M/4	C/8 A/1 M/1	27 ± 3	3 ± 2
7	Quevedo and Coghill, in Preparation	2010	3	F/2 M/1	C/3	27 ± 3	22 ± 1
8	Nahman-Averbuch et al., 2012	2011	9	F/6 M/3	C/6 AA/2 A/1	25 ± 3	10 ± 5
9	Zeidan et al., 2012	2011	10	F/5 M/5	C/9 A/1	27 ± 4	2 ± 2
10	Lobanov et al., 2013	2011	13	F/8 M/5	C/7 AA/1 A/2 M/2 1/1	26 ± 2	4 ± 3
	Total	n/a	116	F/62 M/54	C/94 AA/7 A/8 H/3 M/3 1/1	30 ± 11	5.44 ± 6.81

- = data not available; SD = standard deviation; F = female; M = male; C = Caucasian; AA = African American; A = Asian; H = Hispanic; M = multi-ethnic; I = Indian

Table 2

Structural scan sequences across all studies

Original Study	Sequence	TI (ms)	TR (ms)	Flip Angle (°)	TE (ms)	Matrix Size	Slice Thicknes* (mm)	Sections	In-plane resolution (mm)	FOV (cm)
Coghill et al., 2003	3D spoiled gradient-echo	600	9.10	20	1.98	256 × 192	1.5	124	0.9375 × 0.9375	24
Hadsel et al., 2006	3D spoiled gradient-echo	600	8.59	20	1.88	256 × 196	1.5	124	0.9375 × 0.9375	24
Martucci et al., 2006	3D spoiled gradient-echo	600	8.59	20	1.88	256 × 196	1.5	124	0.9375 × 0.9375	24
Starr et al., 2011	3D spoiled gradient-echo	600	9.10	20	1.98	256 × 196	1.5	124	0.9375 × 0.9375	24
Lobanov et al., 2013	BRAVO	600	11.41	12	4.77	240 × 240	1.5	160	0.9375 × 0.9375	24
Zeidan et al., 2011	3D spoiled gradient-echo	600	11.42	12	4.76	240 × 240	1.0	164	0.9375 × 0.9375	24
Quevedo and Coghill, in Preparation	3D spoiled gradient-echo	600	9.10	20	1.98	256 × 196	1.5	124	0.9375 × 0.9375	24
Nahman-Averbuch et al., 2012	BRAVO	600	11.46	12	4.73	240 × 240	1.5		0.9375 × 0.9375	24
Zeidan et al., 2012	BRAVO	600	11.49	12	4.74	256 × 256	1.0	156	0.9375 × 0.9375	24
Lobanov et al., 2013	BRAVO	600	11.49	12	4.74	240 × 240	1.0	156	0.9375 × 0.9375	24

TI = inversion time; TR = repetition time; TE = echo time; FOV = field of view;

*
no gap between sections