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# Cortical thickness correlates of pain and temperature sensitivity

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ABSTRACT

It is well established that there is individual variability in pain and temperature sensitivity. Functional brain imaging studies have found that interindividual heat pain variability correlates with brain activity in sensory and pain modulation areas. Thus, it is possible that these individual differences are associated with variability in gray matter thickness of cortical regions involved in thermoreception and pain. To test this, we investigated the relationship between thermal thresholds and cortical thickness in 80 healthy subjects. Subjects underwent a psychophysical session to determine their cool detection (CD), warm detection (WD), cold pain (CP), and heat pain (HP) threshold. A high-resolution structural magnetic resonance imaging scan was acquired for each subject. We correlated each threshold measure to cortical thickness of regions associated with thermoreception and pain. The mean (± SD) thresholds were 30.7°C (± 0.8) for CD, 33.8°C (± 0.7) for WD, 11.7°C (± 9.7) for CP, and 45.3°C (± 2.8) for HP. The brain gray matter analysis revealed a strong correlation between greater thermal and pain sensitivity and cortical thickening of the primary somatosensory cortex. Additionally, greater sensitivity to cool stimuli correlated with cortical thickening in the paracentral lobule, and greater WD correlated with cortical thinning in the anterior midcingulate cortex. We also found that greater HP sensitivity correlated with thickening in the posterior midcingulate cortex and the orbitofrontal cortex. These cortical gray matter correlates of thermal and pain sensitivity provide a neural basis for individual differences in thermal sensitivity.



## 1. Introduction

Pain is a unique, complex, and multidimensional experience that is shaped by individual differences in perception and pain sensitivity. However, the brain mechanisms underlying between-subject differences of temperature and pain perception remain poorly understood.

Psychophysical studies on healthy volunteers have reported large individual differences in detection thresholds, pain thresholds, and pain tolerance levels [27,39,47,71]. In addition to these behavioural findings, electroencephalography and functional magnetic resonance imaging (fMRI) studies have identified intersubject variability in subcortical and cortical activations evoked by innocuous and noxious experimental stimuli [6,12,38]. Moreover, Coghill et al. [9] showed that a wide range of pain intensity ratings across subjects correlated with fMRI activations in nociceptive and pain-related brain regions. Specifically, the primary somatosensory cortex (S1), anterior cingulate cortex (ACC), and prefrontal cortex (PFC) had greater pain-evoked activations in highly sensitive individuals than in less sensitive individuals. These findings were said to indicate that individual pain experiences involve different patterns of supraspinal activations. Similarly, an electroencephalography study by Iannetti et al. [30] reported a correlation between subjective pain intensity and the amplitude of pain-evoked responses in specific regions of the insula and S1, thereby supporting the idea that pain intensity coding is distributed over several brain regions and may be different between individuals based on their response to the incoming stimulus. Pain and temperature sensitivity are likely to be impacted by genetic factors; in fact, there is substantial evidence that variation in pain sensitivity is partially mediated by genes [15,34,64,75]. Also, various psychological factors and personality traits (e.g., pain catastrophizing, anxiety) have been associated with individual differences in pain sensitivity [25,49,60]. Taken together, there is strong evidence that the individual variability observed in experimental studies reflects actual interindividual differences in neurophysiology (rather than scale or measurement artifacts), and that neuroanatomical substrates may be contributing factors to individual differences.

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Acute experimental pain activates a number of brain areas associated with the representation and modulation of pain. The most commonly activated areas evoked by acute painful stimuli are S1, secondary somatosensory cortex (S2), insular cortex (IC), ACC, midcingulate cortex (MCC), PFC, basal ganglia, and thalamus (for review, see Apkarian et al. [1]). To date, however, there have been no studies that have investigated structural gray matter correlates and their relation to an individual's experience of thermoreception and pain perception. Therefore, the aim of the present study was to investigate the relationship between thermal thresholds and structural brain morphology. We hypothesized that interindividual differences in these behavioural measures would correlate with gray matter thickness in key cortical regions that are responsible for the processing and modulation of sensory stimuli.

## 2. Materials and methods

### 2.1. Subjects

Eighty healthy right-handed subjects (40 female, 40 male; age range = 19 to 36 years, mean age ± SD = 24.5 ± 4.9 years) were recruited for the study and provided informed written consent to experimental protocols approved by the University Health Network Research Ethics Board. Each subject underwent 2 experimental sessions: one to evaluate thermal detection and pain thresholds, and another to acquire a high-resolution anatomical MRI scan.

### 2.2. Psychophysical session

Cool detection (CD), warm detection (WD), cold pain (CP), and heat pain (HP) thresholds were determined with a 30 × 30-mm Peltier thermode (TSA-II NeuroSensory Analyzer, Medoc Ltd., Ramat Yishai, Israel) that delivered stimuli to the left volar forearm. Thresholds were determined based on method of limits protocols that were computer-controlled with Medoc software and a linked response button. For each modality, the baseline temperature was 32°C. The ramp rates for CD and WD were 1°C/s, and for HP and CP were 1.5°C/s (ascending) and 10°C/s (descending). Three consecutive stimulus trials were used for each detection threshold measurement, and 5 consecutive trials for the pain thresholds. The interstimulus intervals were set at 6 seconds for CD and WD, and 10 seconds for CP and HP. The order of measurement was CD, WD, CP, HP. Subjects were given standardized instructions that are commonly used in psychophysical studies of thermal detection and pain thresholds. To determine CD thresholds, subjects were instructed to press the response button as soon as they felt a cool sensation. For WD thresholds, subjects were instructed to press the response button as soon as they felt a warm sensation. For CP thresholds, subjects were instructed to press the response button the moment they felt that the temperature changed from nonpainful cool to a painful cold sensation. Finally, HP thresholds were determined by instructing subjects to press the response button as soon as they felt a change from an innocuous warm to a painful hot sensation.

For each subject, CD and WD thresholds were determined by averaging the last 2 of the 3 repetitions. The CP and HP thresholds were based on the average of the 3 last measures of the 5 repetitions. To investigate possible sex effects for detection and pain thresholds, we ran separate independent *t* tests for each modality between male and female subjects.

### 2.3. MRI session

Subjects underwent MRI on a 3-T MRI system (GE Medical Systems, Milwaukee, WI, USA) fitted with an 8-channel phased-array head coil. A high-resolution anatomical whole-brain scan (180 axial slices; 256 × 256 matrix; 25.6-cm field of view; 1 × 1 × 1-mm voxels) was acquired using a T1-weighted inversion recovery prepped, 3-dimensional fast spoiled gradient echo (IR-FSGPR) sequence (flip angle = 15°, TE = 3 ms, TR = 7.8 ms, TI = 450 ms). Subjects were instructed to remain still during the MRI acquisition to obtain good image quality.

To assess correlations between gray matter and thermal thresholds, we performed cortical thickness analysis (CTA) based on surface reconstructions using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). The details of these methods have been described elsewhere [10,21,22] and previously used by our group [3,4,43,67]. Briefly, preprocessing steps included intensity normalization, skull stripping, Talairach transformation, hemispheric separation, and tissue segmentation. The white matter/gray matter border (i.e., white surface) and gray matter/cerebrospinal fluid border (i.e., pial surface) were identified and transformed into surfaces. Then, the distance between the 2 surfaces was calculated for every point, for each hemisphere separately. Next, each subject's cortex was anatomically parcellated and each sulcus and gyrus was labeled and aligned to the FreeSurfer's average surface map according to cortical folding patterns and smoothed using a 5-mm full-width half-maximum Gaussian spatial smoothing kernel.

In the CTA, vertex-wise linear correlations were conducted with statistical significance set at $P < .05$, corrected for multiple comparisons based on Monte Carlo permutations with 5000 iterations using AlphaSim (http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim) as previously used by our group [3,4,43,67]. Analysis was restricted to a mask (Fig. 1) that contained S1, S2, paracentral lobule (PCL), ACC, MCC, IC, and PFC. This mask was created using FreeSurfer's parcellation atlas (aparc.a2009s) [14]. The location of the resulting clusters and their respective Brodmann area (BA) was verified based on the Talairach and Tournoux [66] atlas. Age was entered as covariate of no interest. Because the independent *t* tests did not reveal any sex effects (see psychophysical results section for details), we did not include sex in the analysis, as we did not expect to find any morphological brain differences based on temperature and pain sensitivity between male and female subjects.

In FreeSurfer, the cortical mantle is inflated and represented as a 2-dimensional surface that contains triangles that map each point of the cortical surface [10,22]. The points at which the sides of these triangles meet or intersect are called vertices. The standard brain in FreeSurfer has a total surface of 163,842 vertices corresponding to a total surface area of 822,000 $mm^2$. The surface reconstruction is comprised of a number of sheets (number of sheets = 2 × number of vertices of the standard brain). To derive the surface area of each cluster (in $mm^2$), we divided the total surface of the standard brain by the number of sheets. Each sheet had a surface area of 0.502 $mm^2$. Accordingly, to obtain the surface area (in $mm^2$) of our results, the number of vertices in each cluster was multiplied by 0.502.

## 3. Results

### 3.1. Psychophysics

The overall group temperature range and mean (± SD) thresholds for the thermal (CD, WD) and pain (CP, HP) detection are summarized in Table 1. The thresholds for all thermal and pain modalities showed individual variability across the 80 subjects tested, which in turn facilitated our gray matter correlation analysis (see later). The innocuous thermal detection thresholds varied less than the pain thresholds, spanning approximately 3°C to 5°C between subjects (Figs. 2 and 3); the mean CD threshold was 30.7°C ± 0.8°C, and the mean WD threshold was 33.8°C ± 0.7°C.

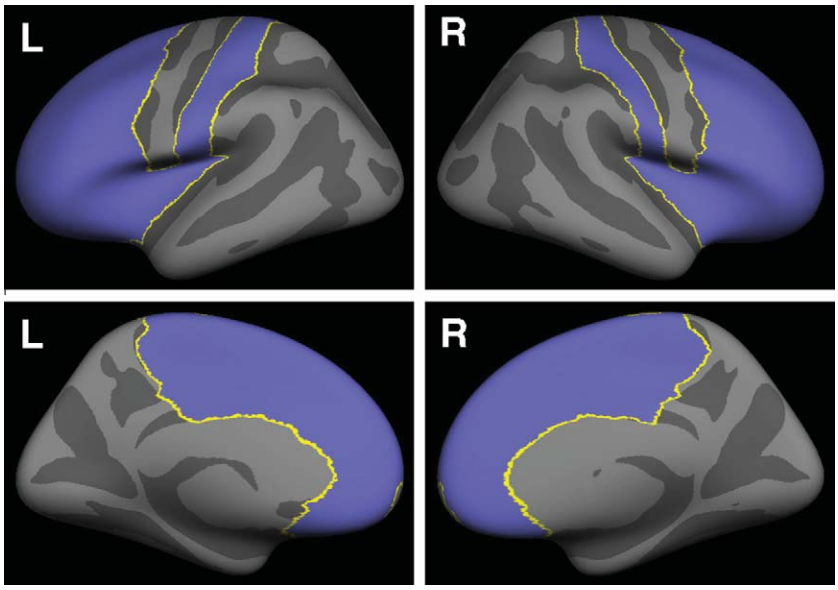


**Fig. 1.** Mask used to perform cortical thickness analysis (CTA). The mask included primary and secondary somatosensory cortices (S1 and S2), paracentral lobule (PCL), anterior and midcingulate cortices (ACC and MCC), insula, and prefrontal cortex (PFC).

**Table 1**
Thermal detection and pain thresholds.

| Modality | Threshold range (°C) | Mean threshold (°C) ± SD |
|---|---|---|
| Cool detection | 27.1–31.8 | 30.7 ± 0.8 |
| Warm detection | 31.8–35.7 | 33.8 ± 0.7 |
| Cold pain | 0.0–28.0 | 11.7 ± 9.7 |
| Heat pain | 38.6–50.0 | 45.3 ± 2.8 |

The individual pain thresholds, however, spanned a much broader range of temperatures, varying by 11°C for HP and 28°C for CP (Figs. 4 and 5). Individual CP thresholds ranged from 28.0°C to 0°C with a mean pain threshold of 11.7°C ± 9.7°C, and individual HP thresholds ranged from 38.6°C to 50.0°C with a mean pain threshold of 45.3°C ± 2.8°C.

A subgroup analysis by sex was also performed to determine whether there were any sex differences in thermal thresholds. The mean thresholds in the group of 40 male subjects were: 30.6°C ± 0.9°C (CD), 33.9°C ± 0.7°C (WD), 10.8°C ± 9.7°C (CP), and 46.0°C ± 2.9°C (HP). The mean thresholds in the group of 40 female subjects were: 30.7°C ± 0.7°C for CD, 33.7°C ± 0.8°C for WD, 11.9°C ± 9.7°C for CP, and 45.4°C ± 2.6°C for HP. Independent *t* tests between male and female subjects revealed no significant sex differences for any of the tested modalities (all $P > .05$).

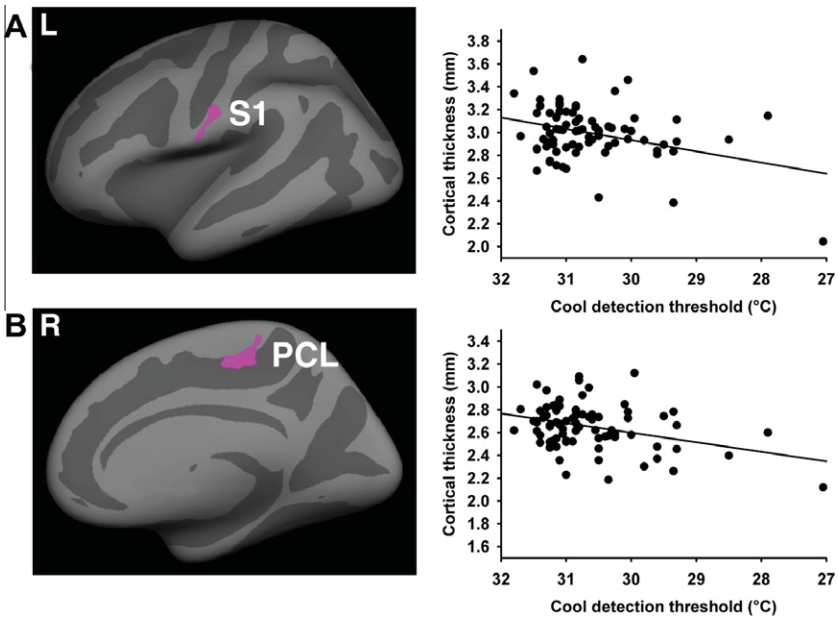


**Fig. 2.** Correlation between cortical gray matter thickness and cool detection threshold (shown in pink). (A) Greater cool detection sensitivity significantly correlates with thickening in cortical gray matter in S1 ($r = 0.34$, $P < .01$). (B) Greater cool detection sensitivity significantly correlates with a thickening in cortical gray matter in PCL ($r = 0.35$, $P < .01$). PCL = paracentral lobule; S1 = primary somatosensory cortex.

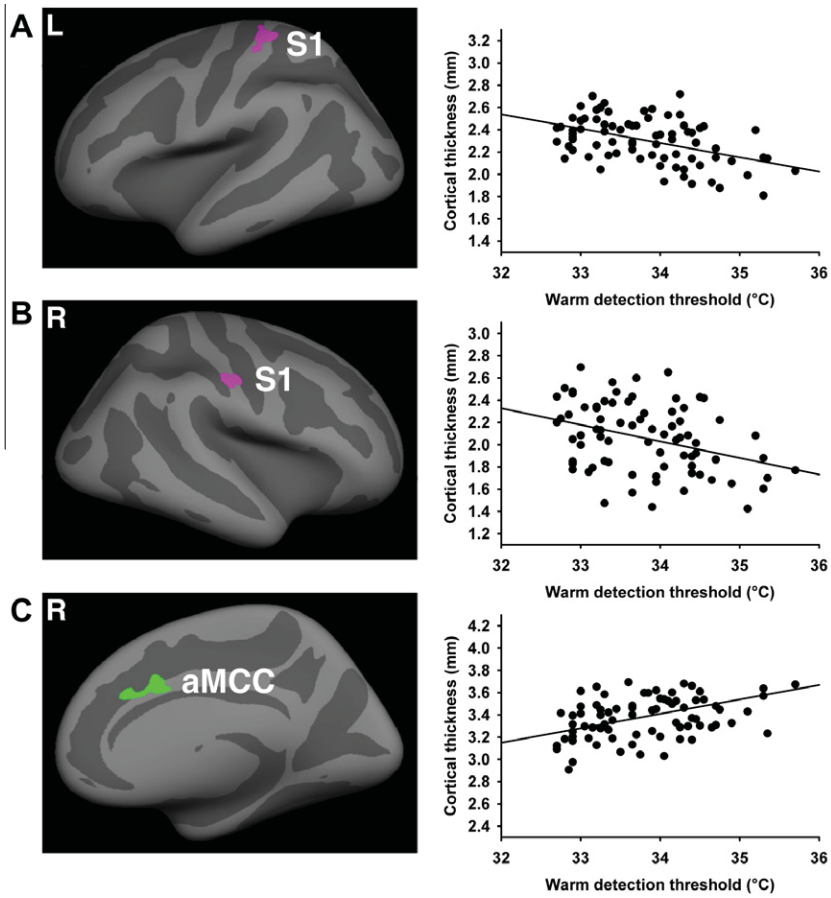


**Fig. 3.** Correlation between cortical gray matter thickness and warm detection threshold. (A) Greater warm detection sensitivity significantly correlates with thickening in cortical gray matter in left S1 ($r = -0.46$, $P < .01$). (B) Greater warm detection sensitivity significantly correlates with thickening in cortical gray matter in right S1 ($r = -0.36$, $P < .01$). (C) Greater warm detection sensitivity significantly correlates with thinning in cortical gray matter in right aMCC ($r = .43$, $P < .01$). Clusters with negative correlations are shown in pink, and clusters with positive correlations are shown in green. aMCC = anterior midcingulate cortex; S1 = primary somatosensory cortex.

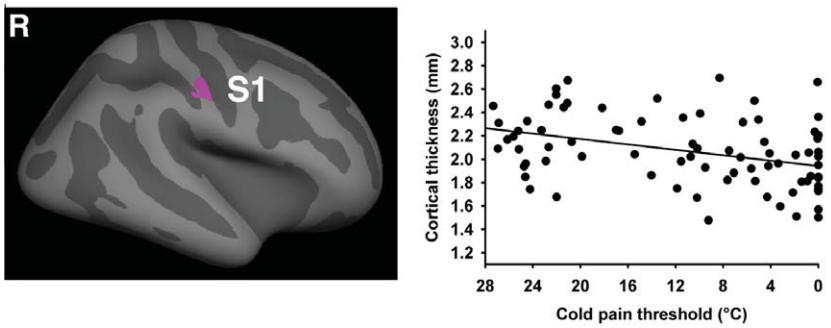


**Fig. 4.** Correlation of cortical gray matter thickness and cold pain threshold (shown in pink). Greater cold pain sensitivity significantly correlates with thickening in cortical gray matter in right S1 ($r = 0.38$, $P < .01$). S1 = primary somatosensory cortex.

### 3.2. Cortical thickness

The cortical thickness of S1 was prominently correlated with thermal thresholds (Table 2, Figs. 2 through 5). The location of cortical thickness within S1 that correlated with HP thresholds and with CP thresholds was nearly identical in surface area and ventrolateral location. A similar-sized region in the ventrolateral S1 correlated with CD and WD (Table 2, Figs. 2 through 5). In addition, the cortical thickness within several other cortical areas was significantly correlated with thermal detection and pain thresholds in individual subjects as described later.

The CTA revealed a significant correlation between innocuous CD threshold and cortical thickness in the left S1 (BA1; $r = 0.34$, $P < .01$; Fig. 2A) and the right PCL (BA5; $r = 0.35$, $P < .01$; Fig. 2B). That is, the S1 and PCL were thicker in those subjects who could detect a cool sensation at only mildly cool temperatures. The S1 finding comprised a region of 178 $mm^2$ predominantly located ventrolaterally in BA1. The PCL finding spanned a region of 221 $mm^2$ (see Table 2 for coordinates).

Individual WD thresholds were negatively correlated with cortical thickness in BA1 of the S1, and included 2 S1 regions: one encompassing a 376 $mm^2$ area of the left S1 ($r = -0.46$, $P < .01$),

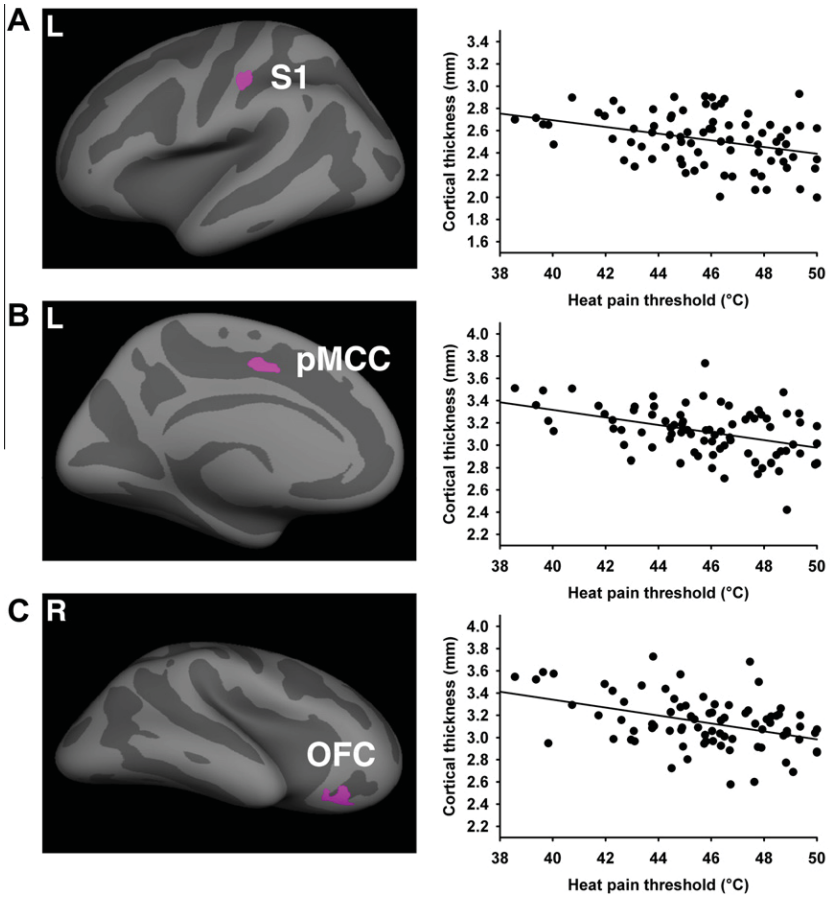


**Fig. 5.** Correlation of cortical gray matter thickness and heat pain threshold (shown in pink). (A) Greater heat pain sensitivity significantly correlates with thickening in left S1 ($r = -0.35$, $P < .01$). (B) Greater heat pain sensitivity significantly correlates with thickening in left pMCC ($r = -0.42$, $P < .01$). (C) Greater heat pain sensitivity significantly correlates with thickening in right OFC ($r = -0.41$, $P < .01$). OFC = orbitofrontal cortex; pMCC = posterior midcingulate cortex; S1 = primary somatosensory cortex.

**Table 2**
Cortical regions significantly correlated with thermal detection and pain thresholds.

| Region | BA | Talairach coordinates | | | Area ($mm^2$) | *T* score | *r* |
|---|---|---|---|---|---|---|---|
| | | x | y | z | | | |
| Cool detection threshold | | | | | | | |
| L S1 | 1 | −59 | −10 | 30 | 178 | 2.26 | 0.34 |
| R PCL | 5 | 11 | −26 | 47 | 221 | 3.28 | 0.35 |
| Warm detection threshold | | | | | | | |
| L S1 | 1 | −31 | −30 | 61 | 376 | −3.89 | −0.46 |
| R S1 | 1 | 52 | −12 | 37 | 220 | −3.04 | −0.36 |
| R aMCC | 24/31 | 8 | 13 | 31 | 225 | 4.31 | 0.43 |
| Cold pain threshold | | | | | | | |
| R S1 | 1 | 52 | −13 | 41 | 248 | 4.20 | 0.38 |
| Heat pain threshold | | | | | | | |
| L S1 | 1 | −50 | −21 | 45 | 233 | −2.41 | −0.35 |
| L pMCC | 32 | −13 | −4 | 41 | 201 | −2.94 | −0.42 |
| R OFC | 11 | 19 | 28 | −14 | 174 | −4.33 | −0.41 |

Peak vertex Talairach coordinates are reported. All results are significant at $P < .05$, corrected for multiple comparisons.
aMCC = anterior midcingulate cortex; BA = Brodmann area; L = left; OFC = orbitofrontal cortex; pMCC = posterior midcingulate cortex; PCL = paracentral lobule; R = right; S1 = primary somatosensory cortex.

and another 220 $mm^2$ area more ventrolateral in the right S1 ($r = -0.36$, $P < .01$). That is, bilateral S1 was thicker in those subjects who could detect a warm sensation at only mildly warm temperatures. WD threshold was also positively correlated with cortical thickness in the anterior MCC (aMCC) (BA 24/31; $r = 0.43$, $P < .01$). Consequently, aMCC was thinner in those subjects who had a lower threshold for detecting innocuous warm stimuli. The regions of cortical thickness correlations with WD and individual WD threshold findings are shown in Fig. 3, and the coordinates of the cortical regions are provided in Table 2.

The result of the group correlation analysis between CP thresholds and cortical thickness as well as the individual subject data are shown in Fig. 4 and Table 2. The analysis indicated that cortical thickness within a 248 $mm^2$ region of BA1 in the right ventrolateral

S1 was significantly correlated with CP thresholds in individual subjects ($r = 0.38$, $P < .01$).

The group correlation analysis between HP thresholds and cortical thickness showed 3 significant negatively correlated cortical areas. One region had a surface area of 233 $mm^2$ and was located in the left S1 (BA1; $r = -0.35$, $P < .01$; Fig. 5A), another region was 201 $mm^2$ and located in the left posterior MCC (pMCC) (BA32; $r = -0.42$, $P < .01$; Fig. 5B), and a third region was 174 $mm^2$ and located within the right orbitofrontal cortex (OFC) (BA11; $r = -0.41$, $P < .01$; Fig. 5C). These findings indicate that subjects who had a lower HP threshold (i.e., higher sensitivity) had greater cortical thickness in S1, pMCC, and OFC.

## 4. Discussion

This study is the first to identify gray matter correlates of thermoreception and pain sensitivity. Our findings reveal a relationship between pain and temperature sensitivity and cortical thickness in brain areas implicated in several types of temperature and pain-related functions. Specifically, the regions identified have longstanding associations with (1) sensory perception of innocuous and noxious thermal stimuli (S1, pMCC), (2) sensorimotor integration (pMCC, PCL), (3) pain anticipation and pain modulation (MCC, OFC), and (4) negative affect, cognitive control, and salience detection (aMCC, OFC).

Our structural findings reveal a predominantly positive correlation between cortical thickness and temperature and pain sensitivity. Specifically, we found that highly sensitive individuals had thicker cortical gray matter in brain regions that are implicated in sensory and pain processing, pain modulation, and affective and cognitive control. From a functional perspective, thicker cortical gray matter may be related to the detection, processing, and modulation of innocuous and noxious stimuli. To date, the substrate of gray matter variability in the brain remains unknown. Gray matter variability could be due to differences in cell volume, synaptic densities, and blood flow or interstitial fluid [23,42]. Structural gray matter changes have also been associated with changes in pain sensitivity. Specifically, a recent longitudinal study provided evidence for brain plasticity (i.e., gray matter increases in nociceptive brain regions) due to repetitive noxious stimulation, which also increased HP thresholds over time [68]. Additionally, chronic pain patients show altered structural changes related to pain characteristics in pain-related brain regions [3,13,24,40,41,43,55,58,74]. Our results corroborate these previous findings by demonstrating correlations between brain morphology and pain and temperature sensitivity.

There was a strong correlation between cortical thickness in S1 and the perception of innocuous and noxious thermal stimuli. The sensory-discriminative processing features of S1 have been demonstrated by classic neurophysiological studies that established that neurons in S1 specifically respond to both innocuous and noxious stimulation [31–33] and that these neurons are responsible for coding the intensity, location, and temporal pattern of sensory stimuli [7,31,32]. Additionally, human imaging studies found that activation of S1 is graded with intensity of noxious stimulation. For example, Porro et al. [53] showed that temporal fMRI patterns correlated with individual pain intensity in S1 and other regions of the cortex. Similarly, S1 was found to be particularly sensitive to pain intensity changes in contrast to other brain regions [44]. S1 can be divided into 4 cytoarchitectonically distinct areas that are arranged rostrocaudally into areas 3a, 3b, 1, and 2. These distinct areas also seem to have functional differences: areas 3b and 1 receive cutaneous tactile input, whereas areas 3a and 2 respond to proprioceptive input. Thus, in accordance with these results, our findings confirm that S1, and specifically BA1, may be involved in the perception of innocuous and noxious thermal stimuli.

The size and the location of the correlated regions, in particular the ventrolateral S1, were very similar for all of our tested modalities. Classically, Penfield and Boldrey [50] demonstrated that S1 in humans contains a predominantly contralateral somatotopic representation of the body. Based on this somatotopic arrangement, our findings seem to be counterintuitive, as we hypothesized to find structural correlates in stimulated S1 regions (i.e., upper limb). One possible explanation for our findings is that they simply reflect general thermal/pain sensitivity, because individuals with a high or low sensitivity at one specific body site are likely to show greater or decreased sensitivity in other regions of the body. Another possibility is that the ventrolateral S1 finding is related to sensory representation of the face [11,45], which is thought to have special biological, emotional, and psychological importance [61]. Finally, previous brain imaging studies are in line with our findings. Some studies found that noxious stimulation induces predominantly functional activations and increases in cerebral blood flow (CBF) in contralateral pain-related cortical areas [1], whereas some studies also found reduced CBF in S1 [2], and particularly in regions that do not contribute to the stimulated body region. For example, reduced CBF has been observed in ipsilateral S1 [52] or in both contralateral and ipsilateral S1 to nonstimulated areas, that is, the leg and face representation of S1 in case of hand stimulation [19]. Because this CBF reduction was observed even without an actual noxious stimulation, this decreased synaptic activity is thought to reflect pain anticipation and/or increased attention toward the stimulus site [19]. In line with these findings, our correlative findings between cortical thickness and thermosensitivity are distributed over a network of bilateral brain regions. Additionally, the stimulation of the forearm in our subjects resulted in structural correlates in face and upper and lower limb somatotopic representations of S1, suggesting that S1 may play a role in pain anticipation and that S1 may be able to enhance the contrast between stimulated and nonstimulated regions, thereby facilitating sensory detection.

Our correlation analysis also revealed that greater sensitivity to warm stimulus detection was associated with a thinner cortex in the aMCC. Experimental studies have repeatedly shown that the aMCC is critically involved in many general functions, not specific to pain, including negative affect and cognitive control [62]. For instance, the MCC has been implicated in salience detection, given its response characteristics to innocuous [16,17,59] and noxious stimulation [18,29]. In addition, Peyron et al. [52] found that acute pain increased CBF in MCC in healthy volunteers. Although many human imaging studies found activation of the cingulate cortex during experimental pain [1], it seems that the cingulate cortex does not have nociceptive-specific regions [69]. For example, nociceptive neurons in the cingulate cortex have large receptive fields, some extending across the whole body surface [63,73]. In monkeys, neurons in the cingulate cortex were activated in anticipation and in response to aversive stimuli and nocifensive behaviour [35,36], providing evidence that the cingulate cortex is involved in the affective-motivational and behavioural dimensions of pain. Functionally, innocuous thermal stimuli have affective components such as feelings of pleasantness and unpleasantness, and these may be useful for survival. Accordingly, innocuous warm stimuli provide pleasant sensations [57], and thus a thinning in aMCC may be related to the detection of nonpainful stimuli, thereby providing a motivational basis for an individual to actively seek a pleasant stimulus.

Interestingly, we found that greater sensitivity to painful heat stimuli correlates with thicker cortex in the right OFC and in the left pMCC. The OFC is implicated in emotional evaluation, decision-making based on the valence of perceived stimuli [57], cognitive

reappraisal [37,54], and in particular in evaluating punishment [46]. The OFC is also thought to participate in generating goal-directed behavioural responses based on prior cognitive evaluations [28,72]. Therefore, our findings suggest that less sensitive subjects may have more effective stimulus evaluation skills and may have more resources to cope with the thermal stimuli than highly sensitive subjects. The pMCC is frequently activated during acute pain [1]. In monkeys, Dum et al. [20] demonstrated that the pMCC contains neurons that respond specifically to nociceptive input from subcortical brain regions, which supposedly underlies pMCC activations during noxious thermal stimulation [69]. Contrary to more anterior parts of the cingulate cortex, the pMCC could not be linked to regulation of primary emotions, such as sadness or fear [69,70]. Based on these findings, we can conclude that pMCC is predominantly implicated in early nocifensive behaviour [69]. Thus, the positive correlation between higher sensitivity to noxious heat stimuli and cortical thickness in pMCC supports evidence that pMCC is responsible for detecting and processing nociceptive input.

Our psychophysical results demonstrate that there is substantial between-subject variability in temperature and pain sensitivity. Previous psychophysical studies reported large ranges of perceptual differences between healthy individuals [27,39,47,71]. Rolke et al. [56] found a similar interindividual variability, as thermal pain thresholds in their 180 healthy volunteers resulted in very large 95% confidence intervals. Consequently, CP thresholds of 29°C and HP thresholds of 37°C must be considered within the normal range. Our data corroborate these findings by demonstrating substantial behavioural variability in our subjects, especially for pain thresholds (i.e., 28°C range for CP and 11.4°C range for HP; Figs. 4 and 5). The significance of studying interindividual differences arises from studies that demonstrate that increased sensitivity to pain may be a risk factor for developing chronic pain later in life. For example, Staud et al. [65] showed that fibromyalgia patients had altered basal pain sensitivity and increased perceptual wind-up pain. This finding is further supported by other research that indicates that chronic pain states are associated with increased sensitivity to experimental pain [5,26,51]. Mechanisms that potentially contribute to individual differences in pain sensitivity include genetic, psychological, and environmental factors [8,48]. Our study reveals that in addition to these proposed mechanisms, the structural brain morphology in specific cortical pain-related regions may also contribute to individual differences in temperature and pain sensitivity.

In conclusion, our findings demonstrate that interindividual differences in temperature and pain sensitivity are correlated with cortical gray matter thickness differences in brain regions that are associated with sensory perception, sensorimotor integration, pain modulation, and affective and cognitive control.

## Conflict of interest statement

The authors have no conflicts of interest to disclose.

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