Cortical Thickness and Pain Sensitivity in Zen Meditators

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Zen meditation has been associated with low sensitivity on both the affective and the sensory dimensions of pain. Given reports of gray matter differences in meditators as well as between chronic pain patients and controls, the present study investigated whether differences in brain morphometry are associated with the low pain sensitivity observed in Zen practitioners. Structural MRI scans were performed and the temperature required to produce moderate pain was assessed in 17 meditators and 18 controls. Meditators had significantly lower pain sensitivity than controls. Assessed across all subjects, lower pain sensitivity was associated with thicker cortex in affective, pain-related brain regions including the anterior cingulate cortex, bilateral parahippocampal gyrus and anterior insula. Comparing groups, meditators were found to have thicker cortex in the dorsal anterior cingulate and bilaterally in secondary somatosensory cortex. More years of meditation experience was associated with thicker gray matter in the anterior cingulate, and hours of experience predicted more gray matter bilaterally in the lower leg area of the primary somatosensory cortex as well as the hand area in the right hemisphere. Results generally suggest that pain sensitivity is related to cortical thickness in pain-related brain regions and that the lower sensitivity observed in meditators may be the product of alterations to brain morphometry from long-term practice.

Keywords: pain, meditation, Zen, mindfulness, cortical thickness

Research on meditation and meditation-related techniques often emphasizes the positive influence of such practices on affective processing (Creswell, Way, Eisenberger, & Lieberman, 2007; Nielsen & Kaszniak, 2006). The cultivation of a state of equanimity toward one's experience, the goal of many meditative practices, is traditionally viewed as vitally important to a healthy mind (Thanissaro, 2000). This Buddhist concept, more generally referred to as *mindfulness*, has been shown to influence a great number of indices, including those measuring depression (Ma & Teasdale, 2004), anxiety (Kabat-Zinn et al., 1992), immune function (Davidson et al., 2003), and pain (Grant & Rainville, 2009; Grossman, Tiefenthaler-Gilmer, Raysz, & Kesper, 2007; Kabat-Zinn, 1982; Kabat-Zinn, Lipworth, & Burney, 1985; Kabat-Zinn, Lipworth, Burney, & Sellers, 1987; McCracken, Gauntlett-Gilbert, & Vowles, 2007).

Consistent with an influence on affective processing, meditation has been found to have a positive impact on chronic pain patients (Grossman et al., 2007; Kabat-Zinn, 1982; Kabat-Zinn et al., 1985; Kabat-Zinn et al., 1987; McCracken et al., 2007). Over the course of 5 years, Kabat-Zinn reported on a group of 225 chronic pain patients who had completed the Mindfulness-Based Stress Reduction (MBSR) program (Kabat-Zinn, 1982, 1985, 1987). Follow-up evaluation at 4 years showed stable improvement on most measures, with the exception of pain intensity. This led the authors to conclude that MBSR teaches an effective coping strategy for pain, whereby the physical sensation of pain remains unchanged, but the patients' emotional reaction toward or even acceptance of the pain is positively altered. The MBSR program has since been used effectively to treat many different chronic pain conditions (Grossman et al., 2007; McCracken et al., 2007) and also appears to increase tolerance to the cold pressor test in healthy subjects (Kingston, Chadwick, Meron, & Skinner, 2007). In addition, improvements specifically in pain acceptance have been reported in

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low-back pain patients following an 8-week meditation program (Morone, Greco, & Weiner, 2007).

More recently, one study has challenged the view that meditation solely influences the affective dimension of pain. Studying healthy individuals with previous training in Zen meditation, we found comparable effects of practice on the affective and sensory aspects of pain (Grant & Rainville, 2009). During exposure to moderate pain, meditators were found to modulate both the unpleasantness and intensity of the stimulation more than controls during a mindful attention condition, and this effect was positively correlated with their experience. Furthermore, the practitioners had significantly lower baseline heat-pain sensitivity than nonmeditating control subjects. Higher trait mindfulness in meditators, coupled with slower respiratory rates that predicted meditative analgesia, suggested that training-related cognitive, affective, or autonomic self-regulation may underlie the observed effects. An additional possibility, stemming from previous work (Hölzel et al., 2008; Lazar et al., 2005; Pagnoni & Cekic, 2007; Vestergaard-Poulsen et al., 2009), is that meditation practice influences the structural organization of the brain in pain-related pathways.

The neural networks underlying the affective and sensorydiscriminative aspects of pain are dissociable (Hofbauer, Rainville, Duncan, & Bushnell, 2001; Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Whereas the lateral thalamus and primary somatosensory cortex (SI) are associated with sensory aspects of noxious processing, the anterior cingulate and insular cortices have been repeatedly associated with the emotional response to pain (Apkarian, Bushnell, Treede, & Zubieta, 2005). Furthermore, the hippocampus has been proposed to mediate emotional and avoidance responses to noxious stimuli (Melzack & Casey, 1967), a suggestion supported by functional MRI (fMRI) studies, which have shown differential hippocampal activation dependant on the anticipated level of pain intensity (Ploghaus et al., 2001). Over the past few years, it has also become evident that a substantial amount of plasticity can occur within the nociceptive pathways. For example, many chronic pain conditions have now been associated with more or less gray matter in pain-related regions (May, 2008). This is consistent with the notion that long-term changes in pain are associated with specific modifications in gray matter, reflecting altered neural processing of nociceptive signals. A similar observation has recently been made in healthy individuals.

In a longitudinal study examining the effect of repeated noxious stimulation on pain sensitivity and gray matter density, Teutsch et al. (2008) found rather surprising results. Receiving 20 min of painful thermal stimulation per day, healthy subjects exhibited reduced pain sensitivity over the course of 8 days. Pain intensity ratings were decreased and pain thresholds increased. This is consistent with a previous study from our lab (Gallez, Albanese, Rainville, & Duncan, 2005) demonstrating spatially specific, reduced pain sensitivity following repeated nociceptive stimulation. In a comparison of gray matter between baseline and Day 8, Teutsch et al. found increased density in pain-processing regions, including those with sensory-discriminative functions such as SI and those involved in pain affect, including the midanterior cingulate cortex. It is important to note that the location of gray matter increase within SI corresponded precisely to the somatotopic region representing the stimulated forearm. This implies that people who repeatedly engage in activities in daily life that involve pain may also have increases in gray matter in somatotopically relevant areas. Considering the fact that meditation is often a painprovoking exercise because of the cross-legged posture, it is possible that a similar phenomenon underlies the lower pain sensitivity previously observed in Zen meditators (Grant & Rainville, 2009). Indeed, morphometric studies have reported trainingrelated differences in gray matter in meditators, compared with nonmeditating control subjects, in regions implicated in pain processing such as the right anterior insula and SI in the vicinity of the leg (Hölzel et al., 2008; Lazar et al., 2005).

In the current study, we sought to determine whether structural differences in the brains of meditators underlie previously observed pain sensitivity differences (Grant & Rainville, 2009). Because meditation is commonly viewed as an emotionally transformative practice (Creswell et al., 2007; Nielsen & Kaszniak, 2006) that has been proposed to underlie the benefit that mindfulness training bestows on chronic pain patients (Kabat-Zinn et al., 1985), one possible outcome of this study is gray matter differences between groups in emotion-related brain regions, which are also known to be involved in pain processing. However, our previous work has shown comparable and even stronger effects of Zen meditation on sensory aspects of pain (Grant & Rainville, 2009). Given that the posture adopted during prolonged meditative practice can be painful and that repeated exposure to noxious stimuli leads to lower pain sensitivity and somatotopically organized gray matter increases (Teutsch et al., 2008), we also explored whether low pain sensitivity in Zen meditators might be associated with gray matter differences in sensory-discriminative cortical regions. To address these possibilities, we acquired high-resolution structural MRI scans from a group of Zen meditators and age- and gender-matched control subjects. Thermal pain sensitivity was assessed and regressed against the thickness of the gray matter across the cortical mantel. On the basis of our previous work with an overlapping sample, we expected that Zen practitioners would exhibit lower pain sensitivity. We hypothesized that lower pain sensitivity would be associated with thicker cortex in sensory and affective pain-processing regions. Lastly, we explored the possibility that differences observed between groups may be related to meditation training by testing the correlation between cortical thickness and time spent meditating. However, note that although training-related effects would be expected to produce significant correlations, such a finding in the present cross-sectional study would not be sufficient to infer causality or rule out the possibility that effects may reflect preexisting individual differences associated with the propensity for meditation.

Method

Participants

The recruitment process involved visits to meditation centers as well as advertisements in local newspapers and online classifieds inviting participants to a study investigating the cognitive modulation of pain. Exclusion criteria included current medication use, history of chronic pain, neurological or psychological illness, claustrophobia, and for control participants, previous experience with meditation or yoga. A list of possible meditators was first compiled (N = 68), consisting of individuals who spanned a large range of experience and meditative traditions. The largest possible sample controlling for homogeneity of training and meeting the

arbitrary requirement of 1,000 hr of experience consisted of 19 Zen practitioners (15 men; see Table 1). Zen is considered to be a meditative tradition emphasizing mindfulness (Deikman, 1982; Goleman, 1997). Meditators from other disciplines were not tested. Twenty control subjects (15 men), matched precisely for age and gender, with no previous experience with meditation or yoga, were subsequently recruited. Two meditators and two controls did not undergo thermal pain sensitivity testing, bringing the sample for that analysis to 35 (17 meditators and 18 controls). Experiments were conducted between September 2006 and October 2007 at the Centre de recherche de l'Institut universitaire de gériatrie de Montréal. All procedures were approved by the local ethics committee (CMER-RNQ 05–06-020). All participants provided written informed consent and received a monetary compensation.

Meditation Experience Questionnaire

Participants completed a questionnaire designed to assess various aspects of their meditative history, including type of practice, number of years practicing, frequency and length of practice in days per week, length of individual sessions in hours, amount of time spent in retreat, and motivation for practicing. Using Cook's Distance and Central Leverage values, we classified a single subject as an outlier in terms of hours of experience with ~45,000 hr compared with the next closest at ~10,000 hr and removed that subject from correlations involving hours of lifetime practice. Control subjects had previously been screened for meditation or yoga experience and thus did not complete this questionnaire. The Five Factor Mindfulness Questionnaire (Baer et al., 2008) was also completed by all participants, but effects related to the five dimensions assessed in this scale will be described in a follow-up report.

Thermal Pain Sensitivity

Thermal stimulation was produced by a computer-controlled Peltier thermode with a 9-cm² contact probe (TSA NeuroSensory Analyzer; Medoc Ltd. Advanced Medical System, Ramat Yishai, Israel). The temperature required to elicit moderate pain was determined in each individual using the ascending method of limits. Each stimulation consisted of a 2-s ascending ramp from 34 °C, a 4-s plateau at the target temperature, followed by a 2-s descending ramp back to 34 °C. Discrete trials began at a target temperature of 42 °C and increased in 1-°C increments to a maximum of 53.0 °C if tolerated. All stimuli were applied to the inner surface of the left calf. The moderate-pain level was defined

 Table 1

 Description of Subjects, Moderate-Pain Level, and Meditation Training

as the temperature required to elicit a pain rating of 6–7 on an 11-point scale on which 0 corresponded to *no pain* and 10 to *extremely painful*. These subject-specific temperatures provided the pain sensitivity index used in the morphometric analyses.

MRI and Cortical Thickness Measurements

Brain images were acquired on a 3 Tesla (T) Siemens Trio (Siemens, Erlangen, Germany). Each participant underwent a high-resolution T-1 weighted structural MRI scan (3D MP-RAGE; TR = 2,300 ms, TE = 2.94 ms, flip angle = 9°, FOV = 256×240 mm, in plane resolution = 1×1 mm, measurement = 1).

Cortical thickness processing and measurements were carried out using an automated analyses pipeline developed at the Montréal Neurological Institute (Lerch & Evans, 2005). Anatomical MRIs were linearly registered and transformed into a common stereotactic space and were corrected for nonuniformity artifacts (Collins, Neelin, Peters, & Evans, 1994; Sled, Zijdenbos, & Evans, 1998). The processed MRIs were then segmented according to their physiological classification (gray matter, white matter, cerebrospinal fluid; Zijdenbos, Forghani, & Evans, 2002). To produce the surfaces of gray and white matter, we applied the constrained Laplacian anatomic segmentation using proximities method (Kim et al., 2005). The white matter surfaces were expanded out to the gray matter-cerebrospinal fluid surface boundary using a surface deformation algorithm (MacDonald, Kabani, Avis, & Evans, 2000). This procedure is ideal for comparison of the two surfaces in that it permits close matching of gray and white matter boundaries. In turn, cortical thickness can be calculated on the basis of the distance between the surfaces. Lastly, individual cortical thickness data were smoothed following surface curvature using a blurring kernel of 20 mm. This technique allows for the identification of cortical thickness changes among the population.

Statistical Analysis

Group differences for the moderate-pain level were assessed with an independent-sample *t* test using SPSS software. About half of the participants of the present study had also participated in our previous psychophysical study (Grant & Rainville, 2009). This between-subjects factor (new vs. returning participants) was included in a two-way analysis of variance (ANOVA) to verify the stability of the meditation-related effect. The test–retest reliability of the individual moderate-pain level was also tested in the returning participants using Pearson correlation. Statistical analysis of

Variable	Meditators n = 19 (15 men)			Controls n = 20 (15 men)		
	М	SD	Range	М	SD	Range
Age (years)	37.6	10.9	22–57	37.5	10.5	21-55
Moderate-pain level (°C) $(n = 35)^*$	50.1	2.3	47–53	48.1	1.0	47-50
Meditation experience $(n = 19)$						
Hours	6,404	8,522	1,229-45,000	_	_	_
Years	14.4	8.39	2-30	—		

* Significant group effect, p < .01.

cortical thickness was performed using SurfStat (Worsley et al., 2009) at individual points on the cortical surface (vertices) using a general linear model controlling for age. Main effects of group (meditators vs. nonmeditators) and pain sensitivity (regression of moderate-pain level with cortical thickness in the entire sample) were computed as well as the interaction between group and pain sensitivity. Lastly, cortical thickness was regressed against hours and years of meditation experience in Zen practitioners. These effects are reported as partial Pearson correlations (i.e., the contribution of the variable after removing the effect of age).

Stemming from our a priori hypotheses, we performed a directed search within pain-related regions of interest (ROIs). Painrelated ROIs were created from a probabilistic meta-analysis of 122 fMRI and positron emission tomography studies (Duerden, Fu, Rainville, & Duncan, 2008) developed using the activation likelihood estimate (ALE) method (Laird et al., 2005). Studies included in the meta-analysis involved the application of a variety of experimental painful stimulus applied to the skin, muscle, or viscera. Brain activation coordinates were converted into standardized stereotactic space and ALE maps were created using a blurring kernel of 8 mm. Regions with the highest probabilistic values across all pain conditions were used as ROIs including bilateral insular cortices, the primary (SI) and secondary (SII) somatosensory cortices, the dorsal anterior cingulate cortex (dACC), and the prefrontal cortex including right Brodmann area (BA) 10/46, and left BA10. Given the hypothesis that reduced emotional reactivity may underlie the pain sensitivity differences previously observed in Zen practitioners, we included an additional ROI based on the coordinates of the peak activation previously associated with painrelated anxiety in the hippocampal formation (HF; Ploghaus et al., 2001). Finally, an ROI (10-mm radius) was created manually, centered over the lower leg representation of SI (i.e., posterior part of the paracentral lobule). The rationale for testing this ROI was that the posture assumed during Zen meditation involves sitting cross-legged. This posture can create considerable pain and numbness with extended periods of practice that may lead to structural changes in the brain.

A two-stage process was used to analyze the cortical thickness data testing our a priori hypotheses. First, significance was tested using small-volume correction based on the number of vertices across all defined ROIs. The second approach involved averaging the thickness values at each vertex within each ROI separately and regressing that value against the variables of interest (i.e., pain sensitivity and meditation experience). All statistical analyses controlled for the age of the subjects. Lastly, a whole brain analysis was conducted for each assessment, cluster corrected for multiple comparisons using random field theory and thresholded at p < .05 (Worsley et al., 1996).

Results

Pain Sensitivity

A significant group difference was found for thermal pain sensitivity, t(35) = 3.34, p = .002. To experience moderate pain, meditators required on average 50.1 °C and control subjects 48.1 °C. It should be noted that approximately half of these participants (49%) also participated in our previous study (Grant & Rainville, 2009), and thus this result should not be considered a completely independent replication of our previous results. A two-way

ANOVA comparing new and returning participants as well as groups (meditators vs. controls) confirmed that new subjects did not differ from the returning subjects: main effect new or returning, F(1, 34) = 0.001, p = .978; main effect group, F(1, 34) = 10.82, p = .003; interaction, F(1, 34) = 0.85, p = .36. Furthermore, in the 17 subjects to return (9 meditators and 8 controls), the test-retest analysis showed that moderate-pain levels were consistent across time (test-retest: r = .76, p < .001). Pain sensitivity, as measured by the moderate-pain level, was not associated with meditation experience (years: r = -.24, p = .35; hours: r = -.24, p = .36).

Group Differences in Cortical Thickness

The ROI analysis revealed that meditators had thicker gray matter than control subjects in several regions known to be involved in pain processing (see Table 2A and Figure 1). Regions included the right dACC (BA24) and SII bilaterally. The dACC was also significant in the whole brain search, but no additional regions were found outside the pain mask. No areas exhibited greater gray matter thickness in control subjects.

Pain Sensitivity Correlations With Cortical Thickness

The temperature required for each subject to report moderate pain was first regressed against cortical thickness for the entire sample. Several pain-related areas showed thicker cortex associated with lower pain sensitivity, that is, a higher moderate-pain level (Table 2B and Figure 2). These areas included the right dACC, HF, SII, and insular cortices. No regions were found where thicker cortex was associated with higher pain sensitivity. At the global search level (whole brain), no additional areas were found, but the HF survived this more strict statistical criterion. The interaction with group revealed that the relationship between cortical thickness and pain sensitivity (i.e., the direction and magnitude of the slope) did not differ between groups even though the meditators had significantly thicker cortex than controls in some areas (ACC and SII). This suggests there is a general relationship between cortical thickness and pain sensitivity, with meditators and controls at opposite ends of the distribution.

Correlation Between Meditation Experience and Cortical Thickness

A correlation between the hours of meditation practice and cortical thickness was seen in the lower leg representation of SI bilaterally (see Table 3A and Figures 3A and 3B), such that more hours of experience were associated with thicker cortex. A similar analysis, using years of meditative experience, revealed that bilateral dACC was also related to cortical thickness in Zen meditators (see Table 3B and Figures 3C and 3D). In each case, more hours of experience were associated with thicker cortex. The same relationship was found in the right hemisphere SI ROI, derived from the pain mask, near the hand representation. This later SI effect was also significant at the global search level, but no other regions, outside the pain mask, were found.

Discussion

Pain Sensitivity

The potential influence of Zen meditative practice on cortical thickness was investigated to probe the mechanisms underlying the

Brain region (BA)	Side	X Y Z MNI space	Vertex-wise <i>t</i> , <i>p</i> : corrected	Average thickness <i>t</i> , <i>p</i> : uncorrected
A. Group difference $(N = 39, df = 37)$				
Anterior cingulate (24)	R	4, 16, 29	$4.14. < .01^{a}$	1.99, <.05
5	L	-8, 0, 42	1.90 ns	0.59 ns
Operculum SII (40/43)	R	57, -25, 25	3.79, <.05	2.58, <.01
	L	-52, -27, 19	2.20 ns	1.93, <.05
Insula (13/14)	R	39, 6, -9	1.93 ns	1.01 ns
	L	-37, 12, -6	2.55 ns	0.54 ns
Parahippocampal gyrus (28)	R	20, -20, -8	2.42 ns	$0.17 \ ns^{\rm b}$
	L	-21, -37, -12	1.54 <i>ns</i>	
Primary somatosensory (1-3)	R	30, -26, 62	1.36 ns	$0.10 \ ns^{b}$
	L	-33, -26, 61	0.60 ns	
Frontal (10/46)	R	47, 42, 0	2.31 ns	1.40 ns
	L	-31, 54, 12	0.88 ns	-0.08 ns
B. Pain sensitivity ($N = 35$, $df = 34$)				
Anterior cingulate (24)	R	4, 12, 27	3.53, <.05	1.51 ns
	L	-3, 2, 37	1.33 ns	0.42 ns
Operculum (52)	R	51, -27, 25	3.37, <.05	2.93, <.01
	L	-40, -24, 20	1.85 ns	1.39 ns
Insula (13/14)	R	51, 2, 6	3.57, <.05	2.49, <.01
	L	-37, 12, -7	2.53 ns	0.48 ns
Parahippocampal gyrus (28)	R	20, -3, -11	4.94, <.001 ^a	$2.60, <.01^{b}$
	L	-21, -36, -13	2.93 ns	
Primary somatosensory (1-3)	R	20, -36, 71	1.54 <i>ns</i>	0.07 <i>ns</i> ^b
	L	-39, -34, 46	0.37 ns	
Frontal (10/46)	R	44, 45, 0	1.95 ns	0.87 <i>ns</i>
	L	-31, 54, 12	0.83 ns	-0.23 ns

Table 2Significant Effects of Cortical Thickness

Note. BA = Brodmann area; R = right; L = left; SII = secondary somatosensory cortex; MNI = Montreal Neurological Institute.

^a The result was significant at the whole brain level. ^b For the average thickness analysis, the region of interest was a single unit spanning both hemispheres.

low pain sensitivity previously observed in these individuals (Grant & Rainville, 2009). With an increased sample size, it was again found that Zen practitioners were less sensitive to thermal pain than control subjects, requiring on average 50 °C versus 48 °C to report moderate pain. This difference is an underestimate as five of 17 meditators tested for moderate pain reached the maximum temperature (53 °C) permitted for stimulation. In contrast, only two of 18 control subjects surpassed 50 °C. Thus, a ceiling effect prevented the true extent of the difference from being measured. Nonetheless, this difference corresponds to an increase of \sim 50%

on a ratio scale of pain perception or 20–25 points on a 0–100 numerical pain scale (Price & Harkins, 1987; Price, McGrath, & Rafii, 1983) and should be considered large.

Emotion-Related Effects

The first hypothesis was that the cortical thickness of brain areas involved in emotion processing, as well as the affective dimension of pain, would be related to pain sensitivity. Overall, considering the entire sample, sensitivity was inversely related to cortical



Figure 1. Meditators have thicker cortex in pain-related regions. A. Thickness values at the peak of the anterior cingulate region of interest (ROI). B. Medial and lateral views of the right hemisphere with *t*-statistic maps projected on an averaged brain revealing areas of statistically different cortical thickness between meditators and nonmeditators. ROIs are traced in white and appear brighter for illustrative purposes. Peak coordinates and statistical values are reported in Table 2A. All effects are adjusted for age.





Figure 2. Thicker cortex is associated with lower pain sensitivity. A. Positive correlation between cortical thickness, at the peak of the parahippocampal gyrus region of interest (ROI), and the moderate-pain level (pain sensitivity) in degrees Celsius. B. Medial and lateral views of the right hemisphere revealing areas where cortical thickness significantly relates to pain sensitivity (thicker cortex = lower pain sensitivity). ROIs are traced in white and appear brighter for illustrative purposes. Peak coordinates and statistical values are reported in Table 2B. All effects are adjusted for age.

thickness in the right dACC (BA24), right anterior insula (rAI), and bilateral HF. In each case, thicker cortex was associated with lower pain sensitivity (i.e., higher moderate-pain level). Each of these regions is discussed in turn.

In terms of emotion in general, the region of dACC reported in the present study is also activated during emotion induction using film excerpts as well as recall of emotional events, possibly reflecting enhanced focal attention to conscious emotional experience (Lane et al., 1998). Greater cortical thickness in this region may thus enhance one's ability to attend to, or be consciously aware of, emotional states, including pain. This same dACC region is among the most commonly activated areas in functional imaging studies of nociception (Apkarian et al., 2005) and has been specifically linked to mediating the affective dimension of pain (Rainville et al., 1997). If indeed the dACC is a mediator of affective responses to nociceptive input, which is not inconsistent with a role in promoting attention toward conscious emotional states, then more gray matter in this region may be indicative of greater control or efficacy of this mediation, thereby reducing pain sensitivity. In support of this, meditators, whose practice is often considered an emotion-regulation technique (Goleman, 2003; Wallace, 2000), had thicker cortex in this region of the ACC than control subjects. Furthermore, there was a significant positive correlation observed between years of meditation experience and thickness in the dACC such that the most experienced meditators had the most gray matter. Lastly, the dACC has been observed as more active during meditation than during control tasks (Baerentsen, Hartvig, Stodkilde-Jorgensen, & Mammen, 2001; Lazar et al., 2003, reviewed in Cahn & Polich, 2006). Taken together, the present results and previous studies suggest that the dACC may be a cortical site that is engaged in and altered by meditative practice. Changes to this region may lead to enhanced awareness and control of emotional experience, including pain.

Thicker gray matter in rAI was also associated with lower pain sensitivity in the present study. This region has known roles in interoception (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004) and perception of body states underlying emotion (Craig, 2008), and it is almost always activated in functional brain imaging studies of acute pain (Apkarian et al., 2005). Consistent with the proposed role of the dACC above, greater cortical thickness of the rAI may represent heightened awareness of the representation of internal body states. Indeed, Craig (2008) suggests that the rAI and ACC together form the neural basis for conscious emotional awareness. However, unlike the ACC, there was no group difference in gray matter in rAI as reported previously in Vipassana and Buddhist Insight meditators (Hölzel et al., 2005), nor was the correlation with meditation experience significant as it was in those studies. It should be noted, however, that

В

 Table 3
 Significant Correlations Between Cortical Thickness and Meditation Experience

Brain region (BA)	Side	X Y Z MNI space	Vertex-wise <i>t</i> , <i>p</i> : corrected	Average thickness t p: uncorrected
A. Hours $(N = 19, df = 18)$				
Anterior cingulate (24)	R	6, 31, 23	1.90 ns	0.23 ns
<i>B a a b b b b b b b b b b</i>	L	-6, -3, 42	1.95 ns	0.71 <i>ns</i>
Operculum SII (40/43)	R	61, -23, 30	1.94 <i>ns</i>	0.27 ns
I the second	L	-61, -22, 28	1.14 <i>ns</i>	0.25 ns
Insula (13/14)	R	57, 7, 9	2.25 ns	-0.08 ns
	L	-37, -9, 8	1.13 ns	0.47 ns
Parahippocampal gyrus (28)	R	25, -21, -28	1.54 <i>ns</i>	$0.87 ns^{\rm b}$
	L	-17, -21, -7	3.57 ns	
Primary somatosensory (1–3)	R	33, -26, 59	$5.42. < .00^{a}$	$2.25. < .05^{b}$
	L	-36, -22, 58	2.49 ns	
Primary somatosensory $(1-3)$ (lower leg)	R	10, -44, 65	3.67 ns	3.55. <.01
	L	-8, -42, 60	3.30 ns	3.28. <.01
Frontal (10/46)	R	47, 44, -12	1.99 ns	0.30 ns
	L	-40, 52, 7	1.50 ns	0.13 ns
B. Years $(N = 19, df = 18)$				
Anterior cingulate (24)	R	7, 22, 31	2.83 ns	2.01. < .05
	L	-6, -3, 42	2.32 ns	1.82. <.05
Operculum SII (40/43)	R	61, -23, 30	1.89 ns	0.14 <i>ns</i>
-F	L	-57, -14, 15	1.21 ns	0.75 ns
Insula (13/14)	R	39. 79	2.27 ns	1.06 ns
	Ĺ	-37, 9, -4	2.43 ns	1 67 ns
Parahippocampal gyrus (28)	R	30, -20, -28	2.49 ns	$0.23 ns^{b}$
r urumppooumpur gyrus (20)	Ĺ	-21, -31, -5	3.17 ns	0120 110
Primary somatosensory (1–3)	R	34, -23, 59	3.06 ns	$1.22 ns^{b}$
(1 5)	Ĺ	-46, -34 , 45	1.62 ns	1122 110
Primary somatosensory (1–3) (lower leg)	R	11, -42, 60	3.05 ns	2.74. <.01
rinning sommoschooly (1 5) (lower log)	L	-4 -36 62	2.22.ns	1 67 ns
Frontal (10/46)	R	44, 48, -12	2.76 ns	1.20 ns
(-0, -0)	Ĺ	-40, 53, 7	1.30 ns	0.11 ns

Note. BA = Brodmann area; R = right; L = left; SII = secondary somatosensory cortex; MNI = Montreal Neurological Institute.

^a The result was significant at the whole brain level. ^b For the average thickness analysis, the region of interest was a single unit spanning both hemispheres.

previous morphometric studies of meditation (Hölzel et al., 2008; Lazar et al., 2005; Pagnoni & Cekic, 2007; Vestergaard-Poulsen et al., 2009) have substantial methodological differences. Although a recent study comparing cortical thickness and gray matter volume, density, and concentration has reported a fairly high correspondence between these measures (Hutton, Draganski, Ashburner, & Weiskopf, 2009), varying meditative traditions, scanner strengths (Han et al., 2006), and statistical methods limit the expected similarities. Nonetheless, the interpretation of both Hölzel et al. (2008) and Lazar et al. (2005) was that meditation trains one to be highly aware of internal experience and thus engages and increases gray matter in interoceptive cortex. However, contrary to predictions, a recent study of Kundalini and Tibetan meditators failed to find any difference in interoceptive acuity, as measured by heartrate detection, between subjects trained in meditation and nonmeditators (Khalsa et al., 2008). Thus, the nature of the involvement of the anterior insula in meditation is unclear and appears to differ across meditative traditions.

The final emotion-related area where cortical thickness predicted pain sensitivity was the HF. The HF has been shown to mediate the emotional response to aversive painful stimulation such that greater activation accompanies anxiously awaited stimuli compared with identical stimuli without anxiety. This structure has also been found more active, concomitantly with the rAI. Seminowicz and Davis (2006) reported increased activity in the HF, as well as the rAI, in association with higher pain catastrophizing in healthy individuals. Similar to the rAI, there was no group difference between meditators and controls and no correlation with meditation experience in the HF. It is interesting that the study by Hölzel et al. (2008) that reported group differences in rAI between meditators and controls also reported differences in gray matter concentration in the hippocampus, very near to the peak found in the current study. Similarly, they also found no correlation with meditation experience. Thus, the rAI and HF may play a different and more general role in pain sensitivity than the ACC, perhaps related to trait-like emotional reactivity, such as catastrophizing or anxiety, that might be more consistent across meditative traditions.

Taken together, the results in emotion-related brain regions, particularly the dACC, are consistent with the possibility that meditation may lead to reduced pain sensitivity, although we cannot strictly exclude preexisting physiological differences. However, Zazen (i.e., sitting meditation) is not practiced to relieve pain but to promote mental clarity and emotional stability (Austin, 1999); therefore, the relationship of cortical thickness and pain sensitivity may relate more generally to heightened control, aware-



Figure 3. Meditation experience predicts thickness of sensory and emotion regions. A. A positive correlation between hours of lifetime meditation practice and cortical thickness in the right primary somatosensory cortex (SI) leg area. B. Medial and overhead views illustrating areas where cortical thickness significantly relates to meditation experience in hours (more hours = thicker cortex). C. A positive correlation between years of practice and cortical thickness in the right anterior cingulate cortex (ACC). D. Medial view of right hemisphere illustrating the area of ACC where more meditation experience in years is associated with thicker cortex. Peak coordinates and statistical values are reported in Table 3. All effects are adjusted for age including Pearson rs (i.e., partial correlation).

ness, or acceptance of one's emotional state. These may be viewed as skills, and part of the concept of mindfulness (Baer, Smith, Hopkins, Krietemeyer, & Toney, 2006), which are allegedly learned through meditation. Just as physical skills are learned and result in gray matter alterations (Draganski & May, 2008), mental skills acquired through meditation may do the same, although a physiological explanation of these effects is still lacking (see below). There is, however, an alternative interpretation for the relationship between these brain regions and pain sensitivity.

Pain Regulation in the ACC

The dACC is putatively involved in pain inhibition (<u>Rainville</u>, Carrier, Hofbauer, Bushnell, & Duncan, 1999; Zubieta et al., 2001). In this view, thicker cortex in the dACC may influence the potential for inhibitory regulation, with more gray matter allowing greater attenuation, thereby resulting in lower pain sensitivity. Support for this interpretation comes from a recent longitudinal pain study of healthy individuals (<u>Teutsch et al., 2008</u>). Over the course of 8 days, subjects' thermal pain thresholds and tolerance rose in response to repeated noxious stimulation, with a concomitant increase in gray matter density in ACC (BA24). Chronic pain patients, who often exhibit hyperalgesia and allodynia, have also been shown to have less gray matter in BA24 (<u>May, 2008</u>). This loss may influence self-regulatory processes, associated with cognitive and emotional function, thought to modulate lower level nociceptive responses through descending pathways affecting brain stem and spinal activity. These findings are consistent with the notion that long-term changes in pain are associated with specific modifications in brain morphometry, reflecting altered neural processing of nociceptive signals. It is interesting that the rAI also has a role in pain modulation. Jasmin, Rabkin, Granato, Boudah, and Ohara (2003) showed that increasing or decreasing GABA transmission in the rAI leads to analgesia and hyperalgesia, respectively. It should be noted that these two alternatives thicker ACC enhancing attentional control and awareness of emotional states and thicker ACC leading to more pain inhibition—are not necessarily mutually exclusive.

Sensory Effects

The second hypothesis of the study was that cortical thickness in brain regions involved in the sensory aspect of nociceptive processing would correlate with pain sensitivity. A single region, right SII, was inversely correlated with sensitivity such that thicker cortex was associated with a higher moderate-pain level. Group differences were also observed, bilaterally in SII, with meditators having thicker cortex than controls. Although neither region of SII correlated with meditation experience, a rather striking relationship was found in the Zen practitioners bilaterally in SI, in the regions receiving input from the lower legs. The thickness of the gray matter in these regions was strongly correlated with the amount of lifetime hours that the individuals had spent meditating, such that more hours were associated with thicker cortex. This remarkable result offers an interesting comparison with the study mentioned above by Teutsch et al. (2008) in which healthy participants were given 20 min of painful forearm stimulation for 8 consecutive days. In that study, contralateral SI, in the vicinity of the forearm representation, was shown to increase in gray matter density, along with subjects' pain thresholds, over the 8 days. This is consistent with findings in a previous study of healthy subjects, in whom we described a spatially specific decrease in pain sensitivity associated with extended exposure to nociceptive stimuli within the context of psychophysical training over a period of several days (Gallez et al., 2005). At first blush, the relation to meditation may not be apparent until one considers that the practice is notoriously associated with pain in the knees and ankles (Austin, 1999). The observation of thicker gray matter in the lower leg areas of SI in meditators may be due to a phenomenon similar to that observed in the above studies (Gallez et al., 2005; Teutsch et al., 2008). Namely, the brains of meditators may be physically altered because of the sensory input associated with the crosslegged posture. Although an intriguing possibility, this interpretation appears incomplete for two reasons. First, unlike Teutsch et al., thermal pain sensitivity did not correlate specifically with cortical thickness in SI in our study. This implies that if cortical thickness is associated with the painful posture, the effect of this repeated exposure to pain from deep tissue may not be sufficient to explain the reduced sensitivity in cutaneous thermal pain perception. Second, an additional area of the right SI cortex, the sensory hand region, also demonstrated a significant increase in thickness that was correlated with hours of meditation experience; however, the hand is not typically subjected to uncomfortable or painful stimulation during meditation.

A complementary explanation for these results lies once again in the processing of somatosensory signals associated with Zen practice; however, pain may not be the necessary component. An aspect of Zen practice that is not often discussed is walking meditation. Zen practice typically involves sitting meditation (Zazen) interspersed with walking meditations (Kinhin; Austin, 1999). During Kinhin, practitioners turn complete attention to the soles of their feet contacting the ground as they walk in unison around the meditation hall. During Zazen, the hands are held in front of the abdomen and serve as a focal point during the sitting meditation. Thus, an alternative explanation for our results in SI is that the increased awareness of the hands and feet, during meditation practice, may lead to an increase in cortical thickness within the corresponding somatotopic area. Consistent with previous studies showing morphometric changes associated with sensorimotor training (Driemeyer, Boyke, Gaser, Buchel, & May, 2008; Gaser & Schlaug, 2003; Ilg et al., 2008), changes in SI may be driven by the voluntary and repeated attentional allocation to the incoming somatosensory signals rather than, or in addition to, the painfulness of the sensory experience associated with the meditative posture. In support of this, Lazar et al. (2005) found thicker cortex in SI also in the vicinity of the leg area, as well as in auditory cortex, in Buddhist Insight meditators. This suggests that the focused attentional processes involved in meditation may promote morphological changes in the cerebral networks underlying the attended representation.

Physiological Considerations

The specific physiological mechanisms underlying changes in cortical thickness are not well understood and could involve a host of phenomena such as an increase in cell size; neuro-, glio-, angio-, or synaptogenesis; or changes in interstitial fluids (Draganski & May, 2008). Given the short time frame of induced gray matter changes observed in several studies (Driemeyer et al., 2008; May et al., 2007; Teutsch et al., 2008) ranging from 5 to 8 days, it is likely that several of these possibilities can be ruled out. Alterations in axonal architecture have been suggested to underlie transient gray matter increases observed during skill acquisition (Ilg et al., 2008). The present finding of a correlation between the hours spent in meditation and thickness in SI suggests that thickness changes may be retained and continue to increase, at least as practice is sustained in time. This is consistent with studies in musicians (Gaser & Schlaug, 2003) where gray matter density in the SI hand representation was shown to correlate with experience level. Clearly, the brain cannot expand indefinitely, and it should be noted that thickening is likely a very subtle effect. Indeed, in the present study, the meditators as a group had thicker cortex in the leg area than controls, but not significantly. The effect was specifically observed in the correlation with meditative experience. It is not yet clear whether these long-term effects reflect the same underlying mechanisms as the short-term changes.

Limitations

Several limitations of the present study should be raised. First, the cross-sectional nature of the design implies that strong causal claims concerning the effect of meditative training on pain sensitivity or cortical thickness cannot be made. For example, we cannot fully exclude the possibility that confounding factors such as expectancy may contribute to the reduced pain sensitivity in meditators (see the discussion of this possibility in Grant & Rainville, 2009). A recent report further suggests that individual differences in expectation-induced analgesia (placebo) relate at least partly to differences in gray matter density within cortical and subcortical structures also associated with dopamine-related personality traits (Schweinhardt, Seminowicz, Jaeger, Duncan, & Bushnell, 2009). However, with only one possible exception (insula/parietal operculum), the cortical areas found to be associated with these variables did not overlap with those related to meditation or reduced pain sensitivity in the present study (e.g., ACC, HF, and SI; see Tables 2 and 3). Although we cannot exclude all possible confounds, differences in pain sensitivity and cortical thickness reported here do not match those related to expectationrelated factors.

Second, as in our previous study (Grant & Rainville, 2009), stimuli were always applied to the subjects' calves, that is, within the site of somatotopic change in cortical thickness. Consistent with the spatially specific analgesia previously reported following daily exposure to pain (Gallez et al., 2005), it is altogether possible that the lower pain sensitivity observed in Zen practitioners is restricted to regions of the legs from the knees down, reflecting a secondary effect of the posture adopted during Zazen. Future studies will need to address this issue by testing pain sensitivity in meditators in an area not influenced directly by the posture or the attentional focus during meditation. Lastly, although we relied on well-accepted statistical methods to control for Type I error, several effects reported here may be considered relatively small, particularly in the ROI average thickness analysis. This may be due to insufficient power or to the statistical approach, which involved averaging vertices within an ROI. Although this was performed because it is more sensitive to weaker but spatially diffuse patterns, possibly due to individual anatomofunctional variability, averaging larger ROIs (i.e., containing more vertices) also has a greater chance of washing out more localized effects.

Conclusion

The goal of the current study was to attempt to dissociate between an affective transformative explanation for reduced pain sensitivity in Zen meditators and sensory habituation stemming from the often painful posture associated with meditative practice. There is evidence that the posture adopted during Zen meditation may result in cortical thickening in brain regions involved in sensation; however, the involvement of nociceptive input is debatable. Increased attention to the feet and hands, focal points of the meditation technique, may be a more parsimonious explanation. However, regions involved in emotion induction, pain affect, and pain modulation were also significantly thicker in meditators compared with nonmeditators, possibly reflecting increased attentional control or decreased emotional reactivity learned through training. This study suggests that the perceptual and emotional changes often attributed to meditation training-observed here in psychophysical measures of pain sensitivity-are associated with structural brain changes in pain-related cortical areas. This provides evidence in support of the notion that meditation strengthens brain processes involved in emotion as well as pain regulation. Future prospective studies should further clarify how much of those differences can be attributed to meditative training.

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