Dissociable Brain Activation Responses to 5-Hz Electrical Pain Stimulation

A High-field Functional Magnetic Resonance Imaging Study

Michael T. Alkire, M.D.,* Nathan S. White, B.S.,† Raymond Hsieh, M.D.,‡ Richard J. Haier, Ph.D.§

Background: To elucidate neural correlates associated with processing of tonic aching pain, the authors used high-field (3-T) functional magnetic resonance imaging with a blocked parametric study design and characterized regional brain responses to electrical stimulation according to stimulus intensity–response functions.

Methods: Pain was induced in six male volunteers using a 5-Hz electrical stimulus applied to the right index finger. Scanning sequences involved different levels of stimulation corresponding to tingling sensation (P1), mild pain (P2), or high pain (P3). Common effects across subjects were sought using a conjunction analyses approach, as implemented in statistical parametric mapping (SPM-99).

Results: The contralateral posterior/mid insula and contralateral primary somatosensory cortex were most associated with encoding stimulus intensity because they showed a positive linear relation between blood oxygenation level–dependent signal responses and increasing stimulation intensity (P1 < P2 < P3). The contralateral secondary somatosensory cortex demonstrated a response function most consistent with a role in pain intensity encoding because it had no significant response during the innocuous condition (P1) but proportionally increased activity with increasingly painful stimulus intensities (0 < P2 < P3). Finally, a portion of the anterior cingulate cortex (area 24) and supplementary motor area 6 demonstrated a high pain–specific response (P3).

Conclusions: The use of response function modeling, conjunction analysis, and high-field imaging reveals dissociable regional responses to a tonic aching electrical pain. Most specifically, the primary somatosensory cortex and insula seem to encode stimulus intensity information, whereas the secondary somatosensory cortex encodes pain intensity information. The cingulate findings are consistent with its proposed role in processing affective–motivational aspects of pain.

FUNCTIONAL neuroimaging techniques, including positron emission tomography, functional magnetic resonance imaging (fMRI), and magnetoencephalography, have played an important role in elucidating how the human brain processes noxious sensory stimuli.[1–6] Early work using these techniques employed relatively straightforward study designs (*i.e.*, categorical designs) that made inferences on brain function by contrasting state-related (pain *vs.* nonpain) brain activity. These studies, following the analysis approach of cognitive subtraction, have been successful in addressing the neuroanatomy of pain and have helped to develop the concept of the central pain matrix, a network of supraspinal structures involved in processing nociceptive information.[4] However, these studies offered little insight into how the observed changes in brain function relate to the different behavioral aspects of the pain experience, which is viewed as a complex amalgam of sensory–discriminative, affective–motivational, and cognitive–evaluative components.[4]

More recent neuroimaging studies using advanced study designs (*i.e.*, parametric and factorial designs) have started to probe the nature of the complex relations between brain function and the sensory, affective, and cognitive components of the pain experience.[2,7–14] As a recent example, Büchel *et al.*[15] (2002) used a parametric single-trial fMRI study design to investigate differential responses of the anterior cingulate cortex (ACC) to laser-induced pain. Büchel *et al.* characterized the responses of the ACC according to a set of stimulus intensity–response functions (SIRFs) as encoding (1) stimulus intensity, voxels identified where blood oxygen level–dependent (BOLD) signal changes increased linearly with a roughly linear increase in delivered stimulus intensity; (2) pain intensity, voxels identified where BOLD signal intensity was not significantly affected by subpainful stimulation intensities but proportionally increased with painful trials; or (3) stimulus perception, voxels identified where BOLD signals differentiated between the presence and absence of subjective stimulus awareness. Using this novel approach, Büchel *et al.* were able to attribute functional roles to different regions in the ACC with respect to different facets of pain processing. A more recent follow-up study by this group reported findings for the rest of the brain.[16] The newer work showed differential SIRFs related to functional changes of activity in the amygdala, prefrontal, insula, and somatosensory cortex.

Here, we implement analysis methods similar to those used by Büchel *et al.* to investigate stimulus intensity–response functions as they apply to regional activations evident throughout the brain in response to a tonic aching-type of pain. We chose to study specifically the neural correlates of a tonic aching-type of pain because anesthesiologists are often involved with treating such pain perioperatively, and electrical pain well approxi-

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mates the pain of tail clamp (*i.e.,* the stimulus used to determine minimum alveolar concentration values in animal models).[17] Taken together, this background suggests an experimental model of tonic aching electrical pain might have utility for future mechanistic work in humans regarding the effects of anesthesia on pain processing. A quantitative tonic aching pain experience is readily provided by the 5-Hz electrical stimulation delivered from a Neurometer (Neurotron, Incorporated, Baltimore, MD) current perception–testing device. The device can be used in a manual mode to deliver titrated pain stimuli in a manner useful for study in an fMRI experiment. Because we were interested in assessing brain responses associated with processing tonic pain, we specifically used a blocked experimental design, rather than an event-related design. Thus, we combine here a blocked parametric study design and modeling of SIRFs with high-field (3-T) fMRI of a tonic aching 5-Hz electrical stimulus.

Materials and Methods

Subjects

Six healthy right-handed male volunteers participated in this study. Subjects had a mean age of 29.5 ± 6 yr (range, 24–41 yr). The study was approved by the University of California (Irvine, California) institutional review board, and all subjects gave written informed consent. Subjects were recruited from the local college campus and graduate schools and were compensated for their participation.

Experimental Protocol: Electrical Stimulation and Pain Rating

For each subject, two gold cup stimulating electrodes were placed on the right index finger such that the delivered electrical stimulation crossed the distal interphalangeal joint. A conductive gel was used, and the electrodes were held in place with an adhesive strip. Stimulation was delivered using the Neurometer device, which gave a constant AC current (5-Hz sine wave) at predefined intensities. Additional cable wire length was added to the Neurometer cable so that the device could be located in the magnetic resonance imaging control room with the electrodes in place on the subject's finger during scanning.

Before scanning, each subject adjusted the stimulus intensity using the method of ascending limits to correspond with a subjective feeling of (1) tingling sensation, P1; (2) mild pain, P2; or (3) high pain, P3. Subjective ratings were performed using the 0–10 numeric pain distress scale. Subjects were told to adjust the intensity of the pain to provide an experience of 3 out of 10 for the mild-pain condition (P2) and 7 out of 10 for the high-pain condition (P3). Subjects adjusted the nonpain-

ful stimulus (*i.e.,* P1) to a point where a noticeable tingling sensation could be consistently felt over a 30-s time frame. The scale used identified 10 out of 10 as the worst pain imaginable and 0 out of 10 as a tingling sensation. All subjects qualitatively described the 5-Hz stimulation from the Neurometer as a deep aching-type of pain relative to the devices other stimulation settings of 250 and 2,000 Hz. The 250-Hz setting was commonly described as a sharp and poking pins-and-needles type of feeling, whereas the 2,000-Hz setting was described as a more tingling, vibrating, burning sensation.

Imaging Protocol: Experimental Design and Image Acquisition

All subjects underwent eight imaging sequences without repositioning in the scanner (one structural scan followed by seven functional scanning sequences). Data were obtained on a Picker/Philips 3-T scanner (Philips Medical Systems, N.A., Bothell, WA). The structural scan was obtained using a high-resolution three-dimensional spoiled gradient recalled acquisition of steady state sequence (field of view = 240 mm; 256 × 256 in-plane resolution; 2.5-mm axial slice thickness; repetition time = 50 ms; flip angle = 50°). This scan was followed by a series of echo planar image acquisitions to obtain the magnetic field map.[18] The field map is used during postprocessing of the raw data to correct for geometric and intensity distortions in echo planar image scans. Each subsequent functional scanning sequence then acquired 90 volumes (22 contiguous 5-mm-thick axial slices using a gradient echo planar imaging T2*-sensitive sequence; repetition time = 3 s, echo time = 40 ms; flip angle = 90°; 128 × 128 in-plane resolution, field of view = 20 cm).

The first functional scanning sequence for each subject measured the BOLD response to tapping of the right index finger in four 30-s on–off blocks (tapping alternating with rest). This session served only to acclimate the subjects to the echo planar image scanning sequence. During pain imaging sessions, subjects remained motionless, with their eyes closed. Before the start of each pain imaging sequence, subjects verified that the electrical stimulus elicited the appropriate targeted pain level. The subjects were not specifically instructed to attend to the pain stimulation during the functional scanning. Six imaging sequences subsequently followed in the pseudo-random order of P3, P2, P1, P2, P3, and P1. Each sequence consisted of alternating 30-s epochs of rest (R, no stimulation) followed by a 30-s period of continuous 5-Hz electrical stimulation applied to the right index finger, for a total of five rest periods and four stimulation periods per run (stimulus onset asynchrony = 20 scans). The intersession period was kept consistent at 3 min across all subjects.

Image Processing and Statistical Analysis

Image processing and statistical analyses were performed using SPM-99 (Wellcome Department of Imaging Neuroscience, London, United Kingdom).[19] For all subjects, all image volumes were realigned to the first volume of the subject's first imaging sequence, spatially normalized to a standard echo planar image template (*i.e.*, Montreal Neurologic Institute) based on the atlas of Talairach and Tournoux,[20] and were spatially and temporally smoothed with an 8-mm and a 4-s isotropic Gaussian filter, respectively. Because high-field fMRI often induces geometric distortions of the BOLD signal in the temporal lobe and orbital frontal regions (susceptibility artifacts), we only considered brain regions superior to the anterior commissure in the current study (specifically, all axial slices above $z = -4$ mm with respect to standard Montreal Neurologic Institute stereotactic space). The first three image volumes of each session were removed to allow for T1 magnetic saturation effects.

The model regressors (explanatory variables) used to estimate the effects of interest consisted of boxcar stimulus functions (representing the alternate stimulus and rest epochs) convolved with a canonical hemodynamic response function. Specific effects of interest were sought using appropriate linear contrasts of the parameter estimates (regression coefficients of the explanatory variables) and comparing these estimates with the residual error variance of the images. Statistical inferences were made according to Gaussian random field theory.[19] Data were analyzed using conjunction analyses within a fixed-effects model to make inferences about the entire group of subjects.[21] Given the relatively small sample size, the conjunction analysis approach helps to localize and identify regional effects that would likely generalize to a larger sample. In essence, this analysis approach does not seek to reject a single null hypothesis that there is no overall (mean) effect across subjects due to the applied electrical stimulation; rather, it seeks to jointly reject multiple null hypotheses that there are no effects in each subject individually. All the above procedures were performed within the context of the general linear model as implemented in SPM-99.

Stimulus Intensity–Response Functions

To make inferences regarding the functional role played by different brain regions in processing the applied electrical stimuli, a set of *a priori* SIRFs were constructed that closely mirrored those developed by Büchel *et al.*[15] These SIRFs modeled the predicted BOLD responses of brain regions responsible for encoding (1) stimulus intensity, voxels identified where BOLD signal changes increased linearly with a roughly linear increase in delivered stimulus intensity; (2) pain intensity, voxels identified where BOLD signal intensity was not significantly affected by the subpainful stimulation intensity but proportionately increased with the increasing pain of the painful sequences; or (3) high pain–specific responses, voxels identified where a significant BOLD signal increase was observed only during the high-pain condition. Stimulus intensity encoding regions were identified by constructing a contrast whose amplitude was linearly modulated over all the stimulus conditions (P1-P3). Pain intensity–encoding regions were identified using a contrast whose amplitude proportionally increased over the pain conditions (P2, P3) and modeled no contribution coming from the innocuous condition (P1). To ensure that the brain regions identified using this contrast were specific only to the painful conditions, an explicit mask ($P < 0.05$, uncorrected) was used to broadly exclude regions that showed activation during the innocuous trials. High pain–specific encoding regions were identified using a contrast modeling significant differences between the high and mild conditions (P3 > P2). An explicit mask ($P < 0.001$, uncorrected) was also used, which specifically excluded those regions showing any significant effect to linearly increasing stimulus intensity. For all examinations, a significance threshold of $P < 0.05$, corrected, was used, except in the case of the high pain–specific encoding SIRF, where we accepted a P value of 0.001, uncorrected, as significant because of the strong *a priori* expectation that the ACC should be identified with this analysis. Büchel *et al.*[15,16] used an identical *a priori* threshold in their recent reports.

Results

Behavioral Data

The relation between subjective pain rating and stimulus intensity was approximately linear for each subject and across the group of subjects, as shown in figure 1. On average, a tingling sensation rating was associated with a mean ($\pm$ SD) stimulus intensity of 55 $\pm$ 26 mA. The mild- and high-pain ratings were associated with mean stimulus intensities of 103 $\pm$ 60 and 153 $\pm$ 97 mA, respectively. The data are shown plotted across the six subjects after normalizing for baseline differences in current intensity thresholds. An overall analysis of variance revealed a significant effect difference across the three levels of normalized stimulus intensity ($P < 0.001$), with all pairwise comparisons showing significant differences, after Bonferroni correction for multiple comparisons ($P < 0.001$ for all).

fMRI Data

All trials from each subject were modeled as separate regressors (columns) in the design matrix. The SIRF was modeled using the magnitude of the responses (*i.e.*, parameter estimates) plotted against condition type (rating). The conjunction of appropriate linear contrasts
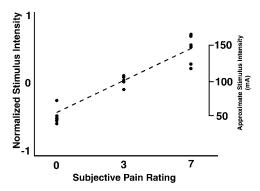
Fig. 1. Relation between subjective pain rating (*x-axis*) and normalized stimulus intensity (*y-axis*). The subjective pain ratings of 0, 3, and 7 correspond to trial types P1, P2, and P3, respectively. For each subject, the stimulus intensity for each trial type was normalized with respect to the overall grand mean (mean over all trials). The ordinate value for any particular *dot* indicates the amount of deviation from this mean. The inserted *y-axis* on the *right* is representative of the average stimulus intensity (in milliamperes) across all six subjects. The mean stimulus intensities across all six subjects were 54.8, 103, and 153.5 for trial types P1, P2, and P3, respectively. The *dotted line* represents the linear regression over all subjects.

allowed us to identify common brain regions (across all subjects) that fit any particular SIRF. The modeled SIRFs are shown in figure 2.

Areas Showing a Stimulus Intensity–related SIRF

Only three brain regions were found with this analysis, as detailed in table 1 and shown in figure 3A. These regions included the contralateral posterior insular cortex, the contralateral secondary somatosensory cortex (SII), and the contralateral primary somatosensory cortex (SI). Noticeably absent from this result are numerous other brain regions, such as the thalamus and the ACC, which have often been associated with central pain processing in multiple previous brain imaging studies.

Areas Showing a Pain Intensity–related SIRF

As shown in figure 3B, the only region that followed this pain intensity SIRF was the contralateral SII cortex. This was the same region of the SII cortex that was previously identified using the stimulus intensity–related SIRF. Whereas this SII region was identified with both SIRFs, close inspection of the BOLD response within this area reveals that its activity fits the SIRF modeling pain

Table 1. Stimulus-evoked Brain Activations

Response Category	Brain Region	MNI Coordinates (x, y, z), mm	Z Score
Stimulus intensity encoding	PI	−40, −20, 12	> 8.0*
	SII	−52, −22, 18	5.67*
	SI	−44, −34, 62	5.10*
Pain intensity encoding	SII	−54, −22, 20	5.83*
High-pain encoding	pACC	2, 12, 32	3.89†
	SMA	4, 10, 68	3.52†

* $P \leq 0.05$, corrected.   † $P \leq 0.001$, uncorrected.

MNI = Montreal Neurological Institute; pACC = posterior anterior cingulate cortex, Brodmann area 24; PI = posterior insula; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; SMA = supplementary motor area, Brodmann area 6.

intensity better than the SIRF modeling stimulus intensity because there was no significant BOLD response during the innocuous condition (P1). Again, noticeably absent from this result are any other brain regions often associated with central processing of pain.

Areas Showing High Pain Intensity–related SIRF

This SIRF shows those brain regions that were activated when the applied stimulus became particularly painful, excluding those regions that increased their activity in response to increasing stimulus intensity. Two regions were found with this analysis, including the anterior portion of the midcingulate cortex and supplementary motor association cortex, as shown in figure 3C and as detailed in table 1. Figure 4 also shows a magnified view of the response in the anterior midcingulate cortex superimposed on the Talairach atlas for better visualization of its anatomic location. The response approaches the posterior edge of the perigenual ACC.

Discussion

The neural correlates of a tonic aching pain, induced with a 5-Hz electrical stimulus, were investigated in humans using high-field (3-T) fMRI. Data were analyzed using SIRFs designed to identify brain regions encoding (1) stimulus intensity information, (2) pain intensity information, and (3) intense pain responses. The results provide strong confirmatory evidence that brain regions neighboring the parietal operculum (*i.e.*, posterior insula
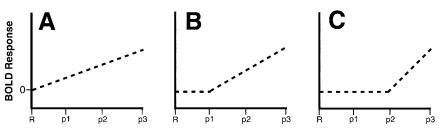

Fig. 2. The stimulus intensity–response functions (SIRFs). The SIRF shown in *A* represents a proportional increase in blood oxygenation level–dependent response with respect to stimulus intensity. Brain regions with this type of response are thought to encode stimulus intensity. The SIRF shown in *B* does not show a response to P1 (*i.e.*, does not differentiate between [R] and P1), but shows a proportional increase over the painful trials (P2, P3). Brain regions with this type of response are thought to encode pain intensity. The SIRF shown in *C* is a step function that does not differentiate between R, P1, and P2, but shows blood oxygen level–dependent (BOLD) response only to P3. This SIRF models brain regions that respond only to high pain (high-pain–specific responses).
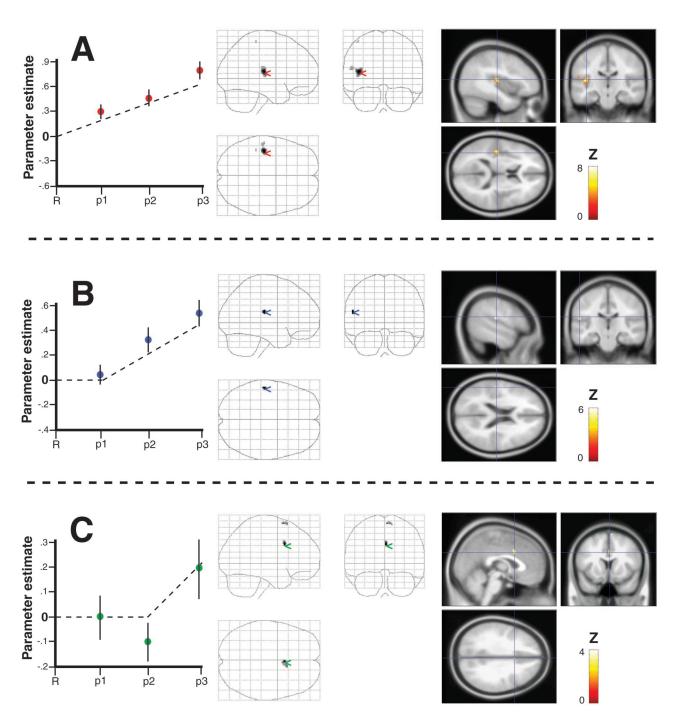
Fig. 3. Statistical parametric mapping results of the modeled stimulus intensity–response functions. The stimulus intensity–response functions (as per fig. 1) are shown in the *first column*, with the *dotted line* representing the modeled response and the *closed circles* representing the measured blood oxygenation level–dependent signal changes (mean ± SEM) for the identified clusters (highlighted with the < symbol). The regional responses are color coded such that *red* = stimulus intensity–related responses (contrast −1, 0, 1); *blue* = pain intensity–related responses (contrast 0, 0.5, 1; masked with 1, 0, 0); and *green* = high pain–specific responses (contrast 0, −1, 1; masked with −1, 0, 1). The *second column* shows the glass brain statistical parametric mapping maximum intensity projection results for the modeled stimulus intensity–response functions (regional cluster coordinates are listed in table 1). Results in the *first* and *second rows* are displayed at $P < 0.05$, corrected for multiple comparisons. The results in the *third row* are displayed at $P < 0.001$, uncorrected. The *third column* shows the regional results displayed on sections of the representative structural magnetic resonance image that was used for normalization. P1 = tingling sensation; P2 = mild pain; P3 = high pain; R = rest.

and SII) as well as SI are important components of the central pain system that are intimately involved with processing the sensory-discriminative aspects of a tonic aching pain. Activity changes within the posterior insula

and SI were found to fit the SIRF modeling stimulus intensity encoding. These regions showed a roughly linear increase in BOLD signal that paralleled the roughly linear increase in the delivered stimulus intensity. In
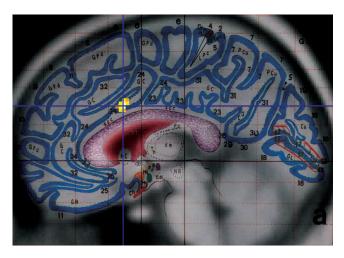
Fig. 4. Regional high pain–specific results (from fig. 3C) projected onto the Talairach atlas. This display clearly localizes this specific functional magnetic resonance imaging conjunction result to the "posterior" anterior cingulate cortex, area 24.[13]

contrast, activity changes within area SII best fit the SIRF modeling pain intensity encoding. The BOLD signal from area SII during the innocuous tingling condition was negligible, whereas the amplitude of this BOLD signal during the painful conditions proportionally increased with respect to the increase in subjective pain intensity. The use of high-field imaging in the current study allowed for better spatial separation of lateral pain pathway system components and made possible the demonstration that a functional distinction in pain processing exists between insular and SII cortical responses. The current findings also support the involvement of the posterior ACC and the supplementary motor association cortex in processing the affective–motivational aspects of an aching pain because only these two regions were identified as being selectively engaged during the high-pain sessions. These findings are discussed more fully below.

Pain Stimulus

There is some evidence that the Neurometer device can selectively activate different pain fibers in both animal and humans.[22-25] The 2,000-Hz stimulation frequency is thought to activate a-β fibers, whereas the 250- and 5-Hz frequencies are thought to primarily activate a-δ and C fibers, respectively.[23] Inui *et al.*[26] developed an intraepidermal electrical stimulation method for use in magnetoencephalographic studies of pain. The stimulation in their study was thought to be specific for A-δ fibers. Their regional magnetoencephalography results map squarely onto SII, in a manner nearly identical to our current fMRI results. This regional overlap in results between studies strongly suggests that 5-Hz electrical stimulation provided by the Neurometer may also have some degree of specificity for activating A-δ fibers. Nevertheless, a direct demonstration of differential peripheral nerve fiber activation by this device, such as that

seen in the work performed on human C-nociceptor activity,[27] remains lacking. Therefore, until the exact capability of this device to activate specific nerve fiber types is established, our results should most cautiously be interpreted as those most likely related to electrical pain stimulation and are not inconsistent with previous fMRI findings using a standard electrical stimulus.[28]

Findings Related to the Sensory Discriminative Aspects of Pain

Much work, encompassing findings from both neuropathology studies and brain imaging studies, supports the idea that the posterior insular cortex and parietal operculum play an important role in the sensory–discriminative aspects of pain processing.[29,30] In one clinical neuropathology study, both pain and tactile processing were disturbed by a brain tumor located in this region, and the associated sensory deficits were reversed with tumor removal.[31] Additional recent study of six patients with lesions involving the parasylvian cortex localized lesion-induced pain sensitivity differences to the parietal operculum and the posterior insula.[32]

The insular cortex receives input from posterior thalamic nuclei and projects to the amygdala and perirhinal cortex. In addition, SII is known to be reciprocally connected with the insular cortex.[33,34] Thus, as noted by Derbyshire *et al.*[2] (1997), "the insula is well situated for the integration of information relating to the affective and reactive components of pain and is included by Gabriel[35] as part of the circuitry related to fear avoidance." The conceptualization of the insula as a bridge between sensory and limbic systems fits well with clinical neuropathology data investigating the syndrome of *asymbolia of pain*. This syndrome, first clinically reported by Schilder and Stengel,[36] is characterized by the ability to recognize pain in a sensory–discriminative manner (*i.e.*, sharp or dull) but with a lack of appropriate motor and emotional responses to a painful stimulation (patients may laugh when a painful stimulus is applied, and they do not physically withdraw from the stimulus). Geschwind[37] proposed that the condition could result from a lesion causing insular damage, which would interrupt connections between SII and the amygdala, a sensory–limbic disconnection syndrome. Berthier *et al.*[38] found strong clinical support for Geschwind's sensory–limbic disconnection proposal in a prospective clinical study of six patients. In the study of Berthier *et al.*, computed tomography data of lesion extent for all six subjects overlapped primarily on the insular cortex.

Recently, activation of SI, SII, and insula in brain imaging pain paradigms has been well documented.[2,6,7,12] However, the functional role played by each of these structures in processing nociceptive information has yet to be fully established. Peyron *et al.*[12] demonstrated in a positron emission tomography study of pain intensity and attentional responses that "only the insular/s so-

matosensory cortices were found to respond whatever the attentional context and might, therefore, subserve the sensory-discriminative dimension of pain (intensity coding)." Coghill *et al.*[7] found in a positron emission tomography study that numerous brain areas, including the insula and SII regions, bilaterally increased activation over a range of stimulation intensities with increasing pain intensity. These previous findings are not inconsistent with our current results because the regions identified here also increased activity over the range of stimulation intensities presented. However, in contrast to these previous studies, our findings can be further segregated because of the increased spatial resolution provided by the high-field magnet and our use of response function modeling. To illustrate further, Timmermann *et al.*,[6] using magnetoencephalography, demonstrated that both SI and SII activation correlated with stimulation intensity, but the two areas differed in their dependence on stimulation parameters. SI activity resembled an exponential function that matched subjects' subjective pain ratings, whereas SII activity showed an S-shaped function with a sharp increase in amplitude only at higher pain intensity stimulations. The patterns of magnetoencephalographic activity found by Timmermann *et al.* and the anatomic locations of their findings are remarkably consistent with the current fMRI results, where both SI and SII were identified with the stimulus intensity–response function, but only the SII activation was found to be best modeled by the more specific pain intensity–encoding SIRF. This suggests neurons in SII may have little or no baseline firing rate related to stimulation intensity, but they are capable of rapidly modulating their firing rates upward as stimulation intensity reaches and surpasses subjective levels of pain. The findings from Bornhovd *et al.*[16] also document similar differences between the response patterns seen in SI and the anterior insula, as compared with those found for SII and the posterior insula. Taken together with our current findings, these imaging and neuropathologic findings help to firmly establish that the insular cortex, SII, and to some extent SI all play a fundamental role in stimulus intensity encoding across a broad range of stimulus intensities, ranging from innocuous to clearly painful stimulation, and thus are likely to be "necessary" components required for the sensory–discriminative processing of aching/throbbing pain.

Findings Related to the Affect-motivation Aspects of Pain

Numerous studies link functional activity of the ACC to pain processing. The ACC is hypothesized to represent a brain region involved with encoding the affective component of pain.[8,9,13,15,39–41] The high pain–specific response found in this study was located in the pACC (fig. 4), in good agreement with recent studies investigating both single-unit activity recorded within this region and

fMRI responses seen at 1.5 T.[13,40,42] Kwan *et al.*[13] conducted a detailed study of the regional activations seen with pain processing in the anterior cingulate and surrounding medial wall areas. They pooled their individual fMRI activations across subjects to create activation maps that best approximated those regions of the ACC associated with the processing of the different pain stimuli studied. Their heat pain–related finding was localized primarily to a small region of the pACC, and our current pACC finding is localized precisely within the borders of their pooled activation map. Our data, based on the statistical conjunction of multisubject activations, show that both procedural methodologies converged toward a remarkably similar endpoint.

In contrast with the findings of Büchel *et al.*[15] (2002), on which our stimulus intensity–response function modeling methodology is based, we did not find any stimulus intensity- or pain intensity–related responses localized to the ACC region. There are numerous differences in methodology between our study and the study of Büchel *et al.* that might explain our failure to find stimulus- and intensity-related effects in the ACC. In addition, these differences in study design apply to the particular findings of Bornhovd *et al.*[16] (2002) as well. We used an electrical stimulus, which may activate more than a single type of pain fiber; they used a laser stimulus, which is likely to be much more specific for only C-fiber activation. We used a boxcar design, with no cognitive expectations placed on the subjects; they used an event-related design that also included rating the stimulus intensity within each trial. Their design emphasized the processing of and the short-term memory components of a very brief pain experience. Our design emphasized what happens in the brain when someone experiences a tonic aching-type of pain. Furthermore, part of the purpose of this work was to identify what brain regions are commonly activated by the stimulus used across the group of subjects studied. We found a statistically reliable convergence of regional effects at high field (3 T), with a sample size of only six subjects, whereas they had nine subjects studied at 1.5 T. Certainly, a larger sample size in this study may have worked to identify other areas of interest, but at the same time, it may have made identification of commonality across the group more difficult. Regardless, given the substantial differences between studies, it would be unwarranted to interpret our lack of finding stimulus or pain intensity–related findings specific to the ACC as a result that is contradictory to the findings of Büchel *et al.* Other work exists that is consistent with our current findings. Peyron *et al.*[12] noted in their intensity and attentional study of pain that "anterior cingulate activity was not found to pertain to the intensity coding network but rather to the attentional neural activity triggered by pain." Furthermore, the Berthier neuropathology data on asymbolia of pain did not reveal any sign of damage to the ACC.[38] Taken

together, these data seem more supportive for a role of the pACC in the sensory–integrative aspect of pain processing, rather than suggesting that the pACC plays a primary role in stimulus or pain intensity–related processing. However, we did not study the effects of increasing pain intensity responses past those causing pain rating of 7 out of 10. This leaves open the possibility that when the ACC comes online (*i.e.*, the pain experience is intense enough), the ACC then regulates its activity upward with further increasing pain intensity.

Conclusion

Here, we used high-field (3-T) fMRI in volunteers to identify brain regions involved in processing pain as induced by 5-Hz electrical stimulation. Conjunction analyses, coupled with stimulus intensity–response function modeling, revealed the insula, SI, and SII are primary sites involved with encoding the sensory–discriminative aspects of a tonic aching/throbbing pain, and the pACC and supplementary motor association cortex sites are involved with encoding the affective–motivational aspects of a tonic aching/throbbing pain.

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