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Coding of Incisional Pain in the Brain

A Functional Magnetic Resonance Imaging Study in Human Volunteers

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ABSTRACT

Introduction: In this study, the activation of different brain areas after an experimental surgical incision was assessed by functional magnetic resonance imaging, and the pathophysiological role of distinct brain activation patterns for pain perception after incision was analyzed.

Methods: Thirty male volunteers (mean age ± SD, 25 ± 5 yr) received an experimental incision (4 mm) within the volar aspect of the right forearm using a ceramic scalper blade, and 14 volunteers (mean age ± SD, 25 ± 4 yr) received a sham procedure. Magnetic resonance images were taken before, during (0–2 min), and after incision or sham procedure (2–4.5, 4.5–10, 24–29, and 44–49 min) at a 3T scanner using a block design. Subjective pain ratings by a numerical pain scale were performed between the scans.

Results: Functional magnetic resonance imaging analysis showed a distinct temporal profile of activity within specific brain regions during and after the injury. Lateralization (predominantly contralateral to the incision) and increased brain activity of the somatosensory cortex, frontal cortex, and limbic system were observed in subjects after incision, when compared with individuals receiving sham procedure. Peak brain activation occurred about 2 min after incision and decreased subsequently. A distinct correlation between evoked pain ratings and brain activity was observed for the anterior cingulate cortex, insular cortex, thalamus, frontal cortex, and somatosensory cortex.

Conclusion: These findings show different and distinct cortical and subcortical activation patterns over a relevant time period after incision. Pain sensitivity hereby has an influence on the activity profile. This may have important implications for encoding ongoing pain after a tissue injury, for example, resting pain in postoperative patients.

What We Already Know about This Topic

- Peripheral and central mechanisms of pain from incision differs from inflammatory or chronic pain
- Brain activation patterns differ with pain type but have not been studied in humans

What This Article Tells Us That Is New

- In normal volunteers, incision of the skin resulted in a distinct temporal pattern of brain activation, which was in many cases correlated with the report of intensity of pain

THERE is increasing evidence for a major role of supraspinal brain mechanisms in the perception and modulation of pain in humans. This is based mainly on experiments using new and improved imaging technologies to understand brain processes, pathways, and networks important for pain in humans.[1,2] Most of the imaging experiments applied a short-lasting painful stimulus noninvasively (*e.g.*, thermal or mechanical stimuli) to the normal skin of healthy volunteers to determine cortical activation patterns relevant for physiologic-nociceptive pain.[3,4] Even though methods and study design differed in these experiments, it has been proposed that a lateral pain system projecting from the ventrobasal nucleus of the thalamus to the primary and secondary somatosensory cortex and insula is involved in discriminative-sensory pain transmission.[3,4] The medial pain system including spinothalamic tract neurons, projecting to the intralaminar and medial thalamic nuclei and further to the cingulate cortex, anterior insula, and frontal cortex, and hippocampus seems to be mainly related to affective-motivational components of pain and cognitive-evaluative aspects of pain processing.[3–6] Similarly, the amygdala, which is interconnected with the anterior cingulate cortex of the medial pain system,[2] plays an important role in cognitive–emotional pain processing and antinociception.[2,5]

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However, more recent functional magnetic resonance imaging (fMRI) studies indicated that nociceptive and clinical pain is encoded differently.[4,7] Clinical pain in contrast to nociceptive pain consists of prolonged, ongoing pain (resting pain) and stimulus-evoked pain (hyperalgesia and allodynia) caused by complex peripheral and central sensitization processes in the spinal cord and brain.[6,7]

To study the role of specific brain areas for perception and modulation of clinical pain, researchers started to perform imaging experiments using standardized human surrogate models for certain pain states such as neuropathic or visceral pain. Stimulus-evoked thermal and mechanical hyperalgesia has been induced by topical application of capsaicin or irradiation with ultraviolet B, and these studies demonstrated that both types of stimulus-evoked pain generate different brain activation patterns.[3,7,8]

Recently, Kawamata *et al.*[9,10] developed a standardized and reliable human model for postoperative incisional pain that parallels the psychophysical characteristics of stimulus-evoked and ongoing pain after surgery. In agreement with several other studies using animal models of postoperative incisional pain, they demonstrated that hypersensitivity caused by an incision is mediated by different mechanisms compared with inflammatory or neuropathic tissue injuries indicating that postoperative pain is a distinct pain paradigm.[8–12] However, little is known so far about cortical processing contributing to the modulation of pain perception after an acute tissue injury in healthy individuals.

Considerable evidence demonstrated different cerebral activation patterns between innocuous and noxious cutaneous stimuli and between different types of pain including visceral and cutaneous pain. In contrast to a nerve injury or inflammation is an incision—a circumscriptive tissue injury with moderate unpleasantness and a distinct duration of pain. Therefore, we hypothesized that a surgical incision primarily activates parts of the sensory-discriminative pain system especially the primary and secondary cortex and the thalamus.

The aim of this study was to adopt the human incisional model of Kawamata *et al.* to assess the role of various brain areas for incision-induced spontaneous nonevoked pain in humans with fMRI.

Materials and Methods

Subjects

Forty-four healthy, male volunteers (mean age ± SD, 25.1 ± 5 yr; right handed) were investigated. All subjects were right handed based on the Edinburgh Handedness Inventory.[13] The volunteers enrolled in this study were free of any preexisting pain syndrome or any current axis I psychiatric diagnosis. Furthermore, they were carefully screened for psychiatric and somatic factors known for altering pain processing such as anxiety or depression.[14] Exclusion criteria for the study were anxiety, somatoform and dissociative, affective, eating, and obsessive-compulsive disorders as well as substance abuse or addiction according to the Composite Diagnostic Interview-Stem Item Screening Questionnaire, a psychiatric screening questionnaire allowing diagnoses according to International Statistical Classification of Diseases and Related Health Problems (ICD-10) and *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, criteria.[15] The Stem Item Screening Questionnaire consists of 16 stem questions from the Composite Diagnostic Interview. All participants signed an informed consent explaining the procedure of the study and the possible risks before testing. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee of the Medical Faculty of the University of Muenster.

Experimental and Imaging Protocol

We used an fMRI-block design with four sessions of image acquisition (sessions 1, 3, and 4: 60 scans = 5 min, session 2: 132 scans = 11 min) and three in between resting periods without scanning (duration: 5 min, 15 min). After the twelfth scan (after 1 min) of session 2, the experimental incision was made. The subjects remained inside the magnetic resonance scanner for the whole time of the experiment (~90 min).

Pain Stimulus and Experimental Pain Ratings. An incision (4 mm long, 5–7 mm deep) was made in the right volar forearm similar to the procedure described by Kawamata *et al.*[9,10] in 30 volunteers. Because the incision was performed during the scans, we used a nonmagnetic No.11 scalpel made of ceramic (SLG-Ceramic, Bernau, Germany) to perform the incision. The blade was pushed into the skin, advanced 5–7 mm through fascia and into muscle tissue and then pulled up from the skin. To avoid any additional stimulation, we decided not to press gauze onto the site of the incision to stop bleeding. Furthermore, 14 volunteers underwent a sham procedure by briefly pressing the handle bar of the scalpel on the skin of the right volar forearm.

Psychophysical Evaluations

Nonevoked Pain. The intensity of this experimental-induced pain was assessed before and after session 1, during incision (subjects were instructed to keep the pain intensity in mind and report it after completion of the scanning session 10 min later), and 10, 20, 30, 40, and 50 min after incision (see fig. 1). Pain was measured eight times during the experiment. Subjects were asked to rate the intensity of nonevoked pain on a numerical rating scale (NRS) ranging from 0 ("no pain") to 100 ("worst pain imaginable").

One investigator stayed in the scanner room during the experiment to perform the incision and to document pain ratings (NRS) and perceived pain qualities (short form of the McGill Pain Questionnaire [SF-MPQ]).

To assess qualitative aspects of pain sensation after incision, the German SF-MPQ was used.[16] The SF-MPQ is based on the full version and has a high degree of consistency. Briefly, a 15-item adjective checklist was rated to the amount of pain being experienced on a 4-point intensity scale (0 =

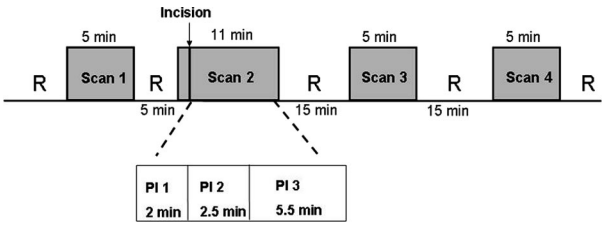

Fig. 1. Experimental block design with single-event stimulus. After the twelfth scan of the second block (after 1 min), the experimental incision was made. For the following analysis of the functional magnetic resonance imaging (fMRI) data, the second block was split into four parts (preincision [1 min], PI = postincisions 1–3). Psychophysical testing for the intensity of the nonevoked pain took place eight times during the course of the experiment. The pain rating during the incision was performed after completion of the second scan (see Methods section for details). Subjects were therefore instructed to memorize their experienced degree of pain during the incision.

"none", 1 = "mild", 2 = "moderate", and 3 = "severe"). The 15 items were split into sensory (11 items) and affective (four items) dimensions of pain providing the best fit to the data.[17]

Analysis. Psychophysical data were analyzed with SPSS 15.0 (SPSS Inc., Chicago, IL). Nonevoked pain ratings were evaluated using Student *t* test or analysis of variance under the assumption of normality and equality of variance (NRS) and Mann–Whitney U test (SF-MPQ) or Kruskal-Wallis test if test for normality failed (Kolmogorow-Smirnow test); *P* values less than 0.05 were considered statistically significant.

Image Acquisition. Magnetic resonance imaging was performed on a 3T scanner (Gyroscan; Philips, Best, Netherlands) using a standard receiver head coil. Before the fMRI datasets, T_1-weighted anatomic spin-echo images (time of repetition = 480 ms, time of echo = 15 ms, flip angle = 90°, matrix dimensions = 256 × 256, field of view = 210 mm, 36 slices) were acquired. For each subject, 312 echo-planar images were obtained (time of repetition = 5 s, time of echo = 35 ms, matrix dimensions = 64 × 64, field of view = 210 mm, 36 oblique slices, pixel size = 3.6 × 3.6 mm, scan time = 1.67 s).

FMRI Data Preprocessing. Statistical parametric mapping (SPM5††), standard routines, and templates were used for preprocessing of fMRI data (realignment, normalization [resulting voxel size 2 × 2 × 2 mm^3], and smoothing [8-mm isotropic Gaussian kernel; high-pass filter cutoff to 160 s]). Each block of image acquisition was defined as a separate session in the realignment procedure.

Blood Oxygenation Level Dependent (BOLD) Cluster Analysis

First-level Analyses. After preprocessing the data, individual data analysis was performed using SPM5. For each participant, preprocessed data were assigned to the following five conditions in the model specification (see fig. 1): session 1 was defined as the baseline condition. Session 2 was split into four parts: the first part (preincision) consisted of the 12 scans (1 min) before the incision; the three following parts (postincisions 1–3) were part of the remaining 120 scans after the incision (24, 30, and 66 scans, respectively); sessions 3 and 4 were spaced by 15 min each The data were globally normalized with the "scaled" option of SPM5 (proportional scaling), because the interruption of the scanning procedure violated the magnetic resonance time series. The motion parameters of the realignment procedure were integrated into the model as regressors to control for false-positive effects caused by head and physiologic motion.

For each of the participants, six BOLD contrast differences (t contrasts) were determined as a function of BOLD signal changes compared with the baseline condition (*preincision, postincision 1*, *postincision 2*, *postincision 3*, *session 3*, and *session 4*) according to the routine procedures implemented in SPM5. These contrasts were entered into the second-level analyses.

Second-level Analyses (within Group). Within group analyses (random effect analysis) were performed for either sham (n = 14) or incision procedure (n = 30) with a one-sided *t* test for each contrast with the NRS score at incision as a cofactor. A correction for multiple comparisons was applied (family-wise error correction, $P = 0.005$ (incision), $T = 7.2$, 10 voxels).

Also, activity differences between different time points were compared to analyze the factor time in more detail (preincision > postincision 1, postincision 1 > postincision 2, postincision 2 > postincision 3) and the reverse contrasts (full-factorial analysis, paired two-tailed *t* tests, uncorrected for multiple comparisons, $P = 0.001$, 10 voxels).

Second-level Analyses (between Groups). To obtain activation maps across subjects representing sham and real incision group during incision and for four contrasts, we designed a two-factorial model with two main factors (analysis of covariance group [sham and incision; two levels] and time [preincision, postincisions 1, 2, and 3; four levels]) in SPM5s "full-factorial option." The NRS scores at incision were added as cofactors in the model to reduce the impact of pain sensitivities on the results (uncorrected for multiple comparisons, $P = 0.001$, 10 voxels). We were interested only in the interaction between both factors ("Group" × "Time") to see whether the temporal activation profile differs between both groups (sham and incision procedure).

Because there was a significant interaction between group and time, this was analyzed further. In *post hoc* analysis, the activation differences between subjects in the sham and incision group were analyzed for each time point (preincision and postincisions 1, 2, and 3) separately (two-tailed *t* test, SPM5, $P = 0.001$ [uncorrected for multiple comparisons], minimum cluster size = 10 voxels; table 1). Individual NRS scores at incision were included in the model as cofactors to reduce the effect of differences in pain perception on results.

In our novel pain model of a single pain event, we assumed a relatively subtle low signal-to-noise ratios of brain activity change to occur as well. We adopted an exploratory approach and used an uncorrected threshold to be able to detect subtle changes in brain activation. To reduce the probability of false-positive results resulting from the uncorrected *P* value, we set a contiguity threshold for cluster volumes of at least 10 voxels.[18]

†† www.fil.ion.ucl.ac.uk/spm. Accessed October 3, 2009.

Table 1. Brain Areas with Increased Activity in Volunteers with Incision Compared with the Sham-operated Subjects

	PI 1: 0–2 min after Incision	PI 2: 2–4.5 min after Incision	PI 3: 4.5–10 min after Incision
Frontal	c BA 10 (−18 58 −4) i BA 10 (30 54 16) c BA 6 (−24 0 46) c BA 9 (−46 32 38) c BA 45 (−52 24 20)	c BA 10 (−18 58 −4) i BA 10 (32 54 14) i BA 8 (14 36 36) c BA 45 (−52 24 14)	c BA 10 (−26 60 −4) i BA 10 (30 56 14) i BA 10 (10 60 0) i BA 8 (14 36 36) i BA 9 (18 44 38) c BA 45 (−42 24 14) i BA 45 (46 20 14)
Limbic	i BA 32 (29 8 40)	i BA 32 (20 8 40) i BA 30 (30 −64 10) c BA 24 (−22 −14 44)	i BA 32 (18 32 24)
Temporal	i BA 39 (34 −52 24)	i BA 39 (34 −52 26)	i BA 39 (34 −52 28)
Parietal	i BA 7 (precuneus) (−18 −68 34) i BA 40 (S II) (50 −34 58)†	i BA 40 (S II) (50 −34 58)*	i BA 7 (precuneus) (−16 −68 40)
Others		c insula (−38 −2 18)	c insula (−38 −2 18) i thalamus (20 −20 −4)

Brain areas of volunteers with an experimental incision (n = 30), which are significantly more activated than volunteers with a sham preparation (n= 14) (second-level analyses [SPM5], two-sample two-tailed *t* test, uncorrected for multiple comparisons, $P = 0.001$, 10 voxels). Visual Analog Scale at incision was added as a cofactor for each subject. With our given threshold, cortical activation with sham preparation was never higher compared with real incision.

* $P = 0.05$, 10 voxels. † $P = 0.01$, 10 voxels.

BA = Brodman area; c = contralateral to incision/sham; i = ipsilateral; PI = postincision.

Anatomical localization of activated brain regions was determined by reference to the standard stereotactic atlas by Talairach and Tournoux.[19]

Second-level Analyses—Correlations. A regression analysis was performed and correlations with NRS during incision and postincisions 1, 2, and 3 each were performed (SPM5, uncorrected for multiple comparisons, $P = 0.001$ [negative correlation] and $P = 0.005$ [positive correlations], threshold 10 voxels), in addition to a correlation between the grade of sensory dimension of pain at t2 (SPM5, uncorrected for multiple comparisons, $P = 0.001$, threshold 10 voxels).

Activation Intensities

BOLD ROI Analysis. Because we expected pain-related differences between both groups in areas of the medial and lateral pain system (cingulate cortex, insular cortex, medial frontal cortex, parietal cortex, thalami, and inferior frontal gyrus[20]) and the amygdale, we performed a region of interest (ROI) analysis for these brain areas. The ROI mask was built with help of the SPM Toolbox "WFU-Pickatlas."[21] Each of the above-mentioned ROI was integrated into the terminal ROI mask and was dilated with the factor 1, so that the mask would not be too inclusive. Mean signal changes were bilaterally assessed during preincision and postincisions 1, 2, and 3 by the tool "Marsbar" in SPM5.

Lateralization effects (paired *t* test) and all other statistical tests were done with the Statistical Package for Social Science (SPSS) V 15.0.

Results

Psychophysical Data

Nonevoked pain intensity (fig. 2) was rated 0 (NRS score 0–100) by all subjects before incision (−17 and −6 min). Nonevoked pain ratings differed significantly for about 30 min with a peak during incision. Mean peri-incisional pain intensity increased to 50.0 ± 4.9 (± SD), while exhibiting a mean of 3.0 ± 2.1 (± SD) during sham incision ($P \leq 0.001$ *vs.* baseline and *vs.* sham, n = 30). Ten minutes after incision, nonevoked pain intensity decreased to 4.8 ± 1.3 (mean ± SD) and remained constant at this level throughout the experiment.

Qualitative aspects of pain sensation as assessed by the SF-MPQ presented significant time-dependent changes during and after the incision ($P \leq 0.05$ *vs.* baseline and *vs.* sham, n = 30) for the following items: stabbing, sharp, hot burning, aching, tender, and exhausting—all but the last belonging to the sensory dimension of pain. Sum scores for the sensory and affective components also differed significantly ($P \pm 0.036$). In addition, a significant enhancement of sensory pain descriptors 15, 35, and 55 min after incision was observed (*vs.* baseline; $P \leq 0.019$). Interestingly, all values reported by the subjects were generally low with averaged single-item responses never exceeding one of the four, corresponding to a "mild" amount of particular pain quality being experienced.

FMRI Data

Random Effect Analysis (within Group). Peak intensity for most areas was reached 0–2 min after incision. Increased brain activity of the somatosensory cortex, frontal cortex, and limbic system was observed in subjects after incision and in sham individuals. Still, temporal incision and sham group activity pattern differed (table 2, fig. 3). Remarkably, the primary and secondary somatosensory cortex was activated during incision (0–2 min), but activity decreased subsequently below our threshold (table 2). In contrast,

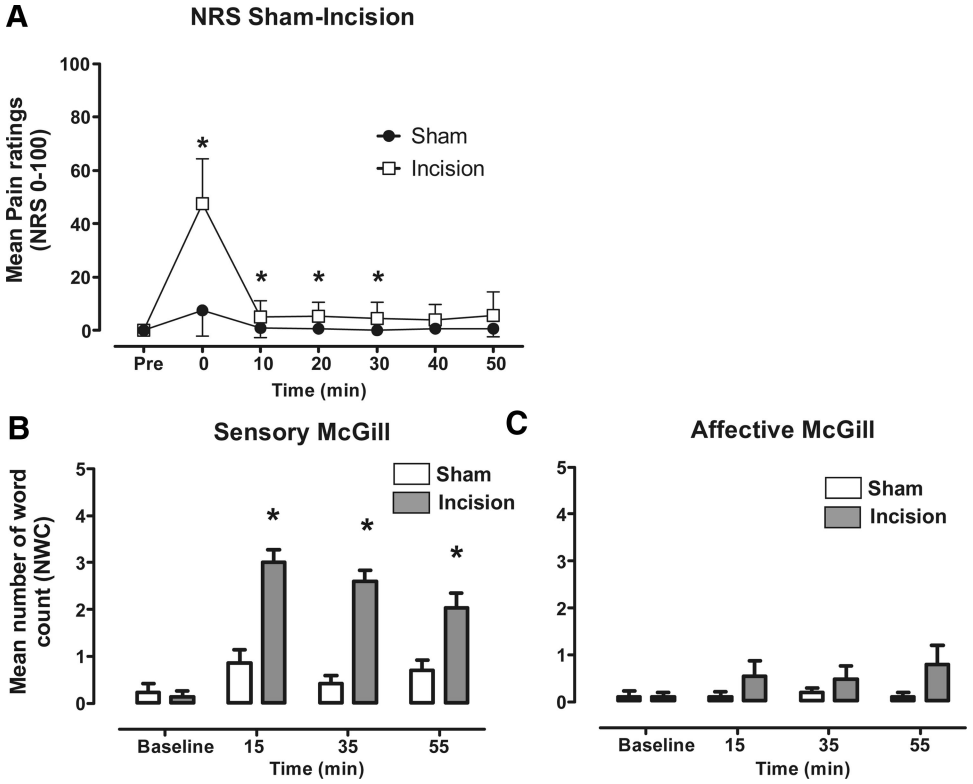

Fig. 2. *A*, Nonevoked pain scores (numerical rating score [NRS] 0–100); *B* and *C*, McGill ratings (separated for left: sensory and right: affective variables). Results are expressed as mean ± SD. *$P < 0.036$ incision *versus* sham when appropriate (nonparametric Mann–Whitney U Test).

the secondary somatosensory cortex was activated during sham procedure and was still active up to 4.5 min after incision (table 2).

No activations in sessions 3 and 4 were observed in a group analysis. The related con-files for these contrasts contained no significant clusters at $P = 0.05$ for many subjects. Therefore, data from sessions 3 and 4 could not be analyzed further. The reason for this finding could be the lack of considerable pain (low NRS scores) after incision during sessions 3 and 4 (see fig. 2). Therefore, we assume that the pain network was only weakly activated and that this small activation cannot be depicted at our minimum threshold of $P = 0.05$.

BOLD Signal Changes between Groups (Interaction Group × Time). The BOLD signal differences between subjects with sham procedure and incision during the course of the experiment were analyzed further, and we found a significant interaction of group and time (fig. 4; uncorrected for multiple comparison, $P = 0.001$, 10 voxels, NRS as cofactor). Significant activation clusters were seen in the ipsilateral primary and secondary somatosensory cortices (parietal postcentral gyrus [BA 2 and BA 3], inferior parietal lobe [BA 40], and the precuneus [parietal lobe, BA 7]), the contralateral parietal postcentral gyrus (BA 7), the bilateral mid-cingulate cortex (BA 31, BA 32, and BA 24), the contralateral anterior insula, the contralateral superior frontal gyrus (BA 9), the bilateral frontal paracentral lobe (BA 5), and the bilateral frontal precentral lobe (BA 6). Another BOLD signal change ($P = 0.01$) was seen in the contralateral thalamus (x, y, and z coordinates: −18, −24, and −4, respectively), which did not survive our contiguity threshold of cluster volume of $P = 0.001$.

Temporal BOLD Profile. To explore the temporal profile after incision in more detail, paired *post hoc t* tests between different time points with NRS at incision as cofactor were performed in each group. The incision group presented only a strong dependence of medial and superior frontal areas on time with our given threshold (uncorrected for multiple comparisons; $P = 0.001$). More specifically, the contralateral frontal precentral gyrus (BA 6), superior frontal gyrus (BA 6), the ipsilateral medial frontal gyrus (BA 6), the ipsilateral inferior frontal gyrus (BA 47) (fig. 3), and the ipsilateral precuneus (BA7) exhibited the highest activity 0–2 min after incision. In contrast, the contralateral medial frontal gyrus (BA 6) reached its maximum in activity later about 4–10 min after incision (table 2).

Differences between Both Groups: Incision *versus* Sham. To further explore the influence of the factor group (sham *vs.* incision) in the observed interaction, *post hoc t* tests (NRS as cofactor) were performed between subjects of both groups at a given time point. Subjects of the incisional group generally revealed higher activations compared with sham subjects; activity was increased contralateral and ipsilateral to the incision (table 1). Increased brain activation of the dorsolateral prefrontal cortex, middle/medial prefrontal cortex, and areas related to somatosensory integration (parietal cortex), anterior insula, and

Table 2. Activated Brain Areas of Volunteers with an Experimental Incision and Sham Preparation

	PI 1: 0–2 min after Incision	PI 2: 2–4.5 min after Incision	PI 3: 4.5–10 min after Incision
Incision			
Frontal	i BA 10 (4 66 16) c BA 6 (−2 32 56) i BA 8 (2 48 38) i BA 47 (54 34 −2) c BA 45 (−60 20 8)	c BA 10 (−2 66 20) c BA 6 (−2 32 56) i BA 8 (2 48 38) i BA 47 (54 34 −2) i BA 46 (−52 26 14) i BA 9 (4 56 32)	c BA 10 (−14 62 20) c BA 6 (−8 2 60) i BA 10 (4 64 0) i BA 10 (2 64 20) i BA 45 (58 28 4) i BA 9 (2 50 36)
Limbic	i BA 19 parahippocampal (34 −46 −6) c BA 19 parahippocampal (−30 −50 −2) c BA 36 (−16 −4 −30)	c BA 32 (0 46 8) c BA 19 parahippocampal (−32 −52 −4) c BA 30 parahippocampal (−28 −48 2)	i BA 32 (2 44 8) c BA 19 parahippocampal (−32 −52 −2)
Temporal	c BA 22 (−46 0 −6) i BA 21 (62 −20 −10) i BA 38 (46 18 −20) c BA 42 (−56 −32 14)	c BA 21 (−52 4 −36) i BA 21 (62 −22 −8) i BA 38 (46 18 −20) c BA 38 (− 34 12 −18)	c BA 21 (−52 4 −36) i BA 38 (46 18 −20) c BA 38 (− 34 12 −18)
Parietal	i BA 40 (S II) (56 −36 52) i BA 3 (S I) (20 −34 70) c BA 3 (S I) −18 −34 72) i BA 7 (14 −50 64)	NA	NA
Others	i caudate (tail) (26 −42 12) c caudate (body) (−4 8 6) i caudate (head) (4 20 2)	i caudate (tail) (26 −42 12) c caudate (head) (−4 10 4) c insula (−42 2 −8) c hippocampus (−24 −44 10)	i caudate (tail) (26 −42 12) c hippocampus (−24 −44 10)
Sham procedure			
Frontal	c BA 6 (−60 2 28) c BA 6 (0 16 42) c BA 46 (−45 32 8) i BA 47 (50 40 −6) c BA 2 (SI) (−54 −26 46)	c BA 6 (−62 0 34) c BA 9 (−60 8 28) c BA 44 (−60 10 12) i BA 8 (2 16 48)	c BA 6 (0 18 46) c BA 9 (−60 8 28) c BA 44 (−58 14 12)
Limbic	c BA 24 (0 24 4) i BA 19 parahippocampal (30 −46 −2) i BA 29 post. cingulate (6 −38 14)	i BA 19 parahippocampal (30 −46 −2) c BA 32 (−4 18 40)	i BA 19 parahippocampal (30 −46 −2)
Temporal	i BA 38 (34 8 −34) c BA 38 (− 44 10 −6)	i BA 38 (34 8 −34) c BA 22 (−46 8 −6)	NA
Parietal	c BA 7 (−30 −68 56) i BA 7 (26 −62 58) i BA 40 (SII) (42 −46 52)	c BA 7 (−32 −62 52) i BA 40 (SII) (56 −54 44)	NA
Others	c caudate (tail) (−14 −34 20) i caudate (head) (8 24 2) i caudate (body) (14 −16 20) c caudate (body) (−12 −18 24) c insula (−42 0 −6)	c caudate (tail) (−18 −34 20) i caudate (head) (8 24 2) i caudate (body) (12 −14 20) c caudate (body) (−12 −18 24)	c caudate (tail) (−18 −34 20) i caudate (body) (12 −14 20) c caudate (body) (−12 −18 24) i thalamus (10 −16 20)

Random-effect analyses. Activated brain areas of volunteers with an experimental incision (n = 30) and of volunteers with a sham preparation (n = 14) with Numerical Rating Scale at incision was added as a cofactor for each subject. (Second-level analyses [SPM5], one-sample *t* test, few correction for multiple comparisons, $T = 7.2$, 10 voxels). With an uncorrected threshold of $P = 0.005$ no activations could be detected for session 3 in both groups and no deactivations could be seen for all conditions in both groups.

BA = Brodman area; c = contralateral to incision/sham; i = ipsilateral; NA = not applicable; PI = postincision.

anterior cingulated cortex was observed in volunteers after incision, compared with the sham group (table 1).

fMRI and Scores of the Psychologic Dimensions of Pain (SF-MPQ) after Incision. To assess the qualitative aspects of pain sensation after incision, the German SF-MPQ was used, and the sensory and affective components of pain were correlated to BOLD activation during incision. We found a correlation between the scores of the sensory dimensions of pain and BOLD activation patterns only. There was a positive correlation between sensory scores and superior frontal gyrus BA 9, medial frontal gyrus (BA 11), and the contralateral caudate (see table 3). Only frontal and mainly ipsilateral brain areas were negatively correlated (BA 6, 7, 8, 10, 45, and BA 46) after incision with the sensory pain scores. Finally, there was no statistically significant difference between the number of word counts for sensory and affective items and BOLD activation patterns.

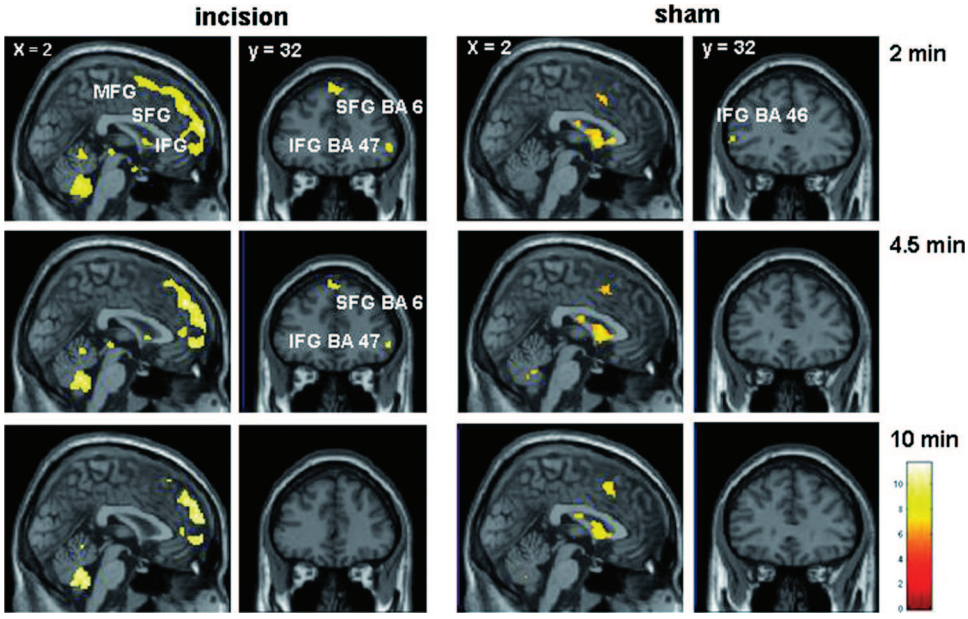

Fig. 3. Random-effect analyses for subjects 0–2, 2–4.5, and 4.5–10 min after incision (n = 30) or sham preparation (n = 14), one sample *t* test; corrected for multiple comparisons, $T = 7.2$, 10 voxels). Pain scores at incision were added as a cofactor. Peak intensity for most areas is reached 0–2 min after incision. Incision and sham group differ significantly (see table 3). BA = Brodman area; MFG = medial frontal gyrus; SFG = superior frontal gyrus; IFG = inferior frontal gyrus.

fMRI and Pain Scores (NRS at Incision). In a second level of SPM analysis with nonevoked pain ratings (NRS at incision) as covariate, there was a positive correlation between the contralateral amygdala (fig. 5) and other areas of the limbic system and NRS pain ratings at incision (table 3). Negative correlations were seen between activation intensities of various brain areas including the ipsilateral ventrolateral thalamus, mainly ipsilateral frontal brain areas and the contralateral insula and nonevoked pain ratings after incision (table 3).

ROI Analyses

Lateralization. Lateralization effects were investigated in areas of the medial and lateral pain system in an ROI analysis. Significant lateralization effects were observed for the anterior cingulate cortex (ACC) during incision (postincisions 2 and 3, trend) and the thalamus during the whole course of the experiment in subjects with incision but not after the sham procedure (table 4, fig. 6). The contralateral side was always stronger activated than the ipsilateral side. No lateralization effects were found for the primary and secondary somatosensory cortex.

Discussion

In this study, we characterized a distinct temporal activation pattern of a cortical pain network during and after a standardized experimental incision in healthy male volunteers. Mean nonevoked pain ratings during incision in our study were comparable with those reported by Kawamata *et al.*[9,10] Three main results were observed in this study: first, a distinct activation pattern with increased brain activity of the secondary somatosensory cortex, frontal cortex, and limbic system occurred in subjects after incision compared with sham individuals (table 1). Second, some lateralization effects were present after incision (table 4) with increased activation contralateral to the incision site. Third, brain activity was modulated by individual nonevoked pain ratings of subjects during incision (table 3).

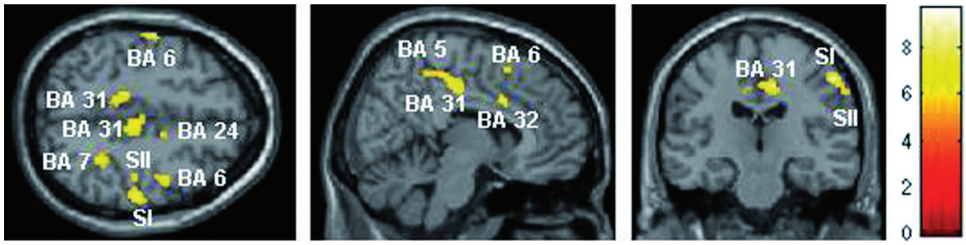

Fig. 4. Group × time images (two-factorial model with two main factors; analysis of covariance, group: [sham and incision; two levels] and time [preincision, postincisions 1, 2, and 3; four levels]). The NRS scores at incision were added as cofactors in the model to reduce the impact of pain sensitivities on the results (uncorrected for multiple comparisons, $P = 0.001$, 10 voxels). There were mainly temporal activation profile differences between both groups (sham and incision procedure) for somatosensory areas (SI and SII), the cingulated gyrus (BA 24, BA 31, and BA 32), and medial frontal cortices (BA 5, BA 6). NRS = numerical rating scale; BA = Brodman area.

Table 3. Correlations between Incisional Induced Brain Activation and Nonevoked Pain Ratings

	PI 1: 0–2 min after Incision	PI 2: 2–4.5 min after Incision	PI 3: 4.5–10 min after Incision
Negative			
Frontal	c BA 6[d] (−16 2 70) l BA 6[e] (34 10 44) c BA 10[e] 0 (32 46 16)[e]	c BA6[d] (−16 2 70) i BA 6[e] (36 8 42) i BA 10[e] (46 48 20) i BA 8[d] (24 14 36)	i BA6[e] (36 8 42) i BA 10[d] (30 52 14) i BA 10[e] (40 44 −6) i BA 8[e] (44 30 46)
Limbic	i BA 32 (20 14 40) c BA 32 (−12 18 24) i BA 31 (12 −30 36)	i BA 32 (18 32 24) c BA 24 (−10 20 24) c BA 24 (−20 −18 46	i BA 32 (20 8 38) c BA 32 (−16 14 24) c BA 24 (−8 20 20) i BA 31 (14 −44 32)
Temporal	NA	c BA 39 (−40 −76 12) i BA 20 (46 −26 −16)	i BA 20 (46 −26 −16)
Parietal	i BA 40[c] (52 −32 52) c BA 2 (−60 −18 28) i BA 2 (48 −30 34) c BA 7 (−14 −54 70)	i BA 40[c] (52 −32 52)	i BA 40[c] (48 −34 54)
Others	c insula (−38 0 20) bilateral cerebellum	c claustrum (−24 22 18) i Thalamus (20 −10 16) bilateral cerebellum	i Globus Pallidus (48 −34 54) i Thalamus (20 −10 16) bilateral cerebellum
Positive			
Frontal	i BA 4 (26 −22 62) c BA 10[f] (−6 62 0)	NA	c BA 9[a] (−10 48 32) i BA 47[b] (46 28 −14)
Limbic	NA	c Uncus BA 28 (−28 −6 −26) c Amygdala (−22 −8 −18) c parahippocsampus BA 36 (−28 −20 −24)	c Uncus BA 28 (−20 4 −24) c Amygdala (−24 0 −24)
Temporal	c BA 21 (−44 4 −32)	i BA 21 (48 10 −36) i BA 38 (36 16 −42)	i BA 21 (48 10 −36) i BA 38 (36 16 −42)
Others	c Cerebellum (−18 −50 −26)	c Cerebellum (−18 −50 −26)	NA

Brain areas of 30 volunteers with an incision. Negative (second-level analysis [SPM5], uncorrected $P = 0.001$, 10 voxels). and positive correlations with nonevoked pain during incision (Numerical Rating Scale) (second-level analysis [SPM5], uncorrected $P = 0.005$, 10 voxels).

BA = Brodman area; c = contralateral to incision/sham; i = ipsilateral; NA = not applicable; PI = postincision.

[a] = superior frontal gyrus; [b] = inferior frontal gyrus lobe; [c] = inferior parietal; [d] = superior frontal; [e] = middle frontal; [f] = medial frontal.

Temporal BOLD Activity Pattern—Lateral Pain System

Brain areas of the lateral nociceptive system including the insula, the primary (SI), and secondary somatosensory cortex (SII) are important for the sensory-discriminative component of pain together with stimulus localization or detection, intensity discrimination, and quality discrimination.[2,4,6] The insula[20,22] has also been discussed to be important for affective/cognitive aspects of pain. Several studies showed that an activation of the insula is associated with negative emotional states and unpleasantness.[7] Probably, the insula has both functions: sensory integration node and evaluation of affective/cognitive aspects of pain, which contribute to the activity observed.

In this study, an increased brain activity during and after incision compared with sham-operated volunteers was found

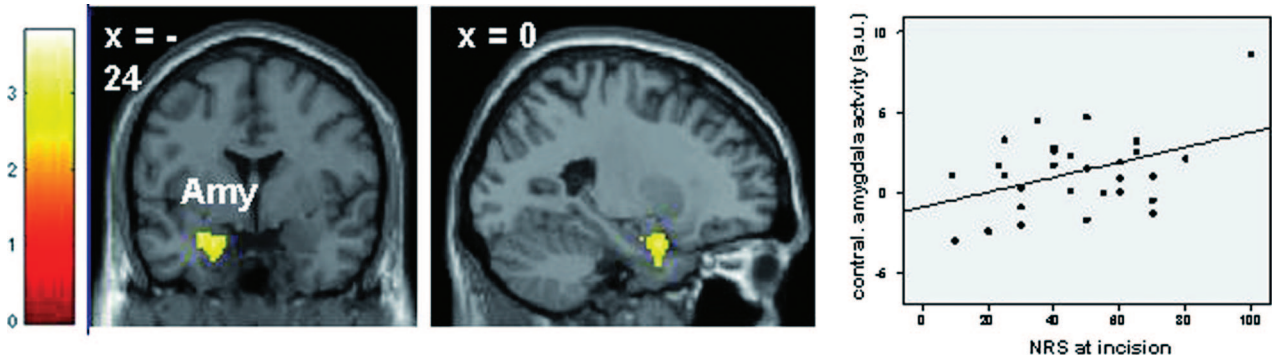

Fig. 5. *A*, Positive blood oxygenation level dependent signal correlation with numerical rating scale (NRS) at incision 4.5–10 min after incision (second-level analysis [SPM5], uncorrected $P = 0.005$, 10 voxels). A strong activation of the contralateral amygdala can be depicted ($x = -24$, $y = 0$, $z = -24$). Illustrative scattergram of positive correlation between the activity of the contralateral amygdala ($x = -24$, $y = 0$, $z = -24$) in a region of interest analysis and NRS scores at incision.

Table 4. Lateralization Differences of Brain Areas Contralateral and Ipsilateral to the Incision Side

Areas and Contrast	Activation Intensity (a.u.) ± SD	*T*	*P* Value*
ACC during incision			
Contralateral	0.54 ± 1.56	2.2	0.037
Ipsilateral	0.09 ± 1.23		
Thalamus pre incision			
Contralateral	1.3 ± 1.9	2.3	0.026
Ipsilateral	0.99 ± 1.66		
Thalamus during incision			
Contralateral	1.98 ± 3.0	2.3	0.031
Ipsilateral	1.63 ± 2.48		
Thalamus 2–4.5 min after incision			
Contralateral	1.89 ± 2.79	2.6	0.015
Ipsilateral	1.48 ± 2.45		
Thalamus 4.5–10 min after incision			
Contralateral	1.78 ± 3.01	2.4	0.022
Ipsilateral	1.32 ± 2.53		

* Paired Student *t* test, *df* = 29.
ACC = anterior cingulate cortex; a.u. = arbitrary units.

for SII but not for SI (table 1). Similarly, Peyron *et al.*[20] demonstrated in a meta-analysis that an activation of SII was seen in most functional pain imaging studies but that the activation of SI occurred only in 50% of the cases. There are several reasons for this finding. First, nociceptive specific projections to SI are sparse and may be interspersed with neurons that respond to nonpainful tactile stimuli,[23,24] suggesting that pain relevant signals from the somatosensory cortex are weak and nociceptive stimuli are needed to increase the signal-to-noise ratio.[22] Therefore, activation of the primary somatosensory cortex was mostly observed after noxious stimuli or evoked pain; however, in this study, we examined nonevoked incision-induced pain. This is also in agreement with other surrogate models of clinical pain, indicating that the activation of SI in response to nonevoked capsaicin-induced pain or visceral distension pain is not consistent.[24–26]

Second, it has been suggested that the activation of the somatosensory cortex depends on pain intensity,[27] and an incision may not be intense enough to robustly activate the SI. However, compared with this study, similar evoked and nonevoked NRS scores have been observed after capsaicin injection activating the somatosensory cortex after this inflammatory tissue injury.[7,24]

Third, psychologic factors including arousal and attention can modulate the activity of the somatosensory cortex[28,29] and may cause an attentional bias in this study. In agreement, we observed an activation of the somatosensory cortex in volunteers after incision and after sham operation, indicating that we may have missed a possible incision-induced activation of the somatosensory cortex.

Temporal BOLD Activity Pattern—Medial Pain System

The frontal cortex, a major part of the medial pain system, receives afferent information from the cingulate gyrus and the thalamus[30] and is related to the affective, cognitive, and attentional processing of painful stimuli.[3,31] There is ample evidence that noxious heat[32] and irritant chemicals including capsaicin[24] activate several brain areas within the prefrontal cortex, including superior frontal cortex (BA 8, 9, and 10), medial frontal gyrus (BA 6, 10, and 46), and inferior frontal gyrus (BA 44, 45, 46, and 47). Accordingly, in this study, the superior (BA 8, 9, and 10) and inferior (BA 45) prefrontal cortex was activated by an incision and partly positively correlated with perception of incisional ongoing pain (tables 1 and 3), indicating that several areas of the prefrontal cortex play an important role for pain processing during and after an incision.

The ACC (Brodmann areas 24, 25, and 32) is regarded as an important area of the limbic system and is associated with

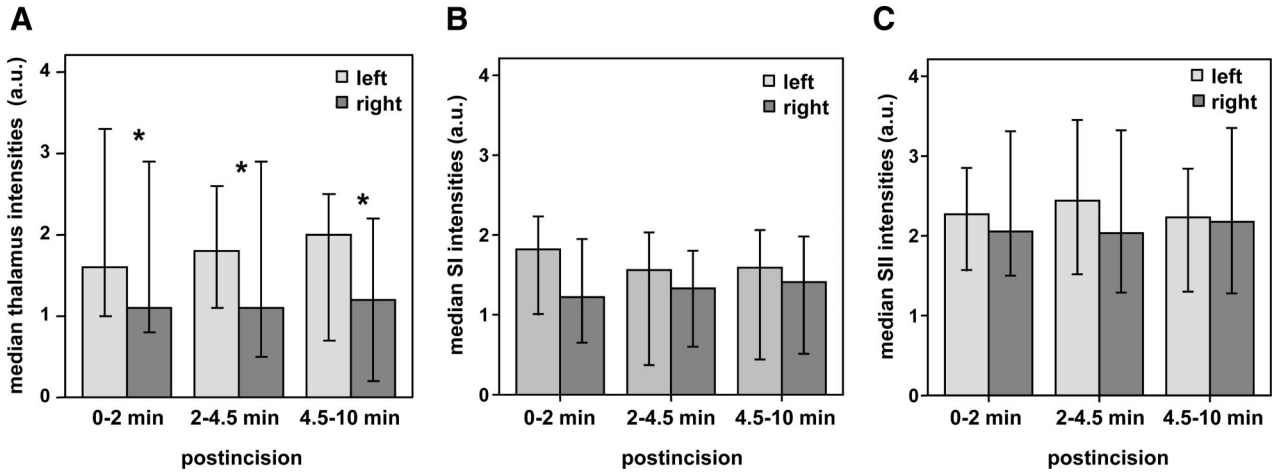

Fig. 6. Box plot of lateralization effects for the activation intensities of (*A*) the thalamus, (*B*) primary sensomotoric (SI), and (*C*) the secondary sensomotoric cortex (SII) in a region of interest analyses. The height of the box characterizes the mean signal intensity in arbitrary units (a.u.), the *whiskers* the SD. There are no lateralization differences for SI and SII in contrast to the thalamus. Here, the contralateral thalamus is generally strongly activated than the ipsilateral side during and after the incision. *$P < 0.05$; paired Student *t* test (see table 4).

the motivational-affective component of the medial pain system. The ACC receives afferent nociceptive input from the thalamus and the amygdala. Also, the ACC is associated with the motivational-affective and cognitive component of the medial pain system.[3,5] Several studies showed that patients with cingulotomies still experience pain but report it as less distressing and bothersome. Moreover, neuroimaging studies demonstrated that noxious stimuli and capsaicin-induced pain activates the ACC.[20,22]

In agreement with these data, we found a significantly greater activation of ACC (BA 24 and 32) after incision compared with sham-operated volunteers, indicating that the ACC is strongly involved in incisional-induced pain unpleasantness coding.

A recent meta-analysis demonstrated that the thalamus was one of the six most reported brain areas involved in pain modulation.[6] Various nuclei of the lateral and medial thalamus receive input from spinothalamic tract neurons and transmit these information to the somatosensory cortex (lateral pain system) or the limbic system (medial pain system). Most studies of acute pain in normal volunteers described a bilateral activation of the thalamus, suggesting that pain from noxious stimuli involves both discriminative and affective networks for pain processing.[6,20,33] In this study, we observed a significant increased activity of the ipsilateral thalamus after incision compared with sham-operated volunteers (fig. 6), supporting the findings by others[34] that these responses may be related to nociceptive input from ipsilateral projections of the spinothalamic tract or from spino-reticular-thalamic pathways.[35]

Temporal BOLD Activity Pattern—Other Brain Areas

The amygdala, which is interconnected with the anterior cingulate cortex of the medial pain system,[2] is considered an important part of the fear- and anxiety-related circuitry that modulates the emotional-affective component of nociception.[36,37] Several neuroimaging studies demonstrated pain-related signal changes of the amygdala in animals and humans (for review see Ref. 36). Bornhövd *et al.*[31] reported a positive correlation between perceived pain intensity and bilateral amygdala activation.[31,36] Similarly, in this study, we obtained a positive correlation between pain intensity and amygdala activity after incision (table 4, fig. 5). This indicates that the amygdala has an integrating function of incision-induced nociception and anxiety.

Correlation between Nonevoked Pain Ratings and Brain Activity

As reported in the previous paragraph, we obtained a positive correlation between pain intensity and activity of several brain areas including the frontal cortex and amygdala after incision (table 4, fig. 4). However, we also observed a negative correlation between nonevoked pain ratings (NRS) and the activity of the somatosensory cortex, thalamus, cingulate cortex, and certain parts of the frontal cortex during and after incision (table 3). Accordingly, several studies of functional pain processing demonstrated a decreased activity in distinct brain areas such as frontal cortex, somatosensory cortex, and cingulate cortex after acute and chronic pain.[38] Apkarian *et al.*[6] demonstrated a decreased cerebral blood flow of the contralateral SI associated with a tonic thermal pain stimulus, suggesting a neuronal inhibition of the somatosensory cortex during sustained pain perception. Furthermore, Coghill *et al.*[37] reported a decreased activity of the posterior cingulate cortex during noxious heat stimulus; nonpainful vibration caused a decreased blood flow in the frontal gyrus. Finally, Bantick *et al.*[34] found a negative correlation of thalamus activation to a painful stimulus during distraction, indicating that the thalamus is involved in an attentional modulation of pain.

Although the exact physiologic relevance and mechanisms are not yet clarified, it has been hypothesized that a decrease in cerebral blood flow may be attributed to a suppression of neuronal activity.[39]

Lateralization of Brain Areas

It is known that both cerebral cortical hemispheres can be engaged in the processing of a unilateral somatosensory stimulus, indicating that both the contralateral and ipsilateral cerebral hemispheres can process information from a unilateral painful stimulus.[40] Accordingly, we obtained a lateralization effect only for the contralateral ACC and the thalamus but not for the somatosensory cortex during and after incision (fig. 6, table 4). This is also in agreement with the meta-analysis by Peyron *et al.*,[20] demonstrating that more than 50% of imaging studies described a bilateral increase in SII activity during painful stimuli. However, in contrast to other brain imaging studies,[20] we observed a bilateral but not a primarily contralateral activation of the SI cortex. Interestingly, in contrast to a pain intensity-dependent activation, Coghill *et al.*[40] observed a right-lateralized, pain intensity–independent activation of several brain areas, including thalamus and frontal cortex processing attentional and awareness components of somatosensory information. In this study, we observed a bilateral or contralateral activation of the frontal cortex and the thalamus during and after incision, respectively, hypothesizing that in contrast to thermal stimulation the activation of these brain areas by an incision is possibly activated pain–intensity dependent.

Limitations

There are some limitations for this study. First, brain activation patterns induced by an incision were correlated with nonevoked pain perception during and after incision but not with stimulus-evoked hyperalgesia. There is now sufficient evidence that distinct brain regions are activated during stimulus-induced pain[6,20] and that different types of hyperalgesia (mechanical or thermal hyperalgesia) cause separate brain activation patterns.[7,41] However, in this study, we focused on brain activation patterns representative for nonevoked pain or resting pain during and after an incision. A separate

study investigating the role of noxious and innocuous stimuli on central pain processing after incision is in progress.

Second, to characterize the brain activation patterns induced by postoperative pain, we used an experimental surrogate pain model in healthy volunteers and did not investigate patients after surgery. However, using a surrogate pain model is one approach to study characteristic sensory disturbances of clinical pain under standardized, reproducible, and stable conditions. Because the pathophysiology of postoperative pain is distinct to acute or chronic pain induced in healthy volunteers, this surrogate model for postoperative pain may close a gap between existing models of acute and chronic pain and the investigation of postoperative patients. Third, even though global scaling is the best approach to analyze this type of data when interruption of the scanning procedure violated the magnetic resonance imaging time series, it may still be suboptimal, because we cannot rule out that unspecific effects of drift and calibration may have influenced our contrasts. For example, Gavrilescu *et al.*[42] reported in a simulation experiment that proportional scaling can induce an increase in the number of deactivated voxels. However, we did not observe this in the random effect analyses (fig. 3).

Conclusion

In this study, we characterized for the first time distinct patterns of brain activity associated with an incision in humans. Furthermore, we identified incision-induced activity in the lateral pain system including the prefrontal cortex and in the medial pain system including thalamus, ACC, and insula and correlated these areas with subjective pain ratings during and after incision.

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