Neural Activity Related to Self- Versus Externally Generated Painful Stimuli Reveals Distinct Differences in the Lateral Pain System in a Parametric fMRI Study

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Abstract: Self-generated sensory stimulation can be distinguished from externally generated stimulation that is otherwise identical. To determine how the brain differentiates external from self-generated noxious stimulation and which structures of the lateral pain system use neural signals to predict the sensory consequences of self-generated painful stimulation, we used functional magnetic resonance imaging to examine healthy human subjects who received thermal-contact stimuli with noxious and non-noxious temperatures on the resting right hand in random order. These stimuli were internally (self-generated) or externally generated. Two additional conditions served as control conditions: to account for stimulus onset uncertainty, acoustic stimuli preceding the same thermal stimuli were used with variable or fixed delays but without any stimulus-eliciting movements. Whereas graded pain-related activity in the insula and secondary somatosensory cortex (SII) was independent of how the stimulus was generated, it was attenuated in the primary somatosensory cortex (SI) during self-generated stimulation. These data agree with recent concepts of the parallel processing of nociceptive signals to the primary and secondary somatosensory cortices. They also suggest that brain areas that encode pain intensity do not distinguish between internally or externally applied noxious stimuli, i.e., this adaptive biological mechanism prevents harm to the individual. The attenuated activation of SI during self-generated painful stimulation might be a result of the predictability of the sensory consequences of the pain-related action. *Hum Brain Mapp* 27:755–765, 2006. © 2006 Wiley-Liss, Inc.

Key words: pain; SI; SII; insula; prediction; fMRI

INTRODUCTION

Pain perception depends strongly on expectation of the sensory consequences of a painful stimulus. By associative pairing of cues of impending pain and pain perception, humans have learned to anticipate and avoid future painful stimuli. The basis of this adaptive biological strategy is largely unknown. For example, it is not known whether the neural substrate for pain anticipation differs from the system involved in nociceptive processing [Bornhovd et al., 2002; Ploghaus et al., 1999; Porro et al., 2002] or if the involved neural pathways differ as to how certain or uncertain the expectation of a painful stimulus is [Ploghaus et al., 2003].

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The expectation of painful stimuli can influence the unpleasantness of painful stimuli [Price et al., 1999; Staub et al., 1971] and even enhance the neural responses to nonpainful somatosensory stimuli [Sawamoto et al., 2000]. These features might be involved in the development of chronic pain syndromes.

One possible behavioral strategy to alleviate the uncertainty of impending pain stimuli is self-generated stimulation. This would require that the brain distinguish between a self-generated and an externally applied painful stimulus. Self-generated tactile stimulation is known to be perceived as weaker than an identical physical stimulus applied externally [Blakemore et al., 1998a]. This is, for instance, the perceptual basis of the phenomenon that persons cannot tickle themselves [Blakemore et al., 1998a, 2000]. Such perceptual modulation is probably accomplished in a feed-forward model that compares the predicted sensory outcome with the actual sensory feedback of a movement [Blakemore et al., 1999a].

To test the hypothesis that a feed-forward model is involved in predicting pain-related consequences of action, we compared the effects of self- versus externally generated painful stimuli on the activation of the lateral pain system, i.e., the primary and secondary somatosensory and insular cortices with respect to individual psychophysical pain perception. To separate pain-related effects from those of purely sensory stimulation, we applied noxious and non-noxious thermal stimuli in a parametric design using the factors mode of stimulus application (self vs. external) and level of uncertainty (certain vs. uncertain) of the impending thermal stimuli, with four graded levels of psychophysical pain perception. Self-generated stimulation is associated with a higher level of onset certainty of the impending stimulus.

Pain-related activity in the primary somatosensory cortex (SI), the secondary somatosensory cortex (SII), and the anterior insula undergoes powerful cognitive modulation [Seminowicz et al., 2004]. Activity in SI was thought to encode pain intensity [Coghill et al., 1999; Porro et al., 1998], but recent data suggest that it is primarily involved in encoding stimulus but not pain intensity [Bornhovd et al., 2002]. Consequently, we hypothesized that activation in the SI attenuates the sensory consequences of self-generated noxious stimuli whereas the SII and insular cortex, which may be involved in signaling biologically relevant pain intensity [Bingel et al., 2003, 2004; Bornhovd et al., 2002], do not. Preliminary data on cerebellar activity related to active versus passive noxious stimulation [Helmchen et al., 2004] and related data on the medial pain system, e.g., the cingulate cortex [Mohr et al., 2005], have been published elsewhere.

SUBJECTS AND METHODS

Subjects

Sixteen healthy, male, right-handed volunteers (age range, 22–41 years; mean $\pm$ standard error of mean = 26.4 ± 6.1 years) gave their informed written consent to participate in

the study, which was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee. All subjects had normal pain thresholds and no history of neurological or psychiatric disease.

Thermal Stimulation

Three different intensities of thermal stimulation (42.5°, 45.5°, or 48.5°C) were delivered repeatedly in randomized order (six repetitions of each stimulus per condition) by a thermode (3 $\times$ 3 cm thermo-conducting surface; TSA II, MEDOC Inc., Israel) at the thenar surface of the right hand. The stimulus intensities were chosen to be below, near, or clearly above the individual pain threshold. The thermo-conducting surface was fixed to a lever, controlled by two ropes that could be pulled by either the investigator or the volunteer's left hand to deliver externally applied or self-generated stimuli to the volunteer's right hand. The ropes fed through tubes along a wooden frame positioned in front of the scanner. To ensure a light, constant pressure during thermal stimulation, a nonmagnetic, metallic block (400 g, 0.7 N/cm² surface pressure) was attached to the back of the thermode.

Before magnetic resonance imaging (MRI) recordings, the individual pain threshold of all subjects was determined psychophysically (by applying a series of stimuli with temperatures increasing or decreasing by 1°/5 s, beginning at 40° and ending at 49°C). Volunteers were exposed to all experimental pain stimuli intensities and trained to use the rating scale (see below). All volunteers were informed about the different modes of stimulus application and that the physical stimulus intensities would differ from trial to trial in a randomized order but not between the conditions.

Experimental Protocol

During scanning one investigator stood next to the scanner to apply and readjust the stimuli and to document the subject's pain rating of each stimulus. The right thenar was supported by a plastic splint to prevent voluntary isometric muscle contraction. Thermal stimulation during rest was either self- or externally generated to determine the differential stimulus-dependent interaction with the graded psychophysiological factors and the two control conditions to account for anticipation or motor-related activation. The first condition (A) contained self-generated painful stimuli. The subject pulled a rope with the left hand after a short verbal command ("action") delivered by headphones. The rope operated a relay that released a lever at the tip of which the thermode was attached (Fig. 1). As soon as the lever was released, the thermode immediately moved to the skin of the right thenar (internal condition) and stimulated it. After each stimulus, the thermode (lever) was pulled back to its initial "resting" position by the investigator. For the sake of comparison, the stimulus setup was especially designed to ensure control equal to that of the second condition and to guarantee the same thermode application pressure, i.e., tactile stimulation and stimulus duration within an identical timing sequence.

Figure 1.

Schematic drawing of the experimental design. The volunteer pulls a rope (blue/black line) with the left hand. This operates a relay that releases a lever at the tip of which is a thermode. As soon as the lever is released, the thermode moves to the skin of the right thenar (internal condition). After each stimulus, the thermode (lever) is returned to its initial resting position by the investigator. In the external condition, the investigator gives the stimuli by means of a different rope (red/gray line). Although in this condition, the volunteer again pulls the (blue/black) rope with his left hand, his rope is now not connected (see Subjects and Methods). The subject's hand movements now have no effect on the thermal stimuli, which only the investigator delivers to the subject's right hand. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

In the second (external) condition (B), the same number and intensities of stimuli were given by the investigator. On the short verbal command ("external") delivered over headphones, the subject again pulled the rope with his left hand; however, this time it was not connected to the lever. The thermode was moved to the subject's right hand by another rope controlled only by the investigator (Fig. 1) after a delay of time (3, 4, or 5 s, randomized), which the investigator observed on a monitor. In this condition the level of stimulus onset uncertainty was higher than that for self-generated stimuli.

In the third (C) and fourth (D) conditions (control conditions), the subjects did not move their left hand at all. They received two different acoustic signals over headphones indicating that a thermal stimulation would follow. In condition C there was no delay (comparable to the internal condition), and in condition D the time intervals varied at random (3, 4, or 5 s, comparable to the external condition). Conditions A, B and C, D thus contained exactly the same

types of events (A, B: signal, movement, stimulation; C, D: signal, stimulation). All four randomly presented conditions included phasic thermal stimulation of the right thenar with the same stimulus intensities applied in random order. In total, 72 thermal stimuli were applied in one session. Each stimulation period (three scans = 10.5 s) was followed by a resting period (six scans = 21 s, beginning with the rating), which served as baseline (excluding the initial rating period).

At the end of each thermal stimulation, the subjects were asked (vocal command "rating" by headphones) to rate the intensity of each stimulus with the left hand using a four-finger scale [Buchel et al., 2002]. P1 was signaled by one finger and indicated a clearly warm but not painful sensation. Two fingers (P2) indicated a stimulus that had just turned from a warm to a lightly painful sensation. Three (P3) or four (P4) fingers expressed increasingly painful sensations, with P4 being the most intensive pain stimulus. This four-finger scale was chosen for only three physical thermal stimuli for the following reasons: (1) to focus the volunteer's attention on the impending different levels of stimulus perception for the subsequent rating (variability to choose); (2) to relate activation patterns to a graded psychophysical response (parametric modulation); (3) to obtain patterns online in the scanner; (4) to have a motor response largely independent of the side of thermal stimulation; and (5) to make our data comparable with previous functional MRI (fMRI) pain studies on stimulus-response functions that used this type of scale [Bornhovd et al., 2002; Buchel et al., 2002].

This experimental design was able to account for anticipatory (certain vs. uncertain timing of stimulus onset) and movement-related effects. Specific differences in the interaction of self- and externally generated thermal stimuli with the perceived stimulus intensities thus could be investigated. The control conditions (C, D) were used to separate the main effects of the covariates (anticipation, motor-related activation) of the stimulus-specific effects from the interaction of condition A versus B and vice versa with the different pain perceptual levels. Categorical comparisons therefore were calculated in a factorial design. The parametric stimulation was used to determine the stimulus intensity-related specificity of the effects. Effects related to motor activation and anticipation did not show a parametric modulation.

Image Acquisition

MRI scanning was carried out on a 1.5-T scanner (Siemens Quantum, Erlangen, Germany; standard head coil). The subject's head was positioned in a standard head coil with foam pads. For each subject, 654 volumes (32 contiguous axial slices covering the whole brain, no gap) were acquired using a gradient echo, echo-planar (EPI) T2*-sensitive sequence (repetition time [TR] 3,500 ms, echo time [TE] 62 ms, flip angle 90 degrees, matrix 64×64 , and isotropic voxel $4 \times 4 \times 4$ mm). Subjects wore a mask to prevent visual stimulation during scanning.

Image Processing and Statistical Analysis

Image processing and statistical analysis were carried out using *SPM2* (Wellcome Dept. of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). All volumes were realigned to the first volume [Friston et al., 1995a], spatially normalized [Friston et al., 1995a] to the standard EPI template of *SPM2*, and finally smoothed with an 8-mm isotropic Gaussian kernel. Data analysis was carried out using a general linear model [GLM; Friston et al., 1994, 1995b,c; Worsley and Friston 1995] for the four conditions (A, B, C, D) and the perceived pain intensities (P1, P2, P3, P4) as functions over the stimulation period (three scans) and one delta function for the rating (event) convolved with the canonical hemodynamic response function as implemented in *SPM2*. The movement parameters from the realignment (*x*, *y*, *z* rotation; *x*, *y*, *z* translation) were defined as covariates of no interest to prevent movement-related artifacts. Data were high-pass filtered with a cutoff of 120 s. Voxelwise regression coefficients for all regressors were estimated using ordinary least squares and restricted maximum likelihood within *SPM2*. Effects were tested with appropriate linear contrasts of the regression coefficients (parameter estimates), resulting in *t*-statistics for every voxel. These *t*-values constituted a statistical parametric map (SPM). For a second-level analysis (random effects) a within-subjects analysis of variance (ANOVA) over the contrasts of the perceived pain intensities was calculated to show the parametric differences for the four conditions using the parameter estimates. With respect to the main aim of this study, i.e., to identify stimulus intensity-related perceptual differences between different forms of stimulus application, the analysis did not focus on temperature-related activation unless otherwise stated. For the parametric analysis of perceived pain intensities, a parametric contrast over P1–P4 $[-1.5 \ -0.5 \ 0.5 \ 1.5]$ was fitted as a linear signal increase from P1 to P4, indicating the stimulus response function (SRF). The time to pain response used for this study was standardized as hemodynamic response function with a default delay of 6 s.

To identify spatial differences in pain-related activation patterns (SRFs) between self-generated and externally applied stimulation, two exclusive, masked parametric contrasts were carried out. The first contrast revealed activations related to a linear, positive SRF for the externally generated condition, whereas self-generated stimulation revealed none, i.e., an attenuated response pattern $[0 \ 0 \ 0 \ 0 \ -1.5 \ -0.5 \ 0.5 \ 1.5 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0]$. The second contrast revealed activations related to a linear, positive SRF for the self-generated condition, but externally generated stimulation revealed none, i.e., an attenuated response pattern $[1.5 \ 0.5 \ -0.5 \ -1.5 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0]$. Within these activations the difference in the parametric response pattern (SRF) was tested for significance with interaction contrasts (A vs. B $[1.5 \ 0.5 \ -0.5 \ -1.5 \ -1.5 \ -0.5 \ 0.5 \ 1.5 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0]$ and B vs. A $[-1.5 \ -0.5 \ 0.5 \ 1.5 \ 1.5 \ 0.5 \ -0.5 \ -1.5 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0]$, $P < 0.05$

uncorrected). A conjunction over the parametric contrasts of conditions A and B [Friston et al., 1999; Price and Friston, 1997] was carried out on the second level ($[0 \ 0 \ 0 \ 0 \ -1.5 \ -0.5 \ 0.5 \ 1.5 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0]$ and $[-1.5 \ -0.5 \ 0.5 \ 1.5 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0 \ 0]$) to specify areas showing the same activation patterns.

For general differences between the two main conditions and the two control conditions, categorical comparisons (ANOVA) of the conditions without respect to their stimulus-related SRFs were used. Categorical comparison of the main effects of condition D > C (D = variable time delay without motor effects, C = stimulation without delay and without motor effects) revealed activations related to anticipation (certainty/uncertainty). Differences between conditions A > C, B > D (A = internal, B = external) revealed activations related to only hand movement. Because the main effect analysis revealed nonspecific effects that did not allow differentiation between the confounding factors (extern/self-generated stimulation, onset uncertainty/certainty), a three-way interaction analysis was carried out to account for the independence of uncertainty (B–A)–(D–C) and certainty (A–B)–(C–D) of the impending stimulus onset. The interaction (B–A)–(D–C) separated the effects of externally applied versus self-generated stimulation from effects related to uncertainty. The interaction (A–B)–(C–D) separated the effects of self-generated versus externally applied stimulation from effects related to certainty. The threshold based on a reduced volume (sphere: $SI = 648 \text{ mm}^3$, otherwise = $4,200 \text{ mm}^3$) was set to a FWE corrected $P < 0.05$ (corrected for multiple comparisons).

RESULTS

Behavioral Data

The individual pain thresholds were on average $46.1 \pm 1.06^\circ\text{C}$ (mean $\pm$ standard error of mean). The lowest stimulus was below and the highest stimulus always above the individual pain threshold. Except for P1, the pain-rating categories were nearly equally distributed (Fig. 2). All subjects perceived painful stimuli (P2–P4) in all four conditions.

To reveal the relationship of the physical stimulus intensity (temperature) and the P levels (perceived stimulus intensity) a regression analysis was carried out. It revealed two slightly different regression slopes: (1) externally applied stimulation, physical stimulus intensity = $1.87 \times P \text{ level} + 41.28^\circ\text{C}$ ($r = 0.93$); and (2) self-generated stimulation, physical stimulus intensity = $1.94 \times P \text{ level} + 41.31^\circ\text{C}$ ($r = 0.93$). The ratings between self-generated and externally applied stimulation, however, were not significantly different (Wilcoxon-test, $P < 0.05$).

Functional MRI Data

In a first step the regions showing stimulus-specific parametric activation were identified using the parametric contrast to model a linear signal increase from P1 to P4. A test for interaction between self-generated and externally ap-

Figure 2.

The histogram shows the mean frequency distribution of the different rating categories (P1–P4) for all four conditions (A, black bars; B, dark gray bars; C, white bars; D, gray bars). Except for P1 the rating categories were distributed nearly equally. All subjects perceived painful stimuli (P2–P4) in all four conditions. Error bars indicate standard deviation.

plied stimulation over the perceived pain intensities showed the differences of the condition-specific SRFs, e.g., linear, positive SRF during self-generated and no modulation or a linear, negative slope during externally applied thermal stimulation or vice versa. The three-way interaction analysis delineated the effects of self-generated versus externally applied stimulation from those related to the level of uncer-

tainty of the impending stimuli ([B-A]–[D-C] and [A-B]–[C-D]). Only the SI activation passed an uncorrected threshold of $P < 0.05$ in the three-way interaction (B-A)–(D-C). Because it did not pass the threshold $P < 0.05$ corrected for multiple comparisons, it was considered a trend. Table I delineates areas of the lateral pain system, which revealed differences in the activation patterns between self-generated

TABLE I. Self- (internal) vs. externally generated stimulation

Contrast	Region		<i>x</i>	<i>y</i>	<i>z</i> (mm)	Z score
External vs. internal (Masked contrast)	SI	L	–30	–32	60	3.02 ^a
	SI	L	–34	–30	58	3.15 ^a
External = internal (Conjunction)	S II	L	–60	–22	28	4.40 ^b
	S II	L	–62	–20	24	4.61 ^c
	S II	L	–40	–18	18	6.50 ^c
	S II	R	46	–14	18	4.65 ^b
	S II	R	54	–18	18	3.85 ^a
	Anterior insula	L	–32	6	6	5.04 ^c
	Anterior insula	L	–30	10	6	4.77 ^c
	Anterior insula	L	–32	14	4	4.75 ^c
	Anterior insula	L	–34	8	0	5.11 ^c
	Anterior insula	L	–32	32	–2	4.58 ^c
	Anterior insula	L	–36	8	–4	5.22 ^c
	Anterior insula	R	34	16	4	5.84 ^c
	Anterior insula	R	36	38	–4	4.31 ^b
	Anterior insula	R	40	30	0	3.87 ^a
	Posterior insula	L	–36	–14	10	6.03 ^c
	Posterior insula	R	38	–14	14	4.01 ^a

Areas of significant activations (^a FWE $P < 0.05$, ^b FWE $P < 0.005$, ^c FWE $P < 0.001$, corrected for multiple comparisons, based on reduced volume corrections; Z scores indicate significance of parametric response pattern) are shown for the contrasts. External vs. internal (externally applied and masked, exclusively self-generated stimulation), showing differences in the interaction of the two conditions with the perceived pain intensity (P1–P4). External = internal (conjunction on the second level over externally applied and self-generated stimulation), showing areas with equal interaction patterns resembling the perceived pain intensity during the self-generated and externally applied stimuli. L, left; R, right side.

and externally applied stimuli from areas showing equal SRFs for both conditions. The different response properties for internal (A) versus external (B) conditions and certain (C) versus uncertain (D) conditions can be illustrated by the relative blood oxygenation level-dependent (BOLD) response (mean $\beta \pm$ standard error of mean) related to the perceived pain intensity using regression plots (Fig. 3).

Primary Somatosensory Cortex

The calculated differences in the parametric activation pattern between self- and externally generated stimuli revealed significant activation in the SI contralateral to the stimulation side (masked contrast; local maximum: $x = -30$, $y = -32$, $z = 60$ and $x = -34$, $y = -30$, $z = 58$; Fig. 3a). During external thermal stimulation, SI activation increased with increasing stimulus intensity (P1–P4). In contrast, during the self-generated stimulation condition there was no increase, indicating a significant interaction between perceived intensity and mode of stimulus application (self vs. external). The trend of a different linear response pattern dependent on self-generated versus externally applied stimulation was significant in the direct interaction contrast (B vs. A, $T = 1.75$; $P < 0.05$). Activation during self-generated, nonpainful tactile stimulation (P1), however, was higher than that during external stimulation. This indicated that the attenuation during self-generated painful stimulation was related specifically to pain. Neither anticipation nor only hand movements could account for this activation pattern. Parametric activation for the certain (C) and uncertain (D) stimulus conditions revealed no significant differences. The three-way interaction (B–A)–(D–C) showed a trend that indicated the different parametric response patterns (external vs. internal condition) of SI were independent of the level of certainty ($x = -34$, $y = -30$, $z = 58$, $T = 1.92$; $P < 0.05$). The same physical thermal stimulus thus elicited a lower, attenuated activation pattern in SI when it was self generated.

Secondary Somatosensory Cortex

In contrast to the activation pattern in SI, activity in SII increased linearly with the applied stimulus intensity, irrespective of the mode of application in all conditions (Fig. 3b; A–D).

Insular Cortex

Anterior and posterior insular cortices showed parametrically modulated SRFs during self- and externally generated thermal stimulation that did not significantly differ from each other. They also showed equal response patterns for the different levels of certainty (Fig. 2c,d; C/D, second level conjunction; local maximum in anterior insula: $x = -36$, $y = 8$, $z = -4$, Fig. 3c; local maximum in posterior insula: $x = -36$, $y = -14$, $z = 10$, Fig. 3d). Accordingly, activation was independent of the mode of application. Interestingly, there were two qualitative differences. First, SRF in the anterior insula was shifted in parallel toward higher activation levels, i.e., for a given pain perceptual level the

activation was higher when the stimuli were self-generated. This was not true for the posterior insula. Second, whereas a linear increase in activation did not precede the first painful perception (P2) in the anterior insula, parametric activation in the posterior insula started with an increase from non-painful P1 to P2, indicating a stimulus-intensity coding SRF.

DISCUSSION

The aim of this study was to clarify the mechanisms involved in the lateral pain system that distinguish self-generated from externally applied painful stimuli. We found attenuated response patterns during self-generated stimulation in SI that may indicate a feed-forward control of the prediction of the sensory consequence of pain-related action. In contrast, the distinctly different activation pattern in SII provides further evidence that SI and SII play two different roles in human pain processing.

Experimental Design

The specific aim of our design was to minimize motor-related confounds and movement artifacts in the MRI scanner by separating the moving hand from the resting stimulation site. This set-up also ensured that the applied pressure of the thermode was identical under all conditions (tactile component) and it exactly determined the timing (and certainty) of the impending stimulus. It is possible, however, that perceptual or activation differences might have been greater if: (1) the subject had moved the stimulus all the way to the contralateral hand; (2) if he had even moved the right hand to the thermode; or (3) if we had used a larger rating scale, but at the cost of methodological confounds. To avoid this, we used four clearly distinguishable pain perception levels as a prerequisite for a parametric analysis involving subjects who used the entire range of ratings [Buchel et al., 2002].

Attenuation of Pain-Related Activation During Self-Produced Stimulation

Both tactile and thermal stimuli activate the primary somatosensory cortex. SI contains nociceptive neurons with small receptive fields [Kenshalo and Willis, 1991]. Although it remains a controversial issue, the activity of SI is thought to be related to the duration and intensity of the stimulus. This was confirmed recently by several [Coghill et al., 2001; Hofbauer et al., 2001] but not all imaging studies [Ringler et al., 2003]. More recently, we and others showed this to be true for purely nociceptive (e.g., laser) stimuli without concomitant tactile stimulation [Bingel et al., 2003; Bornhovd et al., 2002; Kulkarni et al., 2005; Timmermann et al., 2001], in a somatotopic organization [Bingel et al., 2004]. Our activation site was immediately posterior to the central sulcus and in accordance with other imaging pain studies on SI [Bingel et al., 2003; Bushnell et al., 1999; Coghill et al., 2001; Hofbauer et al., 2001; Ploner et al., 1999]. The commonly used WFU_PickAtlas (Wake Forest University; <http://www.ansir.wfubmc.edu>) allocates our coordinates into Brodmann

Figure 3.

Pain-related activations in the SI (a), SII (b), anterior (c) and posterior insula (d) are shown (left) on representative axial slices (L, left; R, right side). Activations corresponding to the linear regression slopes using β values as parameters of the size of the effect (right) are marked by white arrows (coordinates are shown on the ordinate). The linear regression slopes showing the condition-specific SRF of the areas using β values as parameters of the effect are shown for the interaction self- vs. externally applied (A/B) stimulation and certainty/uncertainty (C/D) on the right side. An asterisk (*) in the regression plot indicates a significant differ-

ence (interaction) between the two slopes. For better illustration of the SRF (right side), the parameters of the self-generated condition (A) are indicated in blue, the externally applied condition (B) in red, the certain control condition (C) in light blue, and the uncertain control condition (D) in purple. Activations related to externally applied but masked and to exclusively self-generated stimulations are shown on the representative axial slices (left) in yellow and the areas derived from the second-level conjunction in green.

area 3 (SI). Our linear SRF of SI agrees with previous intensity-related pain studies using fMRI and indicates that activation is related to nociception rather than to purely tactile stimulation [Bornhovd et al., 2002]. SI is thus likely to be important for both sensory localization and intensity discrimination [Bushnell et al., 1999].

In contrast to purely tactile stimulation [Blakemore et al., 1998b], parametric SI activation was attenuated when painful contact–heat stimuli were self-generated but not when externally generated. More specifically, this attenuation seems to be related to pain, because activation was higher for purely tactile, nonpainful stimulation (P1) during self-generated stimuli. If the tactile component were in general responsible for the modulation, one would also expect the SRFs to be shifted in parallel for the two conditions; however, we found different slopes for the conditions. A similar attenuation of activity during self-generated painful stimulation was also found in the posterior part of the anterior cingulate cortex (ACC), supporting its role in sensory nociceptive processing [Buchel et al., 2002; Mohr et al., 2005].

Although the source of this pain-related attenuation of the SI activation remains under investigation, some points have been clarified. First, SI has been shown to be highly modulated by cognitive factors that alter pain perception, including attention [Meftah et al., 2002; Seminowicz et al., 2004], distraction [Petrovic et al., 2000, 2004; Tracey et al., 2002], previous experience [Bushnell et al., 1999], expectation [Sawamoto et al., 2000], anticipation [Porro et al., 2002], and hypnosis [Derbyshire et al., 2004]. These factors might be one reason for the inconsistency of SI activation in pain-imaging studies. Our findings that SI activity is attenuated during self-generated pain, possibly by top-down mechanisms [Staines et al., 2002], therefore expands the concept of context-dependent modulation (self- vs. external stimulation). The acute noxious stimuli used in our study constitute task-relevant sensory input, because they were biologically meaningful and because the experimental task required special attention due to the subsequent pain rating of each individual stimulus. A gating of non-attended nociceptive information is therefore unlikely.

Whereas a shift of attention to a somatosensory or painful stimulus is usually associated with an increase in SI activity [Hamalainen et al., 2002; Hofbauer et al., 2001; Meftah et al., 2002], a shift away from the stimulus elicits neural attenuation [Bantick et al., 2002; Craig et al., 1994; Ohara et al., 2004; Petrovic et al., 2000; Staines et al., 2002]. Due to its fixed latency and thus a higher level of certainty of the impending pain, self-generated stimulation in our study might have been associated with less focused attention than that in the external stimulus condition. External stimulation was applied with variable latencies and accordingly the certainty of onset of the impending stimulus was less. This might have been associated with a higher level of attention to the impending stimulus. We specifically excluded the possibility that the attenuation of activation in self-generated stimuli is related to expectancy or anticipation (condition C/D), but different levels of attention might have still contributed. In

contrast, the perigenual ACC showed decreased activation during externally applied painful stimulation, which was related to the level of onset uncertainty of the impending stimuli [Mohr et al., 2005].

Second, painful stimuli might also inhibit or decrease neural synchronicity in SI [Bushnell et al., 1999]. One could speculate that inhibitory SI neurons underlie a stronger cognitive modulation. It remains to be determined why inhibition should be more active during self-generated stimuli.

Finally, we previously reported distinct differences in cerebellar activation between actively and passively generated noxious stimuli [Helmchen et al., 2004]. A psychophysical interaction (PPI) analysis for these cerebellar sites did not reveal any significant task-related contribution to the somatosensory cortices. Contrary to self-generated tactile stimuli [Blakemore et al., 1999b], the cerebellum therefore does not seem to be the source of the SI attenuation.

Pain-Related Activation Independent of the (External vs. Self-Generated) Conditions

In contrast to SI, SII activation was not attenuated by self-generated thermal noxious stimuli. This difference in cortical activation (SI vs. SII) either requires that different afferent nociceptive information reaches SII or a different mode of nociceptive processing takes place. SII was also shown to be involved in human tactile somatosensory [Binkofski et al., 1999; Del Gratta et al., 2002] and pain processing using positron emission tomography [PET; Casey et al., 1996; Coghill et al., 2001], magnetoencephalography [MEG; Timmermann et al., 2001], and fMRI [Bingel et al., 2003, 2004; Bornhovd et al., 2002; Ringler et al., 2003]. Although SII also has sensory-discriminative functions [Bingel et al., 2004; Schlereth et al., 2003], its activation largely contributes to the intensity dimension of phasic pain [Ringler et al., 2003]. More specifically, parametric analysis has shown that the SRFs of SI are more related to stimulus intensity, whereas those of SII are more related to pain intensity [Bornhovd et al., 2002], i.e., there is a linear increase of BOLD signal with increasing pain perception. One can speculate that unlike tactile information, an attenuation of nociceptive signals in a pain-encoding area (SII) is not biologically useful during self-generated noxious stimuli. Our data thus are compatible with the concept that SII is involved in encoding pain intensity [Bornhovd et al., 2002]. An area with this function does not need to distinguish between self-generated or externally applied noxious stimuli. It primarily detects signals of pain intensity to prevent harm to the organism; therefore, it seems neurobiologically logical that SII activation is not attenuated.

Another argument indicates that SII plays a distinct role in nociceptive processing. In contrast to a serial activation of SI and SII during tactile stimulation [Iwamura, 1998; Schnitzler et al., 1999], both areas are activated simultaneously during noxious stimuli [Ploner et al., 1999; Tarkka and Treede, 1993]. This indicates a parallel cortical processing of nociceptive information. This parallel processing is in accordance with the differential activation of SI and SII during

self-generated stimuli. Unlike tactile stimulation, which shows an attenuation of somatosensory activation in SII during self-generated stimuli [Blakemore et al., 1998b], attenuation was found only in SI and not in SII. This could be further evidence for the functionally relevant direct thalamocortical projections to SII, which bypass SI and ensure the evolutionary meaningful, immediate access of nociceptive information to the motor [Friedman and Murray, 1986], limbic [Lenz and Dougherty, 1997], and memory [Friedman and Murray, 1986] structures to prevent potentially harmful stimuli from reaching the individual. Moreover, it highlights the distinctly different neural mechanisms (SI, SII) underlying the cancellation of self-generated tactile versus nociceptive stimulation. The absence of pain-perceptual differences between self- and externally generated stimulation may indicate that the attenuation of neural activity is related to the sensory prediction of pain-related action and not due merely to perceptual differences. The relevance of imaging data in the absence of behavioral (psychophysical) effects has been demonstrated in the past [O'Craven et al., 1997; Wilkinson and Halligan, 2004].

In accordance with this concept, activation of the anterior and posterior insular cortices also did not show significant differences in the SRF of all conditions (self-generated vs. external) and is therefore compatible with that of SII and the pain intensity-coding area of the ACC [Buchel et al., 2002; Mohr et al., 2005]. The insular cortex is activated during contact-thermal [Brooks et al., 2002; Casey et al., 2001; Coghill et al., 2001; Craig et al., 1996, 2000; Hofbauer et al., 2001; Peyron et al., 2000, 2002; Tolle et al., 1999] and non-tactile painful laser stimulation [Bornhovd et al., 2002]. Anterior and posterior insulae are involved in pain rather than stimulus intensity [Bornhovd et al., 2002]. Accordingly, the insular cortex activation in our subjects was largely independent of how the stimulus was applied, i.e., the SRFs were similar.

CONCLUSIONS

Several lines of evidence indicate that cognitive top-down control mechanisms are involved in endogenous pain control [Bantick et al., 2002; Craig et al., 1994; Ohara et al., 2004; Staines et al., 2002]. For example, an area particularly related to somatosensory discriminative aspects of nociceptive processing (SI) showed attenuated activation during self-generated stimuli, possibly reflecting top-down control mechanisms. Areas largely related to pain perception (e.g., SII, insular cortex) were involved primarily in encoding pain intensity but were largely independent of how the stimulus was applied in our experimental conditions. The attenuation of the SI activation during self-generated stimuli in our subjects implies that prediction of the sensory consequences of pain-related action may be one adaptive strategy to alleviate stimulus intensity, when appropriate. It also reflects fundamental differences between the prediction of the sensory consequences of movements eliciting tactile somatosensory versus nociceptive stimulation.

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