Flexible Cerebral Connectivity Patterns Subserve Contextual Modulations of Pain

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The perception of pain can be significantly modulated by the behavioral context. Here, we investigated how contextual modulations of pain are subserved in the human brain. We independently modulated the attentional and emotional context of painful stimuli and recorded brain activity by using functional magnetic resonance imaging. Our results confirm that attention to pain and a negative emotional context increases pain perception and this is concomitantly associated with increased neural activity in the anterior insular cortex. Connectivity analyses further reveal that during attentional and emotional modulations of pain, the anterior insula selectively and flexibly connects to attentional and emotional brain networks in frontoparietal and medial temporal lobe areas, respectively. We conclude that the flexible functional connectivity of the anterior insula to other functional systems of the brain, for example, attentional and emotional brain networks, subserves the extraordinary sensitivity of the pain experience to contextual modulations.

Keywords: attention, emotion, fMRI, functional connectivity, insular cortex, pain modulation

Introduction

Pain is a highly subjective sensory experience that, more than any other sensory experience, can be modulated by the behavioral context (Melzack and Casey 1968). Particularly, the attentional and emotional state can substantially shape the perception of pain (for review, see Villemure and Bushnell 2002; Wiech et al. 2008; Wiech and Tracey 2009).

Within the brain, the pain experience is subserved by an extended network of brain areas including somatosensory, cingulate, and insular cortices (Apkarian et al. 2005; Tracey and Mantyh 2007). Corresponding to the perceptual effects, the attentional and emotional state can significantly modulate pain-related activations within the cerebral pain network (Villemure and Bushnell 2002; Wiech et al. 2008; Wiech and Tracey 2009). The perception of pain is thus likely to not merely depend on the neural activity of the cerebral pain network but rather on the flexible interaction of the cerebral pain network with other functional systems of the brain. In particular, brain areas related to attentional (Corbetta and Shulman 2002; Pessoa et al. 2003; Dosenbach et al. 2008) and emotional (Dolan 2002; Wager et al. 2008) processes, respectively, may flexibly connect to and interact with other brain areas of the cerebral pain network. Correspondingly, functional imaging studies implicated prefrontal brain areas in pain modulation (Wager et al. 2004), including attentional modulations of pain (Lorenz et al. 2003). A recent functional magnetic resonance imaging (fMRI) study extended these findings by showing different context-dependent corticocortical interactions during attentional and emotional modulations of pain (Villemure and Bushnell 2009) but were probably particularly sensitive to differences rather than similarities between the different contextual modulations of pain.

Here, we therefore investigated functional connectivity during contextual modulations of pain in an fMRI experiment. We applied noxious heat stimuli to healthy human subjects and modulated the attentional and emotional context of pain while keeping the intensity of noxious stimuli constant. We hypothesized that context-dependent functional interactions, that is, flexible functional connectivity patterns between the cerebral pain network and brain areas related to attentional and emotional processes, subserve contextual modulations of pain.

Materials and Methods

Subjects

Eighteen healthy male human subjects with a mean age of 27 years (range, 20–33 years) participated in the experiment. Written informed consent was obtained from all subjects before participation. The study was approved by the local ethics committee and conducted in conformity with the Declaration of Helsinki.

Paradigm

Painful radiant heat stimuli were applied to the dorsum of the right foot (including medial and lateral aspects) in blocks of 15-s duration. The attentional and emotional context of pain was independently modulated in a 2 × 2 factorial design resulting in 4 different conditions (Fig. 1A). Noxious stimulation was kept constant across conditions.

Attention to pain was modulated by task instructions given before each 15-s block of noxious stimulation (Fig. 1B). In the “low-attention” condition, subjects were instructed to count the total number of painful stimuli within each block. In the “high-attention” condition, subjects were asked to count the number of stimuli applied to the left or right half of the foot. The low-attention condition, thus, implied detection of noxious stimuli only, whereas the high-attention condition implied detection plus spatial discrimination of noxious stimuli, which is expected to require more attentional resources than the low-attention condition. After each block, subjects were asked to indicate the respective number of stimuli, that is, the total number of stimuli or the number of stimuli applied to one side of the foot with a button press of the right hand. Performance of the counting task during the low-attention and high-attention conditions of the main experiment confirmed that subjects were performing above the chance level of 25% (39% and 38%, P = 0.024 and P = 0.020, paired t-tests, see below) and thus attending to the painful stimulation. As task difficulty differs between conditions, similar performance in both tasks indicates a successful manipulation of attention.

The emotional context of pain was modulated by the simultaneous presentation of emotional pictures from the International Affective Picture System (IAPS; Lang et al. 2005). The IAPS is a collection of pictures with validated valence and arousal values, which were obtained in 16 separate studies that included approximately 100 participants (see Bradley and Lang 2007 for a review on the theory and applications of the IAPS). These ratings were chosen since they were...
considered to be sufficiently reliable and valid. Moreover, ratings obtained in the present group of subjects would have interfered with the grading of attention to pain and/or would have implied repetition effects. In the "neutral" condition, pictures of neutral valence were presented, whereas in the "negative" condition, pictures of negative valence were presented. Both picture sets were balanced for arousal values. Subjects were instructed to look at the pictures, but no particular task was required with respect to the pictures.

The experiment comprised a $2 \times 2$ factorial design resulting in 4 conditions (Fig. 1A). For each condition, 4 blocks of trials were applied resulting in a total of 16 blocks. Blocks of the different conditions were presented in a pseudorandom sequence. Figure 1B shows the sequence of a single block. Each block began with a visual cue ("count left!", "count right!", or "count total!") that was presented for 2 s. After an interval of 4 s, 6 painful stimuli were applied in a block of 15-s duration. Painful stimuli had a short duration of 4 ms and were separated by an interstimulus interval between 2 and 3 s. During each 15-s block, 6 emotional pictures of neutral or negative valence were presented. Stimulus duration of the pictures was 2 s; interstimulus interval was varied between 0.25 and 0.75 s. Please note that the timing of painful stimuli and emotional pictures was pseudorandomly varied. Thus, the relative timing of painful and visual stimuli varied unpredictably. Six seconds after each block, the subjects were visually instructed to rate the number of stimuli ("total stimulus number?", "right stimulus number?", or "left stimulus number?"). The subjects chose the number of stimuli from a visually presented list of 4 numbers by button presses of the index and middle finger of the right hand. Chance level of the task was, thus, 25%. The rating period had a fixed duration of 5 s. Total duration of a block was 32 s; the interval between blocks was varied between 4.5 and 7.5 s. At the end of the experiment, which was performed in a single series, the subjects were asked to rate the pain intensity during the different attentional and emotional conditions on a visual analogue scale (0–10, anchored at no pain and worst tolerable pain). A post hoc pain rating procedure was chosen since online pain ratings after each block would have continuously required full attentional resources and would therefore have interfered with a grading of attention to pain. As the grading of attention to pain represents a core feature of our study, we deliberately decided to obtain lumped post hoc ratings that, nevertheless, represent an inherent and inevitable limitation of the present study. Prior to the fMRI experiment, a practice session was performed to familiarize the subjects with the tasks and stimulations and to assure correct understanding of the experiment.

**Stimuli**

Painful stimuli were cutaneous laser stimuli that selectively activate nociceptive fibers without concomitant activation of tactile fibers (Plaghki and Mouraux 2003). The laser device was an Nd:YAP laser (DEKA) with a wavelength of 1340 nm and spot diameter of 6 mm.
Stimulus intensity was individually adjusted to evoke moderately painful sensations with an intensity of 5 on a visual analogue scale (0–10, anchored at no pain and worst tolerable pain) requiring a mean stimulus intensity of 3.9 J (range, 3.5–4.5 J). Stimuli were applied to the dorsum of the right foot. Before the experiment, the longitudinal midline of the dorsum of the right foot was marked. All stimuli were applied at a distance of 1–2 cm from the midline. Painful stimulations in all 4 conditions were exactly the same. In each block, 6 painful stimuli with identical physical properties were applied with an interstimulus interval of 2–3 s. Four stimuli were applied to the left and 2 to the right side of the midline or vice versa. Psychophysical pilot experiments showed that these stimulation parameters result in a task performance that was significantly above chance but below 100% in both the high-attention and the low-attention conditions that was confirmed by the performance during the main experiment (see above).

Emotional stimuli were pictures from the IAPS. Two sets of each 24 “neutral” and “negative” pictures were compiled. Neutral and negative pictures differed with respect to valence (5.1 and 2.3, P < 0.001, 2-tailed t-test) but not with respect to arousal values (5.1 and 4.9, P = 0.14, 2-tailed t-test, ratings from 100 healthy subjects; Lang et al. 2005). Both sets included bodily contents. Each picture was presented twice in a pseudorandom sequence throughout the experiment. The pictures were back-projected on a screen subtending a visual angle of about 10°.

Data Acquisition
Magnetic resonance scanning was performed on a 3-T Varian MRI scanner. We used an optimized echo planar imaging ( EPI) T2*-sensitive sequence (Deichmann et al. 2003) in which the influence of in-plane susceptibility gradients is reduced by tilting the imaging slice by 30° from axial to coronal orientation. Through-plane susceptibility gradients were compensated by means of a moderate preparation gradient pulse similar to z-shimming. Each volume comprised 41 axial slices of 3 mm thickness with 3 × 3 mm in-plane resolution, repetition time 3 s, echo time 30 ms, field of view 192 × 192 mm, and matrix size 64 × 64 pixels. At the end of each scanning session, a T1-weighted structural image was acquired for each subject.

Data Analysis
Data were analyzed using FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl/). Preprocessing included removal of the first 4 volumes, motion correction, B0-unwarping using field maps, spatial smoothing using a Gaussian kernel of full-width at half-maximum of 8 mm, and temporal high-pass filtering with a cutoff of 200 s. Data analysis was performed using the general linear model (GLM). Brain activity was characterized by using a mixed-effects general linear modeling procedure composed of fixed-effects first-level individual analysis and random-effects second-level group analysis. The first-level models comprised 6 regressors. Four regressors were the stimulation periods of the 4 conditions (AE, Ac, Ae, and ae). The remaining 2 regressors were the cue and rating periods. All regressors were obtained by convolving a boxcar function of the event duration with the canonical hemodynamic response function (mean lag 6 s and full-width at half-maximum 6 s). Only the first-level contrast images for the stimulation periods were subsequently used for second-level analysis treating individual subjects as a random factor.

To investigate which brain areas of the cerebral pain network are most closely related to the context-dependent experience of pain, we related brain activity during the stimulation periods of the 4 conditions to pain ratings as contrast weights. For the analysis, mean pain ratings were subtracted from pain ratings. The effects of attentional and emotional context were analyzed by contrasting high- and low-attention conditions and negative and neutral emotional conditions, respectively. Activations are reported at a statistical threshold of P < 0.001, uncorrected, except for a priori hypothesized regions, which were thresholded at P < 0.005, uncorrected (only clusters involving 5 or more contiguous voxels are reported) (Phelps et al. 2004; Etkin et al. 2006; Hooker et al. 2006). Please note that these uncorrected thresholds only provide an unquantified control for false positives. Small volume-corrected results for the a priori hypothesized regions were also reported. A priori regions included the pain areas S1, S2, insular, and anterior cingulate cortex (Apkarian et al. 2005; Tracey and Mantyh 2007). Additional emotional a priori areas were the orbitofrontal and ventromedial prefrontal cortex, parahippocampal gyrus, and amygdala (Dolan 2002; Wager et al. 2008), and attentional areas were the superior frontal gyrus and the superior parietal lobule (Corbetta and Shulman 2002; Pessoa et al. 2003).

To investigate context-dependent interactions between areas of the cerebral pain network and attentional and emotional brain areas, we performed psychophysiological interaction analyses (PPIs, Friston et al. 1997). Specifically, we tested for context-dependent changes in the functional connectivity of the anterior insula whose time course represented the physiological variable in the PPI analysis. The bilateral anterior insula was chosen as this brain area showed the closest relationship to the subjective and contextually modulated experience of pain. The activity time courses were extracted from an anatomical mask of the anterior insula based on the Harvard-Oxford-Atlas as implemented in FSL. The posterior border of the anterior insula was set at y = 0 since this coordinate closely corresponds to the border between anterior and posterior insula (Naidich et al. 2004). To compute the PPI regressor, the mean activity was subtracted from the anterior insula time course. Psychological variables were the attentional (high attention and low attention) and emotional (negative and neutral) context. The PPI regressor was computed as the product of the insula activity and a vector coding for the attentional/emotional context (<1 for low-attention trials, 1 for high-attention trials: -1 for neutral emotion, 1 for negative emotion). The GLM for the PPI analyses thus included regressors for the main effects of attention and emotion and for the time course of the anterior insula and the PPI regressor. As we were specifically interested in the differential context-dependent connectivity patterns of the anterior insula to attentional and emotional brain areas, we defined regions of interest as 8-mm spheres centered on peak activations of the main effects of attentional and emotional context. The threshold was set to P < 0.05, small volume corrected.

Results
Pain ratings indicated that the subjects perceived the painful stimuli as more intense during the high-attention than during the low-attention conditions (P = 0.029, paired t-test; Fig. 1 C). Similarly, subjects reported higher pain intensities when they were presented with the negative emotional pictures compared with the neutral pictures (P = 0.002, paired t-test). Thus, as expected from previous studies (for review, see Villemure and Bushnell 2002; Wiech et al. 2008; Wiech and Tracey 2009), the attentional and emotional context of painful stimuli significantly modulated the subjective experience of pain.

Within the brain, we first investigated which areas of the cerebral pain network reflect the subjective experience of pain during modulations of the attentional and emotional context. We therefore correlated subjective pain intensity across the 4 conditions with the neural activity of the cerebral pain network. Results show that only the neural activity in the bilateral anterior insula was significantly associated with the contextually modulated experience of pain (right: 26,22,–2.9; left: –30,12,0, z = 2.6; left: –30,12,0, z = 2.9; Fig. 1 D).

We next investigated which brain areas are sensitive to modulations of the attentional and emotional state. We therefore contrasted brain activity during high and low attention and during negative and neutral emotion. The attentional contrast showed strongest activations in the bilateral frontal eye fields and intraparietal sulci (Fig. 2, upper panel, and Table 1). These brain areas are well known to represent essential parts of a distributed network that controls attention and exerts attentional modulations of sensory processing (Corbetta and Shulman 2002; Pessoa et al. 2003).
Within the cerebral pain network, attention significantly modulated the activity of the bilateral anterior insula (Fig. 2, upper panel). The emotional contrast revealed bilateral activity in the medial temporal lobe extending into parahippocampal gyrus and amygdala (Fig. 2, lower panel, and Table 1), which are both closely related to emotional processes and emotional modulations of sensory processes (Dolan 2002; Wager et al. 2008). Moreover, within the cerebral pain network, emotion was found to modulate the activity of the anterior insula with a slightly more posterior location than attentional effects. No significant interaction was observed between attentional and emotional modulations. These results show that the attentional and emotional modulations of the present study involve well-known brain networks associated with attentional and emotional processes such as frontoparietal and medial temporal lobe areas, respectively. During these attentional and emotional modulations, the subjective experience of pain was particularly related to the neural activity of the anterior insula. The anterior insula is therefore likely to represent a neural target of contextual modulations of pain. In contrast, based on observations in the visual system, frontoparietal and medial temporal lobe areas have been implicated in the attentional and emotional control of sensory processing, respectively (Corbetta and Shulman 2002; Dolan 2002; Pessoa et al. 2003; Wager et al. 2008). It is therefore tempting to assume that these brain areas represent neural sources of contextual modulations of pain. We, thus, hypothesized that the flexible functional connectivity between neural sources and targets, that is, between frontoparietal and medial temporal lobe areas and the anterior insula, subserves the contextual modulations of pain of the present study. In order to test this hypothesis, we performed a PPI (Friston et al. 1997) of the anterior insula during attentional and emotional modulations of pain. PPI analyses revealed changes in functional connectivity between brain areas related to changes in a psychological variable. In our case, the functional connectivity of the anterior insula was related to the attentional and emotional context. During attentional modulation of pain, the results of the PPI analysis revealed changes in functional connectivity between the anterior insula and areas of the frontoparietal attention network but not with brain areas associated with emotional processes in the medial temporal lobe (Fig. 3, left side, and Table 2). Conversely, during the emotional modulation of pain, we observed changes in functional connectivity of the anterior insula to medial temporal lobe areas but not to brain areas of the frontoparietal attentional network (Fig. 3, right side, and Table 2). These observations indicate that contextual modulations of pain significantly influence the functional connectivity of the anterior insula to brain areas associated with attentional and emotional processes. The flexible functional connectivity of the anterior insula to attentional and emotional brain areas may therefore subserve the

Table 1
Effects of attention and emotion

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<th>Area</th>
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<td>Attention</td>
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<td>IPS</td>
<td>L</td>
<td>4.7</td>
<td>−34, −46, 42</td>
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<td>R</td>
<td>4.7</td>
<td>54, −32, 46</td>
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<td>SPL</td>
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<td>4.6</td>
<td>12, −66, 64</td>
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<td>FEF</td>
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<td>4.5</td>
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<td>R</td>
<td>4.5</td>
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<td>Frontal pole</td>
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<td>L</td>
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<td>aINS</td>
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<td>R</td>
<td>3.9</td>
<td>28, 22, 2</td>
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<td>MCC</td>
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<td>3.4</td>
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<td>aINS</td>
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Note: IPS, intraparietal sulcus; L, left; R, right; SPL, superior parietal lobule; FEF, frontal eye field; aINS, anterior insula; MCC, midcingulate cortex; MTL, medial temporal lobe (amygdala and parahippocampal gyrus). All activations were significant at $P < 0.05$, small volume corrected, except for the emotional effects in the right MTL.
extraordinary sensitivity of the pain experience to contextual modulations.

Discussion

Here, we investigated the neural mechanisms of contextual modulations of pain. We independently modulated the attentional and emotional context of pain while keeping the intensity of noxious stimulation constant. Using fMRI, we show that during contextual modulations of pain, the neural activity of the anterior insula is particularly related to the subjective experience of pain. Further analyses reveal that the anterior insula flexibly connects to attentional and emotional brain areas during respective contextual modulations. Our results thus suggest that not only the neural activity of the anterior insula within the cerebral pain network but also, and critically, its momentary functional connectivity to other relevant brain areas represents an important determinant of the pain experience.

Many previous studies agreed that paying attention to pain and/or a negative emotional context can increase the perception of pain (reviewed in Villemure and Bushnell 2002; Wiech et al. 2008; Wiech and Tracey 2009). Most studies on attentional modulations (reviewed in Villemure and Bushnell 2002; Wiech et al. 2008) compared conditions where subjects had to pay attention to pain with control conditions without specific instructions or where subjects had to pay attention to another task. Those studies compared different foci but not necessarily different levels of attentional engagement (Seminowicz and Davis 2007). In contrast, the present paradigm implies a grading of attention to pain that compares different levels rather than different foci of attentional engagement. That way, the paradigm was intended to identify the cerebral targets and sources and, using PPI analyses, functional interactions between targets and sources of attentional control over pain. However, it is important to note that the terms “targets” and “sources” imply a mostly hypothetical causality that cannot directly be inferred from PPI analyses that represent measures of functional but not effective connectivity.

We found attentional activations in the frontal eye field and the intraparietal sulcus bilaterally that corresponds well to sources of attentional control as defined in other modalities (Corbetta and Shulman 2002; Pessoa et al. 2003) and substantiates that the frontoparietal attention network is also involved in the attentional control of pain. This network is likely to reflect endogenous, cognitively driven, and top-down–mediated rather than exogenous, stimulus driven and bottom-up–mediated aspects of attention. Correspondingly, the present results most likely reflect endogenous aspects of attention because stimulus intensity was kept constant, and exogenous aspects should therefore not have differed between conditions. As we modulated the attentional context by a spatial discrimination task, our findings correspond to recent studies on brain mechanisms supporting spatial discrimination of pain (Oshiro et al. 2007, 2009). Those studies found frontoparietal activations including the frontopolar cortex, which is in good accordance with the present results. Notably, in the present study, attentional activations of the prefrontal cortex were located in the frontal eye fields,

Figure 3. Flexible functional connectivity of the anterior insula during attentional and emotional modulations. PPI analyses show that the connectivity of the anterior insula to the frontal eye field but not to the medial temporal lobe covaried with attentional modulations. The connectivity of the anterior insula to the medial temporal lobe but not to the frontal eye field covaried with emotional modulations. For visualization, maps were thresholded at $P < 0.05$, uncorrected. Please note that the PPI analysis was performed as a region-of-interest analysis to attentional and emotional brain areas as defined from the main effects of attention and emotion.

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<td>R</td>
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<td>Emotion</td>
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Note: FEF, frontal eye field; L, left; R, right; MTL, medial temporal lobe (amygdala and parahippocampal gyrus).
whereas pain modulatory activations during heat allodynia (Lorenz et al. 2003) and placebo manipulations (Wager et al. 2004) were located in the dorsolateral prefrontal cortex. The more lateral and anterior locations in those studies may indicate that alldynia and placebo manipulations do represent not only attentional processes but also more complex cognitive operations.

Only few previous studies investigated emotional effects on pain processing (Wiech and Tracey 2009). Ploňhaus et al. (2001) showed that anxiety can modulate pain perception and pain processing in the human brain. Intriguingly, in that study, modulations of pain perception were paralleled by insular cortex activations, which in turn were predicted by the neural activity of the entorhinal cortex. This is in good accordance with the present findings of an emotion-related functional coupling of medial temporal lobe structures with the insula. Another recent study investigated the effects of emotional pictures on pain perception and pain processing (Roy et al. 2009). The authors found that emotional modulations of pain perception were related to the neural activity of the anterior insula and the bilateral parahippocampal gyrus that corresponds well to our present findings. Studies in patients suffering from chronic pain provide further evidence for a role of the anterior insula and the medial temporal lobe including the parahippocampal region and the amygdala for the emotional augmentation of pain (Giesecke et al. 2005; Gundel et al. 2008; Schweinhardt et al. 2008). Moreover, the present location of emotional modulations of the anterior insula corresponds to locations of increased functional connectivity between the ventral anterior insula and the amygdala during peripheral autonomic changes (Mutschler et al. 2009) rather than to the location of dorsal anterior insula–amygdala connectivity observed during passive tasting (Bender et al. 2009). In addition, we observed that the neural activity of the bilateral anterior insula was associated with contextual modulations of pain. Bilateral activations of the anterior insula are well compatible with the proposal that interactions between right and left anterior insula subserve emotional modulations of pain (Craig 2005). However, since we only stimulated the right side of the body, the present study does not allow for unequivocal analyses of hemispheric lateralizations and interactions.

Recent fMRI (Villemure and Bushnell 2009) and electroencephalography (Kenntner-Mabiala et al. 2008) studies directly compared attentional and emotional modulations of pain perception and pain processing. Both studies dissected the pain experience into sensory and affective components. As attentional and emotional modulations of pain affect sensory and affective components of pain differentially, the studies may be particularly sensitive to differences rather than similarities between different contextual modulations of pain. Consequently, the results of these studies indicated that attention and emotion exerted partially different effects on pain perception and pain processing in the human brain, with attention affecting only sensory aspects and emotion affecting both sensory and affective aspects of pain perception and processing. The present findings complement and extend these studies by showing that attentional and emotional modulations of pain actually relate to different patterns of functional connectivity. However, we decided to obtain compound pain ratings rather than to experimentally dissect pain perception. Correspondingly, our analysis may be less sensitive to differences between emotional and attentional modulations of pain but rather aims at common mechanisms of pain modulation. Consequently, our study reveals that attentional and emotional modulations of pain originate from different cerebral sources but can flexibly connect to and act on similar higher order targets within the cerebral pain network, such as the anterior insula.

Our results show that attention and emotion can both modulate the neural activity of the anterior insula. These findings are well compatible with the hypothesis that this brain area integrates sensory and contextual information (Coghill et al. 1994; Paulus and Stein 2006; Starr et al. 2009) to generate a predictive model (Paulus and Stein 2006) and a higher order representation (Craig 2002, 2009; Critchley 2005) of interception, that is, the subjective state of the body. Our results are also in line with the hypothesis that the anterior insula is involved in the supramodal assessment of the magnitude and relevance of external and internal events (Baliki et al. 2009). However, our findings do not necessarily imply that all contextual modulations affect the same neurons within the anterior insula. Rather, emotional and attentional factors may be integrated along a posterior axis (Craig 2009) that would be in accordance with our observation of a more posterior insular activation for the emotional compared with the attentional manipulation. The flexible functional connectivity of anterior insula circuitries with attentional and/or emotional brain networks is thus likely to subserve the continuously changing integration of sensory information with contextual information (Jabbi et al. 2008).

Cerebral connectivity has been increasingly recognized as a crucial determinant of perception and behavior (Eriston 2002) and may be particularly relevant for the perception of pain that, more than other sensory experiences (Rosier et al. 2002), depends on the integration of sensory and contextual processes. Accordingly, imaging studies showed that the functional connectivity of descending pathways from frontoinsular cortices to subcortical structures and the brainstem changes during different modulations of the pain experience (Petrovic et al. 2002; Valet et al. 2004; Bingel et al. 2006; Craggs et al. 2007; Wager et al. 2007; Zaki et al. 2007; Akitsuki and Decety 2009; Eippert et al. 2009). More recent findings revealed that functional connectivity even before a potentially painful event biases the subsequent perception of pain (Ohara et al. 2008; Ploner et al. 2010) and that these effects relate to pain-relevant personality traits (Ploner et al. 2010). Our study extends these findings by revealing a basic and relatively simple mechanism of contextual modulations of pain, that is, the flexible functional connectivity of the anterior insula as a brain area involved in the evaluation of the intensity and behavioral relevance of potentially painful events. This does not imply that the anterior insula is the only target of contextual modulations of pain. However, considering the extensive anatomical connectivity of insula circuitries in monkeys (Mesulam and Mufson 1985) and the supramodal function of the anterior insula (Craig 2002, 2009; Critchley 2005), the anterior insula represents a well-suited target for efficient modulations of pain perception. The present findings thus broaden the concept of the cerebral substrates of pain perception from a circumscribed set of brain areas toward a network approach that takes into account the flexible functional connectivity of the cerebral pain network to other functional systems of the brain. Disturbances of these interactions may yield dysbalances of...
pain perception and thereby contribute to the generation and maintenance of chronic pain (Edwards 2005; Tracey and Mantyh 2007; Apkarian et al. 2009).

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