Cortical correlates of false expectations during pain intensity judgments—a possible manifestation of placebo/nocebo cognitions

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Abstract

We investigated the effects of expectation on intensity ratings and somatosensory evoked magnetic fields and electrical potentials following painful infrared laser stimuli in six healthy subjects. The stimulus series contained trials preceded by different auditory cues which either contained valid, invalid or no information about the upcoming laser intensity. High and low intensities occurred equally probable across cue types. High intensity stimuli induced greater pain than low intensity across all cue types. Furthermore, laser intensity significantly interacted with cue validity: high intensity stimuli were perceived less painful and low intensity stimuli more painful following invalid compared to valid cues. The amplitude of the evoked magnetic field localized within the contralateral secondary somatosensory cortex (SII) at about 165 ms after laser stimuli varied also both with stimulus intensity and cue validity. The evoked electric potential peaked at about 300 ms after laser stimuli and yielded a single dipole source within a region encompassing the caudal anterior cingulate cortex and posterior cingulate cortex. Its amplitude also varied with stimulus intensity, but failed to show any cue validity effects. This result suggests a priming of early cortical nociceptive sensitivity by cues signaling pain severity. A possible contribution of the SII cortex to the manifestation of nocebo/placebo cognitions is discussed.

Keywords: Pain; Attention; Expectancy; Placebo; Nocebo; Laser evoked potentials; Magnetoencephalography; Electroencephalography; Dipole analysis

1. Introduction

Pain is a subjective phenomenon and therefore not only influenced by physical attributes of the stimulus, but also the psychological context in which it occurs. Learning and memory of contextual pain-cues enable an individual to anticipate bodily threat and to adopt immediate protective behaviors to avoid actual tissue damage. Because pain-cues cause the directing of attention to the noxious event they can enhance the actual pain experience (Bushnell et al., 1985; Dowman, 2001) compared to a neutral or distracted situation. Likewise, the placebo effect involves the utilization of cues that signal impending pain relief and can reduce actual pain experience puzzling the evaluation of pharmacological or surgical treatment effects when not tested against a placebo-control (Vase et al., 2002). Thus, attentional processes can obviously bias pain intensity in both directions according to cues signaling negative or positive outcome. In analogy to the term ‘placebo’ (= expect positive outcome), negative polarity of expectation upon pain or other symptoms is nowadays often referred to as nocebo effect (= expect negative outcome).
Attentional modulation of pain has meanwhile been firmly documented using psychophysical (Bushnell et al., 1985; Spence et al., 2002), behavioral (Crombez et al., 1994; Eccleston and Crombez, 1999; Van Damme et al., 2004), and physiological studies (Garcia-Larrea et al., 1997; Legrain et al., 2002; Lorenz and Bromm, 1997; Siedenberg and Treede, 1996). More recently a number of neuromaging studies showed localized effects of attention on pain processing in both the sensory and limbic cortical areas.

Given the fact that attention is not a unified psychological and neurophysiological entity, the manipulations of pain perception used in a given experiment crucially determined the engagement of specific brain structures in various attention-related phenomena, such as anticipation (Ploghaus et al., 1999; Sawamoto et al., 2000), anxiety (Ploghaus et al., 2001), hypnotic suggestions (Hofbauer et al., 2001; Rainville et al., 1997), placebo conditions (Petrovic et al., 2002; Wager et al., 2004) or distraction (Bantick et al., 2002; Tracey et al., 2002). Although some degree of attentional modulation of the primary somatosensory cortex (SI) has been reported (Bushnell et al., 1999; Hofbauer et al., 2001; Mima et al., 1998), the secondary somatosensory cortex (SII) shows more consistent attention-dependent processing of somatosensory input, not only regarding nociceptive (Nakamura et al., 2002; Sawamoto et al., 2000), but also tactile stimuli both in humans (Backes et al., 2000; Fujiwara et al., 2002; Hämäläinen et al., 2002; Hoechstetter et al., 2000; Mima et al., 1998) and in non-human primates (Meftah et al., 2002; Steinmetz et al., 2000). Another key area for pain processing is the cingulate cortex. It belongs to the limbic forebrain structures and is involved in many attentional and cognitive functions related to virtually all sensory modalities including pain (Bush et al., 2000; Vogt et al., 1992).

Both anatomical and functional features indicate a segregation of the cingulate cortex along its caudal-to-rostral extension (Vogt et al., 2003). Mid and caudal portions of the anterior cingulate cortex (ACC) are most consistently activated during functional imaging of human pain reactions using functional magnetic resonance tomography (fMRI), positron emission tomography (PET) (Derbyshire et al., 1998; Petrovic and Ingvar, 2002) and dipole analysis of multi-lead electroencephalography (EEG) and magnetoencephalography (MEG) (Garcia-Larrea et al., 2003).

PET and fMRI are sensitive to hemodynamic reactions following neuronal activity and therefore too slow to differentiate early and late functional stages at which attention may influence pain intensity judgments. In the present study, we took advantage of the high temporal resolution of EEG and MEG to study the effects of expectation and cue utilization on SII and cingulate activities following brief painful infrared laser stimuli applied to the dorsum of the left hand of six healthy male volunteers. It is particularly interesting whether the psychophysical effect of expectancy upon pain perception is related to changes of the perceptual sensitivity of early cortical processes, e.g., in SII or whether it indicates a bias in later processes such as stimulus identification and response selection represented in less modality-specific brain regions such as the cingulate cortex. The combined application of EEG and MEG is favorable because MEG is much more sensitive than EEG to measure SII activity around 150 ms after laser stimuli due to the tangential orientation of its equivalent current dipole (ECD) located in the parietal operculum (Bromm, 2001; Timmermann et al., 2001). In contrast, the radial orientation of the ECD at about 300 ms after laser stimuli renders the EEG more sensitive than MEG to locate pain-relevant cingulate activity (Bromm et al., 2000).

Current status of consensus among the various working groups indicates bilateral SII and ACC sources to account for negative components around 150 ms (N1 and N2) and the positive component at around 400 ms post-stimulus (P2), respectively. With much less consistency than the above-mentioned areas, posterior parietal, medial temporal, and anterior insular regions have been occasionally tagged as possible contributors to LEPs, and the involvement of SI remains controversial (Garcia-Larrea et al., 2003). Contribution of the cognitive P3 to laser-evoked potentials has been also discussed. The laser-P3 has been found to be distinct from the P2 wave according to topographical criteria and differential dependence upon the classical “oddball” factors, but can obviously overlap the P2 wave (Lorenz and Garcia-Larrea, 2003).

In this study, we examined the dependency of SII and ACC activities on expectancy by presenting auditory cues prior to laser stimuli, which either contained valid, invalid or no information about the upcoming stimulus intensity. The use of valid and invalid cues allowed us to compare magnitudes of pain at equally applied laser intensities but correct or false prestimulus expectancies. Although the study design did not involve specific placebo trials in that we did not use fake medications to induce a bias of pain perception, we analyzed how false beliefs and expectations about an upcoming pain, which is one important factor underlying placebo and nocebo cognitions, interact with brain activity evoked by well-controlled painful stimuli.

2. Methods

2.1. Participants

Prior to the experiment the local ethics review board approved the protocol. Six male right-handed medical students (mean age = 25.2 years, SD = 1.5 years) participated in this study after written informed consent and were free to terminate the experiment at any time.
2.2. Pain stimulus, procedure, and pain rating

We delivered brief infrared laser stimuli of 1 ms duration and a beam diameter of 5 mm to the dorsum of the left hand using the Thulium YAG laser (wavelength 1.8 μm). Prior to the test blocks participants were made familiar with the use of the rating scale ranging from 0 (no sensation) to 8 (maximal pain) with a value of 3 indicating the beginning of a stinging or burning pain sensation. Pain threshold was tested by computing the average intensity at which subjects reported a rating value of 3 in three ascending and again first a rating value of 2 in three descending series of laser stimuli using successive intensity increments of 30 mJ. One block of stimuli contained 350 laser pulses of two intensities of equal occurrence probability and in quasi-random order. The low intensity was set one and a half times above each individual’s pain threshold (450–500 mJ), inducing a mild pinprick-like pain sensation. The high intensity was set two times individual pain threshold (600 and 650 mJ) which gave a moderately strong stinging pain sensation and ratings between 4 and 6. In 250 trials a 500 or 2000-Hz tone occurred between eight to ten seconds prior to the laser pulse and indicated whether the respectively low or high intensity laser stimulus would follow. In 80% of these trials the auditory tones validly announced either high or low intensities whereas 20% had invalid cues where subjects either expected a high, but actually received a low intensity or vice versa. One hundred trials (50 of either stimulus intensity) contained a non-informative auditory cue (Windows system jingle) that also alerted subjects to await the next laser stimulus, but did not inform them about its intensity. Three seconds after the laser stimulus another acoustic (buzzing) event prompted a verbal rating using the 9-point numerical scale. When a laser stimulus occurred after informative cues, subjects additionally made a judgment about whether they thought the cue had correctly or incorrectly announced the laser stimulus. In order to enhance task compliance extra payment was granted for accuracy in these judgments. Fig. 1 illustrates the temporal sequence of events in this paradigm. The total duration of the entire block was approximately 90 min. Every 30 min (after trial numbers 120 and 240) within a block there was a brief resting period of approximately 3 min during which participants were allowed to relax, move to a limited extent and readjust their position.

2.3. Data acquisition and analysis of MEG and EEG

The MEG and EEG signals were recorded simultaneously in a magnetically shielded room using 31-channel gradiometer SQUID sensors of 70 mm baseline for the MEG and a 32-channel Synamp amplifier (NeuroScan) for the EEG. Electrode montage followed the international 10–20 system using a nylon cap with attached electrodes (impedance at <5 kΩ). Recordings of the vertical and horizontal electrooculogram were used to reject epochs contaminated by blink artefacts and eye movements. The spatial positions of the electrodes were determined using a 3D digitiser system (Polhemus) and superimposed on a co-registered MRI of the individual heads. MR scanning was performed on a 1.5 T MRI scanner (Siemens Vision). The centre gradiometer of the MEG dewar was placed above C4 of the international 10/20 system. The EEG was recorded with reference to linked ear lobes. The MEG and EEG signals were filtered in the bandwidth between 0.03 and 100 Hz and digitised with a sampling rate of 250 Hz. The recordings were digitally filtered offline with a 70 Hz low pass filter using a Hanning window.
2.4. Equivalent current dipole modeling

Electric and magnetic responses for each trial type were averaged time-locked to the application of the laser stimuli after rejection of epochs which were contaminated by artefacts. Artefact removal was done according to visual inspection of all segments for the presence of ocular or head movements which on average occurred in less than 10% of trials. After re-referencing against common average we focused the analysis of EEG potentials on a time range from 200 to 500 ms post-stimulus when the N2-P2 components of laser-evoked potentials (LEP) generated in the caudal anterior and posterior cingulate cortex are known to occur (Bentley et al., 2002, 2003; Timmermann et al., 2001; Kakigi et al., 1999; Ploner et al., 2002). Sources of the averaged responses were calculated as equivalent current dipoles (ECD) at periods of mean global filed or potential maxima using the boundary element method (BEM) (Fuchs et al., 1998) for EEG, and a 3-shell-sphere model as volume conductor for MEG data using the CURRY Software (Philips Research, Hamburg, Germany) with a single moving dipole model. The location, orientation, and strength of the dipoles were localized within the individual brain morphology determined from magnetic resonance images (MRI).

It should be noted that it was not the goal of this study to extend the previous knowledge (see Section 1) about the dipole localization of laser-evoked potentials (LEP) and magnetic fields (LEF) given the small number of subjects in this study. With the present study we a priori restricted our analysis on the early contralateral SII activity using the MEG in combination with EEG to analyze late ACC activity. We therefore applied a simple and straightforward one moving dipole approach to demonstrate that our main parameter used for further statistical analysis, i.e., the peak amplitude of the mean global electric potential (pMGP) and magnetic field (pMGF) curves, coincides with a latency period where a spatially stable ECD can be fitted within the expected brain regions with a goodness of fit (GOF) better than 80% over a life-time of at least 15 ms. MGF and MGP curves are determined by computing the root mean square of each data point averaged over all squid sensors and scalp positions. They reflect the global magnetic and electric responses of the brain to the stimulus and are composed of characteristic peaks at maximum dipolar activities. Although the dipole strength and the global field/potential amplitude are highly correlated, the signal-to-noise ratio affects these measures differentially. This difference is due to the fact that the dipole strength is derived from a model fit whereas the global field/potential amplitude represents directly the measured variance rendering the mean global field/potentials amplitude in most instances more reliable and sensitive towards experimental manipulations than the estimated dipole strength.

2.5. Statistical analysis

Intensity ratings and physiological parameters were analyzed using two-by-three factorial repeated-measures analyses of variance (ANOVA) testing effects of intensity (low vs. high) and cuetype (valid, invalid, and non-informative). Main or interaction effects with 2 or more degrees of freedom were corrected by application of the Greenhouse-Geisser ε-values. The source of significant main and interaction effects were explored by post hoc paired t tests.

3. Results

3.1. Psychophysics

The intensity of the laser stimulus had a significant effect on the ratings ($F(1,5) = 54.1; p < .01$) due to the high intensity being more painful than the low intensity stimuli across all cuetypes ($t = 7.4; p < .01$). Although there was no main effect of cuetype and no cuetype-by-intensity interaction, the difference of ratings between valid and invalid trials was significantly different between low and high intensities ($t = 2.77; p = .04$) (Fig. 2). Valid trials yielded significantly lower ratings than invalid trials following low intensity stimuli ($t = 2.52; p = .05$), whereas valid trials yielded higher ratings than invalid trials following high intensity stimuli, which was
marginally significant (t = 2.34; p = .07). This effect is also reflected by a significant cue validity-by-intensity interaction (F(1, 5) = 7.7; p < .05) when we refined the ANOVA to a two-by-two factorial design with cue validity (valid and invalid) and intensity (low and high) as effects. Thus, when subjects expected a high intensity laser stimulus following an invalid cue they perceived a low intensity stimulus more painful than when they expected the same laser stimulus to be of low intensity in validly cued trials. Along the same line, expectation of a low intensity stimulus following an invalid cue rendered high intensity stimuli less painful than the same intensity being validly cued.

Following the rating subjects also made a judgment about whether they had received a correct or incorrect cue for high or low intensity stimuli. The percentage of errors in these judgments is given in Fig. 3. It demonstrates that both stimulus intensity (F(1, 5) = 6.7; p < .05) and cue validity (F(1, 5) = 18.2; p < .01) exerted significant main effects on this measure. Thus, high intensity stimuli were more often judged as low intensity stimuli than were low intensity stimuli judged as high intensity stimuli. Furthermore, invalid cues increased the rate of false judgments for both intensities. These results show that we were successful in manipulating the magnitude of experienced pain following identically applied laser stimulus intensities dependent on prestimulus expectancies.

3.2. MEG activity

The peak in the mean global magnetic field power (pMGP) calculated from the average laser-evoked activity of the 31 SQUID gradiometers appeared at about 160 ms (range: 132–188 ms) after stimulus onset. This activity was significantly influenced by stimulus intensity across all cue types (F(1, 5) = 30.8; p < .01) due to greater activity after high as compared to low laser intensity (t = 5.6; p < .01). After computation of the iso-

field maps of each individual’s data at the peak latency of the MGF curve we fitted equivalent current dipoles using each individual’s MRI as volume conductor model. All subjects showed a single dipole within the parieto-opercular region suggesting activation of SII cortex with values for the goodness of fit ranging between 80 and 98%. Table 1 represents latency and dipole parameters of the SII activity and the corresponding intensity rating following high and low stimulus intensities according to validly and invalidly cued trials. Fig. 4 illustrates the effects of stimulus intensity (left and right columns) and cue validity (top and bottom section) on the isofield maps (top row) and reconstructed dipoles (bottom row) at 140 ms after stimulus onset in a representative subject (#4). It demonstrates that the strength of the dipole (represented by its length) is not only influenced by the physical stimulus intensity but also by the validity of the cue information. Whereas an invalidly cued high intensity stimulus yields a smaller dipole compared to the same intensity being validly cued, an invalidly cued low intensity stimulus evoked a greater dipole than when this intensity has been validly cued. The ANOVA confirmed this effect at group level for the peak amplitude of the mean global field (pMGF): whereas cue type had no main effect on the amplitude of pMGF (F(1, 5) = 1.4; p = .3), it significantly interacted with laser intensity (F(2, 6, 5) = 9.2; p = .02 corrected) (Fig. 2, middle). This effect was mainly due to the manipulation of cue validity yielding different effects between low and high intensity stimuli. Compared with validly cued trials invalidly cued trials induced increases of pMGF amplitudes after low intensity stimuli (t = 3.33; p = .02), but decreases following high intensity stimuli (t = 3.43; p = .02). Again, when we refined the ANOVA to only cue validity and intensity effects within a 2 x 2 factorial design the interaction between these effects was highly significant (F(1, 5) = 16.7; p < .01).

Thus, intensity ratings and SII activity showed a remarkable consistency regarding the effect of cue validity, which is illustrated in Fig. 5. It represents a close linear correlation (r = .93; p < .0001) of the individual degree of change of pMGF amplitude following invalid compared to valid cues plotted as a function of the change of perceived pain intensity according to cue validity.

3.3. EEG activity

The peak of activity in the mean global electric potential curve (pMGF) calculated from averaged laser-evoked activity of the 31 scalp electrodes appeared around 300 ms after stimulus onset (range: 260–340 ms). This peak accounts for the major P2 positivity at the vertex position known from numerous LEP studies (see Bромm and Lorenz, 1998) and illustrated in the waveform of the grand average across all subjects (Fig. 6). As
expected, stimulus intensity significantly influenced pMGP across all cuetypes \((F(1,5) = 19.8; p < .01)\) due to greater activity following high compared to low intensity stimuli \((t = 4.45; p < .01)\). Additionally, there was a significant effect of cuetype upon pMGP \((F(2, 8.2) = 5.0; p = .04 \text{ corrected})\). Because the difference between validly and invalidly cued trials was not significant \((t = 0.86; p = .43)\) we tested the difference between non-informative trials against the mean of valid and invalid trials (=informative trials), which was weakly significant \((t = 2.6; p < .05 \text{ uncorrected})\). ECD fitted for the individual isopotential maps at pMGP in each individual’s MRI were consistently located in the caudal part of the anterior cingulate cortex or posterior section of the cingulate cortex (PCC) and explained more than 95% of the measured variance (range 84.6–99.9%; Table 2). Fig. 7 illustrates the isopotential maps and reconstructed dipoles for high and low intensity following valid and invalid cues in the same subjects as in Fig. 4.

### 4. Discussion

The present study examined the effects of false expectations on the magnitude of perceived pain and brain magnetic and electric activity in six healthy male subjects. Pain was evoked by brief infrared laser stimuli randomly applied at two different intensities to the dorsum of the left hand. Laser intensities of each trial were either validly or invalidly cued by different pitched tones 8–10 s prior to the laser stimulus, or were preceded by an auditory event without information about the upcoming intensity. Aside from the effects of applied laser intensity on perceived pain intensity,
results indicate that when subjects expect a low intensity stimulus after an invalid cue but actually receive a high intensity stimulus they report significantly lower pain intensity in comparison to the same high intensity being validly cued. Similarly, subjects judge a low intensity stimulus as significantly more painful when they have been informed to receive a high intensity stimulus compared to validly cued trials of the same low intensity. Consistent with the ratings, subjects’ identifications of correct and false cues yielded relatively more errors for invalidly than for validly cued trials. This result confirms that we were able to manipulate subjective pain intensity judgments at identically applied stimulus intensities dependent on anticipation.

In a remarkable correlation with subjective intensity judgments, the amplitude of contralateral magnetic activity at about 160 ms after stimulus onset depends on both applied laser intensity and cue validity. As expected, the isocontour maps of magnetic activity at this latency were modeled by a single equivalent current dipole (ECD) generated within SII, whereas an ECD generated in caudal anterior cingulate cortex (ACC) or the posterior section of the cingulate cortex (PCC) accounted for the positive-ongoing electric activity with
peak maximum around 300 ms. This topology of laser evoked responses is consistent with numerous previous studies (Bentley et al., 2002, 2003; Bromm, 2004; Vogel et al., 2003; Bromm and Chen, 1995; Bromm et al., 2000; Garcia-Larrea et al., 2003; Kakigi et al., 1999, 2000; Spiegel et al., 1996; Tarkka and Treede, 1993; Treede et al., 1999, 2000, 2003).

SII represents one of the earliest stages of attention-dependent processing of somatosensory input, not only regarding noiceptive (Nakamura et al., 2002; Sawamoto et al., 2000) but also tactile stimuli both in humans (Backes et al., 2000; Fujiwara et al., 2002; Hoechstetter et al., 2000; Maugiere et al., 1997; Mima et al., 1998) and non-human primates (Meftah et al., 2002; Steinmetz et al., 2000). However, some results are at odds with this view (Garcia-Larrea et al., 1997; Yamashita et al., 1999, 2000).

Partly inconsistent findings regarding attentional modulation of SII may be related to differences in statistical sensitivity and the methods used to manipulate attention. Lorenz and Garcia-Larrea (2003) recently reviewed the evidence of existence of multiple sources of modulatory effects upon pain perception as revealed by laser evoked magnetic and electric brain activity. Thus, non-specific arousal can affect noiceptive activity of SII, presumably controlled by activation of the ascending reticular activation pathways. Additionally, there is an inter-modal attention effect reducing pain whenever attention is actively shifted towards other sensory modalities or tasks. Notably, arousal and attentional engagement seem to increase SII activity only to a certain ‘saturation’ level (Nakamura et al., 2002), beyond which introduction of further attentional load, such as the change from non-informative to informative cues fails to further augment SII responses. Divergent results of previous studies may therefore be explained by the fact that SII activity has been investigated in different states of susceptibility to arousal and attentional engagement. However, cuing paradigms such as the one used in this study confirm an additional intra-modal sensory gain effect, by which SII activity is primed according to spatial and intensity expectancies during the utilization of perceptual cues. Legrain et al. (2002) observed an enhancement of the amplitude of the temporo-parietal N1 component that is most likely generated in SII following infrared laser stimuli (Spiegel et al., 1996), when painful stimuli are presented within compared to outside an expected body location.

Although less precise than SI, SII represents a somatotopic organization of laser-evoked hemodynamic activities (Bingel et al., 2003). Moreover, the SII region has close anatomical and functional connections to the insula which has been found to be influenced by expectation of painful stimuli (Plohaus et al., 1999; Sawamoto et al., 2000). The insula has been suggested to represent a ‘limbic substrate’ of thermosensory and noiceptive information (Craig, 2003; Craig et al., 2000). It is therefore possible that this region modulates the sensory gain of SII noiceptive neurons based on anticipation of future events, regarding both their intensity and spatial distribution. In contrast to SI-responses, which exhibit a steady increase of activation with applied stimulus intensity, SII responses yield a stepwise increase when laser stimuli exceed pain threshold (Bornhövd et al., 2002; Timmermann et al., 2001). This behavior suggests a more complex function of SII subserving detection of, orienting towards and contextual learning of potentially damaging stimuli. Apart from a higher level of fear induced by cues announcing the high pain intensity (Van Damme et al., 2004), the greater likelihood of validly than invalidly cued trials in our study may have facilitated responses of noiceptive SII neurons due to learning and memory, consistent with similar observations in the monkey (Dong et al., 1994).
An interesting result of this study is that the type of attentional modulation observed in magnetic SII responses differed from that observed in electrical caudal ACC/PCC responses following laser stimuli. Unlike SII activity, the caudal ACC/PCC activity was generally enhanced following laser stimuli preceded by the informative compared to the non-informative cues. However, caudal ACC/PCC failed to be affected by the validity of the cue, an effect markedly present in SII. These findings suggest that the sensitivity of the caudal ACC/PCC towards cues relates to the induction of a stronger stimulus-related orienting and cognitive engagement when stimuli have been anticipated or associated with task demands (Mesulam et al., 2001).

This is consistent with findings that cingulate cortex activity following nociceptive stimuli generally varies more with perceived pain than with applied stimulus intensity (Coghill et al., 1999; Garcia-Larrea et al., 1997) especially when pain is manipulated by attentional shifts (Garcia-Larrea et al., 1997). However, caudal ACC/PCC is obviously not affected by processes that more specifically mediate the direction of an anticipatory bias of pain intensity discriminations depending on positive or negative expectations.

The anatomical and functional heterogeneity of the cingulate cortex (Mesulam et al., 2001; Vogt et al., 2003) which appears to encompass different sub-regions with different stimulus–response functions following noxious stimuli (Büchel et al., 2002) deserves some further elaboration here. It has been suggested that the cingulate cortex subserves a general role in assigning attentional resources to task stimuli, with viscero-autonomic and emotional processes represented in anterior and cognitive–evaluative functions represented in posterior sec-

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tions (Bush et al., 2000; Vogt et al., 1992). Furthermore, areas involved in the processing of modulatory influences, such as anticipation (Ploghaus et al., 1999), distraction (Frankenstein et al., 2001; Petrovic et al., 2002), stroop interference (Bantick et al., 2002; Derbyshire et al., 1998) or placebo cognitions (Petrovic and Ingvar, 2002) are consistently localized anteriorly to subregions responding to pain per se. Consistent with numerous PET and fMRI studies dipole reconstruction of multi-lead LEP and LEF also localized pain-relevant activity within the mid-caudal ACC when spherical head models were used for dipole reconstruction (Bromm and Chen, 1995; Tarkka and Treede, 1993). However, more recent applications of realistic head models derived from the individual MRI yielded laser-evoked dipole activity within the border region between caudal ACC and posterior cingulate cortex (PCC) (Bentley et al., 2002, 2003; Bromm, 2004). It is thus possible that despite an overlap within the caudal ACC, EEG, and MEG tend to localize pain-relevant activity more posterior than PET and fMRI. Finally, the nature of the pain stimulus appears to be relevant. Derbyshire (2002) suggested that the cingulate is more anteriorly activated following tonic compared to phasic experimental pain. Tonic pain in turn recruits endogenous opioidergic inhibition in the anterior cingulate (Zubieta et al., 2001) which is linked to the

Fig. 7. Isocontour maps and localization of equivalent dipoles of electrical activity 300 ms after stimulus onset in a single subject (4).
periaqueductual grey (PAG) region of the brainstem, a key area of descending inhibitory pain modulation pathways. It is possible that sustained and volitional control of attention during the expectation of pain or during the presence of a longer lasting pain stimulus may recruit rostral ACC areas as correlate of behavioral adaptation, emotional engagement and descending control. In turn, the strength of caudal ACC and PCC activity appears to follow brief painful stimuli, perhaps reflecting more automatic orientation to the spatial origin of salient and threatening events being enhanced when perceptual cues inform about location and intensity of the upcoming pain stimulus. Evidence also indicates that reward enhances task-related activation in caudal portions of the anterior cingulate (Bush et al., 2002), which might have contributed to greater cingulate activity associated with informative cues where we rewarded accurate detection of correct and false cues.

The proposed contribution of the ACC to the control of attention during the processing of painful stimuli has been implicated in placebo analgesia. Previous neuroimaging studies using PET and fMRI point towards the rostral anterior cingulate cortex as a crucial region for both placebo and opioid analgesia (Petrovic et al., 2002), probably controlled by the prefrontal cortex (Wager et al., 2004), in that the latter region might link contextual sensory information with endogenous descending inhibition. Although the present study did not involve specific manipulations to induce placebo analgesia, in that we did not use fake medications to bias subjects’ pain reactions, results indicate possible mechanisms of this phenomenon. Accordingly, placebo analgesia could result in situational contexts providing cues, such as the view of a trustful doctor or a syringe, that signal upcoming relief from ongoing pain or less painfulness of a certain medical procedure, and render pain-relevant brain structures such as the SII cortex less sensitive towards the actual pain. The cingulate activity observed in this study is certainly too far posterior to match the rostral ACC in which activity varied with placebo effects in the studies of Petrovic et al. (2002) and Wager et al. (2004). We believe that rostral ACC activities might be too slow and weakly synchronized with repeated stimulation to be recognized by evoked and averaged MEG/EEG activities in our study. Furthermore, as we elaborated above, the rostral ACC most likely houses a different and probably placebo-relevant attentional process than that represented by the caudal ACC/PCC sub region that we found not to yield activity varying with the direction of cue-induced expectations. It is, therefore, possible that placebo analgesia underlies various sensory, cognitive, and emotional mechanisms that interact with each other in a given context. This is consistent with the view that placebo analgesia is not a unique neurobiological entity but involve different phenomena in addition to expectation, e.g., conscious or unconscious conditioning learning (Benedetti and Amanzio, 1997; Price and Barrell, 2000). Our study suggests the possibility that pain related cues mediate sensory gain changes of the nociceptive system at the level of SII cortex reflecting a comparably rapid process that might contribute to placebo and nocebo effects.

To sum up and conclude, the present study indicates an interesting double dissociation of caudal ACC/PCC and SII activities following nociceptive infrared laser stimuli regarding attentional engagement and perceptual cue utilization: activity in caudal ACC/PCC, but not in SII increased when laser stimuli are preceded by cues that induced greater levels of task engagement characterized by the degree of effort applied during (rewarded) intensity discrimination. In contrast, activity in SII, but not in caudal ACC/PCC was highly correlated with the degree to which subjective pain intensity judgments were influenced by prestimulus expectancy, both in the direction of pain increases or decreases depending on the polarity of the cue. We think that this phenomenon might contribute to respective nocebo or placebo cognitions. Notably, the high temporal resolution of MEG and EEG in this study allows the conclusion that false expectations during cue utilization influences pain intensity judgments by modulating the sensory gain of nociceptive stimuli at an early cortical process whereas task-related effects related to mental effort, orienting, target identification or response selection concern later stages represented in less modality-specific limbic brain structures.

Acknowledgments

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References


Bentley, D.E., Derbyshire, S.W., Youell, P.D., Jones, A.K.P., 2003. Caudal cingulate cortex involvement in pain processing: an inter-indi-


