Pain 120 (2006) 8–15

PAIN

www.elsevier.com/locate/pain

Research papers

Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network

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Received 31 January 2005; received in revised form 19 July 2005; accepted 18 August 2005

Abstract

Placebo analgesia is one of the most striking examples of the cognitive modulation of pain perception and the underlying mechanisms are finally beginning to be understood. According to pharmacological studies, the endogenous opioid system is essential for placebo analgesia. Recent functional imaging data provides evidence that the rostral anterior cingulate cortex (rACC) represents a crucial cortical area for this type of endogenous pain control. We therefore hypothesized that placebo analgesia recruits other brain areas outside the rACC and that interactions of the rACC with these brain areas mediate opioid-dependent endogenous antinociception as part of a top–down mechanism. Nineteen healthy subjects received and rated painful laser stimuli to the dorsum of both hands, one of them treated with a fake analgesic cream (placebo). Painful stimulation was preceded by an auditory cue, indicating the side of the next laser stimulation. BOLD-responses to the painful laser-stimulation during the placebo and no-placebo condition were assessed using event-related fMRI. After having confirmed placebo related activity in the rACC, a connectivity analysis identified placebo dependent contributions of rACC activity with bilateral amygdalae and the periaqueductal gray (PAG). This finding supports the view that placebo analgesia depends on the enhanced functional connectivity of the rACC with subcortical brain structures that are crucial for conditioned learning and descending inhibition of nociception.

Keywords: Pain; Placebo; rACC; fMRI; PAG; Amygdala; PPI

1. Introduction

Behavioral context can modulate neuronal activity in nociceptive and non-nociceptive somatosensory pathways (Melzack, 1999; Sawamoto et al., 2000; Wall, 1999). Placebo analgesia is one of the most striking examples of the cognitive modulation of pain perception. It represents a situation where the administration of an ineffective substance produces an analgesic effect when the subject is convinced that the substance is a potent painkiller. Even though the placebo phenomenon is well recognized, the underlying mechanisms and neural systems remain obscure. Pharmacological studies indicate that placebo analgesia can be antagonized by the opioid-antagonist naloxone, implicating that at least some aspects of placebo analgesia depend on the endogenous opioid-system (Benedetti et al., 1999; Levine et al., 1978; Wall, 1999). Recent neuroimaging data point towards the rostral anterior cingulate cortex (rACC) as a crucial cortical region involved in placebo analgesia. In a previous positron emission tomography (PET) study Petrovic and colleagues (2002) demonstrated similarity in regional brain activation of exogenous opioid administration and systemic placebo analgesia, thus providing evidence of a link between placebo analgesia and the opioid system. According to their study, the anterior cingulate cortex yielded increased activity during both placebo and opioid analgesia (Petrovic et al., 2002). Using fMRI,

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0304-3959/$20.00
doi:10.1016/j.pain.2005.08.027

a recent study further confirmed rACC involvement in placebo analgesia in combination with anticipatory activation of the dorsolateral prefrontal cortex (DLPFC) (Wager et al., 2004). The prevailing evidence thus supports the role of the rostral ACC in linking pain perception with pain modulation pathways following the processing of contextual cues that initiate placebo-related expectations. The main aim of the present study was to investigate subcortical 'effectors' that might be recruited by the rACC in placebo analgesia. We hypothesized, that similar to exogenous opioid analgesia, the rACC interacts with subcortical brain areas involved in opioid-mediated endogenous antinociception such as the amygdala (Fanselow, 1994) and the PAG (Petrovic et al., 2002) during placebo analgesia. To test this hypothesis, healthy subjects received and rated painful Tm-YAG-laser stimuli to the dorsum of both hands, one of them treated with a fake analgesic cream (placebo). Painful stimulation was preceded by an auditory cue, indicating the side of the next laser stimulation. BOLD-responses to the painful laser-stimulation during the placebo and no-placebo condition were assessed using event-related fMRI. After identifying placebo related activity in the rACC, a psycho-physiological interaction analysis (PPI) (Friston et al., 1997) was conducted to test for its possible placebo dependent contributions to other brain areas.

2. Methods

2.1. Subjects

Nineteen healthy (four female), right-handed subjects from the local Medical School aged 18–32 years (mean 24 ± 5 SEM) gave written informed consent to participate in the study, which was conducted in accord with the declaration of Helsinki and approved by the local Ethics committee. All subjects had normal pain thresholds at both sites of stimulus application, no history of neurological or psychiatric disease, particularly no history of pain syndrome, and were free to withdraw from the study at any time.

2.2. Experimental protocol

Prior to the experiment, the subjects familiarized themselves with the laser stimuli and were trained to rate the perceived pain intensity with hand signs on a numerical rank scale (NRS) ranging from 0 (no sensation) to 4 (maximum pain used in the experiment). On this scale, '2' denotes the pain threshold. In addition, individual pain thresholds for the sites of stimulus application were determined outside the scanner. Subjects were informed that the different pain intensities administered during the threshold session would be the same as those applied during the scanning session.

The subjects were informed that the purpose of the current study was to investigate the neural correlates of the pain reducing potency of a new analgetic cream to be used for pain relief during intravenous catherization in children. In reality, the cream consisted of a standard basic skin cream. Its putative effect was supposed to last for 15–20 min and then decay within a short period of time. We were therefore able to employ a cross-over design and apply the placebo cream on both hands of all volunteers on a single day. There was a pause of 15 min between successive applications. Subjects were investigated in two scanning sessions. The placebo-cream was applied to the right hand in one session and to the left hand in the other scanning session, with the order randomized across subjects. The non-placebo hand was treated with an 'inactive' control cream supposed to account for a standardized procedure and identical mechanical skin stimulation, as one expects in a controlled pharmacological study. To reinforce placebo induced expectation, we conditioned the subjects by applying two more series of four laser stimuli to each hand immediately prior to the actual scanning procedure. However, while the subjects expected identical stimuli on both hands, we covertly lowered the applied laser energy on the placebo hand from 600 to 450 mJ. This conditioning procedure is known to amplify the ensuing placebo effect.

Within each session of the actual fMRI experiment, laser pain stimuli were randomly applied to both hands (placebo and no-placebo hand) to directly compare pain related responses under the 'placebo' and 'no-placebo' conditions. A vocal cue ('right' or 'left') signaled which hand would be stimulated next via headphones. Five to seven seconds after the cue, four consecutive laser pain stimuli of 600 mJ each were applied to the respective hand every 6–8 s. To avoid sensitization and habituation, the stimulus site was randomly changed after each stimulus. The choice of parameters for the painful stimulus applied to the hand (600 mJ and 1 ms duration) was based on previous fMRI and psychophysical experiments indicating that a 600 mJ stimulus evokes a very brief, but clearly 'pin prick-like' painful sensation without any warmth or tactile components (Bingel et al., 2002; Buchel et al., 2002) and reliably activates SI, SII and the insula (Bingel et al., 2003; Bornhovd et al., 2002). Seven seconds after the fourth laser stimulus, another vocal command ('rating') prompted the subject to rate the average sensation for the last four painful stimuli with hand signs on the numerical rank scale (NRS) ranging from 0 (no sensation) to 4 (maximum pain used in the experiment). A total of 10 times four consecutive laser stimuli were applied to each (the 'placebo' and the 'no-placebo') hand in each scanning session. The time course of one session and a single trial is shown in Fig. 1.

2.3. Laser stimulation

A Tm-YAG-infrared-laser (Neurolaser, Wavelight, Starnberg Germany) was used to apply computer-controlled brief, radiant pain stimuli. The Tm-YAG laser emits near-infrared radiation (wavelength 1.96 μm, spot diameter 5 mm, pulse duration 1 ms) with a penetration depth of 360 μm into human skin. The laser stimulus allows restriction of the emitted heat energy to the termination area of primary nociceptive afferents (20–570 μm), without damaging the epidermis or affecting the subcutaneous tissue (Spiegel et al., 2000).

2.4. Image acquisition

MR scanning was performed on a 1.5 T MRI system (Siemens Vision) with a standard headcoil. Thirty-two axial slices (slice thickness: 3 mm, 1 mm gap) were acquired using a gradient echo echo planar (EPI) T2*-sensitive sequence (TR = 2.6 s, TE = 40 ms,

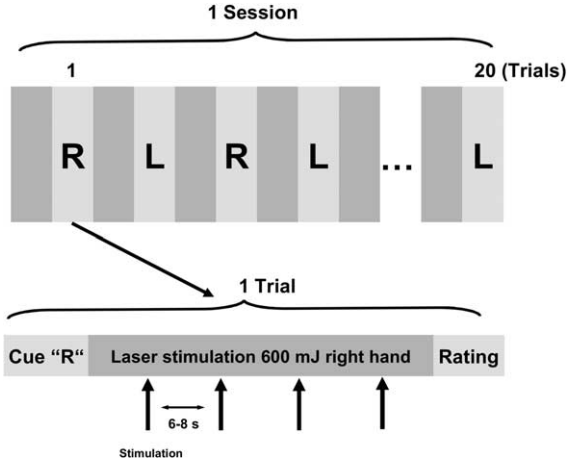

Fig. 1. Study design: each of the two consecutive scanning sessions consisted of 20 trials. During one session, the placebo cream was applied to the left hand and in the other to the right hand, with session order counterbalanced over subjects. Within each trial, a vocal cue signaled pain on either the right or the left hand. Between 5 and 7 s after the cue, four consecutive 600 mJ laser-pain stimuli (each every 6–8 s) were applied to the cued hand. Five seconds after the fourth pain stimulus, a vocal command requested the manual rating on a 0–4 rating scale.

flip angle 90°, matrix 64×64, field of view 210×210 mm). A high resolution (1×1×1 mm voxel size) T_1 weighted structural MRI was acquired for each volunteer using a 3D FLASH sequence.

2.5. Image processing and statistical analysis

Image processing and statistical analysis were carried out using SPM2 (www.fil.ion.ucl.ac.uk/spm). All volumes were realigned to the first volume, spatially normalized (Friston et al., 1995) to a standard EPI template (Evans et al., 1993) and finally smoothed using a 8 mm full-width at half-maximum isotropic Gaussian kernel. Data analysis was performed using the general linear model (GLM) and modeling the different conditions (cue placebo side, cue normal side, pain placebo side, pain non-placebo side, rating) as delta functions convolved with a canonical hemodynamic response function as implemented in SPM2. An event-related approach was used since the stimulus onset asynchrony was randomized and not constant. A design matrix was prepared for each single session with a significant placebo effect (please see Psychophysics) and included each of the five regressors (see above). Regression coefficients for all regressors were estimated using least squares within SPM2. Specific effects were tested with appropriate linear contrasts of the parameter estimates for the HRF regressor of all trial types, resulting in a *t*-statistic for each voxel. These *t*-statistics constitute a statistical parametric map (SPM). SPM's are interpreted by referring to the probabilistic behaviour of Gaussian random fields.

Data were analyzed for each subject individually (first-level analysis) and for the group (second level analysis). Separate contrast images for each of the five regressors were then generated. At the group level, a random effects approach (Friston et al., 1999) was applied using non-sphericity correction. Since we were specifically interested in the neural basis of cognitive pain control, correction was based on our regions of interest, which included classical pain areas (thalamus, insula, SII, SI) and the medial wall extending from rACC over the perigenual cingulate gyrus into vmPFC (significance levels of activations in SI, SII, insula, and the medial wall were corrected for a 15 mm sphere, thalamus for a 8 mm sphere).

2.6. Psycho-physiological interaction

To investigate placebo dependent contributions of the rACC to other brain areas, a psycho-physiological interaction (PPI) (Friston et al., 1997) analysis was performed. A psycho-physiological interaction means, that the contribution of one area to another significantly changes with the experimental or psychological context. In other words, the PPI analysis reveals which areas show activation patterns covarying with rACC (physiological variable) activity depending on whether pain is applied in the placebo or no-placebo condition (psychological variable). Characteristic time series were extracted from a sphere (6 mm radius) centered on the rostral anterior cingulate maximum of the placebo > no placebo contrast for each individual volunteer using the first eigen-timeseries (principal component) of this area. The PPI regressor was computed as the element-by-element product of the mean-corrected rACC activity and a vector coding for the differential effect of noxious stimulation during the psychological conditions: placebo or no-placebo (1 for placebo noxious stimulation, −1 for no-placebo noxious stimulation). Our analysis of connectivity was thus specific for context-dependent rACC influences that occurred over and above any task effects and context-independent rACC influences. Brain sites receiving contextual influences of the rACC that were stronger during the placebo condition than during no-placebo conditions were determined by a *t*-test. Since we were specifically interested in context dependent contribution of the rACC to subcortical brain areas involved in endogenous pain control, we restricted our analysis to the most thoroughly described pain modulating circuit (Fields, 2000), including the amygdala, PAG and the rostral ventromedial medulla (RVM) in the brainstem. Significance levels of activations in these subcortical areas were corrected for an 8 mm sphere.

3. Results

3.1. Psychophysics

The behavioral placebo effect was assessed within each subject for each session by comparing pain ratings on the neutral hand with pain ratings on the placebo hand by a *t*-test. A significant ($P<0.05$) placebo response was observed in 18 sessions (10 from the first and 8 from the second scanning session). In these sessions, the mean rating for the placebo hand was 1.5 compared to 2.5 on NRS, ($P<0.05$).

3.2. Imaging data

Nineteen subjects were scanned in this experiment; one subject had to be excluded due to movement artefacts. For two subjects, we only acquired one session as they withdrew from the experiment after the first scanning session. For 18

of these 34 sessions, we found a significant behavioral placebo effect. These sessions were included in the data analysis 'placebo responses'. Subsequently, the data analysis of the 'non-responsive-sessions' included data from 16 sessions.

3.3. Main effects of hand painful stimulation

Painful laser stimulation of the hand led to statistically significant activation in primary and secondary somatosensory cortices, cingulate cortex, the insula, medial temporal gyrus approaching the occipito-temporal junction and the dorsolateral-prefrontal cortex. Subcortical responses were seen bilaterally in medial and lateral thalamic nuclei, amygdala, brainstem including PAG, putamen and, the cerebellum (Table 1a).

3.4. Response during actual painful stimulation/ Placebo-related response:

To identify the neuronal source of placebo analgesia, we tested for BOLD signal that was greater under the placebo condition as compared to the no-placebo condition. This test revealed a distinct and circumscribed activation in the rostral ACC [3, 42, −18; $Z=3.8$, $P<0.05$, Table 1b, Fig. 2]. To account for the issue of lateralization (contralateral bias) of potential placebo related responses (Bingel et al., 2003; Brooks et al., 2002), the same analysis was also performed using a $R-L$ flipping procedure of datasets obtained from sessions when placebo analgesia involved the left hand. The placebo-hand was thereby consistently represented in the same hemisphere over all subjects. However, we did not find any additional, lateralized/somatotopically-organized activation in this analysis.

To investigate whether reduced pain perception during the placebo condition was associated with reduced activation in the afferent somatosensory neuraxis, we performed an ANOVA of pain related responses including each brain area showing a main effect of painful stimulation (Table 1a) depending on the experimental condition (placebo vs. no-placebo). This analysis revealed a significant effect for the factor condition (placebo vs. no-placebo), with reduced pain related activation during the placebo condition $F(1,17)=13.1$, $P<0.05$.

3.5. Activation pattern in non-responders and group × condition interaction.

To further substantiate the relationship of rACC activity and placebo analgesia, we performed the identical data analysis for those sessions without a significant placebo response. Interestingly, we did not find any placebo related rACC activity (placebo > no-placebo) in this analysis, not even at very low thresholds (0.05 uncorrected). Finally, we performed an interaction analysis including all data in a single analysis (repeated measurement ANOVA). This analysis included the factors group (placebo-response vs. no placebo response) and condition (pain under placebo condition vs. pain under no placebo condition). Intuitively, the interaction denotes a stronger placebo related response (placebo > no-placebo) in the placebo responsive group as compared to the non-responsive group. This analysis revealed significant activation in the rACC [0, 36, −9, for x,y,z, $P<0.05$, $Z=3.6$].

3.6. Time course of placebo related activation

To evaluate the underlying temporal dynamics of placebo analgesia, we performed an additional finite

Table 1

Region	Coordinate (x,y,z in mm)		Voxel-level (Z), R/L
	R	L	
(a) Main effect of painful laser-stimulation (pooled over left and right sided stimulation			
SI	42, −42, 48	−54, −42, 48	5.0*/5.1*
SII	57, −21, 21	−60, −15, 15	6.1*/4.9*
STG/MTG	63, −51, 12	−60, −36, 12	4.2+/4.0+
Insula	39, −6, 0	−39, 6, 3	5.5*/5.3*
Mid-cingulate	3, 30, 39	−3, 18, 48	5.4*/6.4*
RACC	6, 39, 9	−6, 42, 12	4.0*/4.8*
Thalamus	9, −18, 9	−12, −9, 0	4.8*/4.2*
Amygdala	18, −3, −15	−18, 0, −15	5.0*/4.6+
Cerebellum	30, −63, −33	−33, −72, −21	5.6*/5.1*
Putamen	18, 12, −3	−15, 15, 0	6.1*/5.4*
(b) Placebo-related activity (plac > nplac)			
RACC	3, 42, −18	−3, 39, −18	3.8*/3.5+
(c) Co-players of placebo analgesia (PPI-analysis)			
Amygdala	15, −6, −21	−18, −12, −21	4.0*/3.8*
PAG	3, −21, −3	–	3.2*/
Pons	0, −12, −9	–	2.8+/

*<0.05 corrected; +<0.001 uncorrected; SI, primary; SII, secondary somatosensory cortex; STG, superior; MTG, medial temporal gyrus; rACC, rostral anterior cingulate cortex.

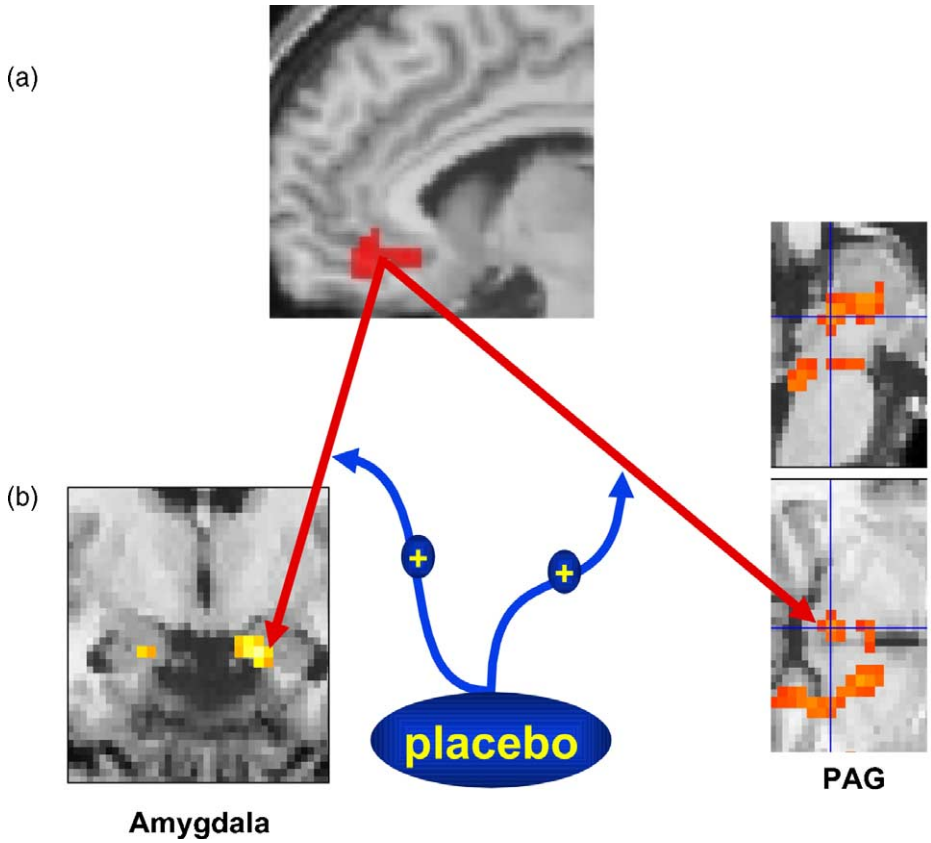

Fig. 2. (a) Placebo related activation in the rACC. Placebo (red) related activation overlaid on a structural T_1-weighted MRI as used for spatial normalization. Placebo-related responses were identified by testing for activations, which were greater under the placebo condition compared to the no-placebo condition; (b) rACC recruitment of subcortical antinociceptive network: a psycho-physiological interaction analysis (PPI) was conducted to test for placebo dependent contributions of the rACC to other brain areas. Placebo analgesia activity in the rACC covaried with that in bilateral amygdalae, PAG, and the pons.

impulse response (FIR) basis set analysis in order to to illustrate the time course of activation over eleven, 3 s time bins following the presentation of the cue, depending on the experimental condition (placebo vs. no-placebo). The FIR model includes all 18 sessions with a significant placebo effect. We plotted the time course of activity from the peak voxel derived from the group×condition interaction analysis [0, 36, −9] (Fig. 3). Interestingly, this plot reveals that the major difference between the placebo and non-placebo blocks is seen 9–21 s after cue onset. Taking the hemodynamic response delay into account, this means that the difference due to the placebo effect in the rACC was maximal during the application of the first three painful stimuli. rACC activity at the beginning of a block (cue) and the end was similar for both—the placebo and the no-placebo condition.

3.7. Psycho-physiological interaction analysis

To test for placebo dependent contributions of the rACC to other brain areas, a psycho-physiological interaction analysis was conducted as described in the methods section. Activity in the rACC covaried with activity in bilateral amygdalae [15, −6, −21/−18, −12, −21; Z=4.0/3.8; $P<0.05$] and the periaqueductual gray (PAG) [3, −24, −3, Z=3.2, $P<0.05$] during the placebo condition (Table 1c, Fig. 2). No significant effect was observed in the rostral ventromedial medulla.

4. Discussion

Two important findings emerge from this study: (i) as proposed by two previous studies (Petrovic et al., 2002; Wager et al., 2004), the rACC seems to represent an important cortical area involved in placebo analgesia; (ii) during placebo analgesia, rACC activity covaries with activity in a subcortical antinociceptive network including bilateral amygdalae and the PAG. This suggests that the rACC recruits a subcortical antinociceptive network to link cognition (in this case expectation of analgesia) with endogenous pain control/antinociception.

To identify the neural substrates that mediate placebo-analgesia, we tested for brain areas displaying greater activation during the placebo condition compared to the no-placebo condition. Such a response pattern renders it likely that this area modulates pain perception. The only brain area showing this behavior was the rostral anterior cingulate cortex (rACC). Our interpretation that the rACC activity is

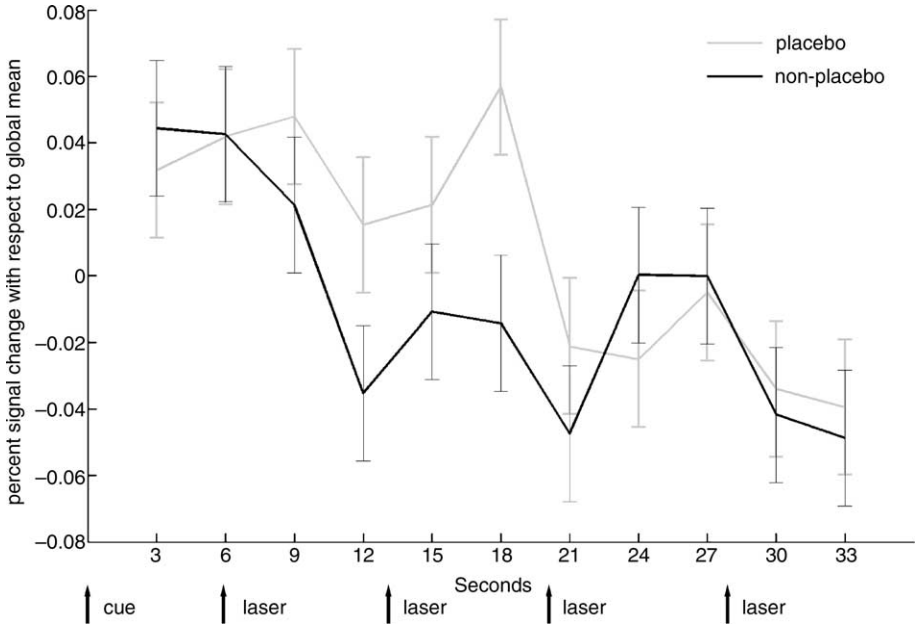

Fig. 3. Time course of BOLD signal in the rACC for the placebo (grey) and no-placebo conditions (black). This plot demonstrates the time course of activity [percent signal change with respect to global mean] from the peak voxel derived from the group×condition interaction analysis [0, 36, −9, for *x*,*y*,*z*]. The plot is derived from a finite impulse response (FIR) basis set analysis illustrating the time course of activation over eleven, 3 s time bins following the presentation of the cue. The data are presented with their 90% confidence intervals. The major difference between the placebo and non-placebo blocks is seen 9–21 s after cue onset. Taking the hemodynamic response delay into account, this means that the difference due to the placebo effect in the rACC was maximal during the application of the first 2–3 painful stimuli. rACC activity at the beginning of the block (cue) and the end was similar for both—the placebo and the no-placebo condition.

tightly linked to a placebo response is underlined by the fact that the placebo vs. no-placebo condition BOLD signal difference was significantly stronger in those sessions where a significant placebo analgesia effect was also observed behaviorally (group×condition interaction).

Our finding of rACC activation related to placebo analgesia is in line with a previous PET study on placebo analgesia by Petrovic and colleagues, who studied similarities between intravenous opioid analgesia and placebo analgesia induced by a fake analgesic i.v. injection (Petrovic et al., 2002). Their study demonstrated a shared neuronal mechanism for endogenous and exogenous antinociception; namely, a significant contribution of the anterior cingulate cortex to both placebo and opioid analgesia, thereby establishing evidence for earlier ideas of the involvement of the endogenous opioid system in placebo analgesia.

Within the stimulation block (lasting about 30 s), the BOLD signal difference between the placebo and non-placebo conditions was greatest for the period of pain stimulation, with a maximum for the first 2–3 pain stimuli. Importantly, no effect was observed at the time point of the cue. Given that placebo analgesia was induced on only one side of the body, it appears tempting to relate our findings to the somatotopy of placebo analgesia (Benedetti et al., 1999). However, we did not formally test for somatotopic specificity, since painful stimuli were only presented at one body part at a time. Therefore, our results indicate a dynamic, temporally specific placebo analgesia mechanism, in which the rACC is only active when painful stimuli are actually applied in combination with the knowledge of a substance that is thought to reduce the sensation of these painful stimuli. This suggests a significant phasic component of the dynamics of placebo analgesia, even though our experimental setting cannot exclude an underlying tonic aspect.

As one would expect, and in accord with the study by Wager et al. (2004), we found that reduced pain perception is reflected in decreased activation in the pain system. This result supports the view that placebo analgesia is not merely the consequence of an altered evaluation of unaltered afferent neuronal information, but that the mechanism of placebo analgesia does indeed shape incoming nociceptive information in the brain.

4.1. Mechanisms of placebo analgesia

After having identified the rACC as a source of placebo analgesia, we tried to further characterize the underlying mechanisms of placebo analgesia. It appeared likely that during placebo analgesia, the rACC does not directly modulate pain processing, but rather exerts its effect through subcortical pain modulating circuitry. Given the growing evidence that placebo analgesia involves opiate-dependent mechanisms (Benedetti et al., 1999; Levine et al., 1978; Wall, 1999), we hypothesized that the rACC recruits a subordinate system involved in opioid-dependent endogenous antinociception to mediate placebo analgesia. The most thoroughly described pain modulating circuit includes the amygdala, PAG and the rostral ventromedial

medulla (RVM) in the brainstem. Through descending projections, this circuit controls both spinal and trigeminal dorsal horn pain transmission neurons, and mediates both opioid and stimulation produced analgesia (Basbaum & Fields, 1984; Fields, 2000).

To test whether a similar network is involved in placebo analgesia, we sought areas that covaried with rACC activation; in other words, areas that show a stronger coupling with rACC during the placebo condition. A psychophysiological interaction analysis showed that activity in the rACC covaried with activity in bilateral amygdalae and the periaqueductual gray (PAG) during the placebo condition. This indicates that during placebo analgesia, the rACC interacts with subcortical structures involved in endogenous antinociception to produce the placebo-induced reduction in pain perception. Our finding that placebo analgesia involves mechanisms of descending modulation confirms earlier reports (Petrovic et al., 2002), that described increased coupling between the activation of the rACC and activity in the brainstem during both opioid and placebo analgesia. The rACC has one of the highest cortical concentrations of opioid receptors (Willoch et al., 1999) and the lower opioid system, including the PAG, is under the control of the opioid rich areas in the rACC through direct or indirect projections (Vogt et al., 1993).

4.2. PAG

The periaqueductal gray (PAG) plays a key role in descending mechanisms that modulate spinal nociceptive activity (Behbehani, 1995; Fields, 2000; Helmstetter et al., 1998). According to its cortical anatomical interconnections, it is ideally suited to integrate inputs from the limbic forebrain with ascending nociceptive input from the dorsal horn. Data from rats, cats and monkeys demonstrate significant cortical inputs to the PAG from a pain related network, including somatosensory areas, the insular cortex, medial prefrontal cortex, and from multiple areas of the ACC, including those that receive nociceptive input (An et al., 1998; Mantyh, 1982).

The PAG is part of an opioid linked circuit that controls nociceptive neurons in the dorsal horn. A major efferent projection of the PAG is to the rostral ventromedial medulla (RVM), which projects abundantly and selectively to pain transmitting neurons in the dorsal horn of the spinal cord and the trigeminal nucleus. When opioid agonists are injected into the PAG, RVM, as well as the amygdalae, a powerful analgesic effect is produced (Burkey et al., 1996; Fields et al., 1991; Helmstetter & Bellgowan, 1993). Most interestingly, the PAG can produce antinociceptive effects, which are somatotopically organized. Both the stimulation and the injection of morphine at different loci produce analgesia in different body parts (Soper & Melzack, 1982; Yaksh et al., 1976). Thus, the PAG represents an ideal relay station to link the target directed expectation of placebo analgesia with the opioid system.

4.3. Amygdala

The amygdala appears to represent a major relay station for both afferent and efferent (anti-) nociceptive information processing. For afferent information processing (nociception), the amydala receives pain related information through spino-(trigemino)-amygdala pathways projecting to large receptive field nociceptive neurons (Bernard & Besson, 1988). In one of our recent fMRI studies, we documented a robust activation of bilateral amydgalae to unilateral laser stimuli, which was in accord with the electrophysiological observation that 50% of these neurons respond similarly to stimulation of all body parts (Bernard et al., 1992; Bingel et al., 2002). These response properties and its extensive connections to anterior cingulate cortex support the view that this area contributes to emotional processing (i.e. aversive nature) of painful events rather than sensory-discriminative aspects of pain.

As supported by our present findings of amygdala involvement in placebo analgesia, the amygdala activation seen in pain studies might also reflect activation of a ‘defensive behavioral system’, which controls transmission of nociceptive impulses to the brain through modulatory circuits. The amygdala contains massive projections to the periaqueductal gray matter (PAG) and is found to contribute to fear, stress, and expectation induced analgesia, most of which appear to depend on the release of endogenous opioids (Borszcz & Streltsov, 2000; Fields, 2000; Fox & Sorenson, 1994; Mena et al., 1995).

Alternatively to antinociceptive mechanisms, one may also view the amygdala involvement in placebo analgesia as a conditioned-learning mechanism. Apart from expectation, current concepts of placebo analgesia emphasize the importance of learning through conditioning. Unlike expectation, which always involves the conscious process of engaging the modulation that underlies placebo analgesia, conditioning describes the adoption of an altered response over time that is linked to a conditioning stimulus and that is not necessarily coupled to awareness (Benedetti et al., 2003). Along these lines, the prefrontal cortex and the amygdalae could both converge onto the endogenous pain modulation pathways through interaction with the rostral ACC, providing a brain anatomical basis for the dual modes of placebo analgesia characterized by expectation and conditioning processes.

5. Conclusion

Our data support previous evidence that the rACC is not only involved in pain perception, but also plays a key role in modulating pain perception—in this case, the generation of placebo analgesia. During placebo analgesia, rACC activity covaries with activity in the PAG and bilateral amygdalae—both subcortical structures classically involved in endogenous antinociception. Our results provide further support for

the idea that the rACC resembles a crucial cognitive control area for exogenous and endogenous antinociception that recruits subcortical pain modulatory mechanisms.

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