CHAPTER 16

Pain Anticipation in the Cingulate Gyrus

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Chapter contents

Our ability to anticipate the consequences of motor events, environmental stimuli, or decision processes is a fundamental aspect of consciousness and it offers unique adaptive advantages (Ingvar, 1985). Previous acquired knowledge, in combination with currently available information, provides the basis for understanding as to how we generate anticipatory responses. Anticipation is a highly complex condition where different factors such as attention, preparation and motivation, fear, or anxiety can come into play. Such mechanisms allow anticipatory adaptation and coping with neutral and emotional stimuli, thus influencing subsequent behavior (Lazarus, 1991; Posada *et al.*, 2001). A description of current theories on anticipation is beyond the scope of this chapter (for review, see Kirsch, 1999).

Given its unique role at the interface of cognitive, affective, and motor functions as discussed in Chapters 5 and 8–13, the cingulate cortex is a likely substrate for anticipatory mechanisms. Indeed, physiological and functional imaging studies have disclosed the role of cingulate regions in different experimental models of anticipation. For instance, electrophysiological studies performed in non-human primates have shown anticipatory activity of anterior cingulate neurons during expectation of the visual cue triggering task onset, or during the delay period in delayed response tasks (Niki and Watanabe, 1976, 1979); anticipatory activity of different neurons could be related to orienting attention before stimulus onset, to a preparatory set for emitting appropriate behavioral responses, or to time estimation processes. Other studies have shown cingulate neurons displaying activity related to the degree of reward expectancy (Shidara and Richmond, 2002; Matsumoto, *et al.*, 2003) or to motor preparation depending on an expected reward (Shima and Tanji, 1998; Matsumoto *et al.*, 2003).

In humans, the cingulate cortex appears to be heavily involved in the anticipation of cognitive and emotional processes. In a positron emission tomography (PET) study, Murtha *et al.* (1996) found significantly increased cerebral blood flow in the anterior cingulate cortex (ACC) during anticipatory states to different cognitive tasks, such as naming pictures or carrying on semantic judgments. More recently, using functional magnetic resonance imaging (fMRI), other authors have revealed cingulate cortex activations related to the expectancy of emotional pictures (Bermpohl *et al.*, 2006; Nitschke *et al.*, 2006) or to the degree of uncertainty (risk) inherent in a decision, to the level of autonomic arousal, or both, during the delay period between reward-related decisions and their outcomes as shown in Figure 16.1 (Critchley *et al.*, 2001).

It is also worth mentioning that the cingulate cortex, together with the supplementary motor area (SMA) and thalamus, have been identified as the source of the contingent negative variation (CNV), a slow event-related potential generated over several seconds following an eliciting event (Ioannides *et al.,* 1994; Nagai *et al.,* 2004; Fig. 16.2). Similarly, source modeling results suggest the ACC as the generator of fear-induced

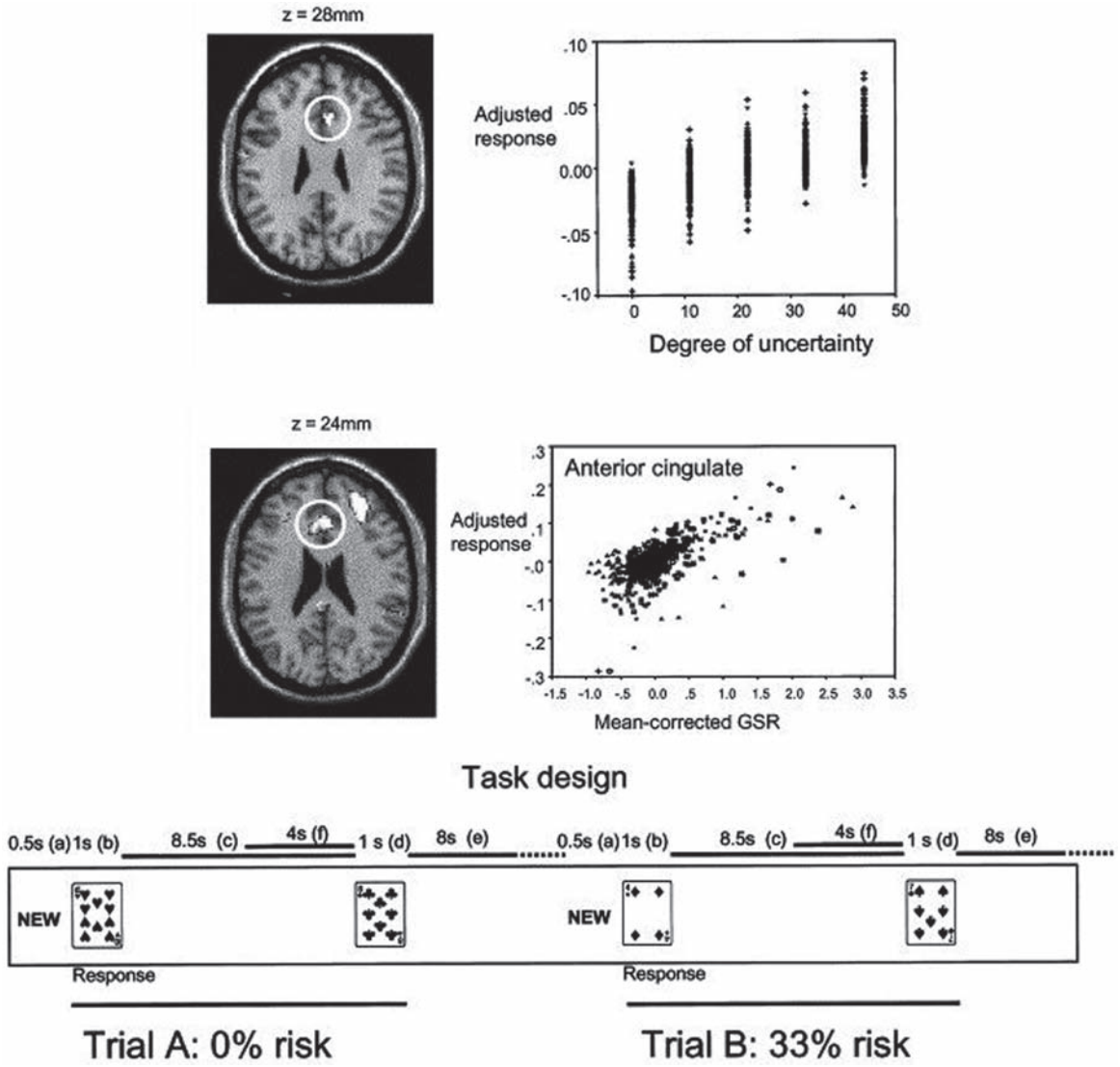

Fig. 16.1 fMRI activity in the ACC positively co-varying with the degree of uncertainty (risk) inherent in a decision (*top*) and with the galvanic skin response (GSR: *middle*) during the delay period between reward-related decisions and their outcomes. Subjects performed a two-choice decision-making task (*bottom*) based on visual presentation on cards and on the prediction of whether the next card would be higher or lower. Correct decisions were associated with monetary gain, incorrect decisions were associated with monetary loss. Adjacent portions of the cingulate gyrus were modulated according to the degree of uncertainty (risk) inherent in the decision, by arousal indexed by GSR, or conjointly by arousal and uncertainty. (From: Critchley *et al.*, 2001, with permission).

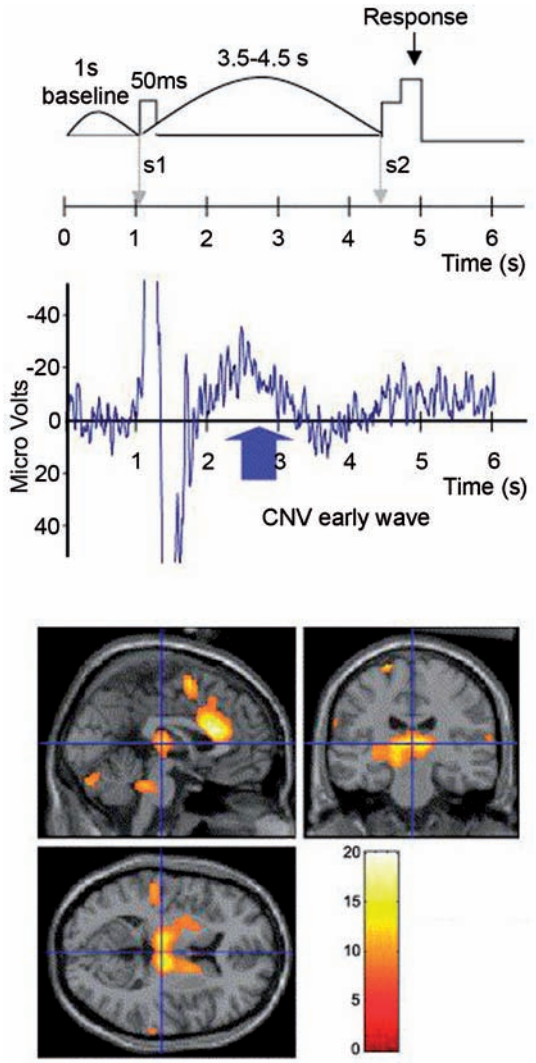

Fig. 16.2 Cingulate activity co-varying with the amplitude of CNV during a forewarned reaction time task. EEG and fMRI data were simultaneously recorded while the subjects performed the task (*top*). Regional brain activity correlating with trial-by-trial changes in measured CNV amplitude was detected in the rostral midcingulate cortex, bilateral thalamus and supplementary motor area (*bottom*). S1: warning acoustic stimulus; S2: imperative stimulus instructing subjects to emit a motor response. (Modified from: Nagai *et al.*, 2004, with permission).

Stimulus-Preceding Negativity, a slow cortical potential which follows visual cues in a threat-of-shock paradigm (Böcker *et al.*, 2001). These results, taken together; point out the role of anterior and midcingulate regions in different aspects of anticipation, both of neutral and of affectively relevant events.

Goals of This Chapter

Throughout this chapter, we focus mainly on the involvement of the cingulate cortex in the anticipation of somatosensory input and specifically of pain. This issue has important theoretical and clinical implications, given the role of the cingulate cortex in the mechanisms of pain and analgesia (see Chapters 14 and 15). A specific question is that whether anticipation is able to affect the activity of pain-related populations in the cingulate cortex and in the pain matrix in general. Indeed, it has long been hypothesized (James, 1892) that essentially the same brain regions were implicated both in the anticipation and in the perception of a stimulus; this hypothesis has now been directly tested by electrophysiological and functional imaging studies in humans and non-human primates. Also, when appropriate, we will briefly compare the activity of the cingulate cortex during anticipation of pain and during anticipation of other aversive or reward events. The specific goals of this chapter include the following:

1 Assess electrophysiological evidence of neurons active during pain anticipation in the cingulate cortex.

2 Evaluate evidence from functional imaging studies of activity changes related to somatosensory anticipation in different portions of the cingulate gyrus in healthy volunteers and in pain patients.

3 Appraise the modulation of basal- and stimulus-evoked activity of pain-related populations in the cingulate cortex and in other pain-related areas.

4 Consider anticipation of pain and analgesia in terms of the potential underlying mechanisms and cingulate circuits.

Electrophysiological Studies of Pain "Anticipatory" Cingulate Neurons

Cingulate neurons that are active during the period preceding the appearance of painful stimuli in pain-avoidance tasks have been described in different species, namely rats (Takenouchi *et al.*, 1999), rabbits (Freeman *et al.*, 1996), and monkeys (Nishijo *et al.*, 1997; Koyama *et al.*, 1998, 2000, 2001). Moreover, there is preliminary electrophysiological evidence for pain anticipatory neurons in the human cingulate cortex (Hutchison *et al.*, 1999).

The studies by Nishijo *et al.* (1997) and Koyama *et al.* (1998, 2000, 2001) in macaque monkeys are of particular interest. They tested the characteristics of neurons in the midcingulate cortex (MCC), while animals were performing visually-directed pain-avoidance or reward tasks, which were randomly interspersed within the same recording sessions. In the Nishijo *et al.* study (1997), 116 out of 550 isolated neurons responded during one or more phases of the operant task. Among them, eight displayed gradually increasing activity in the delay phase between a start tone signaling trial

initiation and visual cues, and were therefore called "anticipatory" neurons. The experimental design adopted by Koyama *et al.* is depicted in Figure 16.3. In pain-avoidance trials, the monkey began each trial by pressing a lever. One second thereafter, a predictive cue was presented at the centre of the computer monitor for 0.5–1.5 s and, subsequently, a red light signaling an ensuing noxious stimulus (discrimination cue) appeared for 1 s. The monkey had to respond by releasing the lever during the red light presentation, in order to avoid a painful electric shock at its disappearance. In reward trials, a green light was the discriminative cue. Out of 775 neurons, 196 task-related neurons were found and, among them, 36 exhibited increased discharge frequency after the appearance of a visual fixation cue that signaled trial onset, but did not provide any information as to the kind of task ("anticipatory" units).

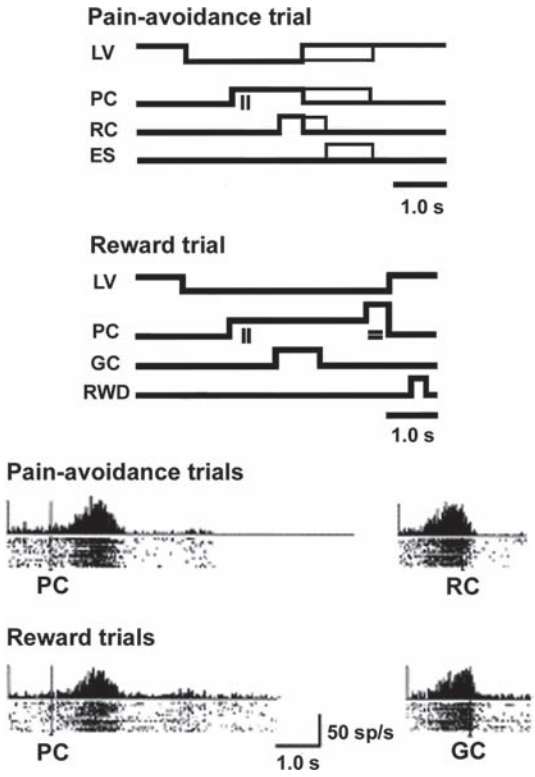

Fig. 16.3 Anticipation-related electrophysiological responses in monkey cingulate cortex. *Top:* Schematic representation of pain-avoidance and reward trials. ES, electric stimulation; GC, green cue; LV, lever; PC, prediction cue; RC, red cue; RWD, reward. Thin lines specify the time range of stimuli and responses. *Bottom:* Representative data for a neuron that showed significant activation during the prediction period in pain-avoidance and reward trials. This neuron showed gradually increasing firing after the appearance of the prediction cue, returning to the spontaneous baseline rate soon after the appearance of the red or green discrimination cue. (From: Koyama *et al.*, 2001, with permission).

Unlike putative "time estimation" units (e.g., Niki and Watanabe, 1979), the activity of anticipatory units was typically gradually increasing after the appearance of the prediction cue; it returned to baseline values soon after the appearance of the discriminative cue (see Fig. 16.3). Several other task-related cingulate neurons (36 out of 116 in the Nishijo *et al.* population and 77 out of 196 in the Koyama *et al.* studies) responded selectively during the visual discrimination period (namely, after the appearance of a discriminative cue). The majority displayed differential responses to rewarding or aversive cues, suggesting that their activity was not a function of arousal or attention. No activation was usually observed during the fixation period preceding the visual cue, or during the monkey motor response. On these grounds, the activity of these neurons cannot be ascribed to simple perceptual or motor processes. Rather, they could be involved in the cognitive appreciation of stimuli, or in the selection of appropriate adaptive responses. Other neurons responded differently during the same kind of bar pressing, performed with different purposes (to obtain reward or to avoid shock; Nishijo *et al.*, 1997).

The percentage of cingulate neurons showing pain anticipatory responses in the above-mentioned studies may seem rather small. It should be underlined, however, that the cingulate cortex is a complex structure, where different neural populations are intermingled. Indeed, several other single-unit electrophysiological studies in trained monkeys have found that the majority of neurons in specific portions of the anterior or midcingulate cortices were not responsive or showed differential responses to the specific task under examination (e.g., Niki and Watanabe, 1979; Shima and Tanji, 1998; Ito *et al.*, 2003; Matsumoto *et al.*, 2003). Functional imaging studies in humans also provide evidence for spatially contiguous neural populations with different response characteristics (e.g., Critchley *et al.*, 2001; Büchel *et al.*, 2002).

An interesting issue concerns the sensory properties of cingulate anticipatory neurons (Koyama *et al.*, 1998). Approximately 50% of neurons active during anticipation of a noxious transcutaneous electric shock may be nociceptive-specific, since they responded also to painful stimulation of the contralateral leg, but not to tactile input. The remaining anticipatory neurons were not affected by noxious stimulation and, according to the authors, could be more generally involved in aversive conditioning. It is not known whether the two sub-populations were intermingled or whether they clustered in different portions within MCC.

Electrophysiological evidence for complex properties of cingulate-nociceptive neurons in humans come from the study of Hutchison *et al.* (1999), who performed microelectrode exploration of the MCC in patients

undergoing bilateral cingulotomy for chronic depression or obsessive-compulsive disorder. In four patients, 11 MCC nociceptive-specific neurons were identified that responded (9 excited, 2 inhibited) to contralateral noxious thermal and/or noxious mechanical stimuli. Three of these neurons also appeared to respond to the observation of a potentially painful stimulus, namely when the patient watched pinpricks being applied to the examiner's fingers. When pinpricks were again applied to the patient, the activity of one neuron increased before the skin was contacted, suggesting a response related to pain anticipation as shown in Figure 16.4.

Altogether, these findings show an integrated neuronal network within the cingulate cortex for anticipating, evaluating and responding to salient environmental stimuli. A subset of this network, including cingulate nociceptive neurons, seem to be specifically active during anticipation of noxious stimuli. The overlap of circuits active during anticipation and experience of pain, suggested by electrophysiological studies at the single-cell level, has been further demonstrated by mapping studies in humans.

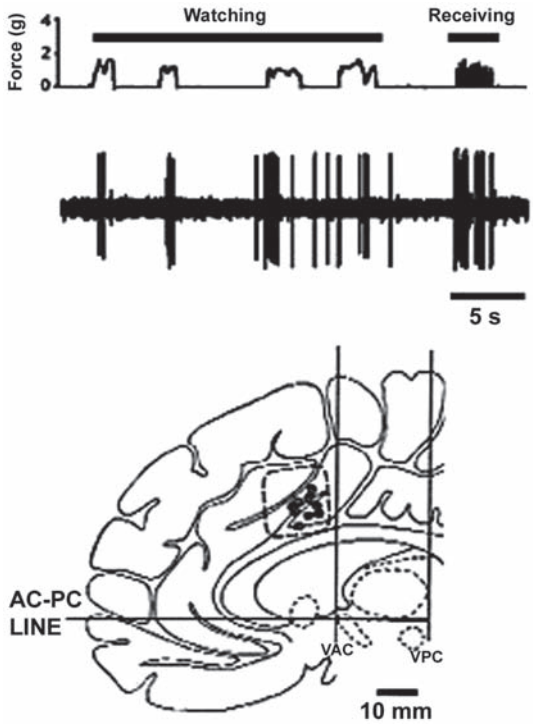

Fig. 16.4 Cingulate neuron responding during perception, observation and anticipation of painful stimuli in humans. This cell responded when the patient watched pinpricks being applied to the examiner's fingers. When pinpricks were again applied to the patient, the response started before the skin was contacted, suggesting a response to pain anticipation. The recording sites are shown on the sagittal section at the bottom (From: Hutchison *et al.*,1999, with permission). AC-PC Line, horizontal line through the anterior and posterior commissures.

Functional Imaging Studies of Anticipation of Somatosensory Input in Humans

PET studies from different groups have provided evidence that anticipation *per se*, in the absence of actual somatosensory input, affects regional cerebral blood flow (rCBF) in specific cortical areas in healthy volunteers (Drevets *et al*., 1995; Chua *et al*., 1999; Hsieh *et al*., 1999; Naliboff *et al*., 2001; Mayer *et al*., 2005). Over the last few years, the characteristics and spatiotemporal distribution of somatosensory anticipation-related changes in brain activity have been described in more detail using fMRI (Ploghaus *et al*., 1999; Carlsson *et al*., 2000; Sawamoto *et al*., 2000; Porro *et al*., 2002, 2003; Jensen *et al*., 2003; Singer *et al*., 2004; Koyama *et al*., 2005; Berns et *al*., 2006). With few exceptions (e.g., Wager *et al*., 2004), these fMRI studies have disclosed anticipation-related foci in different portions of the cingulate cortex, mainly in the anterior MCC (aMCC) and pregenual ACC (pACC). It is worth mentioning that different cingulate regions show responses of different signs during anticipation of painful electric shocks; for instance, Chua *et al*., (1999) showed positive correlations between anxiety scores and rCBF levels in the left aMCC, whereas blood-flow decreases were found in pACC in the PET study by Simpson *et al.* (2001).

The anticipation-related pattern of cingulate activity seems to differ at least in part according to the degree of uncertainty inherent in the paradigm. Indeed, Hsieh *et al*. (1999) demonstrated that cognitive appraisal of impending somatic pain may differentially modulate brain activity depending on previous experience and available information on the kind of stimulus. When normal subjects anticipated an unknown painful event, increased regional blood flow levels were found in the anterior (area 32′/9) and posterior (area 24′) portions of the MCC, as well as in the ventromedial prefrontal cortex (approximately corresponding to Brodmann area 12) and in the periaqueductal gray matter. By contrast, blood flow decreased in areas 12 and 24′ during anticipation of a pre-trained known but unavoidable pain. These opposite patterns of brain activity paralleled different responses on the behavioral level – anxiety and directing attention toward the unknown stimulus, or fear and diverging attention from the known source of distress (Hsieh *et al.,* 1999; Ploghaus *et al*., 2003).

An interesting issue is whether anticipation of pain involves different cingulate subregions from those active during anticipation of non-noxious stimuli. Ploghaus and colleagues (1999) described foci in the medial frontal lobe, anterior insular and cerebellar cortex that were selectively activated during certain

anticipation of acute thermal pain but not during anticipation of warmth or during actual thermal stimulation. Based on their antero-posterior coordinates (*y* axis) in individual subjects, anticipation of pain-related foci in the medial frontal cortex appeared to be either in the aMCC or in dorsal pACC (mean Talairach coordinates –7, 47, 16). In most of the subjects, pain-related foci were more posteriorly located in the MCC as shown in Figure 16.5. The authors surmised that, given their rather close proximity to pain-related foci, the anticipation regions could exert some form of local interaction leading to the prediction of pain and/or to changes in autonomic, affective or motor functions (Ploghaus *et al*., 1999). Another study (Jensen *et al*., 2003) showed that the aMCC, together with ventral striatum and bilateral anterior insula, was activated during anticipation (5 s) of an aversive event (painful electric shock). Interestingly, the activation occurred whether or not the subject could actively avoid the aversive stimulus. An involvement of dorsal pACC and rostral cingulate motor area during anticipation, but not actual perception, of emotional pictures has also been described in a recent fMRI study (Bermpohl *et al*., 2006).

Using a different experimental paradigm characterized by more prolonged waiting (up to 60 s) and stimulation periods (lasting several minutes), Porro *et al*. (2002, 2003) demonstrated a more complex involvement of cingulate areas during anticipation. Another important difference with the study by Ploghaus *et al*. is that subjects were not aware of the quality of the impending stimulus (either painful or not painful: "uncertain" anticipation), and that they had never experienced the same kind of noxious stimulus before. Moreover, a long baseline period preceded the anticipatory cue, thus allowing a differentiation of a simple rest condition from anticipation of somatosensory input. The results showed that mean fMRI signals in both posterior cingulate cortex (PCC) and MCC were increased during the anticipatory phase, but only MCC showed increased activity during the period immediately following the stimulation (either tactile or painful) as shown in Figure 16.6. By contrast, pACC often displayed a composite array of areas showing that fMRI signal increases or decreases during anticipation. These findings suggest that large populations of neurons in the cingulate cortex are involved during uncertain expectation of pain. It may be hypothesized that the fMRI signal increases in PCC, which was not activated to a significant extent during actual somatosensory input, were related to enhanced monitoring of the body state (see below) or to non-specific arousal. We and others have suggested that the differences with the Ploghaus' study (increased activity not only in pACC and aMCC, but also in more posterior parts of the cingulate cortex), are related mainly to the degree of uncertainty

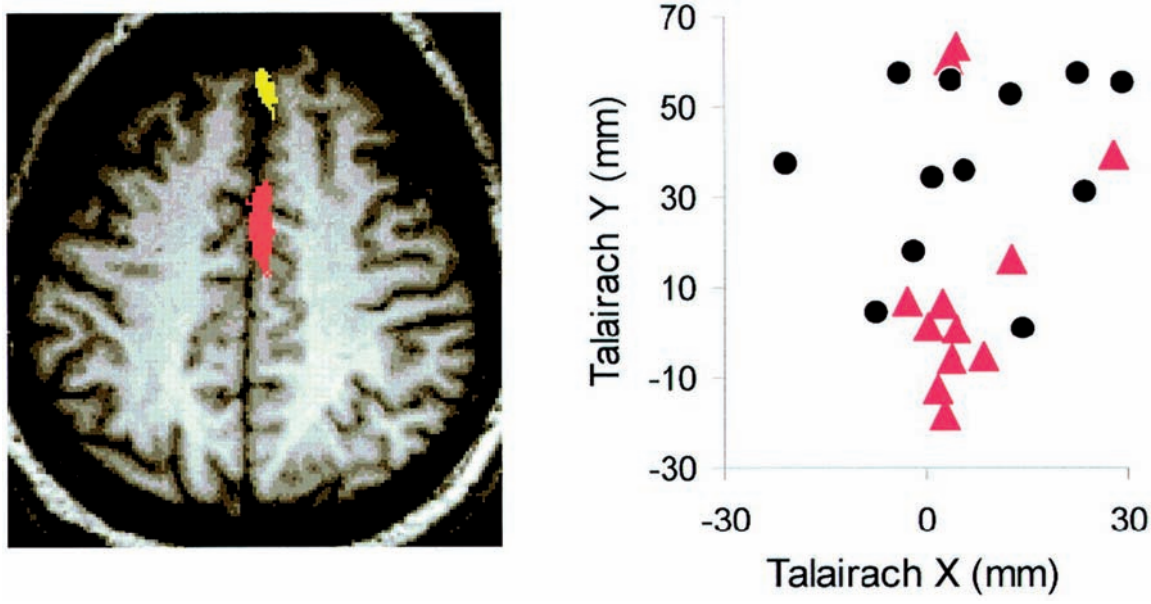

Fig. 16.5 Location of anticipation- and pain-related fMRI activations in the cingulate/medial frontal cortex, in a paradigm involving certain expectation of pain. *Left:* Group map showing the location of clusters in the medial frontal cortex/anterior cingulate, showing signal changes specifically time-locked to the anticipation phase of noxious input (yellow) or to noxious heat stimulation (red). *Right*: Talairach coordinates in individual subjects of anticipation-related (black circles) or pain-related (red triangles) clusters. (From: Ploghaus *et al*., 1999, with permission).

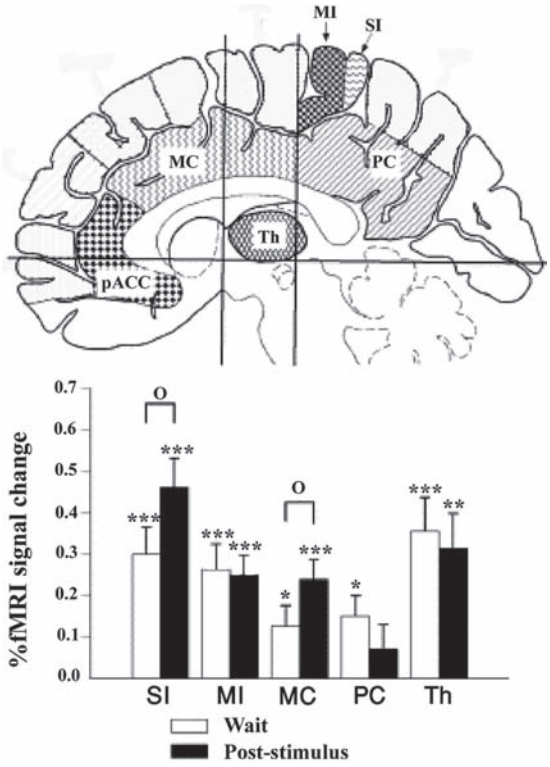

Fig. 16.6 Mean changes in fMRI activity during anticipation of a potentially noxious stimulus to one foot, and during the first minute after stimulus onset. *Top:* Schematic drawing of the mesial hemispheric wall, showing the location and extent of the regions of interest (ROIs). MC, midcingulate cortex; MI, primary motor cortex; pACC, perigenual anterior cingulate cortex; PC, posterior cingulate cortex; SI, primary somatosensory cortex; Th, thalamus. *Bottom:* Mean (+SEM, $n = 56$) normalized percent fMRI signal changes from baseline in selected ROIs, during the 42-s preceding stimulus onset (Wait) and in the post-stimulus period. *, **, *** = significantly higher than baseline at $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively. O = values from the post-stimulus period higher than those from the Waiting period, $p < 0.05$. (Modified from: Porro *et al*., 2003, with permission).

inherent in the paradigm (Ploghaus *et al*., 2003; Porro *et al*., 2003).

In a recent event-related fMRI study (Lui *et al*. in preparation), we studied brain activity during brief periods of anticipation and actual processing of mechanically induced pain. A visual cue informed the subjects about the timing, but not the intensity (noxious or non-noxious) of the impending stimulus ("uncertain" anticipation). We found one focus in the right pACC which was uniquely active during the anticipatory period, but not following actual noxious stimuli. The coordinates of this anticipation-related focus appeared to closely overlap those of foci active during anticipation of the placebo effect (Petrovic *et al*., 2005; see below) and are close to those found by Ploghaus *et al*. (1999) during certain expectation of pain. Thus, activated foci in this area do not appear to be specific of certain expectation and associated fear-related processes (Ploghaus *et al*., 2003).

Interestingly, cingulate activation has also been demonstrated during anticipation of visceral pain (Naliboff *et al*., 2001; Mayer *et al*., 2005; Yaguez *et al*., 2005). In an fMRI study involving aversive conditioning of painful esophageal distention in healthy volunteers, brain activity during pure anticipation of pain and conditioning extinction resembled what was seen during actual stimulation; in contrast, anticipation of an innocuous somatic stimulus induced lesser activity, confined to the posterior parietal cortex (Yaguez *et al*., 2005). Similarly, rCBF increases in the pACC and in the adjacent medial prefrontal, and orbitofrontal cortices were seen not only during actual inflation at painful pressure (45–60 mmHg) of a latex balloon catheter inserted into the rectum, but also during scans in which pressure pulses were expected but not given (Naliboff *et al*., 2001; Mayer *et al*., 2005).

There is some evidence that the anticipation-related pattern of CBF changes can be modulated by pre-existing pain syndromes. Indeed, in patients suffering from irritable bowel syndrome (IBS), anticipation of visceral distension was associated with higher rCBF increases in aMCC and PCC than in healthy controls (Naliboff *et al*., 2001). These changes possibly reflect arousal and hypervigilance to potentially aversive stimuli (see Crombez *et al*., 2005), inasmuch as they were reduced in IBS patients after repeated exposure to the same experimental protocol; by contrast, anticipation-related activation in pACC, and the responses to actual visceral stimuli in the thalamus and insula were unchanged (Naliboff *et al*., 2006). These results have implications for the understanding of the mechanisms underlying visceral hypersensitivity in disease conditions such as functional gastrointestinal disorders (Aziz, 2006).

Cognitive factors related to anticipation are also likely to be important in other chronic pain syndromes. For instance, in fibromyalgic patients undergoing blunt pressure stimuli, pain catastrophizing (namely, characterization of pain as awful, horrible and unbearable) was positively correlated with fMRI activation in the contralateral MCC and medial frontal gyrus; it has been hypothesized that these functional changes reflect altered anticipation of, and attention to, somatic stimuli (Gracely *et al*., 2004). Anticipation and fear-avoidance beliefs have been shown to limit behavioral performance of patients with low back pain (Pfingsten *et al*., 2001); expectations, negative affect, and fear avoidance beliefs are interrelated constructs that have predictive value for future pain and disability (Boersma and Linton, 2006). Longitudinal functional imaging studies in patients at risk of developing chronic somatic pain are

needed to help elucidate the role of cingulate areas in this regard.

To summarize, imaging techniques in humans have consistently shown foci of activation in aMCC/pACC during anticipation of somatic and visceral pain, which show higher changes than those associated with anticipation of non-noxious input. Uncertain anticipation is also associated with increased fMRI signal changes in PCC, whereas pACC show a composite pattern of activity increases and decreases. An important implication of these findings is that anticipation effects must be taken into account when designing experiments aimed at investigating cingulate involvement in pain mechanisms, in order to disentangle nociceptive information processing from its anticipation. Pain anticipation-related activity in specific cingulate regions can be enhanced in pain patients, which may reflect fear-related processes and hypervigilance and contribute to the development and maintenance of chronic pain syndromes.

Anticipation-related Modulation of Basal and Evoked Activity in Cingulate Clusters Processing Somatosensory Information

As partially mentioned above, several studies have shown spatial overlap between the brain areas activated during anticipated and actual somatosensory input (Carlsson *et al.*, 2000; Porro *et al.*, 2002, 2003; Singer *et al.*, 2004; Koyama *et al.*, 2005; Yaguez *et al.*, 2005; Berns *et al.*, 2006). A crucial question with regard to pain mechanisms is whether cortical nociceptive populations are directly affected by anticipation. Anticipation-related effects may in principle be exerted in two ways: through changes of basal activity (namely, in the absence of actual stimulation) of nociceptive circuits and through changes of stimulus-evoked activity. There is now evidence that both the effects can occur in the human brain, including the cingulate cortex.

As for the first effect, it has been recently shown that during uncertain anticipation of pain, cingulate, parietal, and insular cortical clusters encoding pain intensity undergo fMRI signal changes of the same sign as those displayed during pain, although less intense (on average, 30–40% as large: Porro *et al.* 2002, 2003) (Fig. 16.7). Several clusters showed gradually increasing activity from the anticipatory cue to stimulus onset, followed by larger increases during actual pain perception. In a recent study involving anticipation of a painful electric shock, two components of the response of pain-related cortical areas (including pMCC) during anticipation were hypothesized, a dread term

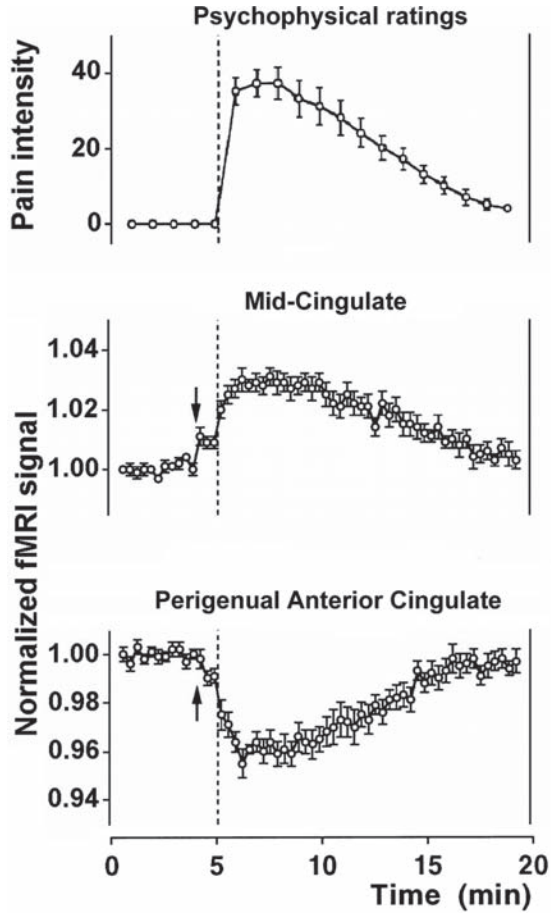

Fig. 16.7 Changes of basal activity of nociceptive clusters in the cingulate cortex during uncertain anticipation of pain. Time profiles of the mean (±SEM, $n = 24$) intensity of perceived pain (*top row*) and of changes of fMRI signal intensity in clusters displaying increases (*middle row*) or decreases (*bottom row*) significantly related to the individual psychophysical pain intensity curve, in subjects injected s.c. with ascorbic acid. Note the fMRI signal changes after the "warning" signal (arrows), of the same sign as those occurring during actual noxious stimulation. Vertical lines indicate time of injection. (From: Porro *et al.*,1998).

declining over time, and an exponentially increasing time-discounted consumption term (Berns *et al.*, 2006). It is worth mentioning that, despite the differences of the adopted experimental paradigms, all the above-mentioned studies demonstrated widespread anticipation-related changes throughout the pain matrix.

As for the second potential effect of anticipation in the modulation of evoked responses, a modulation in somatosensory-related activity in specific portions of the cingulate cortex is illustrated by a study of Sawamoto and colleagues (2000). Uncertain expectation of pain was followed by increases of the innocuous heat-related activity of clusters in the MCC and parietal

operculum/posterior insula, in parallel with increases of the perceived unpleasantness induced by the same thermal stimuli as shown in Figure 16.8. These findings constitute a first clear demonstration that anticipation can modify information processing of ensuing stimuli.

Increased activity occurring after anticipatory cues in nociceptive clusters of MCC and anterior insula has also been noted during certain expectation of either self or others' pain. In a fMRI study aimed at investigating the neural substrates of empathy for pain (Singer *et al*., 2004), two peaks of fMRI signals were found during "self pain" trials in nociceptive clusters of contralateral aMCC: the first one 2–4 s after a visual anticipation cue signaling impending pain, and the second one following the onset of the pain stimulus (3–4 s after the anticipation cue).

Koyama *et al*. (2005) studied the psychophysical and fMRI correlates of expectation of pain in a different experimental model, where longer durations of the waiting interval were associated with increasing intensities of noxious heat stimuli. As the magnitude of expected pain increased, fMRI signal changes increased in the aMCC, thalamus, insula, prefrontal, and parietal cortical regions. Manipulation of actual delivered stimuli showed that expectations of lower pain intensities powerfully reduced both the subjective experience of pain and the activation of a partially overlapping array of brain regions, including MCC, insular cortex, and primary somatosensory cortex (SI) (Koyama *et al*., 2005).

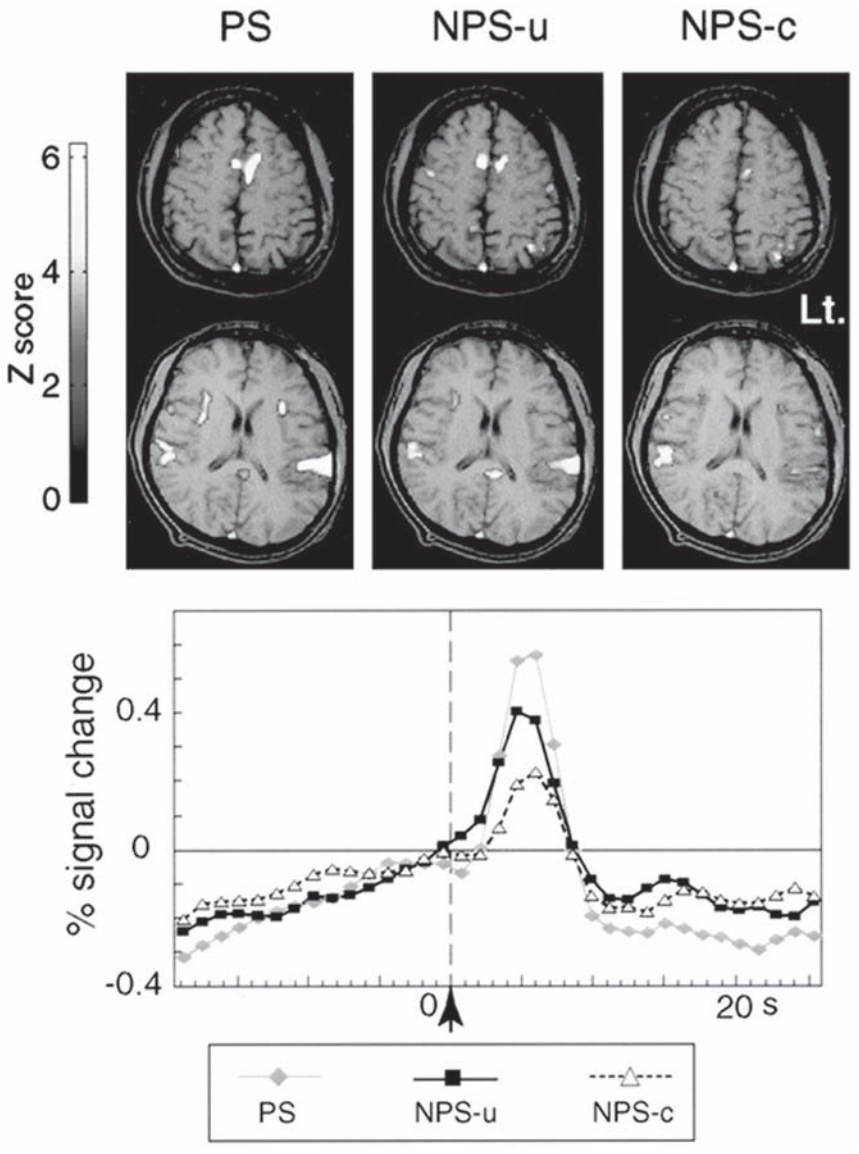

Fig. 16.8 Anticipation-induced modulation of the activity of clusters related to certain painful (PS) or non-painful (NPS-u, NPS-c) laser heat stimulation. Stimulus intensity was identical in the NPS-u and NPS-c conditions; however, in the former, the subjects did not know whether the stimulus would be noxious or non-noxious (u = uncertain context), whereas in the latter condition they were explicitly assured that the stimuli were non-painful (c = certain context). *Top*: Maps showing the location and extent of activated clusters in the three conditions in a representative subject. *Bottom*: Averaged time course data of fMRI signal changes in the cingulate cortex in the three conditions. The vertical dashed line indicates the time of the stimulus presentation. Note the higher post-stimulus peak in the NPS-u than in the NPS-c condition. (From: Sawamoto *et al*., 2000, with permission).

In another recent fMRI work by Mohr *et al.* (2005), stimulus-evoked signals in the pACC linearly decreased with increasing intensity of laser stimulation (and of perceived pain) when uncertainty about the timing of stimulus onset (randomly varying from 3 to 5 s) was present. An opposite stimulus-response function (increased signals with increased stimulus intensity) was found when stimuli immediately followed the warning cue (namely, in a "certain" condition: Mohr *et al.*, 2005).

Altogether, these findings suggest a direct influence of anticipation of pain on the basal activity of cingulate somatosensory systems, as well as modulation of processing subsequent stimuli. These results thus support the hypothesis advanced by William James (1892) in which essentially the same brain regions were implicated in the anticipation and perception of a stimulus. The shaping effect on the activity of the pain matrix may well explain why anticipation can influence the perception of subsequent noxious stimuli, a well-known effect in experimental studies and in the clinical setting (Price, 1999).

Potential Factors Underlying Changes of Cingulate Activity During Anticipation of Pain

Although the above-mentioned findings clearly demonstrate the involvement of the cingulate gyrus in anticipation of painful somatosensory input, the underlying mechanisms are still to be thoroughly clarified. Available evidence suggests a complex pattern of activity which is likely related to different factors, among which are selective attention, anxiety and arousal, and mental representation of stimuli.

Spatial orienting of attention toward the expected body area is likely to occur during anticipation, if the site of stimulation is known in advance (Van Damme *et al.*, 2004). This hypothesis may explain the somatotopically-specific modulation of baseline activity in different portions of the postcentral gyrus during uncertain expectation of pain, with selective fMRI signal increases in the appropriate SI portion of the contralateral hemisphere (Porro *et al.*, 2002). The cingulate gyrus has been identified as a major component of a network subserving the dynamic reallocation of spatial attention in the extrapersonal space (Mesulam *et al.*, 2001). A recent fMRI study suggests indeed that the posterior cingulate and medial prefrontal cortex are involved in internally generated anticipatory biases toward locations, where significant events are expected to occur, thus establishing a neural interface between attention and motivation (Small *et al.*, 2003). If the same applies to orienting attention in the personal domain, this might help to explain the selective involvement of the posterior cingulate cortex during anticipation of pain (Porro *et al.*, 2003).

Another mechanism which comes into play during anticipation is a non-specific increase in vigilance (arousal). As mentioned above, Critchley *et al.* (2001) showed that during the delay period between reward-related decisions and their outcomes, activity in the right aMCC/pACC cortex and dorsolateral prefrontal cortex positively co-varied with the level of autonomic arousal, indexed by changes in the galvanic skin conductance response (Fig. 16.1). Adjacent portions of the cingulate gyrus were modulated by the degree of uncertainty (risk) inherent in the decision, or conjointly by arousal and uncertainty (Critchley *et al.*, 2001). Thus, activity in this region seems to be implicated in mediating cognitive and somatic dimensions of anticipation. Porro *et al.* (2003) found cingulate clusters whose fMRI signal time courses were related to the heart rate (HR) profile, showing specific changes of activity during uncertain anticipation of pain as shown in Figure 16.9. The HR clusters had different functional characteristics from, and showed limited spatial overlap with, nociceptive clusters. Thus, these clusters are unlikely to be directly involved in pain mechanisms, whereas they are probably related to emotional changes during uncertain anticipation (Porro *et al.*, 2003). Anxiety and dread can be associated at various degrees with uncertain expectation, and can affect the activity of specific cingulate clusters (Ploghaus *et al.*, 2001; Berns *et al.*, 2006).

Finally, if the stimulus is known in advance, a mental representation of the impending event is likely to occur. It has been suggested that the ACC, insula and prefrontal cortex (PFC) work together to this end (Koyama *et al.*, 2005), incorporating information from brain regions associated with affective memory recall, such as the amygdala and parahippocampal regions. This hypothesis is supported by an increasing number of studies. For instance, several cingulate regions are activated in healthy volunteers during hypnotic suggestions of pain in the absence of sensory input (Derbyshire *et al.*, 2004; Raij *et al.*, 2005) or while observing pictures of people with their hands or feet in painful situations and imagining the level of perceived pain (Jackson *et al.*, 2006). Moreover, aMCC changes its activity during suggestions of increased or decreased unpleasantness of painful thermal stimuli (Rainville *et al.*, 1997). During suggestion-induced pain, activity in aMCC/pACC correlates with the subjective reality estimates (Raij *et al.*, 2005). The relative contribution of these different cognitive and emotional factors is likely to vary both in physiological and pathological states, depending on previous history and, possibly, individual differences (e.g., Berns *et al.*, 2006).

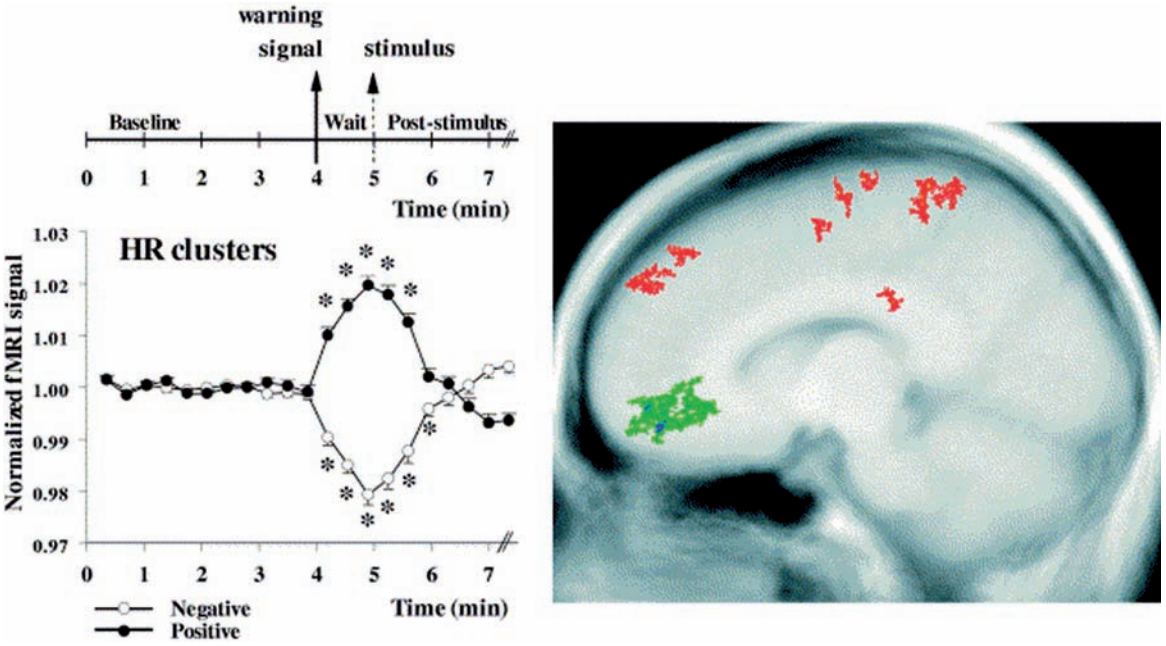

Fig. 16.9 Cortical clusters related to changes in heart rate (HR) during anticipation. *Left:* Time profiles of mean (+SEM, $n = 56$) normalized changes of functional magnetic resonance imaging (fMRI) signal intensity in the clusters displaying positive or negative correlations with the mean HR profile. * = significantly different from baseline (analysis of variance, simple contrasts) at $p < 0.001$. *Right:* Cumulative maps showing the location and extent of neural clusters positively (red-yellow) or negatively (blue-green) related to the HR profile, superimposed to the averaged anatomical image of a paramedian sagittal plane ($|x| = 6$ mm) from the 56 subjects. Positive HR clusters are frequently encountered in individual subjects also in aMCC. However, their spatial location is quite variable and they are therefore missing in the cumulative map. (From: Porro *et al.*, 2003, with permission).

Anticipation of Pain and Analgesia: Common Modulatory Sites Within Cingulate Cortex?

Anticipation of analgesia is another process of paramount relevance for our understanding of the cognitive modulation of pain (Colloca and Benedetti, 2005). Recently, functional imaging studies have begun disclosing the brain circuits involved in the placebo analgesia process, and the placebo effects on the pain matrix (Petrovic *et al.*, 2002; Wager *et al.*, 2004). Anticipation of analgesia induced by placebo increases the activity in aMCC/pACC in healthy volunteers, while decreasing brain activity in other pain-related brain regions (see Chapter 15). Accordingly, in a recent PET study aimed at identifying the specific versus non-specific correlates of acupuncture in patients, Pariente *et al.* (2005) showed that aMCC was more active when they expected a real treatment than during overt sham acupuncture. It has been proposed that both placebo- and opioid-mediated analgesic effects involve a cingulate-brainstem descending circuit (Petrovic *et al.*, 2002; Wager *et al.*, 2004; Pariente *et al.*, 2005). Interestingly, the aMCC is known to be involved in primary reward or in the context of expectation of a reward in other experimental and clinical conditions (de la Fuente-Fernandez *et al.*, 2001; O'Doherty *et al.*, 2002; Ernst *et al.*, 2004). A recent event-related fMRI study (Petrovic *et al.*, 2005) demonstrated that foci in the aMCC/pACC and orbitofrontal cortex are also involved in the expectation of anxiety relief (emotional placebo): the placebo-dependent increase in aMCC signals correlated with the treatment expectation as shown in Figure 16.10. These data are consistent with the hypothesis that placebo analgesia is a special case of reward processing, and that the placebo analgesic effect can be ascribed at least in part to a general process of modulation induced by the subjects' expectations (Petrovic *et al.*, 2005), for which the rostral cingulate cortex can be a crucial node.

In patients suffering from irritable bowel syndrome, Lieberman *et al.* (2004) found that increases in right ventrolateral PFC activity from pre- to post-placebo predicted self-reported symptom improvement, and this relationship was mediated by decreases in dorsal MCC activity. These results are consistent with the disruption theory, which proposes that activation of

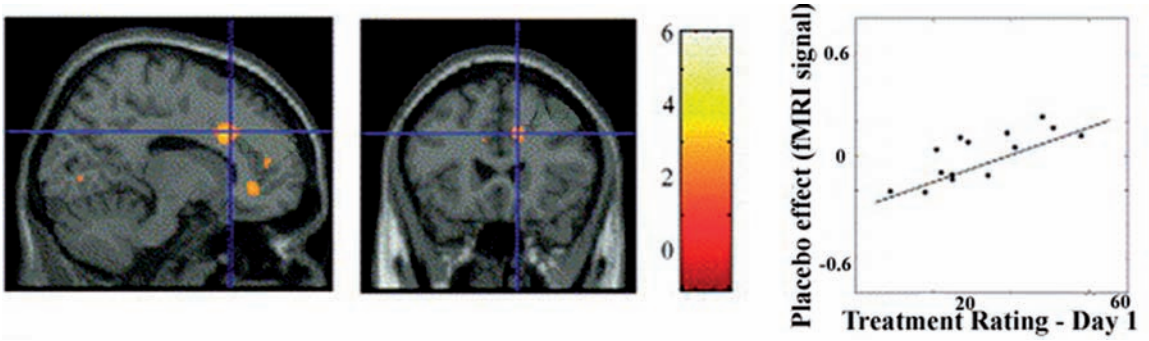

Fig. 16.10 Correlation between treatment expectation and placebo processing in the cingulate gyrus. To induce treatment expectation, on day 1 the subjects were given an anxiolitic drug to reduce the perceived unpleasantness related to the presentation of unpleasant pictures. On day 2, the subjects viewed the same pictures while undergoing the placebo fMRI experiment (namely, they were informed that they would receive the same drug as in day 1, whereas they received only saline). The effect of the pharmacological treatment to relieve anxiety on day 1 correlated positively with the fMRI signals *(right)* in different foci of aMCC/pACC *(left)*. (From: Petrovic *et al.*, 2005, with permission).

prefrontal regions associated with thinking about affective processes diminishes the reactivity of brain regions involved in the automatic generation of negative affect. It is worth mentioning that apparently adjacent foci in the aMCC/pACC appear to be "sources" or "sites" of placebo-induced modulation in the pain system (Wager *et al.*, 2004; see Fig. 16.11).

The location of peak changes within the aMCC/pACC active during the anticipation of pain or placebo, or showing placebo-induced modulation of nociceptive activity are shown in Figure 16.11. Different populations are largely intermingled in the aMCC, which thus appear to be at the interface of modulatory and nociceptive systems. On the basis of converging information from different studies, it is likely that more rostral pACC sites constitute a higher-order link in the circuits underlying cognitive modulation of the pain and emotion system. Functional connectivity measures suggest that, during expectation of analgesia, aMCC/pACC portions are linked with dorsolateral, prefrontal, and orbitofrontal cortical regions and may influence the activity of subcortical regions such as the periaqueductal gray matter (Petrovic *et al.*, 2002; Lieberman *et al.*, 2004). However, so far, causal relationships between the activity of these brain regions could not be assessed. Studies of effective connectivity will help elucidating how different portions of the cingulate gyrus influence each other and are linked to different cortical and subcortical areas during anticipation of pain.

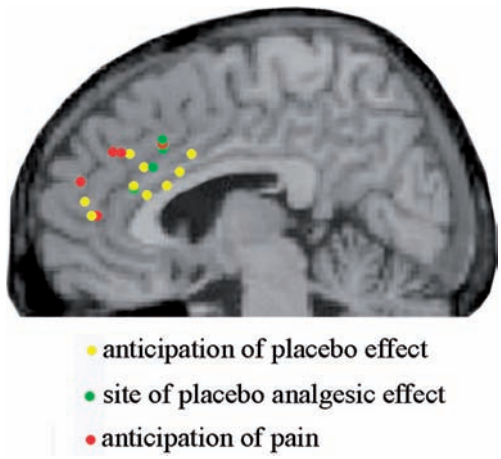

Fig. 16.11 Peak coordinates of cingulate clusters showing fMRI signal changes during anticipation of pain (red) or anticipation of placebo effects (yellow: "sources"), or showing placebo-induced modulation ("sites") of nociceptive activity (green). Only clusters with peak coordinates within 20 mm from midline were included (data from both hemispheres); they were projected on the same parasagittal plane ($|x| = 6$ mm) for the sake of simplicity. Data from: Ploghaus *et al.*, 1999; Jensen *et al.*, 2003; Porro *et al.*, 2003; Lieberman *et al.*, 2004; Koyama *et al.*, 2005; Petrovic *et al.*, 2005; Lui *et al.* (in preparation).

Summary and Future Perspectives

Cingulate Cortex as a Key for Anticipating and Modulating Painful Experiences

The electrophysiological findings in non-human primates summarized above show an integrated neuronal network within the cingulate cortex for anticipating, evaluating and responding to salient environmental stimuli; some cingulate nociceptive neurons seem to be specifically active during anticipation of noxious stimuli. These results have been confirmed and extended by functional imaging studies in humans, which have consistently shown foci of activation in aMCC/pACC during anticipation of somatic and visceral pain.

Uncertain anticipation is also associated with increased fMRI signal changes in PCC, whereas pACC shows a composite pattern of activity increases and decreases.

Several studies have shown at least partial spatial overlap between the cingulate areas activated during anticipated and actual somatosensory input. Furthermore, a direct influence of anticipation of pain on the basal activity of cingulate somatosensory systems, as well as modulation of processing noxious and non-noxious stimuli, has been demonstrated. The shaping effect of anticipation on the activity of cingulate nociceptive circuits may contribute to its effects on the perception of subsequent noxious stimuli.

Available evidence suggests that anticipation-related activity in the cingulate cortex is likely related to different factors, among which are selective attention, anxiety and arousal, mental representation of impending stimuli. It may be hypothesized that anticipation of pain and of analgesia shares at least in part common sites within the rostral cingulate cortex, taking part in a cortico-subcortical network involved in modulating the response of the pain matrix.

Although the ability to predict the likelihood of pain or other unpleasant events is an important adaptive behavior under physiological circumstances, expectation can also cause disabling fear and avoidance in some individuals, thus contributing to the development of chronic pain (Price, 1999; Boersma and Linton, 2006). Aversive conditioning is indeed likely to play an important role in specific experimental paradigms and in pain patients (see Ploghaus *et al.*, 2003; Yaguez *et al.*, 2005). There is evidence that anticipation-related activity in MCC and PCC is enhanced in pain patients, possibly reflecting hypervigilance to potentially aversive stimuli. Further studies on the involvement of the cingulate cortex in the pathophysiology and pharmacology of anticipation of aversive events are therefore necessary on both theoretical and clinical grounds.

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