CHAPTER 20

Thalamocingulate Mechanisms of Precentral Cortex Stimulation for Central Pain

Luis Garcia-Larrea, Joseph Maarrawi and Roland Peyron

Chapter contents

Experimental studies in animals have demonstrated the strong inhibitory influences that electrical stimulation at different levels of the nervous system can exert on pain transmission, thus prompting the use of neurostimulation strategies for the relief of chronic pain in humans. The neural targets of stimulation procedures have been mostly the sensory pathways mediating transmission of non-noxious information (e.g., large afferent peripheral fibers, spinal dorsal columns, and thalamic sensory nuclei), and to a lesser extent brainstem structures exerting descending antinociceptive influences (reviews in Gybels & Kupers, 1995; Holsheimer, 1997; Wallace *et al.* 2004). Although, stimulation of central motor fibers was also shown to inhibit afferent transmission in the dorsal horn and to produce analgesic effects in man (Lindblom & Ottosson, 1957; Field & Adams, 1974), the use of motor cortex stimulation (MCS) for pain control was documented only during the early 1990s by Tsubokawa *et al.* (1991, 1993a). Following these seminal reports, MCS has been progressively included in the armamentarium of functional surgeons treating chronic pain, with reported success rates of 50–70% depending on the localization and characteristics of pain syndromes (Tsubokawa *et al.*, 1993; Meyerson *et al.*, 1993; Mertens *et al.*, 1999; Nguyen *et al.*, 2000; Carroll *et al.*, 2000; Nuti *et al.*, 2005). As the procedure is applied only to patients with long-lasting, severe refractory pain, such results make of this surgical procedure a promising therapy for this chronic condition.

Although MCS induces significant pain relief in a proportion of patients whose pain has resisted every analgesic or co-analgesic drugs, the mechanisms whereby this beneficial effect is achieved remain hypothetical. Whatever the precise actions underlying MCS clinical effects, these are likely to be mediated by regional changes in synaptic activity, which may, in turn, be reflected by corresponding regional changes in cerebral blood flow (CBF; Sokoloff *et al.*, 1991). During the last 10 years, our group has assessed CBF changes using positron-emission tomography (PET) in patients undergoing MCS in an effort to characterize the regions involved in its therapeutic action.

Goals of This Chapter

As it is unlikely that alleviation of chronic pain results from a direct action of stimulation on motor cortex, a broader functional model needs to be addressed that might account for such relief. Our previous work underscores the anterior cingulate cortex (ACC) as one of the potential sites where such responses are mediated, and functional imaging provides a powerful analytical tool to evaluate this mechanism. The specific goals of this chapter include the following:

1 Review the functional imaging literature on the consequences of precentral stimulation.

2 Relate the time course of PET activation of anterior cingulate cortex, to stimulation and analgesia.

4 Describe changes on functional connectivity during MCS.

5 Provide a circuit model to account for the role of anterior cingulate cortex in mediating analgesia evoked by MCS.

Early PET and Electrophysiological Studies of Precentral Cortex Stimulation for Pain Control

Early hypotheses on MCS mechanisms considered that precentral gyrus stimulation activated through corticocortical fibers, non-nociceptive somatosensory neurons that in turn would inhibit hyperactive nociceptive units within SI (Tsubokawa *et al.* 1993a). Although, this view received support by the finding of histochemical changes within the sensory cortex of rats exposed to chronic motor stimulation (Tsubokawa *et al.*, 1993b), electrophysiological and PET-scan studies in patients receiving MCS have failed so far to demonstrate significant changes within primary motor or sensory cortices. Instead, significant increases in regional cerebral blood flow (rCBF) were observed in structures *distant* from the motor cortex, such as the thalamus, striatum, brainstem, and ACC.

First rCBF measurements during MCS

Peyron *et al.* (1995) were the first to describe, using PET-scan in two patients, rCBF changes directly related to MCS for pain control. In each patient, MCS-related increases in rCBF, ranging from 6% to 16%, were noted within the thalamus, ACC/orbitofrontal cortex, and brainstem. Subsequent group analysis of 10 consecutive patients (Garcia-Larrea *et al.*, 1999) largely confirmed these data: the most significant increases in rCBF during a short MCS session were found within the ventral-lateral thalamus, in regions directly connected with the stimulated motor cortex, followed by the medial thalamus, insula, subgenual ACC, and brainstem as shown in Figure 20.1. Conversely, no significant modifications of rCBF were observed in the sensorimotor cortex, and the somatosensory-evoked potentials (SEPs) were not affected by MCS, indicating that SI excitability did not change during application of the procedure. These results lead us to conclude that descending axons, rather than apical dendrites or cell

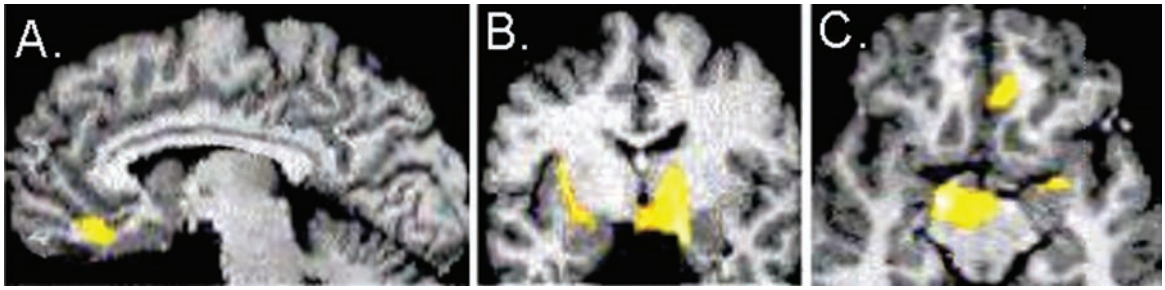

Fig. 20.1 Sagittal (A.), Coronal (B.), and Axial (C.) MRI sections normalized to Talairach space. Regions with significant (z> 3.5; yellow) increases in blood flow during motor cortex stimulation, including the thalamus ipsilateral to stimulation, the insular and sACC/orbitofrontal cortices, and the brainstem. In contrast, no significant rCBF change was observed in the motor or somatosensory cortices directly underlying the stimulator. From Garcia-Larrea et al. (1999).

bodies, are primarily activated by MCS, in accordance with previous theoretical considerations and empirical studies (Katayama *et al.*, 1988; Nowak & Bullier, 1998a,b).

A number of ensuing results served to refine this model. They were concerned with (1) the relation between activity in different structures and clinical pain relief; (2) the effects of MCS at the spinal level, and (3) the effects of MCS on cognitive activity.

Relation of thalamic and cingulate changes with clinical pain relief

Our results underscored the fact that thalamic activation, although probably important, was not a *sufficient* condition for clinical effect, as it could be observed also in patients without significant pain relief (Peyron *et al.*, 1995). When regional normalized flow in the lateral thalamus of each patient was calculated using regions of interest (ROI), it was not significantly different in patients with good clinical effect of MCS (pain relief >80%) relative to those with poor to very poor efficacy (pain relief <30%). Conversely, blood flow increase in area 32 of ACC during MCS was significantly higher in patients with good analgesic efficacy than in others as shown in Figure 20.2.

Modulation of spinal reflexes by MCS

Spinal nociceptive reflexes were investigated in seven patients receiving MCS with varying clinical effect. In three of them, spinal nociceptive reflexes were significantly depressed during MCS; in a similar manner as it had been described during spinal cord stimulation (Garcia-Larrea *et al.*, 1999, 2000), while in no instance was an *enhancement* of such nociceptive responses observed during MCS. Two of the three patients with MCS-related reflex attenuation were experiencing good or very good clinical pain relief from the procedure, while the other reported a selective decrease in allodynic pain during MCS, although the procedure was unsatisfactory on spontaneous pain. None of the four patients whose nociceptive reflexes remained unmodified by MCS was satisfied with the clinical effect of neurostimulation.

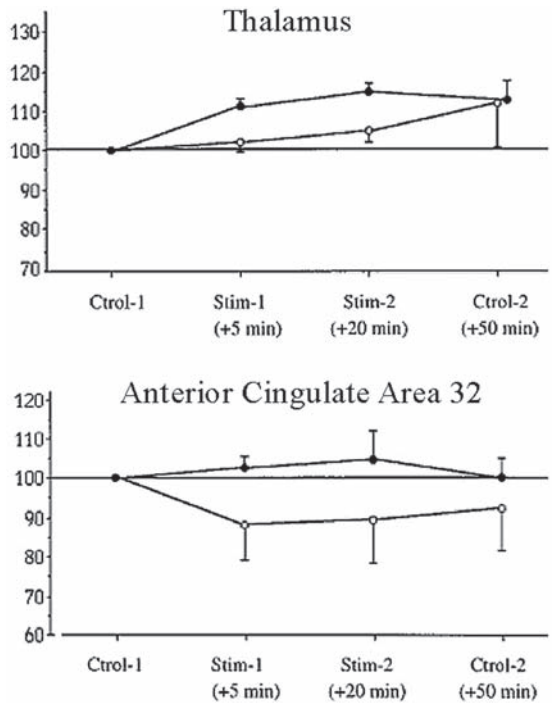

Fig. 20.2 ROI analysis of the lateral thalamus and area 32 in pACC in patients with very good (>80%, open circle) or insufficient (<20%, black dots) pain relief. X axis: experimental conditions (Control 1 and Control 2, MCS off). Y axis: normalized radioactivity within ROI. While lateral thalamic CBF appears to increase in all patients (albeit to a greater extent in those with good clinical effect), pACC CBF shows very different trends in patients with good and bad clinical effect. From Garcia-Larrea et al. (1999).

Cognitive effects of MCS

Montes *et al*. (2002) analyzed cognitive-evoked potentials and behavioural performance during a target-detection task in 11 patients submitted to MCS. While sensory responses remained unaffected by MCS, there was a significant delay of brain potentials reflecting target detection in the older patients, rapidly reversible after MCS discontinuation. No effect was observed in patients younger than 50 years. Cognitive effects of MCS appeared as mild and non-specific, directly related to the stimulation period (i.e., with no post-effect), in a manner reminding of cognitive effects reported during transcranial magnetic MCS (Jing *et al*., 2001).

Toward a First Model of MCS Mechanisms

Models of MCS activation had to be adjusted to account for these results: Although, the primary thalamic changes appeared to concern the lateral thalamus (and/or basal ganglia), parallel or secondary activation of medial thalamic regions, either by direct connection from motor cortex (Powell & Cowan, 1967) or via the reticularis and ventral anterior thalamic nuclei, were postulated to trigger a cascade of synaptic events influencing activity in other pain-related structures, including the anterior cingulate gyrus, insula, and upper brainstem. It was deemed conceivable that thalamic functional changes should reach a threshold in order to activate other areas, and that a lack of clinical effect might result from failure to attain such threshold. Activation of thalamic nuclei connected with motor and premotor cortices was considered as a crucial (although not sufficient) step for allowing the pain-relieving activity of this procedure, while pregenual anterior cingulate cortex (pACC) and upper brainstem appeared as more directly related to clinical effects. It was, therefore, concluded that the cortical and brainstem structures activated by MCS might modify the pain experience at least at two different levels:

1 The ACC has been the target of neurosurgical lesions that specifically reduced the emotional component of chronic pain (e.g., Foltz & White, 1962; Talbot *et al*., 1995; Chapter 18). Among the cingulate subdivisions, the pACC/orbitofrontal boundary activated by MCS appears particularly involved in the affective components of pain (Devinsky *et al*., 1995; Vogt *et al*., 1996, Vogt, 2005), and generally the processing of emotional stimuli (see discussion below). We therefore, suggested that the analgesic effects of MCS might partly derive from a transient blunting of the distressful reaction to pain, rather than to an actual decrease of its intensity.

2 Changes in spinal reflexes during cortical stimulation supported the implication of descending mechanisms leading to inhibition of pain impulses at the dorsal horn level. Early investigators noted that central motor fibers may inhibit afferent transmission in the dorsal horn (Lindblom & Ottosson, 1957; Andersen *et al*., 1962), and this effect might be at the basis of flexion reflex depression in patients. This putative mechanism was postulated by Fields and Adams (1974) (see also Adams *et al*., 1974), who stimulated corticospinal fibers in the internal capsule to inhibit nociceptive neurons at the spinal level. Descending inhibition triggered by direct MCS was considered to explain putatively the efficacy of the procedure upon the 'evoked components' of pain (i.e., allodynia and hyperalgesia), even in patients who may remain unsatisfied of the overall pain relief (Garcia-Larrea *et al*., 1999).

Time-course of rCBF Changes During MCS

A point that remained unexplained in the models described above is that the clinical effects of MCS are generally delayed relative to the actual periods of cortical stimulation. Patients almost never experience sudden pain relief concomitant with stimulation, and rather describe a progressive relief during the hours or days following utilization of the device. The clinical consequence is that, while MCS is generally used in discontinuous mode, with alternating 'on' and 'off' periods, the clinical relief, when present, remains continuous. This aspect of clinical effects differs from the rapid rCBF changes investigated in classical PET-scan experiments, and prompted us to investigate specifically the temporal dynamics of different regional brain activities during MCS treatment.

In the first PET-scan experiments, the temporal dynamics of rCBF changes singled out, to a certain extent, the ACC from other activated regions. While in most regions the relatively abrupt rCBF increase following MCS onset was reversible shortly after stimulation offset, in the pACC such increase had not yet reverted to pre-stimulation values 30 min after MCS discontinuation as shown in Figure 20.3. This aspect was confirmed by statistical comparisons between the pre- and post-stimulation control conditions, where two spots of increased rCBF during the post-stimulation period (as compared with the pre-MCS baseline) appeared in both right and left ACC/orbitofrontal boundaries, indicative of a remnant effect on CBF after MCS offset.

Anterior Cingulate Cortex and Late-onset Effects of MCS

Peyron *et al*. (1999a,b, 2006) devised PET-scan experiments to study specifically the timing and localization of those MCS effects that outlast the actual application of the procedure. Thus, patients were recorded not

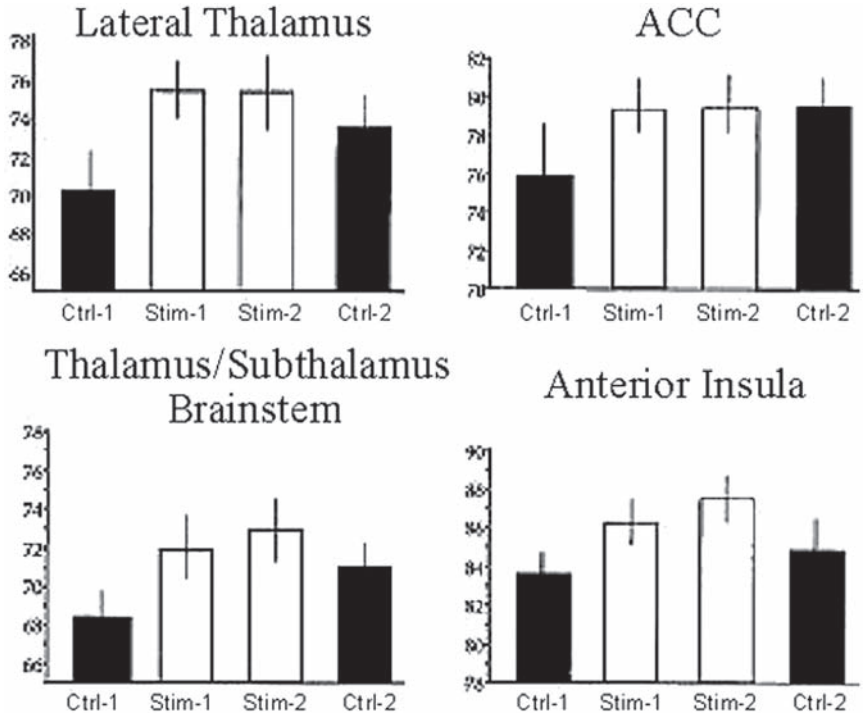

Fig. 20.3 Temporal dynamics of rCBF changes in the regions with MCS-related rCBF increase. X axis, experimental conditions; Y axis, normalized radioactivity within regions studied. In all of cases there was an abrupt rCBF increase during the first MCS scan (5 min after onset), which remained rather stable during the 2nd scan (20 min after MCS onset). These effects were reversible during the second control condition (30 min after stimulation offset) except in the ACC/orbitofrontal boundary, where rCBF had not yet reverted to pre-stimulation values 30 min after MCS discontinuation. From Garcia-Larrea et al. (1999).

only during MCS activation, but also and especially, in sequential manner during almost 2 hours following discontinuation of the procedure. The results, illustrated in Figure 20.4, showed a delayed activation of the pACC that was strengthened following MCS offset and reached a maximum, more than 60 min later. Interestingly, such protracted activation was restricted to the pregenual and subgenual ACC and did not involve MCC (area 24′), that has been associated with phasic attention and orienting reactions to pain (Peyron *et al.*, 1999a,b, 2000). The reasons for differences with the earlier studies is that they did not concern the period following MCS discontinuation and also the period of active MCS stimulation was much shorter (10′ versus 30′). Thus, activation of the lateral thalamus during the 'on' period is probably a phasic and short lasting phenomenon that was 'averaged out' in most recent analyses (discussed in Peyron *et al.*, 2006). Indeed, the design in this latter study is so different from the previous ones that direct comparisons seem unwarranted.

In this same study, a protracted activation of the rostral mesencephalon, in a region consistent with the location of the periaqueductal gray matter (PAG), was also apparent shortly after the activity in pACC had reached its maximal significance (Figure 20.4, at 60-min post-MCS offset). Given the important and reciprocal connections between pACC and PAG (An *et al.*, 1998; Freedman *et al.*, 2000; Chapter 15); such double activation, argued in favor of top–down mechanisms implicating ACC to PAG activation, and contributing to the analgesic effects of MCS. In addition, it was interesting to note that the anatomical localization of regions activated after MCS offset, corresponded to regions rich in opioid receptors in both experimental animals and man (Jones *et al.*, 1991; Vogt *et al.*, 2001). These findings allowed putting forward the hypothesis that, part of the long-lasting effects of MCS might rely on activation of endogenous opioid systems (see below).

The functional relations between pACC and other regions with prolonged activation after MCS were studied by Peyron *et al* (2007), who analyzed CBF using PET in 19 consecutive patients treated with MCS for refractory neuropathic pain. Patients were studied during a 35-min period of MCS, and then during a 75-min period after the stimulation had been discontinued, the results being compared with a resting condition. Turning on the stimulator was associated with very restricted CBF increase in the contralateral midcingulate area 24′ and in the ipsilateral and contralateral dorsolateral prefrontal cortex (DLPF). Again, the post-stimulus period was associated with a much larger matrix of CBF increase which included the pACC, MCC, orbitofrontal cortex, thalamus, basal ganglia, and PAG.

The possible interactions between activated regions were then assessed through 'functional connectivity', defined as the temporal correlation of neurophysiological rCBF events between distributed brain areas. Such analysis stands on the idea that, regions with covarying patterns of blood flow during a specific condition are most likely in functional exchange with each other

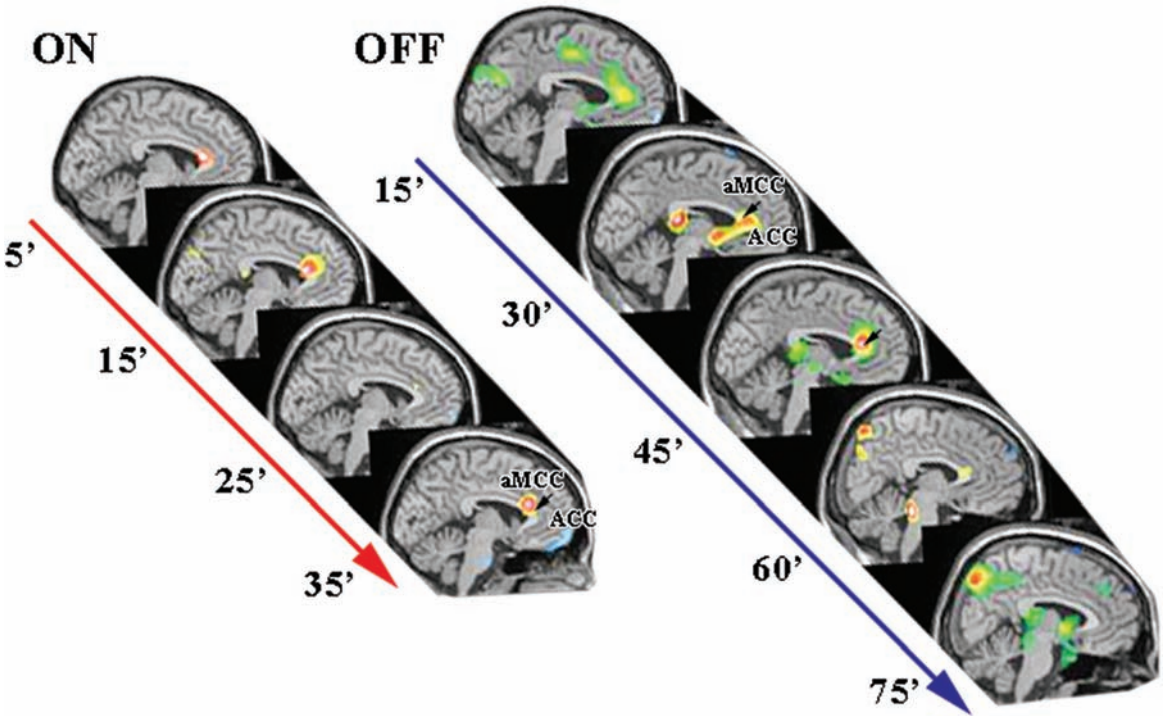

Fig. 20.4 Midsagittal views of PET scans obtained sequentially, 5–35 min following MCS onset (left sequence, 'ON'), and then 15–75 min following MCS discontinuation (right sequence, 'OFF'). Note the late increase in rCBF in the pACC is maximal at 30–45 min following MCS arrest, and the protracted activation of the posterior mesencephalon, consistent with PAG 60 min after MCS arrest. The black arrows indicate the borders between aMCC and ACC and the pivotal differences between activity while the stimulator was on or off, are apparent.

(Friston *et al*, 1996, 1997). The functional connectivity analysis is shown in Figure 20.5. It showed that pACC activations were significantly correlated with those of PAG, basal ganglia and lower pons, supporting the activation of descending ACC-to-PAG connections. Furthermore, enhanced CBF in pACC and subgenual anterior cingulate cortex (sACC), orbitofrontal cortex, striatum, thalamus, and PAG was correlated with the overall pain relief reported under MCS. These results suggest that the procedure may act in part through delayed and descending (top–down) inhibitory controls that involve DLPF, orbitofrontal and pACC as well as basal ganglia, thalamus, and brainstem (PAG and lower pons).

Anterior Cingulate Cortex, Chronic Pain, and Analgesia

Vogt *et al*. (1996) suggested that, the affective reaction associated with pain unpleasantness would be principally integrated in the pACC areas 32, 24, and 25, whereas midcingulate activation (the one most commonly seen in PET and functional magnetic resonance imaging [fMRI] studies of pain) would be associated with cognitive processes, especially response selection and motor inhibition. While the implication of MCC in orienting and attentional reactions to pain stimuli remains a robust finding (Valet *et al*., 2004; reviews in Peyron *et al*., 2000; Garcia-Larrea *et al*., 2003), the conception that pain affect is strictly contingent on the pACC has not been supported by other imaging studies. For instance, Rainville *et al*. (1997) reported a linear relationship between hypnotically modulated subjective unpleasantness and CBF in the MCC, rather than in pACC; and Tölle *et al*. (1999) found that pain unpleasantness correlated positively with CBF in the MCC. Also, in studies assessing the reaction to the unpleasant character of stimuli such as frightful animals, facial expressions of disgust, unpleasant musical dissonance or words with negative semantic content, the main increases in CBF have been observed in the middle and posterior sections of the ACC rather than in its perigenual portions (Frederikson *et al*., 1995; Morris *et al*., 1998; Blood *et al*., 1999).

Structural and functional changes in the pACC have been, on the contrary, consistently associated with mood alterations. Notably, rCBF decreases at rest have been described in the ACC of depressed or bipolar patients (Drevets *et al*., 1997), as well as reduction of

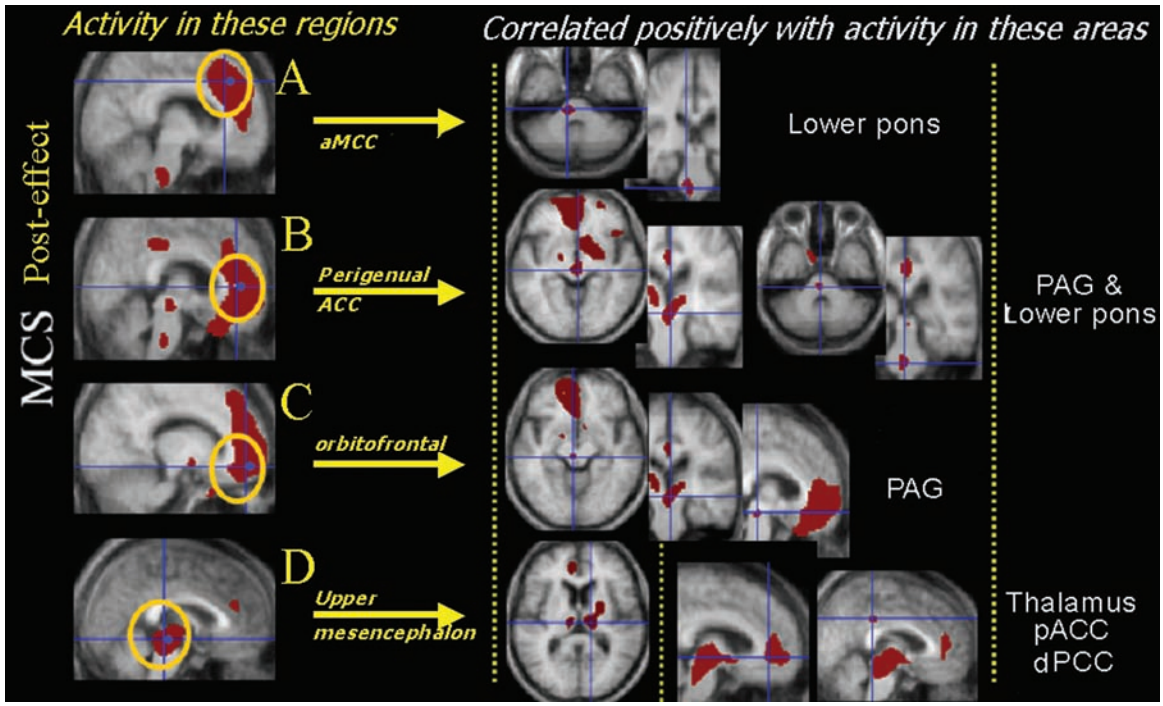

Fig. 20.5 Functional connectivity (FC) analysis, as reflected by rCBF change correlation between distributed brain areas The left column shows the regions activated following MCS discontinuation (OFF phase late activation). For each row, images in the right panel depict the brain areas whose rCBF correlated significantly with corresponding regions in the left column. The pACC activations (left column, 2nd and 3rd rows) were significantly correlated with activity in PAG, basal ganglia and lower pons, supporting the activation of descending ACC-to-PAG connections.

gray and white-matter cortical volume (Lopez-Larson *et al*, 2002), and reduced glial cell number and density (Rajkowska, 2002). Although, these and other studies have not distinguished between abnormalities associated with the depressive and manic phases of the disorder, the sACC and associated ventral prefrontal cortex is currently considered critical for the *production of affective states* and related behavior (Phillips *et al*, 2003, Vogt *et al*, 2003). Decreased blood flow in pACC and medial prefrontal cortex has also been observed during the phase of anticipation of an impending pain stimulus (Simpson *et al*., 2001; Porro *et al*., 2002), and, more recently, it was shown that the blood oxygen level dependent (BOLD) signal decrease during pain anticipation became exacerbated during actual pain (Creac'ch *et al*., 2006). As the most anxious subjects were those who exhibited the least CBF decrease, this finding was interpreted as possibly reflecting a coping strategy against anticipatory anxiety (Simpson *et al*., 2001). Whatever the interpretation, mood alteration, stress, and anxiety appear as the subjective states most closely associated to rCBF changes in sACC, and support the conceptual view that makes of these areas a part of 'ventral affective system' involved in identification of the emotional significance of a stimulus, production of affective states, and automatic regulation of emotional responses, and comprising also the amygdala, anterior insula, and ventral striatum (Phillips *et al*., 2003).

While acute experimental pain in healthy subjects is generally associated with activation of the MCC (Peyron *et al*., 2000, Derbyshire, 2000), the pACC has generally failed to show any consistent increase to experimental pain in healthy subjects (but see below), and have on the contrary shown an *inverse* relation with clinical pain. Thus, a *decrease* of sACC blood flow has been reported in patients with chronic neuropathic pain at rest (Hsieh *et al*, 1995), and a 'blunted' response of the ACC has been observed during provocation of clinical allodynia (Hsieh *et al*., 1995; Peyron *et al*., 1998), suggesting that the lessened reaction of these regions to allodynic stimuli might represent one adaptive mechanism characteristic of patients with chronic pain (Peyron *et al*., 2000). An alternative (or complementary) view comes from data showing rCBF decrease in ACC and medial prefrontal cortices during anticipation of pain (Hsieh *et al*., 1999; Simpson *et al*., 2001; Porro *et al*., 2002; Creac'h *et al*., 2006). The question arises as to whether anticipation of an intensely distressful and well-learned sensation, rather than the sensation itself,

might also contribute to the blunted ACC response in allodynia.

Analgesic procedures that relieve pain tend to correct these abnormalities and thus increase rCBF within the sACC and orbitofrontal cortices as shown in Figure 20.6. This has been observed both in response to pharmacological interventions (Hsieh *et al.*, 1995), neurostimulation procedures of various types (Peyron *et al.*, 1995, Duncan *et al.*, 1998; Davis *et al.*, 2000; Willoch *et al.*, 2003; Saitoh *et al.*, 2004), and other non-pharmacological interventions entailing analgesia, such as conscious distraction from the nociceptive stimulus (Frankenstein *et al.*, 2001; Valet *et al.*, 2004). Our recent results (Peyron *et al.*, 2007) further show that such enhanced activity in CBF, when triggered by MCS, may outlast by several hours, the actual duration of stimulation (see Section **4**), thus suggesting the contribution of neurotransmitter-mediated tonic actions.

Although most reports in healthy controls or patients failed to show pain-related ACC activations (see above), recent studies have suggested that medial prefrontal and ACC areas might increase their activity in specific relation with the *unpleasantness* of experimental pain (see Chapter 19). Thus, Lorenz and Casey (2005) showed that for identical pain intensity, increased degrees of unpleasantness were associated with increased pACC and medial frontal activity, and Kulkarni *et al.,* (2005) observed that the rCBF in pACC and orbitofrontal cortices increased when subjects focused their attention on pain unpleasantness, and decreased when attention was directed to pain localization. It is hard to explain, why activity in the same perigenual regions should increase both by pain and by the relief of pain. One may argue that different mechanisms and networks may be operating within the same macroscopic regions, and that current imaging techniques are unable to resolve possible differences in their respective spatial distribution or temporal dynamics.

Another, more appealing possibility is that, increased signal in medial frontal and ACC regions may subserve some activity directed at *controlling pain*, via extensive connections with limbic areas and the PAG. It would then be logical that the more disagreeable the sensation, the more enhanced would be the reactive activity in those areas, explaining the association not only with pain unpleasantness, but also with the 'subjective impression of reality' in hypnotically induced pain (Raij *et al.*, 2005). This would also be consistent with the fact that external manipulations aiming at controlling pain, whether opioids, placebo or cortical stimulation, may enhance such systems for pain control and therefore enhance local activity. Whatever the explanation, the fact that rCBF increase in MCS can be detected only a few minutes after stimulation onset (Peyron *et al.*, 1995; Garcia-Larrea *et al*, 1999), at a moment when patients do not yet report significant changes in their ongoing pain, suggests that such modifications of brain activity are, at least in part, likely to contribute to clinical relief, rather than being a simple consequence of it.

The Role of ACC in MCS-Evoked Analgesia

Areas on the sACC and orbitofrontal cortex receive direct or indirect information from both the external and the internal milieu via interconnections including (but not restricted to) the amygdala, hypothalamus, anterior insula, striatum, and PAG (Carmichael & Price, 1995; Phillips *et al.*, 2003). Such anatomical relationships suggest a role in the integration of information gathered from the internal and external environment, as well as an 'effector' role in generating affective states. MCS, by imposing a different metabolic activity in these areas, may modify or bias the production of affective states, by changing the end-line interpretation of neuropathic pain signals. While the precise mechanisms underlying such effects are unknown, the notion that MCS may activate simultaneously, a ventral affective network supported by the results of functional connectivity obtained in these patients, in whom protracted activity in perigenual areas was significantly correlated with that of the striatum, the orbitofrontal cortex and the PAG (Peyron *et al.*, 2007).

The strong connections between the sACC and the PAG in the upper brainstem, as well as the activity coupling of the two structures following MCS, seem to confirm our early suggestion that descending inhibitory controls may play a role in the pain-relieving effects of MCS (see above). The PAG in the mesencephalon, the nucleus raphe magnus, and adjacent structures of the rostral ventromedial medulla constitute the efferent channel of a pain-control system that descends onto the spinal cord. In addition to the effects on spinal nociceptive reflexes, recent evidence indicates that endogenous motor cortex activation inhibits neurons to the dorsal horn in primates (Seki *et al.*, 2003), and that, such inhibition may become specific for pain inputs in case of electrical MCS (Senapati *et al.*, 2005).

In our experience, both pACC and PAG activations were positively related to clinical pain relief (Garcia-Larrea *et al.*, 1999; Peyron *et al.*, 2007), thus making of these regions a pivotal area for the passage from neurophysiological to clinical effects. As the effects upon sACC and PAG are protracted and long-lasting, they are not likely to represent simple *on/off* consequences of stimulation periods, but rather reflect a long-term modulation of endogenous neurotransmitters. Two distinctive features of these areas are noteworthy in that sense: (1) they correspond to the regions

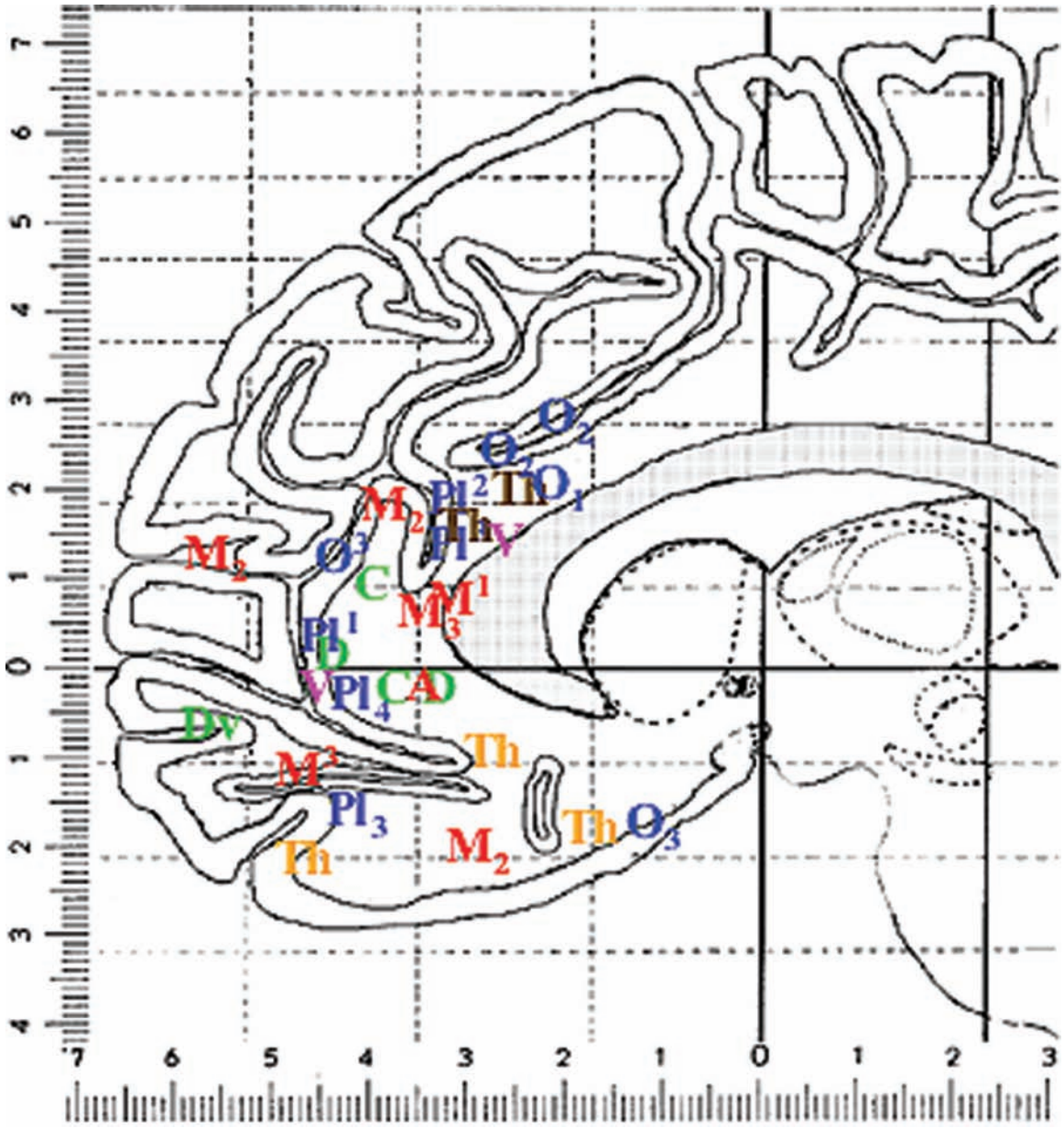

Fig. 20.6 Sites of peak activity changes in anterior cingulate/orbitofrontal cortices, as reported in previous studies investigating analgesic drugs or processes that concur to modulate pain intensity. Each color represents one modality of pain modulation: O (blue): Opioid-related changes in activity (O1: Adler et al., 1997, O2: Firetsone et al., 1996, O3: Petrovic et al., 2002). A (red): Effects of anesthetic blocks (Hsieh et al., 1995) Pl (blue): Placebo-related changes in activity (Pl1: Casey et al., 2000, Pl2: Wager et al., 2004, Pl3: Petrovic et al., 2002, Pl4: Bingel et al., 2004). Green letters represent physiological activities associated with modulation of ACC activity during pain. C (green): Controllability of pain-related activities (Salomons et al., 2004), D (Green): Distraction from pain (D: Bantick et al., 2002, Dv: Valet et al., 2004). Th (orange): thalamic stimulation for pain relief (Kupers et al., 2000, brown, Davis et al., 2000): V (magenta): stimulation of trigeminal ganglion in patients with trigeminopathic pain (Willoch et al., 2003). M (red): motor cortex stimulation for pain relief (M1: Garcia-Larrea et al., 1999, M2: Saitoh et al., 2004, M3: Peyron et al., 2005).

with high density of opioid receptors (Kuhar *et al*., 1973; Jones *et al*., 1991), and (2) they are included in the cortical–subcortical network activated during opioid analgesia in humans (Adler *et al*., 1997; Firestone *et al*., 1996; Casey *et al*., 2000; Petrovic *et al*., 2002). Although, these features strengthen an 'opioid connection', the question of whether long-lasting MCS effects are mediated through endogenous opioids or through other neurotransmitter remains open. A recent report in patients chronically implanted suggests indeed a positive relation between MCS-induced opioid secretion and clinical relief (Maarrawi *et al*., 2007)

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