CHAPTER 18

Neurophysiology of Cingulate Pain Responses and Neurosurgical Pain Interventions

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Chapter contents

Pain is generally considered to consist of at least two distinct dimensions, the sensory-discriminative component and the motivational-affective component (Melzack & Casey, 1968). The sensory-discriminative component encompasses qualities such as the intensity, location, and descriptive qualities of pain. The motivational-affective component may be characterized as "unpleasantness," representing the negative valence which motivates the behavior evoked by pain, and generating pain's affective tone (LeDoux, 1996; Price, 2000). Evidence suggesting the presence of a discrete motivational-affective component of pain were derived from the early observations of analgesia after cingulotomy. Specifically, after lesions involving the anterior cingulate cortex (ACC – anterior to the marginal branch of the cingulate sulcus which includes midcingulate cortex – MCC –) patients with chronic pain reported that they continued to have pain, but that it was "not particularly bothersome" (Foltz & White, 1962). This observation led to the conclusion that the ACC is involved in the motivational-affective component of pain. Many observations since that time have demonstrated that the cingulate gyrus has a role in pain unpleasantness, attention, and cognition.

The mechanisms of corticocortical processing are poorly understood; particularly in terms of parietal lobe interactions and it has not been clear to what extent pain activation and attention mechanisms drive similar parts of the cingulate gyrus. Attention-related tasks such as verbal fluency or Stroop (Lezak, 1995) activate MCC based on group analysis and direct comparisons indicate separate regions within the ACC for attention versus pain-related activation (Davis *et al.*, 1997; Derbyshire *et al.*, 1998). We have used laser-evoked potentials (LEPs) in conjunction with subdural recording electrodes to evaluate the nociceptive properties of cingulate cortex. Analysis of LEPs indicates that the MCC encodes pain intensity and is modulated by attention. Cortical activation, as measured by ERD, is modulated by the analgesic effect of distraction, independent of the distraction task. Although the precise pathways by which somatosensory and cingulate cortices interact are still unknown, these findings of the various functional imaging modalities provide a platform for exploring these issues with great precision.

Goals of the Chapter

This chapter describes the role of the ACC in primate pain processing and in the treatment of pain. It reviews the physiology of pain pathways to the ACC via the medial thalamus and modulation of these inputs by the ACC are related to pain sensation or pain-related behaviors. Finally, we review the effect of lesions of the cingulate gyrus on chronic and experimental pain. The focus is on human studies when available.

Anatomy

The spinothalamic tract (STT) is the classic nociceptive pathway associated with the sensation of pain (Perl, 1984; Willis, 1985). Afferent Aδ and C fibers enter the spinal cord and ascend or descend lateral to the dorsal rootlets as Lissaur's tract. They then enter the dorsal horn and synapse in the superficial lamina (Rexed I) or deep laminae (III to V) of the dorsal horn. The fibers of the spinal neurons then cross to the contralateral portion of the spinal cord via the anterior white commissure to travel to the thalamus and forebrain limbic structures. The STT consists of two components: one in the ventral lateral spinal funiculus, and the other in the dorsal lateral funiculus (Apkarian & Hodge, 1989a, 1989b; Cusick *et al.*, 1989; Craig, 1991; Ralston & Ralston, 1992). The axons of the cells arising in the deeper spinal lamina project via the ventral lateral funiculus, and the axons of the cells arising from the more superficial lamina project via the dorsal lateral funiculus (Apkarian & Hodge, 1989a). There is also evidence that primary afferent nociceptive fibers arising from viscera synapse on neurons near the central canal and ascend in the midline of the posterior funiculus as the post-synaptic dorsal column pathway (Vierck & Luck, 1979; Vierck *et al.*, 1990; Nagaro *et al.*, 1993; Willis *et al.*, 1999).

Human STT terminations have been demonstrated by silver staining at autopsy in patients post-cordotomy. These STT terminations are in thalamic nuclei including the intralaminar nuclei, (central lateral and parafascicular), and the medial dorsal nucleus (Mehler, 1962, 1969). Quantitative analysis suggests that the terminations of the dorsal and ventral parts of the STT are largely overlapping in these nuclei in monkeys (Apkarian & Hodge, 1989b). STT terminations are also found in striatal structures and in limbic structures such as the hypothalamus and the amygdala (Newman *et al.*, 1996).

Silver staining at autopsy in patients with thalamic lesions suggests that the cingulate cortex anterior to the marginal branch of the cingulate sulcus (Fig. 18.1) receives input from medial, pain-related thalamic nuclei (Van Buren & Borke, 1972). These include the parafascicular and the medial dorsal nuclei, both of which receive STT input (Mehler, 1962, 1969). In monkeys, Brodmann's area 24 of the ACC receives inputs from the intralaminar nuclei (central lateral and parafascicular) and subnuclei of the mediodorsal nucleus (parvocellular and densocellular; Vogt *et al.*, 1987; Chapters 4 and 14) which receive STT inputs (Mehler *et al.*, 1960; Kerr, 1975; Berkley, 1980; Burton & Craig, 1983; Apkarian & Hodge, 1989b).

Functional Imaging

The advent of functional imaging has greatly advanced our understanding of the cortical areas involved in pain processing. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have shown multiple areas of increased regional cerebral blood flow (rCBF) or blood oxygenation level-dependent (BOLD) signal increases in response to painful stimuli. These cortical areas include: the primary somatosensory cortex (SI), cortex around the sylvian fissure (PS, parasylvian cortex), prefrontal cortex, supplementary motor area (SMA) and the cingulate gyrus. These studies provide evidence to support the role of the midcingulate cortex (MCC), just anterior to the central sulcus in the processing of pain (Jones *et al.*, 1991; Talbot *et al.*, 1991; Casey *et al.*, 1994, 1996; Coghill *et al.*, 1994; Craig *et al.*, 1996; Vogt *et al.*, 1996; Derbyshire *et al.*, 1997; Rainville *et al.*, 1997; Ploghaus *et al.*, 1999; Lorenz *et al.*, 2003; Moulton *et al.*, 2005).

Activation during noxious stimulation has been identified in multiple locations within the cingulate

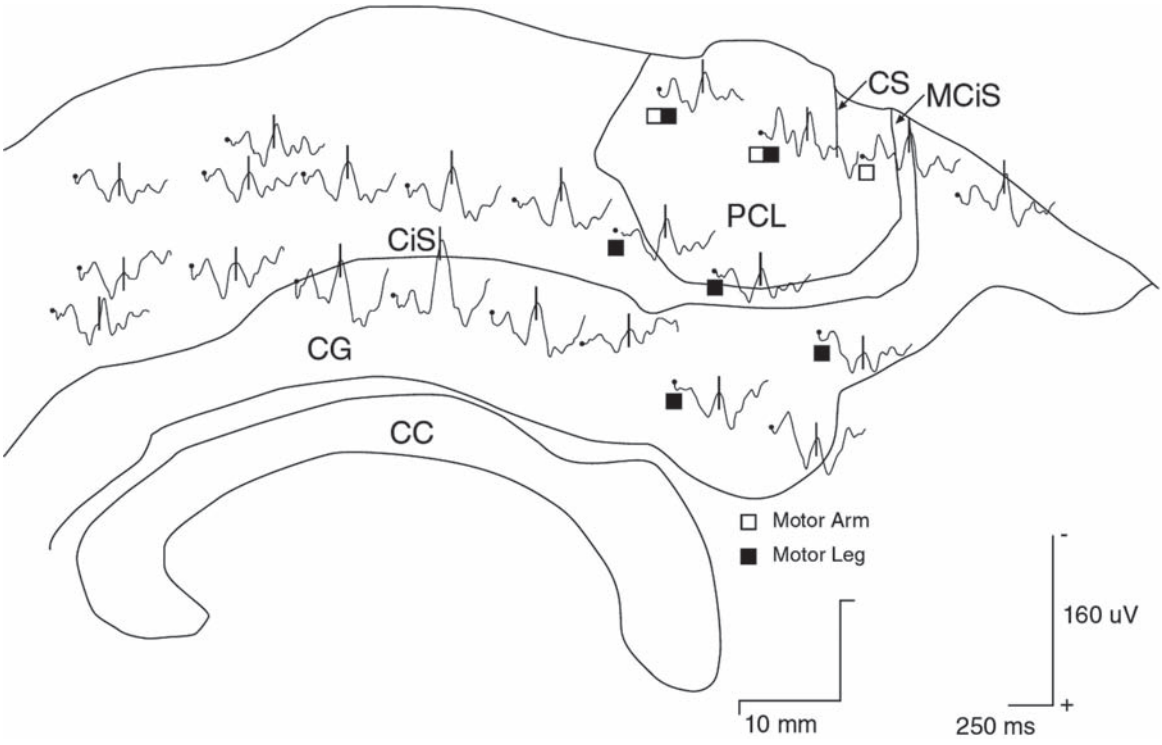

Fig. 18.1 Topographical representation of LEPs over the right medial wall in response to stimulation of the contralateral face. Traces 0–500 ms; vertical line at 250 ms. Stimulation evoked movements of arm and leg as indicated in the list of symbols. CC – corpus callosum, CG – cingulate gyrus, CiS – cingulate sulcus, CS – central sulcus, MCiS – marginal branch of the cingulate sulcus, posterior margin of the paracental lobule composed of the pre- and post-central gyri, MF – medial frontal including anterior and middle CG, PCL - paracentral lobule composed of the pre- and post-central gyri. Adapted from Lenz *et al.* (1998b).

cortex anterior to the marginal branch of the cingulate sulcus as shown in Figure 18.1 (Davis *et al.*, 1995, 1997; Rainville *et al.*, 1997; Becerra *et al.*, 1999; Ploghaus *et al.*, 1999; Moulton *et al.*, 2005). These studies have also demonstrated widespread cortical areas apparently encoding the actual and perceived intensity of the noxious stimulus (Coghill *et al.*, 1997, 1999).

Imaging studies have also demonstrated functional differences which depend on location along the rostral-caudal axis of the cingulate gyrus. Pain-related cerebral blood flow increase or BOLD activation is frequently found in the MCC (Hsieh *et al.*, 1995; Davis *et al.*, 1997; Derbyshire & Jones, 1998). This area is also activated when the unpleasantness of pain is increased by hypnosis, without altering the intensity of the pain (Rainville *et al.*, 1997).

Attention related tasks (e.g. verbal fluency or Stroop; Lezak, 1995) activate MCC based on group analysis, but individual responses showed more widespread activation of the medial frontal cortex [Davis *et al.*, 1997; Derbyshire *et al.*, 1998). Direct comparisons indicate separate regions within the ACC for attentional versus pain-related activation [Davis *et al.*, 1997; Derbyshire *et al.*, 1998). ACC is activated when subjects experience capsaicin-induced heat allodynia, but not when experiencing normal (non-sensitized) heat pain (Lorenz *et al.*, 2002) However, the ACC can be activated by the expectation of pain (Ploghaus *et al.*, 1999), anxiety surrounding pain (Ploghaus *et al.*, 2001), or by intravenous opiates (Wagner *et al.*, 2001).

Neurophysiology

Animal and human electrophysiologic evidence also supports the role of the medial thalamus and cingulate gyrus in pain processing. The presence of neurons which respond to painful stimuli has been demonstrated in the medial thalamus (Bushnell & Duncan, 1989). Anatomic confirmation of such cells has been demonstrated in the central lateral, the parafascicular, and the medial dorsal nuclei of monkeys (Perl & Whitlock, 1961; Casey, 1966). In monkeys, these cells responded exclusively to noxious stimulation in large receptive fields (Perl & Whitlock, 1961; Casey, 1966), although during some states of consciousness, there was convergence with other sensory modalities.

Studies of human medial thalamus have identified nociceptive neurons in the central median/parafascicularis nuclear complex (Sano *et al*., 1970; Ishijima *et al*., 1975; Tsubokawa & Moriyasu, 1975). One group of cells responded in a short latency to the application of noxious stimuli. A second group of cells responded following a long latency and showed prolonged afterdischarges. Both types of cells had receptive fields that were large and often bilateral. Analogous neurons in the monkey medial thalamus showed the capacity to encode noxious stimulus intensity, despite having large, spatially diffuse receptive fields (Bushnell & Duncan, 1989). Thus, these cells may be involved in the intensity discriminative aspect of pain. Nociceptive cells were not reported in more recent human microelectrode studies, apparently directed toward the same nuclei (Rinaldi *et al*., 1991; Jeanmonod *et al*., 1993).

Pain has been reported in response to stimulation of the medial thalamus during thalamotomy in patients with chronic pain (Sugita *et al*., 1972; Sano, 1979). Two types of stimulation-evoked sensation have been reported following stimulation in medial thalamus (Sano, 1979). The first type was described as a diffuse, burning pain referred to the contralateral half of the body or on occasion the whole body which may have been evoked by stimulation of the central median/parafascicularis nuclei. The patient's chronic pain was said to be exacerbated by stimulation at these sites. The second type of sensation was a generalized "unpleasant" sensation, not localized to a particular body part which may have been evoked by stimulation of the medial dorsal and periventricular nuclei. Stimulation-evoked pain was not reported in the more recent human microelectrode studies directed toward the medial and intralaminar thalamus (Rinaldi *et al*., 1991; Jeanmonod *et al*., 1993).

Cortical responses to noxious stimuli have been reported in human and animal studies. Neurons in ACC of rabbits and rats respond to noxious stimuli (Sikes & Vogt, 1992; Yamamura *et al*., 1996). Based on observations made just prior to cingulotomy, neurons in the human ACC responded to painful cutaneous stimuli or to pain-related events, e.g. observation or anticipation of the application of a painful stimulus (Hutchison *et al*., 1999). Similar anticipatory and nociceptive neuronal responses were recorded in the ACC of monkeys while performing an avoidance task (Koyama *et al*., 1998).

Figure 18.1 demonstrates the presence of nociceptive activity in the ACC based on EEG potentials recorded directly from the cortex (electrocorticography) in response to application of a noxious cutaneous laser (laser evoked potentials – LEPs; Lenz *et al*., 1998b). These consist of a negative wave (N2) followed by a positive wave (P2). Scalp LEPs having vertex maximums (Carmon *et al*., 1978; Bromm & Treede, 1984) may arise in part from generators in the ACC, as assessed by scalp source analysis (Tarkka & Treede, 1993; Chen & Bromm, 1995; Kitamura *et al*., 1995).

LEP N2 and P2 peaks were also recorded from high lateral convexity near the primary somatic sensory cortex hand area (SI region, Fig. 18.2), and near the sylvian fissure (parasylvian region; Ohara *et al*., 2004a). LEP N2 and P2 peaks in the SI region were distributed over both pre- and post-central cortical areas. For the PS cortex, both N2 and P2 were maximal near the junction of central sulcus and sylvian fissure with polarity reversal (Fig. 18.2A and B). Over the medial frontal region, both N2 and P2 peaks were distributed over the cingulate sulcus and the supplementary motor area, with polarity reversal near the cingulate sulcus (Lenz *et al*., 1998a; Vogel *et al*., 2003; Ohara *et al*., 2004a, 2004b).

Neurophysiology of Attention to Pain

Using subdural grids placed over the medial wall of the cerebral hemispheres nociceptive input was localized to the MCC, just anterior to the marginal branch of the cingulate sulcus (Fig. 18.1). The location of this potential overlaps with that of attention-related activation reported in imaging studies (Davis *et al*., 1997; Derbyshire *et al*., 1998). This proximity has been confirmed in studies of LEPs, while the subject is either attending the laser stimulus (counting stimuli) versus distracted from the laser (reading for comprehension; Ohara *et al*., 2004c).

During attention versus distraction increased N2 and P2 peaks were observed over SI, PS and ACC (Fig. 3A). A late positive potential (LP, Fig. 3B) was recorded over ACC and dorsal area 6 (Lenz & Treede, 2002; Ohara *et al*., 2004c) only during attention to the laser. Thus, the LP potential has "an all or none" or binary quality and is not merely changed in degree with changes in the attentional state. The location of this peak was recorded within and dorsal to the ACC, consistent with the location, where binary pain-related activations have been observed in imaging studies of the response to painful stimuli (Coghill *et al*., 1999; Bornhovd *et al*., 2002; Buchel *et al*., 2002).

Therefore, two types of attention-related effects upon laser-evoked potentials are demonstrated in Figure 18.3. The first is the analog modulation of N2 and P2 waves which are increased during attention versus distraction (Fig. 18.3A, N2 and P2 peaks). The morphology and distribution of these peaks are clearly different from the binary potentials which are seen during attention but not during distraction (Fig. 18.3B, LP peaks). The emergence of potentials during attention that are absent during distraction (LP) in an ACC and dorsal

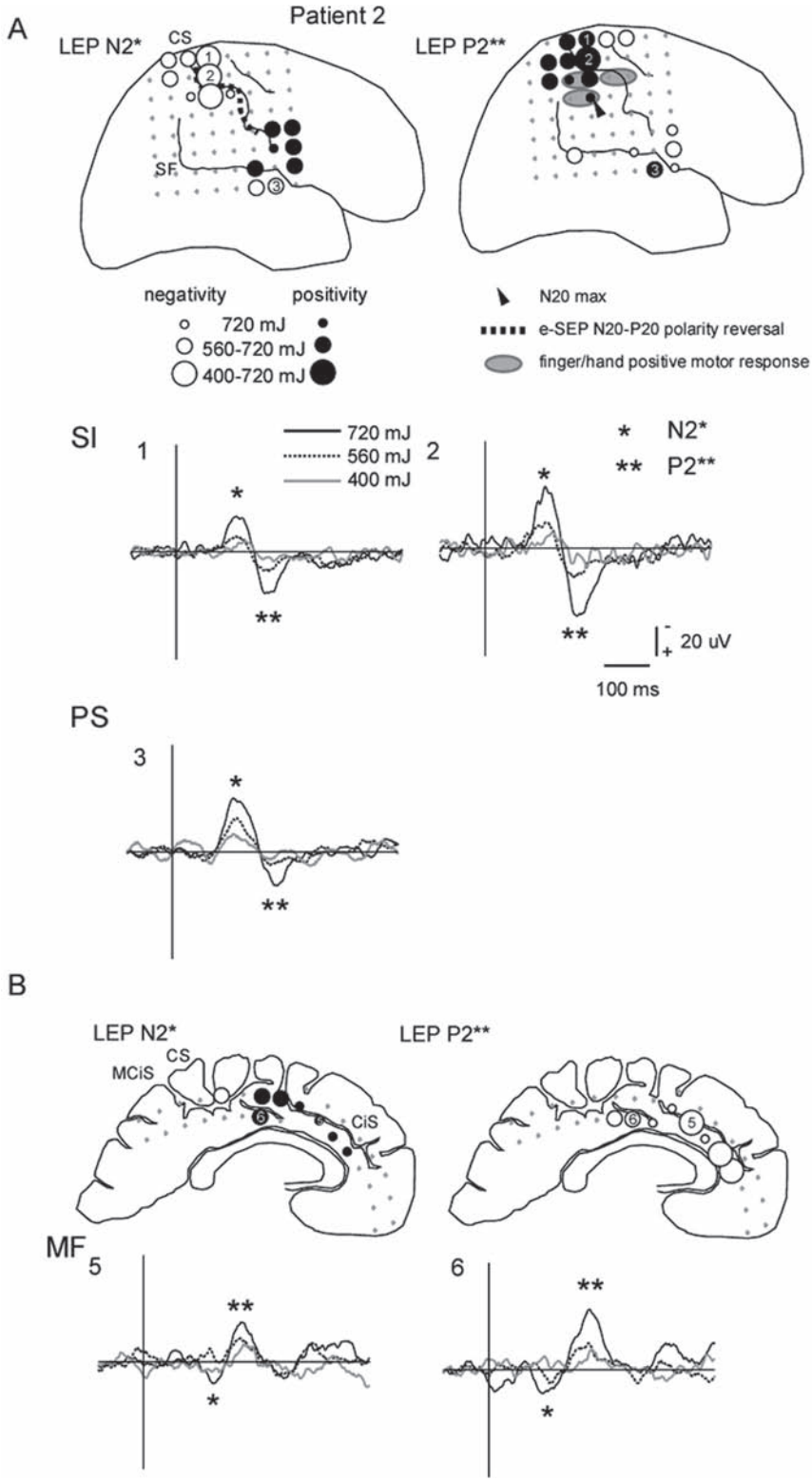

Fig. 18.2 Distribution of LEP N2* and P2** peaks over the convexity (A) and the medial surface (B) of the hemisphere. Significant LEP N2* and P2** peaks were recorded from electrodes over SI, parasylvian and medial frontal regions. Sample LEP waveforms (recorded versus average reference) are shown for two electrodes in each region (marked 1–6 in the figurines). Note that the amplitudes of N2* (*) and P2** (**) at individual electrodes as well as the number of electrodes with significant LEPs were graded with laser energy in all three regions. Representative LEP waveforms (recorded versus average reference) are also shown (marked 1–5 in the figurines). Note that there were no electrodes below the sylvian fissure in this patient. The amplitudes of N2* (*) and P2** (**) at individual electrodes as well as the number of electrodes with significant LEPs were graded with laser energy in all three regions. Conventions as in Fig. 18.1. SF, sylvian fissure Adapted from Ohara *et al.* (2004).

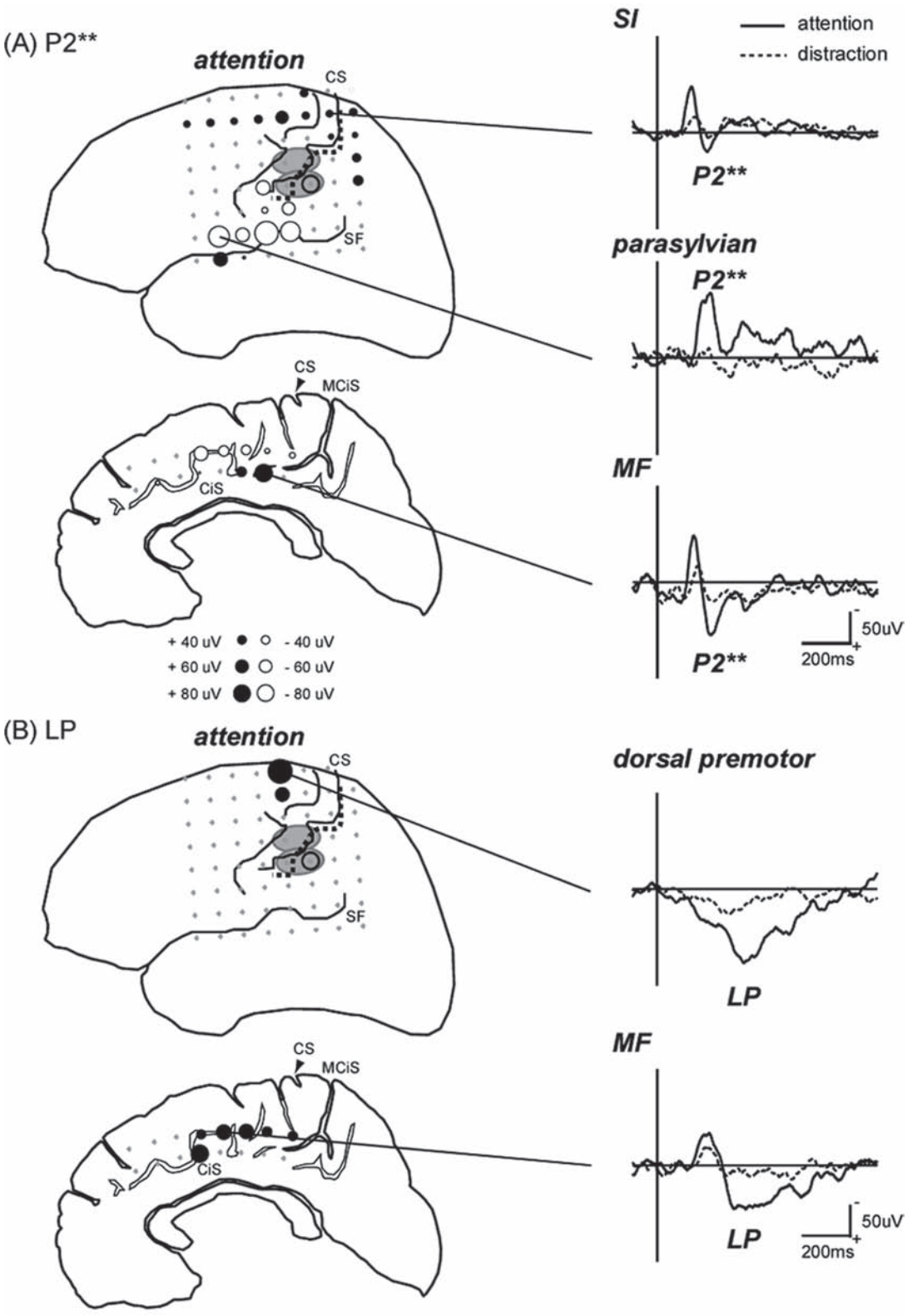

Fig. 18.3 Distribution of negative (N2 – not labeled)(A), positive P2 (A) and LP (B) peaks of the laser evoked subdural potential during attention and distraction conditions and representative waveforms. A, P2 peaks were recorded from primary somatosensory (Taliarich coordinates; Talairach & Tournoux, 1988) for SI: 37, −25, 59, PS: 63, -(12, -(6 and medial frontal including ACC (MF: -(1, -(16, 33) cortex regions. The amplitude of the P2** peak was strongly enhanced during the attention task. B, LP was recorded from the MF region and a part of the lateral premotor area (38, -(11, 48) only during the attention condition (counting the laser stimuli) but not the distraction condition. Schematic maps show the distribution of N2* amplitude during the attention condition. Note the clear N2* amplitude difference between attention (counting) and distraction (reading) conditions. Adapted from Ohara *et al.* (2004).

premotor cortex suggests that these cortical areas are "sources". A recent model defines "sources" as structures which are specific to attention and are not involved in other functions related to the task (Posner, 2000). In the same model, "sites" are structures where attention acts during task performance to alter computations involved in the task (Posner, 2000), like the gain of LEPs which is increased during the attention task. Increased LEPs at SI, PS and ACC during directed attention may identify these cortical structures as "sites" for directed attention (Posner, 2000).

The ACC and dorsal premotor cortex may be "sources" for directed attention, consistent with their role as a part of the executive attentional system involved in target selection or response (Corbetta *et al.*, 1991; Bench *et al.*, 1993; Devinsky *et al.*, 1995; Picard & Strick, 1996). This suggestion is consistent with the finding that cingulotomy impairs intention and spontaneous response production (Cohen *et al.*, 1999).

The binary nature of attention-related LPs is reminiscent of the cortical potentials related to the alertness or attention evoked by infrequent events, like the P300 potential. The amplitude of the P300 for laser/painful stimuli is independent of stimulus amplitude (Becker *et al.*, 1993; Zaslansky *et al.*, 1995; Bornhovd *et al.*, 2002) and stimulus location. Therefore, the LP and P300 are both independent of stimulus amplitude, consistent with functional imaging studies demonstrating brain regions where the application of a specific, painful, stimulus activates the region, while further increases in stimulus intensity do not produce increased activation (Coghill *et al.*, 1999; Bornhovd *et al.*, 2002). The LP may indicate an alarm evoked by painful stimuli in somewhat the same way that the P300 indicates a state of alertness evoked by infrequent events (Picton, 1992; Lenz *et al.*, 2000). The LP is evoked when the subject is required to detect (count) the painful stimulus, while the P300 occurs when the subject is required to detect the infrequent event (button push). Therefore, both potentials may be alarm signal attention or alertness which are triggered by a stimulus level but otherwise may be independent of stimulus parameters (Coghill *et al.*, 1999; Bornhovd *et al.*, 2002).

The studies of LEPs during attention versus distraction demonstrate attentional modulation of activity in the midcingulate gyrus (Fig. 18.3). Studies of cortical activation of the middle cingulate cortex also reflects, not just the effect of distraction, but the analgesic effect of distraction. Our measure of cortical activation is event-related modulation of EEG spectral energy which has been demonstrated during multiple behaviors including movement (Pfurtscheller & Aranibar, 1977; Pfurtscheller, 1981; Stancak & Pfurtscheller, 1995; Pfurtscheller *et al.*, 1996; Crone *et al.*, 1998; Ohara *et al.*, 2000), vision (Tallon-Baudry *et al.*, 1996), audition (Crone *et al.*, 2001a), language (Crone *et al.*, 2001b) and nociception (Mouraux *et al.*, 2003).

Event-related spectral EEG responses are analyzed over different frequency bands (Pfurtscheller, 1999) that exhibit different temporal-, spatial-, and task-dependent response characteristics, suggesting that they reflect different aspects of cerebral processing. For example, EEG spectral energy in the alpha range (8–13 Hz) are regionally suppressed (ERD) by task-specific cortical processing (Pfurtscheller & Aranibar, 1977; Tiihonen *et al.*, 1991; Bastiaansen *et al.*, 1999), but may also be modulated by attention (Boiten *et al.*, 1992; Klimesch *et al.*, 1992, 1998; Dujardin *et al.*, 1993; Sterman, 1999; Suffczynski *et al.*, 2001).

In Figure 18.4A, the spatial distribution of alpha ERD overlapped but was not identical to that of the LEP peaks (N2*, P2** or both; Fig. 18.3B; Ohara *et al.*, 2004), and was more widespread during the attention condition than during the distraction condition. This was particularly so when distraction was associated with a lower perceived pain intensity – an analgesic effect of distraction. Attention to the laser stimulus was associated with more intense and widespread ERD over the PS region (Fig. 18.4A, left), where it was nearly absent with distraction, regardless of perceived intensity (Fig. 18.4A, middle and right).

Under the distraction condition, there was a lower perceived intensity in one of the three runs even though the laser energy was constant across all three runs (Fig. 18.4A, middle and right panels; Ohara *et al.*, 2004). This lower perceived pain intensity, suggesting a greater analgesic effect of distraction was correlated with much less alpha ERD over medial frontal and SI cortices (Fig. 18.4, middle versus right) than the effect of distraction without analgesia (Fig. 18.4, left versus right).

The ERD results suggest that the MCC (posterior ACC) is also a "site" where distraction-related analgesic effects. This is consistent with the site of where an inverse relationship has been demonstrated between mu receptor binding and affective pain ratings resulting from administration of a tonic pain stimulus (Zubieta *et al.*, 2001) PET blood flow increases after opiate administration (Wagner *et al.*, 2001) have been demonstrated ACC, anterior to the site of ERD effects shown in Figure 18.4.

It is not surprising that LEPs are modulated by cognitive processes like attention. However, LEP signals recorded over the medial frontal cortex are also related to stimulus intensity and/or the ratings of the intensity of the evoked pain. Figure 18.2 shows potentials recorded in response to three separate levels of energy (weak, medium and strong) of laser stimulation. N2 and P2 peaks at the maxima over medial frontal, PS, and SI cortex were both significantly graded by energy and with

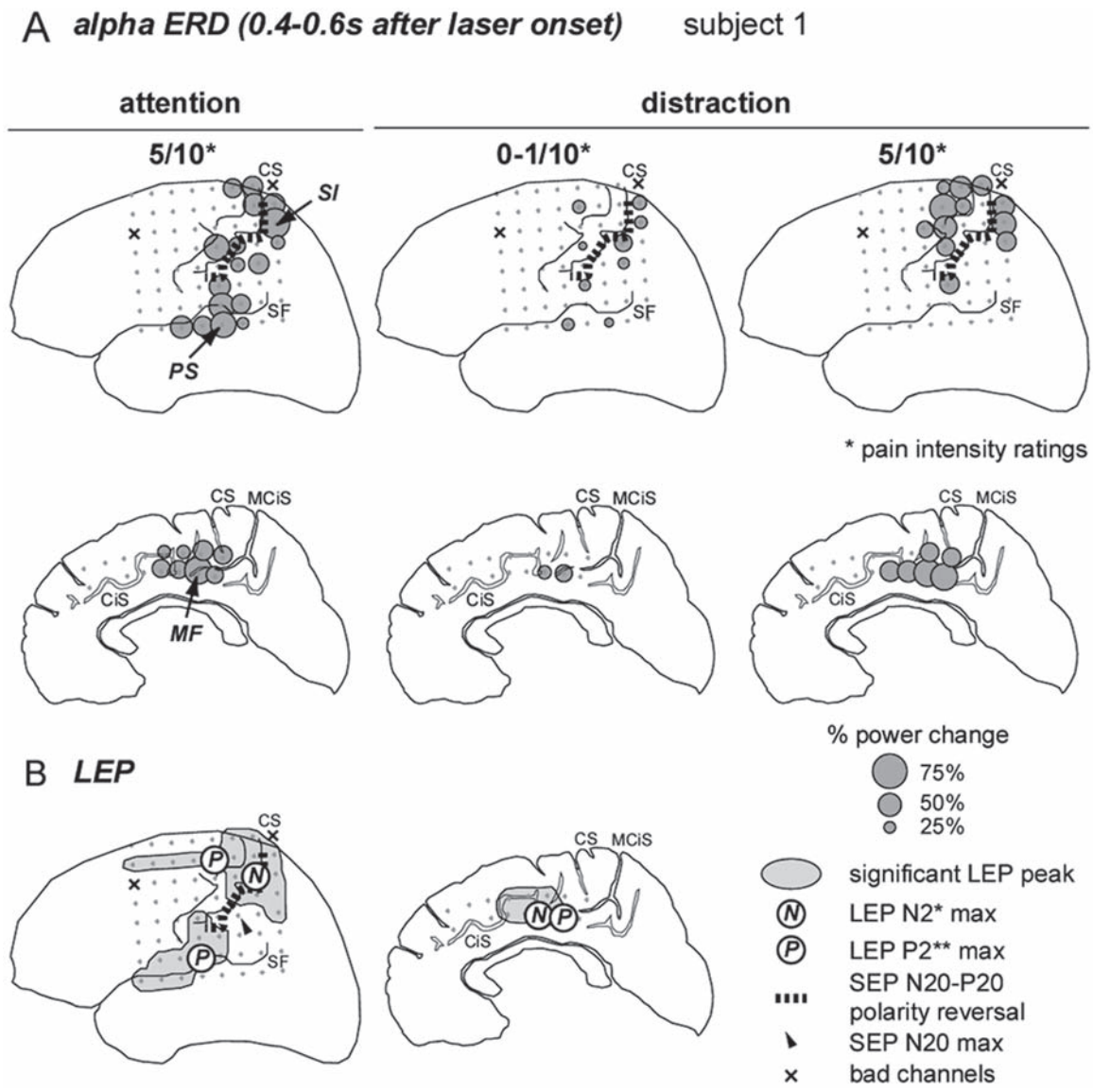

Fig. 18.4 Spatial distributions of LEP N2*/P2** peaks during the attention condition and alpha ERD during the attention and two distraction conditions. During the attention condition, statistically significant ERD in alpha range (6–12 Hz, 0-4-06s after laser onset) was distributed over the SI, PS and MF cortices (A, left column), which overlapped with, but not equal to, the LEP distribution (B). The arrows indicate the electrodes used for demonstrating time-frequency representation of spectral response to painful stimulation over each of three regions (SI, PS and MF). To the contrary, during the distraction condition, the distribution of the alpha ERD was reduced when subject felt less pain (0–1/10 in pain intensity, A, middle column). However, even with distraction, alpha ERD showed much wider distribution with higher pain intensity (5/10, A, right column). Note that the distraction task, with either low or high pain intensity, not associated with the alpha ERD over the PS as compared with the attention condition. Adapted from Ohara *et al.* (2004).

pain intensity ratings. Both PS and medial frontal regions seem less responsive to weak painful stimulation than SI, because of lack of significant peaks with the weak laser pulse. Thus, analysis of LEPs indicates that the MCC encodes pain intensity and is modulated by attention. Cortical activation, as measured by ERD, is modulated by the analgesic effect of distraction, independent of the distraction task.

Experimental Lesion Studies

The rationale for cingulotomy for pain is related to imaging studies (see above) and to studies of rodent models of subacute or chronic pain (Donahue *et al.*, 2001; Lagraize *et al.*, 2004; Senapati *et al.*, 2005). A model of inflammatory pain was produced by injection of formalin into the forepaw, and a model of neuropathic,

chronic pain and mechanical hypersensitivity was produced by an L5 nerve root ligation. Pain-related behaviors were decreased by an electrolytic lesion of the ACC in the inflammatory pain model (Donahue *et al*., 2001). In the neuropathic pain model, mechanical hypersensitivity was unchanged while escape/avoidance behaviors were decreased (Lagraize *et al*., 2004).

Studies of experimental pain before and after cingulotomy in a patient with psychiatric disease have yielded results different (Davis *et al*., 1994) from those anticipated by the early literature of cingulotomy for chronic pain (Foltz & White, 1962). One study demonstrated increased perceptions of both the intensity and unpleasantness of painful hot stimuli post-cingulotomy, although the heat pain threshold was increased (Davis *et al*., 1994). That is to say, there was decreased sensitivity to heat at threshold, but increased intensity and unpleasantness of supratheshold stimuli.

A similar case study demonstrated that detection and pain thresholds for innocuous and noxious thermal stimuli were unchanged post-operatively, except for a slight increase in cold pain sensitivity (Greenspan *et al*., 2008). Ratings of the same types of stimuli were remarkable only for increased unpleasantness and intensity ratings of painful stimuli. These two reports demonstrate increased pain intensity and unpleasantness despite partial destruction of the ACC, unlike the surgical reports. Therefore, the increased unpleasantness of experimental pain following cingulotomy contrasts with that of chronic pain which was reported to be less "bothersome" or unpleasant following cingulotomy (Foltz & White, 1962).

Another psychophysical study examined the effects on experimental pain of anterior capsulotomy in a patient with psychiatric disease. This lesion interrupts afferent and efferent fibers to the ACC and other frontal lobe structures (Talbot *et al*., 1995). Post-capsulotomy effects upon thermal pain perception included decreased intensity and unpleasantness ratings for suprathreshold stimuli. When tested by the cold pressor test, which involves immersing one hand in an ice water bath, the patient rated the ice water as less-painful, but he had much shorter immersion times, consistent with decreased tolerance. His behavioral reactions, however, were not consistent with decreased tolerance, as he was perplexed that his hand came out of the water bath so quickly. The capsulotomy may have disrupted pathways that altered voluntary motor control, such that the subject was no longer able to inhibit spinal withdrawal reflexes.

It was suggested that capsulotomy blocks the subcortical input to and so disinhibits anterior cingulate which reduces both the intensity and unpleasantness of noxious stimuli (Talbot *et al*., 1995). This interpretation could reconcile the decreased ratings following capsulotomy with the increased ratings following cingulotomy. The effect of cingulotomy would decrease cingulate activity leading to increased intensity and unpleasantness. Post-capsulotomy, decreased unpleasantness ratings of thermal stimuli, including the cold pressor, post-capsulotomy are more consistent with the less "bothersome" or unpleasant nature of chronic pain which may occur following capsulotomy. Clearly, the relationship between the ACC and experimental pain versus chronic or cancer pain is more complicated than assumed initially (Foltz & White, 1962).

Cingulotomy for Pain

The ACC and associated structures was first suggested to be a target for psychiatric surgery by Fulton, based on studies in monkeys (Pribram & Fulton, 1954). This procedure was initially done as an open procedure (Whitty *et al*., 1952). Subsequently, a lesion of the rostral cingulate fasciculus was carried stereotactically based on the radiologic visualization of air or contrast injected into the frontal horns of the lateral ventricles (Fig. 18.5). This approach was adopted for treatment of chronic pain and psychiatric disease (Foltz & White, 1962; Ballantine *et al*., 1967).

The largest reported series of cingulotomy cases for chronic pain treated 123 patients, and included both the ventriculogram (air or contrast) era and the MRI era (Ballantine & Giriunas, 1988). Procedures were judged to be successful if the patient reported no pain without any analgesic medication or was comfortable on non-narcotic analgesics. Among 35 patients with cancer, 57% had significant relief. Among 98 patients with non-cancer pain, the largest group was those with failed back syndrome (61 patients) of whom 74% benefited from cingulotomy. Numbers were much smaller in other groups such as patients with chronic abdominal pain of whom 5/6 were improved or phantom limb pain of whom 3/5 reported improvement. Patients with pain from post-herpetic neuralgia or post-stroke pain were never benefited, although numbers were very small (Ballantine & Giriunas, 1988).

The advent of modern imaging techniques has lead to MRI-guided cingulotomy (Hassenbusch *et al*., 1990; Cosgrove & Rauch, 2003). MRI cingulotomy is based on radiologic localization with coronal, T1 weighted images spanning the entire anterior cingulate cortex and frontal horns of the lateral ventricles. Targets are chosen 2–5 mm above the roof of the lateral ventricle, 7 mm from the midline, and 20–25 mm posterior to the tip of the frontal horn (Fig. 18.5). Microelectrode recording may be used to confirm the location of the cingulate gyrus (Richter *et al*., 2004) which can be directly visualized on the MRI scan.

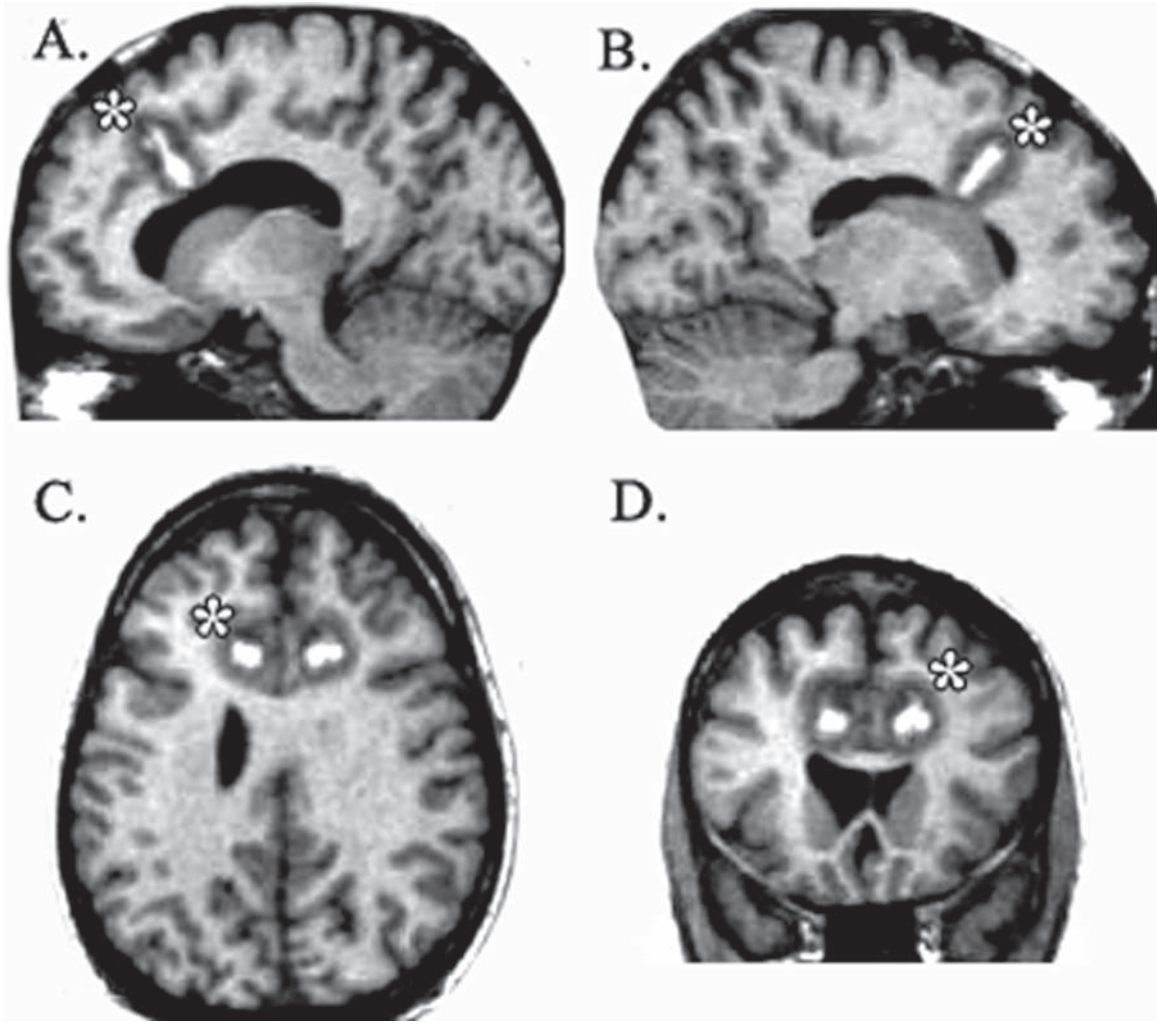

Fig. 18.5 Magnetic resonance imaging post-cingulotomy. T1 weighted, sagittal (A and B), axial (C) and coronal (D) views of a patient 1-week post-cingulotomy. The bright signals surrounded by a gray signal are the lesions (asterisks).

A radio-frequency electrode is introduced to the target, and the lesions are made. An additional lesion can be made above by withdrawing the electrode 5–10 mm (Cosgrove & Rauch, 2003).

There are several recent series of cingulotomy for treatment of chronic neuropathic pain and cancer pain. A study of MRI stereotactic bilateral cingulotomy for treatment of three patients with widespread metastatic cancer reported significant relief of pain in two out of three patients, based on reduction in pain medication requirements and subjective pain relief (Wong *et al*., 1997). Wilkinson reported 23 patients that underwent 28 bilateral cingulotomies for chronic neuropathic pain, including 5 who had enlargement of the lesion. These patients had a variety of pain syndromes, including phantom limb pain, "failed back syndrome", vascular claudication, and atypical facial pain. Seventy-two percent of patients reported significant improvement in their pain, and 55 patients discontinued opiates (Wilkinson *et al*., 1999).

Another series of cingulotomy for pain included patients with cancer and nociceptive ($n = 6$) and neuropathic pain ($n = 2$) of which four had an excellent result and four had a poor to fair result (Pillay & Hassenbusch, 1992). The remaining patients had pain secondary to neurofibromatosis and post-stroke central pain with excellent and poor results, respectively. There do not appear to have been complications in this series. Finally, transient benefit was reported in a case of "whole body sympathetically maintained pain" (Santo, 1990).

The complications of this procedure are those that can occur with any stereotactic neurosurgical procedure

including intracranial hemorrhage, infection, and seizure. In Wilkinson's series of 23 patients, two patients had seizures intra-operatively, and five had late seizures. Four of those patients were placed on phenytoin with adequate control of their seizures and one had pseudo-seizures not requiring treatment. No hemorrhages were reported, and no patients died as a result of the procedure (Wilkinson *et al*., 1999).

A lower incidence of complications was reported in the large Massachusetts General Hospital series (714 cingulotomies, 414 patients) performed for either chronic pain or psychiatric disease. There were no deaths and no infections. Two patients became hemiplegic secondary to acute subdural hematomas, one developed a chronic subdural hematoma, and five patients had seizures controlled by phenytoin (Ballantine & Giriunas, 1988).

Neuropsychological testing of patients with bilateral cingulotomy for chronic pain displayed worse executive function, attention, and self-initiated behavior, while language, motor control, and memory were not affected (Cohen *et al*., 1999). Another group reported that all patients had a transient flattening of affect post-operatively, and 2 of 23 patients had an aphasia that resolved in 48 h. One patient exhibited repetitive hand washing lasting several days (Wilkinson *et al*., 1999).

Ablation of the Limbic Thalamus

The management of neuropathic pain has also been reported by ablation of thalamic nuclei including the central lateral, central median, midline, and the posterior aspect of the median dorsal nucleus as well as posterior, limitans and medial pulvinar (Hirai & Jones, 1989; Jeanmonod *et al*., 1994, 1996, 2001). A large series of patients with neuropathic pain ($n = 69$) were subjected to this procedure and studied after variable follow-up (13 months average, range 1–48 months; Jeanmonod *et al*., 1994, 1996). The success of the procedure was judged by the patient's subjective rating, which was reported to show 70% relief in peripheral and 60% in central neuropathic pain. Overall, 67% of patients were reported to show improvement including 20% with complete relief. No complications were reported (Jeanmonod *et al*., 1994). However, the efficacy and safety of this procedure for treatment of neuropathic or nociceptive pain are unclear (Gybels & Sweet, 1989). Lesions of the intralaminar or centromedian nuclei may produce successful pain relief and minimize symptoms of opiate withdrawal (Gildenberg & DeVaul, 1985).

The recent series of gamma knife medial thalamotomy reported greater than 3 months follow-up (average 12 months) in 15 patients. Nine patients had greater than 50% pain relief of whom four reported complete pain relief. Complications occurred in 4/17 cases followed over 3 months. There were four cases of hemiplegia. Among these four one resolved, two were improving at the time of the report, and one died of radiation necrosis following a contralateral, medial thalamotomy (Young *et al*., 1995). This is consistent with the risk of neurologic complications of functional radiosurgical procedures, when employed for treatment of movement disorders (Okun *et al*., 2001; Kondziolka, 2002).

Linear accelerator thalamotomy targeting the central median and parafascicular nuclei for the treatment of peripheral and central neuropathic pain has been reported in three cases (Frighetto *et al*., 2004). The lesion was made at standard coordinates. Post-operatively immediate pain relief was reported in all the three cases based on the assessment of the treating physician. No complications were reported.

Emerging Approaches to Cingulate Surgery

In the field of movement disorders, destructive procedures such as thalamotomy, have been largely replaced by deep brain stimulation (DBS). The latter is reversible, modifiable, and has a much lower rate of neurological deficits (Schuurman *et al*., 2000). A single study reports the use of DBS deep to area 25 of subgenual ACC for treatment of depression (Mayberg *et al*., 2005). A double blind controlled trial of anterior capsular stimulation was carried out in six patients with severe, refractory obsessive-compulsive disorder (OCD; Nuttin *et al*., 2003). Stimulation reduced core symptoms and Global Severity Scores for OCD over follow-up of up to 21 months. The degree of improvement does not appear to have been statistically significant. These radiosurgical and DBS techniques may well have a role in the future of surgical procedures on the limbic thalamus and cingulum bundle for the treatment of pain.

Cingulotomy Alterations in the Cognitive Aspects of Pain Processing

The dichotomy between the effects of cingulotomy on acute and chronic pain is difficult to reconcile. However, recent functional imaging studies examining pain and expectations may provide some insight (Porro *et al*., 2002; Koyama *et al*., 2005; Chapter 16). Both studies identified an overlap between pain and expectation-related activation in the ACC. Koyama *et al*. (2005 Chapter 16) proposed that this overlap may reflect a crucial interface between cognitive information and afferent processing of nociceptive information. Surgical disruption of the ACC may substantially alter this interaction. Thus, pain with substantial cognitive involvement, such as chronic pain, may be more susceptible to

disruption of the ACC than an acute pain that is driven largely by a brief burst of nociceptive activity. While this explanation is admittedly speculative, the subjective experience of pain has long been known to be heavily influenced by cognitive factors. The anatomy and physiology of the ACC indicate that it is well positioned to subserve this critical aspect of pain.

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