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Topical review

Cortical representation of pain: functional characterization of nociceptive areas near the lateral sulcus

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Abstract

Many lines of evidence implicate the somatosensory areas near the lateral sulcus (Sylvian fissure) in the cortical representation of pain. Anatomical tracing studies in the monkey show nociceptive projection pathways to the vicinity of the secondary somatosensory cortex in the parietal operculum, and to anterior parts of insular cortex deep inside the Sylvian fissure. Clinical observations demonstrate alterations in pain sensation following lesions in these two areas in human parasylvian cortex. Imaging studies in humans reveal increased blood flow in parasylvian cortex, both contralaterally and ipsilaterally, in response to painful stimuli. Painful stimuli (such as laser radiant heat) evoke potentials with a scalp maximum at anterior temporal positions (T3 and T4). Several dipole source analyses as well as subdural recordings have confirmed that the earliest evoked potential following painful laser stimulation of the skin derives from sources in the parietal operculum. Thus, imaging and electrophysiological studies in humans suggest that parasylvian cortex is activated by painful stimuli, and is one of the first cortical relay stations in the central processing of these stimuli. There is mounting evidence for closely located but separate representations of pain (deep parietal operculum and anterior insula) and touch (secondary somatosensory cortex and posterior insula) in parasylvian cortex. This anatomical separation may be one of the reasons why single unit recordings of nociceptive neurons are scarce within regions comprising low-threshold mechanoreceptive neurons. The functional significance (sensory-discriminative, affective-motivational, cognitive-evaluative) of the closely spaced parasylvian cortical areas in acute and chronic pain is only poorly understood. It is likely that some of these areas are involved in sensory-limbic projection pathways that may subserve the recognition of potentially tissue damaging stimuli as well as pain memory.

Keywords: Nociception; Secondary somatosensory cortex; Parietal operculum; Insula

1. Introduction

In the course of the past decade, pain has finally joined the other sensory modalities in that its conscious perception is thought to depend on an intact neocortex. This view has replaced the old position that pain is the only sensation that is derived from thalamic rather than cortical activity (Head and Holmes, 1911). Pain perception cannot be separated from consciousness, because pain only exists when it is perceived (Bromm, 1995). Following an injury, pain is the consequence of activation of the nociceptive system, which is a part of the somatosensory system. The term 'nociception' refers to signal processing of noxious stimulus input, independent of its conscious perception. Rather than revealing a 'pain centre' in the brain, the many reports on the cortical representation of pain of the past decade have dramatically increased our knowledge on nociceptive areas in the cerebral cortex (for review see Treede et al., 1999b). Much of this increase in knowledge was due to advances in the imaging technologies of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These imaging studies have also renewed the interest in human electrophysiological data obtained by either magneto-encephalographic (MEG) or evoked poten-

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tial techniques (EEG/EP), including invasive subdural and intracerebral recordings.

The neocortex surrounding the lateral sulcus (Sylvian fissure) is one of the regions that is found most consistently to be activated in PET studies using painful stimulation of skin (Talbot et al., 1991; Craig et al., 1996; Casey and Minoshima, 1997), muscle (Svensson et al., 1997) or viscera (Aziz et al., 1997). Several earlier EEG/EP and MEG studies had already documented pain-related activation in this area (Bromm and Treede, 1991; Treede, 1994; Bromm and Chen, 1995; Bromm and Lorenz, 1998). Moreover, among the cortical lesions, lesions of parasylvian cortex are most likely to cause alteration of pain perception (Biemond, 1956; Greenspan and Winfield, 1992; Schmahmann and Leifer, 1992; Greenspan et al., 1999); conversely, seizures originating in parasylvian cortex can be painful (Blume et al., 1992; Scholz et al., 1999). Anatomical data have shown that nociceptive input to that region can largely bypass the primary somatosensory cortex in the postcentral gyrus by direct thalamo-cortical projections (Apkarian, 1995; Craig and Dostrovsky, 1997).

In spite of this tremendous body of evidence supporting a decisive role of parasylvian cortex in pain perception, the precise nature of these roles remains contentious. The aim of this topical review is to summarize the evidence supporting such a decisive role of parasylvian cortex, and to outline possible reasons why our knowledge of its functions is still rather limited. This topical review was inspired by discussions at a topical workshop at the Ninth World Congress on Pain in Vienna (Treede et al., 1999a).

2. Connectivity of the parietal operculum and the insula

The secondary somatosensory cortex (SII) is situated in the upper bank of the Sylvian fissure as part of the frontoparietal operculum, the 'top cover' of the insula (Fig. 1). The primary auditory cortex (Heschl's transverse gyrus) is part of the temporal operculum in the lower bank of the Sylvian fissure, and is thus situated approximately opposite of SII across the Sylvian fissure. The size of the left parietal operculum in humans usually exceeds that of its counterpart in the right hemisphere by a similar factor as the planum temporale in the lower bank of the Sylvian fissure (Kennedy et al., 1998), but the functional significance of this hemispheric asymmetry is unknown.

The existence of another somatosensory area outside the primary somatosensory cortex (SI) was already apparent in early studies of cortical electrophysiology (for review see Burton, 1986). This observation led to the general concept of multiple cortical representations of sensory systems. More recent studies have shown that parasylvian cortex in primates contains at least two adjacent somatosensory areas (Burton et al., 1995; Krubitzer et al., 1995). Further somatosensory areas are situated in the inferior parietal cortex, the posterior insula and retroinsular cortex, as well as mesial parts of areas 5 and 7 (see Caselli, 1993). PET studies using tactile stimuli in humans revealed multiple somatosensory areas extending from the upper bank of the Sylvian fissure into retroinsular cortex and anterior insula (Burton et al., 1993). A similar set of somatosensory areas was observed in fMRI studies (Davis et al., 1998; Gelnar et al., 1998; Hodge et al., 1998; Darbar et al., 1999; Disbrow et al., 2000). Both the parietal operculum and the insula (situated opposite of SII across the circular sulcus of the insula, see Fig.1) thus contain several somatosensory association areas.

To identify the nociceptive parts of these parasylvian somatosensory areas, anatomists have followed the projection pathways originating in the nociceptive areas of the spinal cord (lamina I and V) up to the thalamus and further to the cerebral cortex. In the monkey, spinothalamic terminations were found in several nuclei in the lateral thalamus (VPL/VPM, VPI, VMpo), which in turn project to SI, SII and the insula (Apkarian, 1995; Craig and Dostrovsky, 1997). Some of these terminations, especially within VPL/VPM, are in clear registry with the body map for tactile inputs from the dorsal column nuclei to the same region, whereas the spinothalamic terminations in VPI and VMpo appear to be distinct from tactile inputs (Gingold et al., 1991; Apkarian and Shi, 1994; Craig et al., 1994). Therefore, the interrelationship between the cortical representation of pain and touch might be different in different cortical regions. The parietal operculum receives projections from large numbers of neurons with spinothalamic inputs (Stevens et al., 1993), which are located in VPI where about 50% of the neurons are nociceptive (Apkarian and Shi, 1994). The insula receives its nociceptive projections largely from neurons in VMpo (Craig et al., 1994).

In humans, the thalamic ventrocaudal nucleus (Vc), the inferior subnucleus of Vc (Vcpc), and the posterior subnucleus of Vc (Vcpor) project to parasylvian cortex (Lenz and Dougherty, 1997). Whereas Vc primarily projects to SI, Vcpc projects to anterior insular cortex, and Vcpor projects to the inferior parietal lobule including the parietal operculum and SII. Cells that respond to painful stimuli have been recorded in all three of these thalamic nuclei and in the ventral medial posterior nucleus VMpo (Lenz et al., 1993). Moreover, intraoperative stimulation evokes somatic pain, visceral pain and memories of previously perceived pain (Lenz et al., 1995).

Single unit recordings in SII revealed a closely spaced somatotopy (face anterolateral, foot posteromedial) and a significant proportion of bilateral receptive fields (for review see Burton, 1986). These recordings, however, were from low-threshold neurons that presumably subserve tactile functions. There are a few physiological studies in parasylvian cortex that use functional criteria to identify nociceptive neurons (Robinson and Burton, 1980; Dong et al., 1989). Some nociceptive neurons with large receptive fields have been described in the caudal part of SII and in neighbouring areas 7b and retroinsular cortex, but the core of SII appears to contain few nociceptive neurons. Although

the secondary somatosensory cortex receives appropriate spinothalamic projections, evidence from single cell recordings for nociceptive neurons along the upper bank of the lateral sulcus thus is limited. Electrophysiological studies in this region usually use mechanical search stimuli. If the nociceptive area in parasylvian cortex were separate from the tactile area, there is the intriguing possibility that these studies have systematically missed the nociceptive neurons (see below).

3. Electrophysiological signals from parasylvian cortex in human subjects

Pain-related evoked potentials are known since the 1960s (Spreng and Ichioka, 1964). The fact that painful stimuli can evoke these potentials in a similar way as e.g. auditory stimuli is consistent with the existence of nociceptive areas in the cerebral cortex (for review see Chen, 1993; Chudler and Dong, 1983; Scharein and Bromm, 1998). Pain-related evoked potentials, however, were not generally recognized to provide conclusive evidence for these areas, because the potentials had a wide distribution on the scalp suggesting a very diffuse projection or deep sources. Localized sources that were activated by painful stimulation were first identified in a source analysis of MEG (Hari and Kaukoranta, 1985). For stimulation of the nasal mucosa the source was near SII, whereas for tooth pulp stimulation the source was anterior to SII, in the frontal operculum. The latency for activation of these sources was about 50 ms shorter than the latency for the widespread potentials (vertex potentials). Sources within or near SII were also identified in recordings of scalp evoked potentials using different painful stimuli such as laser radiant heat (Treede et al., 1988; Kunde and Treede, 1993; Miyazaki et al., 1994; Xu et al., 1995) or stimulation of the esophagus (Aziz et al., 1995; Hecht et al., 1999). These sources project to the scalp as a negativity in anterior temporal electrodes (T3 and T4) and a positivity in the midline. In contrast to SII and its vicinity, activation of SI by noxious stimulation in humans has rarely been reported. Whenever present, SI sources were activated simultaneously with SII sources or even later (Tarkka and Treede, 1993; Ploner et al., 1999). This is in contrast to the source pattern activated by electrical stimulation of tactile afferents, where SI is activated within 20 ms and SII follows with about 100 ms delay (e.g. Kany and Treede, 1997; Frot and Mauguière, 1999). These functional data from human electrophysiology support the concept from anatomical data in monkey, that nociceptive input reaches SII mostly by direct projection from VPI, whereas tactile input reaches this region by a projection pathway via SI.

SII activity in response to experimental pain stimuli seems to be tonically pre-primed by subcortical structures that control the arousal state. Experiments with tranquilizing or hypnotic drugs showed a significant reduction of pain-induced activity of sources in parasylvian cortex. The same was found with the dissociative anaesthetic ketamine: an i.v. bolus of 0.5 mg/kg (S+)-ketamine induces a brief period of unconsciousness (3–10 min) during which the activity of parasylvian sources in response to brief laser heat stimuli is drastically attenuated (Bromm et al., 2000). If we assume that SII is involved in the sensory-discrimina-

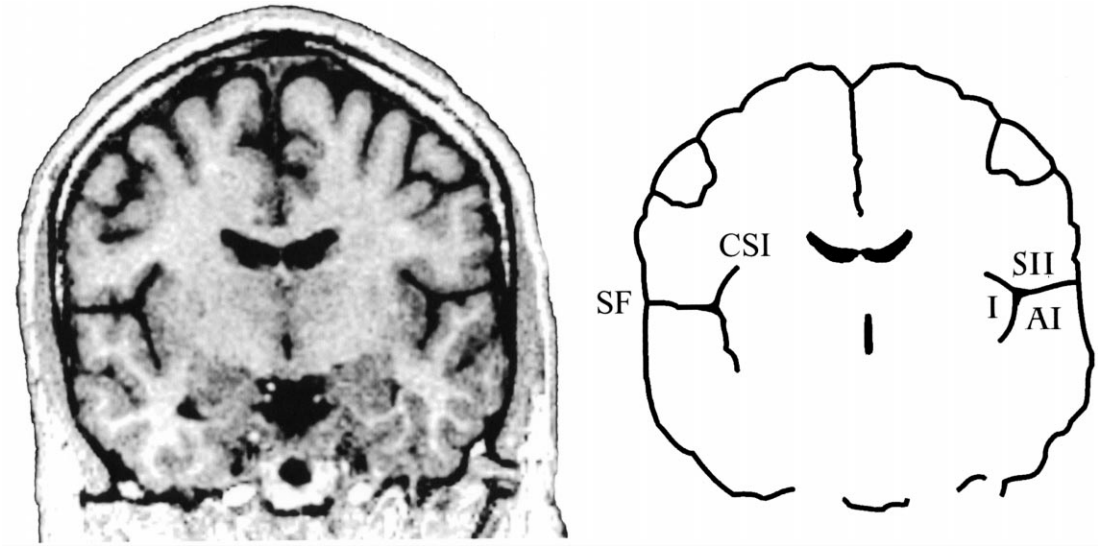

Fig. 1. Cortical areas around the Sylvian fissure in the human brain. (Left) Magnetic resonance image of a coronal section through the brain of a healthy human subject. (Right) Schematic outlines of this section. The secondary somatosensory cortex (SII) is situated in the upper bank of the Sylvian fissure (SF). The primary auditory cortex (AI) is situated in the opposite, lower bank of the Sylvian fissure, in Heschl's transverse gyrus. On the medial side, SII is situated close to the insular cortex (I), which lies on the opposite bank of the circular sulcus of the insula (CSI). The cortex above the Sylvian fissure contains multiple somatosensory areas, the functions of which are largely unknown. Nociceptive areas in this region overlap only partly with tactile areas and the classical SII region. Nociceptive areas are also found in parts of the insular cortex.

tive component of pain, we may conclude that this component plays a major role in the understanding of the analgesic effects of general anaesthesia.

Recordings of laser-evoked potentials (LEPs) from subdural grids in patients scheduled for epilepsy surgery revealed waveforms that were similar in shape to scalp recordings. Following stimulation of contralateral or ipsilateral face or hand, maximal amplitudes of the initial negativity were recorded from electrodes just above the Sylvian fissure and behind the central sulcus, i.e. overlying the parietal operculum (Lenz et al., 1998). These subdural recordings confirm the predictions of dipole source modeling studies (Tarkka and Treede, 1993; Bromm and Chen, 1995; Valeriani et al., 1996) and MEG studies (Kakigi et al., 1995; Ploner et al., 1999).

By comparing the polarity and amplitude distributions of laser-evoked potentials and auditory evoked potentials, the location of the nociceptive area in the parietal operculum is estimated to be across the Sylvian fissure from the primary auditory cortex, and a few mm more anterior (Lenz et al., 2000). The orientation of the LEP dipole is not at right angles to the Sylvian fissure, but at right angles to the surface of the brain, suggesting that the generator of the parasylvian LEP was not located in the upper bank of the Sylvian fissure in SII. More likely, the generator of the parasylvian LEP was located in the insula or in the deep surface of the parietal operculum. A study using stereotactically implanted depth electrodes reported maximal LEP amplitudes at several sites with a mean *x*-coordinate of 44 ± 7 mm (i.e. about 20 mm below the surface of the brain) along the parietal operculum in different patients (Frot et al., 1999). Polarity reversals, which indicate that the recordings were close to a dipolar source, were found only at the inner surface of the parietal operculum (i.e. the outer bank of the circular sulcus of the insula, cf. Fig. 1). These electrophysiological findings in humans support anatomical and imaging study results about the existence of nociceptive areas in parasylvian cortex. On the other hand, the electrophysiological data suggest that these areas are outside the classical SII region.

4. Are tactile and nociceptive areas in parasylvian cortex separate?

Subdural and depth recordings of laser-evoked potentials suggested that the nociceptive area in parasylvian cortex is situated at the inner surface of the parietal operculum (see above). This area is approximately halfway between the traditional SII and the insula. A recent clinical study compared the patterns of lesions in parasylvian cortex that lead to loss of pain sensitivity with those that do not affect pain sensitivity (Greenspan et al., 1999). The common feature of patients with normal pain thresholds in spite of parasylvian lesions was the apparent sparing of the parietal operculum. This series of cases thus supports the significance of the parietal operculum for normal pain perception.

These data raise the question whether nociceptive and tactile somatosensory areas may be separate within the parietal operculum. One of the earliest electrophysiological studies in monkey suggested that posterior SII included polysensory and nociceptive neurons, whereas anterior SII consisted of tactile neurons (Whitsel et al., 1969). An extensive study on the encoding properties of nociceptive neurons in monkey parietal operculum characterized cells in posterior parietal area 7b rather than SII (Dong et al., 1994). In humans, the scalp topography of the initial LEP negativity (presumed to originate in parasylvian cortex) is slightly shifted compared with its counterpart following electrical stimulation of tactile afferents (Kunde and Treede, 1993). In MEG source analysis studies, the LEP sources were found deep inside the parietal operculum (Kakigi et al., 1995), whereas with electrical nerve stimulation of tactile afferents the sources were spread along the upper bank of the Sylvian fissure (Maeda et al., 1999). Depth recordings from stereotactically implanted electrodes gave maximal signals for painful laser heat and non-painful electrical stimulation at about the same coordinates (Frot and Mauguière, 1999; Frot et al., 1999), but in those studies only a small number of electrode tracks was available for analysis. In PET studies, tactile tasks (including attention) activate an SII focus within the upper bank of the Sylvian fissure (Burton et al., 1993, 1999). A direct comparison of vibrotactile and painful heat stimulation using PET showed that both stimuli activated a similar region in what was labeled as SII (Coghill et al., 1994). Painful stimuli were more effective in activating the anterior insula, a region linked with both somatosensory and limbic systems. High-resolution fMRI studies of vibrotactile and thermal pain tasks showed only about 30% of overlap in activated areas within the parietal operculum (Gelnar et al., 1999).

In summary, there seems to be considerable overlap in tactile and nociceptive areas in the parietal operculum, but human data show a trend towards a deeper location of the nociceptive area (closer to the circular sulcus of the insula than to the Sylvian fissure). This proposition is supported by the observation of pain intensity dependent fMRI responses in this deeper location, but the lack of such an effect in the more lateral somatosensory areas (Moulton et al., 2000). This difference in location may be the reason, why single unit data from nociceptive neurons in the parietal operculum are scarce. There is also evidence from fMRI studies that the anterior insula may be involved in pain, whereas the posterior insula may be involved in touch (Davis et al., 1998).

5. Sensory-limbic projections, experiential responses, and pain memory

Although the nociceptive region within the parietal operculum appears to be distinct from the tactile region, it is

conceivable that the two regions share corresponding functions in two parallel pathways. For the tactile system, there is evidence that areas in the parietal operculum are more sensitive to task-dependent modulation than SI (Hsiao et al., 1993) and may be involved in feature extraction such as roughness discrimination and object size detection (Ledberg et al., 1995). Single neurons in SII often exhibit weak responses to passively presented tactile stimuli and larger receptive fields than those in SI, but this loss in information on stimulus location and intensity is offset by gains in specificity for spatial patterns such as gratings and by specific activation during active touch tasks (Sinclair and Burton, 1993). As such, one of the functions of SII may be tactile object recognition. For this function, most of the input to SII is assumed to derive from SI, and the output is directed towards the insular cortex and the parahippocampal gyrus (Friedman et al., 1986). This pattern of connections is similar to that of inferior temporal cortex which is implicated in the visual discrimination of objects.

By analogy, one of the functions of the nociceptive region within the deep parietal operculum may be the recognition of the noxious nature of a stimulus. This hypothesis is supported by the characteristics of the spino-thalamo-cortical projection to nociceptive neurons in the parietal operculum, which is mostly directly from the thalamic nucleus VPI whereas tactile input is mostly indirect from VPL via SI (Apkarian and Shi, 1994). About 50% of VPI neurons are nociceptive, mostly responding only to noxious stimuli (nociceptive specific), whereas only 10% of neurons in VPL are nociceptive, and those are mostly of the wide-dynamic-range type that encodes stimulus intensities throughout the ranges of tactile and noxious stimuli. Consistent with the functions discussed above, patients with lesions in the parietal operculum suffer from both impaired tactile object recognition (Caselli, 1993) and deficits in pain perception (Biemond, 1956; Greenspan and Winfield, 1992; Greenspan et al., 1999).

In addition to potential functions in the sensory-discriminative component of pain, other functions have been proposed for parasylvian cortex. A cognitive-evaluative function of the parietal operculum is suggested by the parallel effects of a cognitive distracting task on the perceived intensity and the cerebral perfusion increase induced by the cold pressor pain test (Petrovic et al., 2000). Affective-motivational functions of the anterior insula are suggested by the observation that lesions in that region appear to produce asymbolia for pain and increases in pain tolerance (Berthier et al., 1988; Greenspan et al., 1999). Previously experienced pain associated with a strong affective dimension (angina pectoris, labor pain) has been reproduced by stimulation of those postero-inferior regions of the human thalamus that project to parietal operculum and insular cortex (Lenz et al., 1997). This type of pain was only elicited in patients with prior experience of such pain, whereas similar pain but without a strong affective component was elicited in patients without the previous experience of such pain (Lenz et al., 1995). These results suggest that the strong affective component of pain elicited by thalamic stimulation is the result of prior experience and learning, and that the thalamic stimulation apparently activated a memory trace. The suggested pathway for this sensory-limbic model of pain memory consists of parallel projections from postero-inferior thalamus to parietal operculum and insula, a projection from parietal operculum to the insula, and parallel projections from the insula to the hippocampus (via the parahippocampal gyrus) and to the amygdala (Lenz et al., 1997).

The affective-motivational component of pain perception has often been associated with the anterior cingulate gyrus (Vogt et al., 1996; Rainville et al., 1997). Whereas the affective functions of the anterior cingulate gyrus may be related to the integration of general affect, cognition and response selection (cf. Devinsky et al., 1995), those of the insula appear to be more closely related to memory. The insula is also known as a visceral sensory and visceral motor area (for review see Augustine, 1996), and may thus serve a sensory integrative function for pain, taste and other visceral sensations.

6. Conclusions

Many lines of evidence indicate that the parietal operculum and the anterior insula are involved in the cortical representation of pain. Electrophysiological data in humans and clinical observations in patients with cortical lesions suggest that the inner surface of the parietal operculum, between the classical SII area and the insula, contains a nociceptive area that is activated very early after the onset of phasic noxious stimuli. These findings are consistent with the results of some of the more recent high-resolution fMRI studies of nociceptive signal processing in this region. For tactile signal processing, single unit electrophysiology as well as functional studies support the hypothesis that SII is part of a pathway for tactile object recognition and tactile learning. In contrast, single unit electrophysiology has so far failed to describe any reasonable population of nociceptive cells in SII. Since those studies have always been conducted by identifying SII using tactile stimuli and then searching for nociceptive neurons in the same location, the putative nociceptive region within the inner surface of the parietal operculum and outside the classical SII region has not been explored systematically. The lack of knowledge about the response properties of nociceptive neurons in parasylvian cortex is a major obstacle for our understanding of the functional roles of this region for pain perception. Largely by analogy to tactile signal processing, it may be hypothesized that these roles involve the identification of noxious stimuli and pain memory. More detailed studies on the properties of single neurons, the task dependence of signals from source analyses and functional imaging, and the consequences of lesions in this region are necessary to verify or disprove this hypothesis.

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