5.45 Nociceptive Processing in the Cerebral Cortex

R D Treede, Ruprecht-Karls-University Heidelberg, Heidelberg, Germany

A V Apkarian, Northwestern University, Chicago, IL, USA

Glossary

ACC anterior cingulate cortex (n.b.: some authors use this as a summary term for ACC and MCC)
CBP Chronic back pain
CRPS Complex regional pain syndrome
EEG Electro-encephalography
fMRI Functional magnetic resonance imaging
IBS Irritable bowel syndrome
IC Insular cortex
MCC mid-cingulate cortex (n.b.: some authors call this region the posterior part of ACC)
MEG Magneto-encephalography
MRS Magnetic resonance spectroscopy

OIC Operculo-insular cortex, consisting of insular cortex plus the frontal, parietal and temporal operculum.
PAG Periaqueductal grey
PET Positron emission tomography
PFC prefrontal cortex
PHN Postherpetic neuralgia
SI Primary somatosensory cortex
SII Secondary soamtosensory cortex
SCI Spinal cord injury
SPECT Single photon emission computed tomography
Th Thalamus

5.45.1   Introduction

Conscious perception of external stimuli requires encoding by sensory organs, processing within the respective sensory system, and activation of the appropriate sensory cortical areas. Based on a small case series of infra- and supratentorial brain lesions, Head H. and Holmes G. (1911) postulated that the sensation of pain is an exception to this rule and that its conscious perception occurs in the essential organ of the thalamus. In spite of evidence to the contrary from clinical reports (Marshall, J., 1951; Biemond, A., 1956), evoked potentials in humans (Spreng, M. and Ichioka, M., 1964; Duclaux, R. *et al.*, 1974; Carmon, A. *et al.*, 1976; Chen, A. C. N. *et al.*, 1979; Bromm, B. and Treede, R. D., 1984), single unit recordings in animals (Lamour, Y. *et al.*, 1982; Kenshalo, D. R. and Isensee, O., 1983), neuroanatomical tracing (Gingold, S. I. *et al.*, 1991), and some early PET studies (Buchsbaum, M. S. *et al.*, 1984), it was maintained for a long time that the cortical representation of pain is a *quantité negligable*.

This situation changed, when the modern neuroimaging techniques of positron emission tomography (PET) and later functional magnetic resonance imaging (fMRI) demonstrated systematic metabolic and perfusion changes in a large number of cortical areas following painful stimuli (Talbot, J. D. *et al.*, 1991; Jones, A. K. P. *et al.*, 1991a; Apkarian, A. V. *et al.*, 1992; Davis, K. D. *et al.*, 1995). These findings were supported by invasive and noninvasive electrophysiological studies in humans, using magnetoencephalography (MEG), electroencephalography (EEG), subdural recordings directly from the surface of the brain, and depth recordings during stereotactic procedures (for a systematic review see Apkarian, A. V. *et al.*, 2005).

Meanwhile it has been recognized that painful stimuli activate a vast network of cortical areas, including the primary and secondary somatosensory cortex (SI, SII), the insula, posterior parietal cortex, anterior and mid-cingulate cortex, and parts of the prefrontal cortex (PFC; Figure 1). These areas are involved in the generation of painful percepts as well as in the descending control of pain (for review see Kenshalo, D. R. and Willis, W. D., 1991; Treede, R. D. *et al.*, 1999; Price, D. D., 2000; Apkarian, A. V. *et al.*, 2005). Most of these areas are also involved in other sensory, emotional, cognitive, motor or autonomic functions. Hence, the nociceptive system converges with other systems for the generation of the conscious percept of pain. In that sense, the nociceptive system is not different from the visual system, for example. But it is still an open question, to what extent any cortical regions can be considered as nociceptive specific.

In this chapter we will briefly review the methods used to assess nociceptive processing in the human brain, present connectivity and functional properties of each of the principal cortical regions of the nociceptive system, and summarize the roles of the cerebral cortex in various aspects of pain perception and pain modulation.
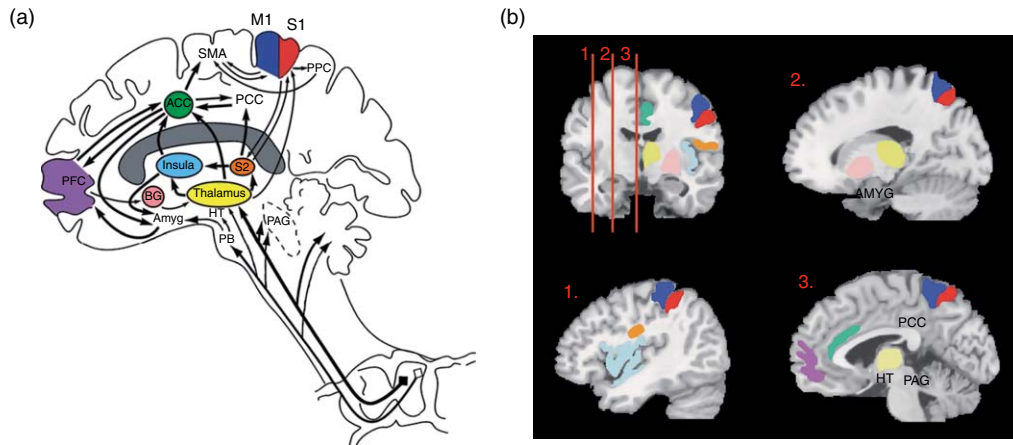
Figure 1 Cortical regions involved in pain perception, their interconnectivity and ascending pathways. Locations of brain regions involved in pain perception are color coded in a schematic drawing and in an example magnetic resonance image (MRI). (a) Schematic diagram shows the regions, their interconnectivity, and afferent pathways. (b) The areas corresponding to those shown in the schematic are shown in an anatomical MRI, on a coronal slice and three sagittal slices as indicated on the coronal slice: primary and secondary somatosensory cortices (S1, S2, red and orange), anterior and mid-cingulate cortex (ACC, green), insula (blue), thalamus (yellow), prefrontal cortex (PFC, purple), primary and supplementary motor cortex (M1 and SMA), posterior parietal cortex (PPC), posterior cingulate cortex (PCC), basal ganglia (BG, pink), hypothalamus (HT), amygdala (AMYG), parabrachial nuclei (PB), and periaqueductal gray (PAG). Reproduced from Apkarian, A. V., Bushnell, C., Treede, R. D., and Zubieta, J. K. 2005. Human brain mechanisms of pain perception and regulation in health and disease. Eur. J. Pain 9, 463–484.

5.45.2 Methods to Study Nociceptive Processing in the Human Cerebral Cortex

Table 1 summarizes properties of the different brain imaging techniques that have been used to define the nociceptive network in the human brain. The most direct approach to learn about the functions of cortical neurons is direct intracellular or extracellular recording of their electrical activity during sensory stimulation and in different contexts. This technique is mostly restricted to animal studies (Kenshalo, D. R. and Isensee, O., 1983; Dong, W. K. et al., 1994) and has rarely been possible in humans (Hutchison, W. D. et al., 1999). Field potentials within the brain invert their polarity, when an electrode track passes through or close to their generator source. This technique has been used in the course of presurgical epilepsy diagnostics (Frot, M. and Mauguière, F., 1999), but since the electrode tracks are related to the clinical indications, only few parts of the brain have been sampled that way. Presurgical epilepsy diagnostics using subdural electrode grids samples a much larger part of the brain surface, and dipole source analysis can be used to estimate the depths of the generators below the grids (Vogel, H. et al., 2003). All of these invasive recordings in the human brain need to be interpreted with caution, because the cortical pathology that provided the indication for the procedure (e.g., epilepsy, tumors) may have altered nociceptive signal processing.

EEG and MEG are noninvasive techniques for the direct assessment of electrical activity in the brain. Mathematical algorithms are available to estimate the location of the generators within the brain from the signals recorded at the surface of the head with an accuracy of about 10 mm (Scherg, M., 1992; Pascual-Marqui, R. D. et al., 1994; Hari, R. and Forss, N., 1999). EEG and MEG techniques provide accurate timing information. As a result, both methods have been used mainly to identify the arrival of information to various cortical regions (stimulus-evoked potentials). Spontaneous fluctuations in EEG and MEG would provide a view of the interactions between cortical areas. However, the application of the latter to painful states has remained minimal (Chen, A. C. N., 1993; Ohara, S. et al., 2006). MEG detects brain magnetic activity, a signal that is proportional and orthogonal to the local electrical activity. Depending on the orientation of a local generator source and the gyral geometry of the brain region, evoked potentials in different brain areas may be better detected by MEG or EEG. The main weakness of EEG and MEG methods is their limited spatial resolution (on the order of 1 cm for both methods).

PET, single photon emission-computed tomography (SPECT), and fMRI measure brain activity

Table 1 Brain mapping techniques, their properties, and application in pain studies

Method	Energy source	Spatial resolution (mm)	Temporal resolution (s)	Constraints	Output measured	Application in pain studies
EEG/MEG	Intrinsic electricity	10	0.001	Lack of unique localization	Electrophysiology of brain events	Increasing in use, mainly for detecting temporal sequences
fMRI	Radio waves, magnetic fields	4–5	4–10	Immobilization, loud, cooperation	Relative cerebral blood flow	Most used, mainly for localizing brain activity
MRS	Radio waves, magnetic fields	10	10–100	Immobilization, loud	Relative chemical concentrations	Recently used, for detecting long term changes in brain chemistry
Nuclear (PET/SPECT)	Radiation	5–10	60–1000	Radiation limits, immobilization	Physiology, neurochemistry, absolute values	Decreasing in use, becoming limited to neurochemistry
Brain imaging techniques available but rarely or not yet used in pain studies						
Single or multiunit electrophysiology	Intrinsic electricity	0.01–1	0.001	Invasive, direct access to brain	Electrophysiology	
Near infrared spectroscopy and imaging	Infrared light	0.05	0.05	Immobilization, surface > depth, limited field of view	Relative cerebral blood flow	
Transcranial magnetic/electric stimulation	Magnetic/electric fields	10	0.01	Risk of seizures, immobilization, loud	Electrophysiology, conduction times	
Structural MRI	Radio waves, magnetic fields	1	N/A	Immobilization, loud	Structure, vasculature, white matter	
Postmortem	N/A	0.001	N/A	Postmortem	Microarchitecture, chemoarchitecture	

EEG, electroencephalography; MEG, magnetoencephalography; fMRI, functional magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; SPECT, single photon emission-computed tomography; N/A, not applicable.

indirectly by imaging changes in blood flow, blood oxygenation, or local metabolic changes (Peyron, R. *et al.*, 2000; Davis, K. D., 2003). All three methods can provide similar spatial resolution, although PET and fMRI methodologies are now far more advanced than SPECT. The statistical models and experimental designs available for PET and fMRI are robust and very rich. Therefore, these two techniques are currently most extensively used for detecting brain circuitry underlying many cognitive states, including pain. The temporal resolution of PET and SPECT is in the order of tens of seconds, while for fMRI it is shorter. PET and SPECT provide the additional opportunity for examining *in vivo* biochemistry and pharmacology by imaging the distributions of specific neurotransmitters or receptors. Recent MRI methods, like magnetic resonance spectroscopy (MRS), have also provided the ability to examine brain biochemistry. This approach is

developing rapidly and has the potential to become a major method in the near future for studying brain chemistry. In addition, voxel based morphometry allows to image structural changes related to disease states (May, A. *et al.*, 1999).

5.45.3 Cortical Regions that are Part of the Nociceptive System

5.45.3.1 The Primary Somatosensory Cortex

The primary somatosensory cortex (SI) is located in the anterior part of the parietal lobe, where it constitutes the postcentral gyrus. It consists of Brodmann areas 1, 2, 3a, and 3b (Figure 2(a)). Areas 3b and 1 receive cutaneous tactile input, areas 3a and 2 proprioceptive input.
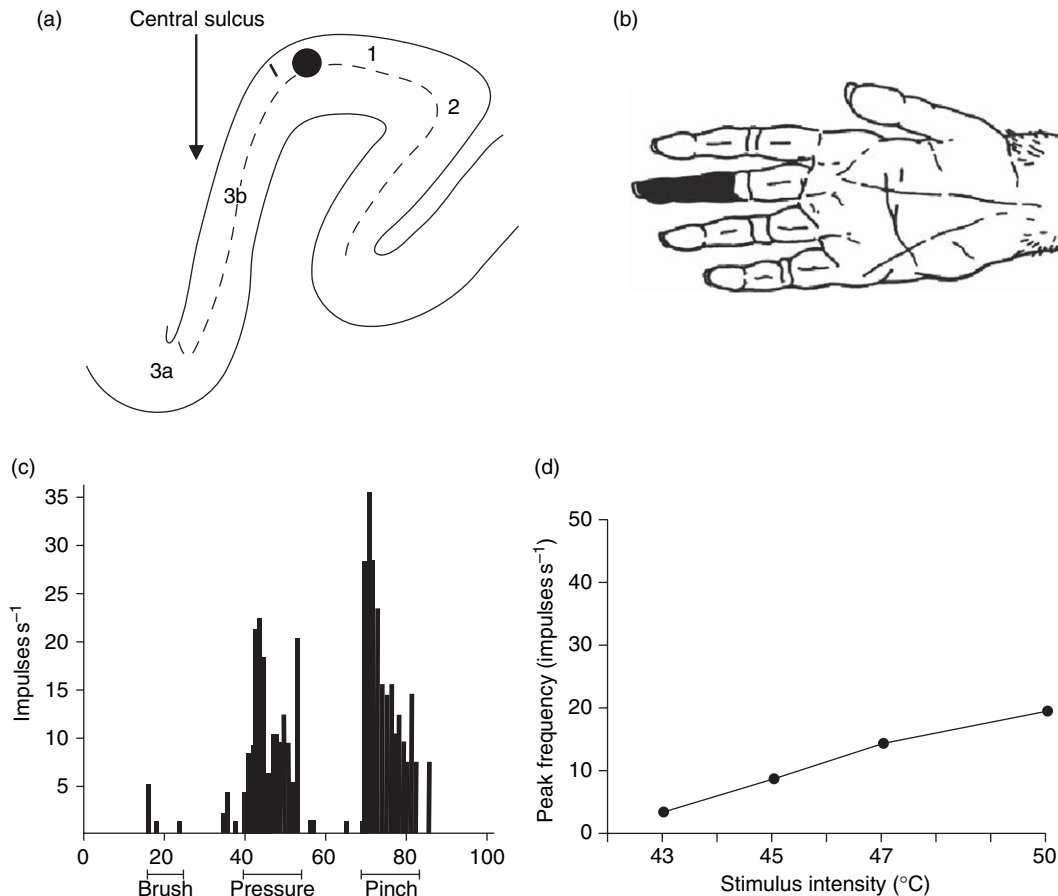
Figure 2 Nociceptive specific neuron in the primary somatosensory cortex (SI). (a) Left: SI consists of Brodmann areas 1, 2, 3a, and 3b in the postcentral gyrus. Black dot: location of the recorded neuron. (b) The small receptive field is consistent with a role in spatial discrimination. (c) Stimulus response function to painful mechanical stimuli. (d) Stimulus response function to painful heat stimuli. Modified from Kenshalo, D. R., Iwata, K., Sholas, M., and Thomas, D. A. 2000. Response properties and organization of nociceptive neurons in area 1 of monkey primary somatosensory cortex. J. Neurophysiol. 84, 719–729.

Nociceptive input to monkey SI was demonstrated anatomically. SI receives direct spinothalamocortical input from the ventrobasal nuclei, in particular the ventro-posterolateral (VPL) nucleus (Gingold, S. I. et al., 1991). Nociceptive neurons in SI are found in clusters, raising the possibility that SI may contain nociceptive specific columns (Lamour, Y. et al., 1983). Since evidence for nociceptive neurons in the most superficial cortical layers is lacking, this hypothesis has not yet been confirmed. Nociceptive neurons are rare in monkey SI and have mainly been found in area 1 (Kenshalo, D. R. et al., 2000), whereas optical imaging techniques have also suggested nociceptive input to area 3a (Tommerdahl, M. et al., 1996). Thus, nociceptive signal processing within SI may be spatially distinct from tactile signal processing that is primarily directed to area 3b. There is also some EEG and MEG evidence in humans that nociceptive areas may be situated more medially within SI than tactile areas with the same receptive fields, suggesting that nociceptive and tactile signal processing may occur in different subareas of SI (Ploner, M. et al. 2000; Schlereth, T. et al., 2003). Nociceptive input to human SI has been confirmed by subdural recordings (Kanda, M. et al., 2000; Ohara, S. et al., 2004). About 75% of the PET and fMRI studies reported activation of SI (Bushnell, M. C. et al., 1999; Apkarian, A. V. et al., 2005).

Nociceptive neurons in SI have small receptive fields (Figure 2(b)) that are somatotopically arranged, and hence are ideally suited to code for the location of nociceptive stimuli (Kenshalo, D. R. and Isensee, O., 1983). Somatotopy of nociceptive processing in the human SI has been confirmed by EEG and PET studies (Tarkka, I. M. and Treede, R. D., 1993; Andersson, J. L. R. et al., 1997). Action potential discharges of nociceptive SI neurons in monkey are modulated by the intensity of both mechanical and heat stimuli (Figures 2(c) and 2(d)) and their discharges correlate with detection speed (Kenshalo, D. R. et al., 1988). These findings suggest that nociceptive SI neurons are involved in the coding of pain intensity. This conclusion has been confirmed by a PET study of hypnotic modulation of perceived pain intensity that also modulated perfusion of SI (Hofbauer, R. K. et al., 2001) and by correlation analysis (Timmermann, L. et al., 2001).

5.45.3.2 Parasylvian Cortex: the Operculo-Insular Region

The parasylvian cortex has a complicated macroscopic structure and only some of its cytoarchitectonic areas have been charted in detail (Eickhoff, S. B. et al., 2006). In lateral views of the brain, the Sylvian fissure runs above the temporal lobe and separates it from the parietal and frontal lobes above the fissure. Hidden deep inside the Sylvian fissure lies a further lobe of the brain: the insula (Figure 3(a)). The insula is covered by the
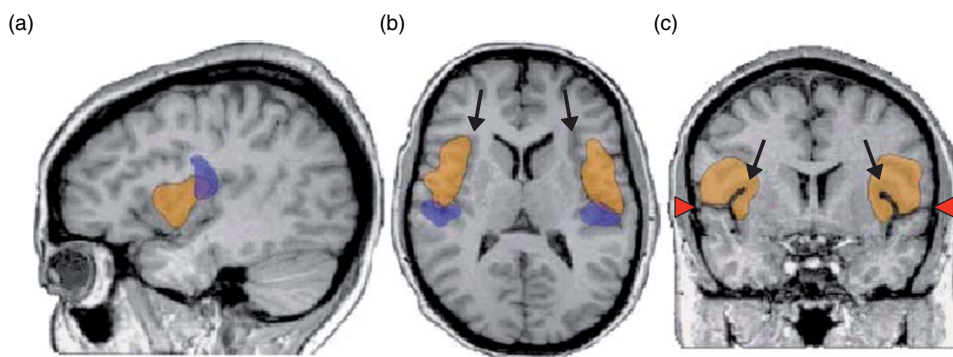
Figure 3 Nociceptive regions in parasylvian cortex. (a) Sagittal section shows the insula as a triangular region deep inside the Sylvian fissure. (b) Transaxial section illustrates the secondary somatosensory cortex (SII) as identified by tactile stimuli (blue) and regions responsive to nociceptive stimulation (orange) that extend further rostrally and medially. (c) Coronal section shows that the temporal operculum covers the insula below the Sylvian fissure, and frontal and parietal opercula cover the insula above the fissure. Frontal and parietal opercula consist of an outer part on the convexity of the brain, a horizontal part above the Sylvian Fissure, and an inner vertical part facing the insula across its circular sulcus. Arrowheads: Sylvian fissure (lateral sulcus). Arrows: circular sulcus of the insula. Modified from Treede, R. D., Baumgärtner, U., and Lenz, F. A. 2007. Nociceptive Processing in the Secondary Somatosensory Cortex. In: Encyclopedia of Pain (eds. R. F. Schmidt and W. D. Willis), pp. 1376–1379. Springer.

temporal, parietal and frontal opercula. Coronal sections reveal that the parasylvian cortex consists of the insula itself, the inner vertical surface of the opercula, the horizontal banks of the Sylvian fissure, and most laterally the outer surface of the convexity of the brain (Figure 3(c)).

The majority of human imaging studies showed consistent activation of the parasylvian cortex during painful stimulation, and this activation overlapped only partly with that by tactile stimuli (Treede, R. D. *et al.*, 2007). Lesions in parasylvian cortex cause deficits in pain perception (Greenspan, J. D. *et al.*, 1999), and intracortical electrical stimulation of this region is painful (Ostrowsky, K. *et al.*, 2002). Thus, this region is a good candidate to contain some nociceptive specific cortical areas, if they exist.

About 75% of the PET and fMRI studies reported activation of the SII region, and 94% found activation of the insula (Treede, R. D. *et al.*, 2000; Apkarian, A. V. *et al.*, 2005). But due to the curvature and oblique course of the Sylvian fissure (Özcan, M. *et al.*, 2005), activated areas are often misallocated, even across major sulci. Whereas the operculo-insular cortex in the parasylvian region has been recognized as one of the most important nociceptive cortical areas, its precise anatomical and functional organization has yet to be determined. In particular it is not yet known, whether insula and operculum subserve distinct functions or form one uniform area.

5.45.3.2.1 The secondary somatosensory cortex (SII)

The secondary somatosensory cortex is located in the superior bank of the Sylvian fissure, where it makes up a major part of the parietal operculum (Figures 1(b), 3(b), and 3(c)). Nociceptive input to monkey SII was demonstrated anatomically. SII receives direct spino-thalamo-cortical input from the ventrobasal nuclei, in particular the ventro-postero-inferior nucleus VPI (Stevens, R. T. *et al.*, 1993). Nociceptive input to human SII has been confirmed by subdural recordings (Lenz, F. A. *et al.*, 1998a).

Single neuron recordings in SII have largely focused on the tactile representation (Robinson, C. J. and Burton, H. 1980; Fitzgerald, P. J. *et al.*, 2006). The SII region contains multiple somatotopic representations of the body, suggesting the existence of several subregions (Disbrow, E. *et al.*, 2000, Fitzgerald, P. J. *et al.*, 2004). Although most neurons in SII have contralateral receptive fields, this is the first part of the somatosensory system with a sizable proportion of bilateral receptive fields. Hence, most imaging and electrophysiological studies in humans have shown a bilateral response to unilateral stimulation, with a contralateral preponderance. Functionally, SII is considered to play a role in tactile object recognition and memory (Seitz, R. J. *et al.*, 1991).

Evoked potential recordings in humans following brief laser heat stimuli showed that SII was activated simultaneously with or even earlier than SI (Ploner, M. *et al.*, 1999; Schlereth, T. *et al.*, 2003). Combined anterograde and retrograde tracer studies in monkey (Apkarian, A. V. and Shi, T., 1994) support the concept that nociceptive input reaches SII more directly than tactile input. Hence, SII has been supposed to be important for the recognition of painful stimuli as such.

In contrast to the abundance of evidence for nociceptive activation of the SII region from human studies, there are few single neuron recordings in this area showing specific nociceptive responses (Treede, R. D. *et al.*, 2000). In monkey, some convergence with visual input encoding the approach of a sharp object to the face has raised the possibility of a representation of threat. These neurons, however, were not in SII proper but in area 7b which is adjacent to SII in monkey but not in humans (Dong, W. K. *et al.*, 1994). These neurons are now considered to be part of the posterior parietal cortex (see below). Since neurons in all studies on SII were searched using mechanical skin stimulation, it is possible that these studies missed nociceptive specific neurons, because many primary nociceptive afferents are mechanically insensitive (Treede, R. D. *et al.*, 1998). Thus, an intriguing possibility is that tactile and nociceptive inputs are represented in different areas within the SII region.

5.45.3.2.2 The frontal operculum

Dipole source analysis of laser-evoked potentials (LEPs) in healthy volunteers, and subdural and depth recordings in patients undergoing epilepsy surgery have identified an area in the inner vertical surface of the frontal operculum (Figure 4(a)) that was activated by painful heat stimuli with a shorter latency (about 150 ms) than any other cortical area (Tarkka, I. M. and Treede, R. D., 1993; Valeriani, M. *et al.*, 1996; Ploner, M. *et al.*, 1999; Frot, M. and Mauguière, F., 2003; Schlereth, T. *et al.*, 2003; Vogel, H. *et al.*, 2003). This area anterior of the tactile SII area has a different somatotopic orientation (face: anterior, foot: posterior) than SII itself (face: lateral, foot: medial; Vogel, H. *et al.*, 2003). The thalamic source of nociceptive input to this region is not yet
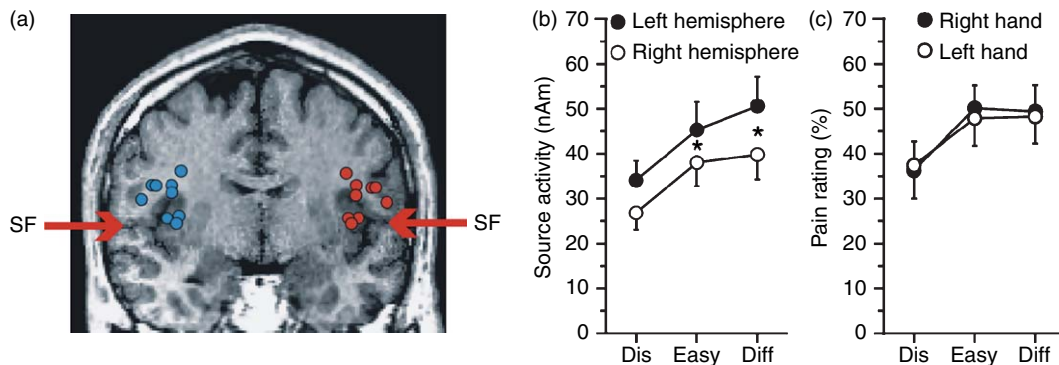
Figure 4 Nociceptive input to the frontal operculum. (a) Projection of dipole source locations for the first component of laser-evoked potentials (LEPs) onto a coronal magnetic resonance image slice at Talairach y = −6 mm. The distribution around the roof of the circular insular sulcus, ranging from the inner vertical face of the frontal operculum to the adjacent dorsal insula matches the projection area of the nociceptive thalamic nucleus VMpo. (b) Task effects and interhemispheric differences. (c) The hemispheric asymmetry of opercular activation (left hemisphere > right hemisphere) was not reflected or caused by different visual analog score pain ratings between both hands. Dis, distraction task; Easy, easy spatial and intensity discrimination tasks; diff, difficult discrimination tasks. ANOVA:* P < 0.05. Modified from Schlereth, T., Baumgärtner, U., Magerl, W., Stoeter, P., and Treede, R. D. 2003. Left-hemisphere dominance in early nociceptive processing in the human parasylvian cortex. Neuroimage 20, 441–454.

clear: it may be VPI like for the posteriorly adjacent SII, or it may be VMpo like for the medially adjacent dorsal insula. Somatotopy in the frontal operculum would be consistent with that of a VMpo projection target (Craig, A. D., 1995). Nociceptive input to the frontal operculum in humans has been confirmed by subdural and depth recordings (Lenz, F. A. et al., 1998a; Frot, M. et al., 1999). Responses in this area are modulated during spatial and intensity discrimination tasks and show a left-hemisphere dominance (Figures 4(b) and 4(c)).

5.45.3.2.3 The insula

The insula is located deep inside the Sylvian fissure, where it can be visualized as a triangular shape in sagittal sections (Figure 3(a)). It often contains two long sulci in its posterior part and three short sulci rostrally. Several functional subdivisions of the insula have been suggested (Dieterich, M. et al., 2003; Schweinhardt, P. et al., 2006), but there is no consensus yet. Parts of the insula subserve varied functions in the somatosensory, vestibular, gustatory and autonomic nervous system, which led to the suggestion that this region serves for a central representation of the internal state of the body (Craig, A. D., 2002). This concept is consistent with the interoceptive aspects of nociception.

Another source of nociceptive input into the parasylvian cortex is the posterior inferior part of the ventrobasal nucleus (Lenz, F. A. et al., 1993), a region designated as VMpo by some authors (Craig, A. D. et al., 1994). VMpo projects to the dorsal insula and the adjacent frontal operculum. Nociceptive input to the insula in humans has been confirmed by depth recordings (Frot, M. et al., 2003). The somatotopic representation of pain in the dorsal insula in monkey (face: anterior, foot: posterior) is orthogonal to that in SII (face: lateral, foot: medial; Baumgärtner, U. et al., 2006b). Direct electrical stimulation of the insula is painful with a strong affective component (Ostrowsky, K. et al., 2002).

5.45.3.3 The Posterior Parietal Cortex

The posterior parietal cortex is located adjacent and posterior to SI. It comprises Brodmann areas 5 and 7 (Figure 5(c)). Nociceptive input to this region is suggested by studies in monkey that reported short-latency responses to nociceptive stimuli in area 7b; the same neurons also responded to visual stimuli of sharp objects directed at their receptive field (Dong, W. K. et al., 1994). In the tactile system, this region is part of a dorsally directed stream involved in stimulus location, convergence with visual information and the generation of spatial information for motor control. Nociceptive input to this region in humans has not yet been explored with subdural recordings, but there is some evidence from EEG
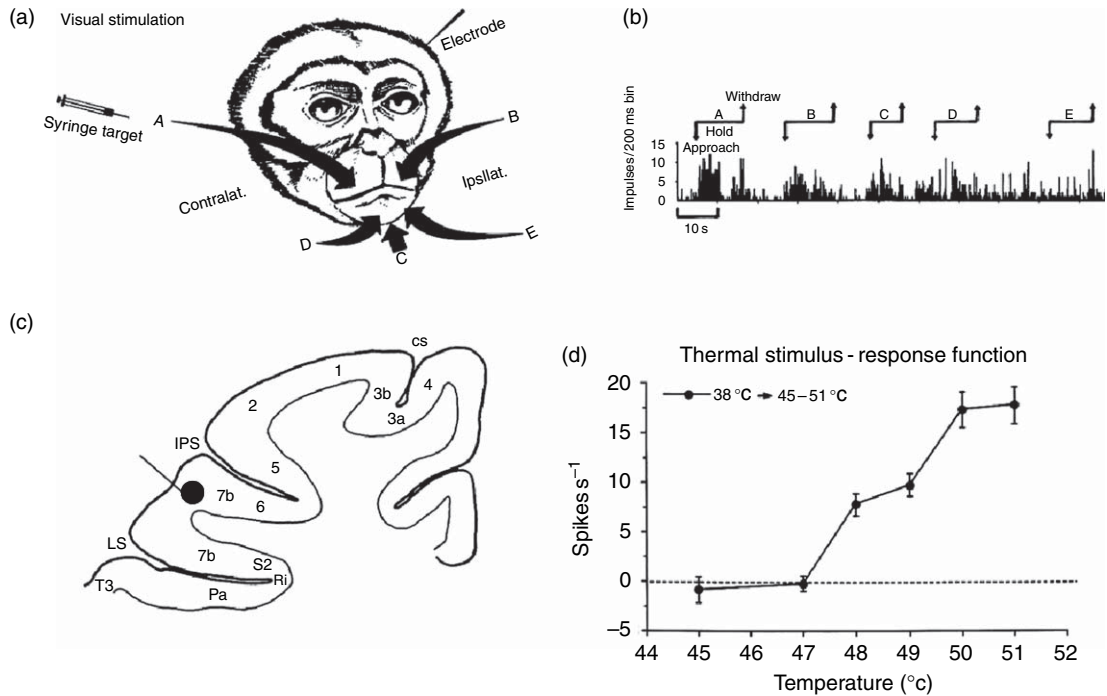
Figure 5 Nociceptive neuron in posterior parietal cortex (Area 7b threat neuron). (a) Bilateral receptive field in the orofacial region; seeing a syringe approach the receptive field was also an adequate stimulus. (b) Responses to the stimuli shown in (a). (c) Location of the recorded neuron on a coronal section that passes through both the central sulcus (CS) and the Sylvian fissure (LS: lateral sulcus). (d) Stimulus response function to painful heat stimuli. IPS, Intraparietal sulcus. Modified from Dong, W. K., Chudler, E. H., Sugiyama, K., Roberts, V. J., and Hayashi, T. 1994. Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. J. Neurophysiol. 72, 542–564.

and MEG studies in humans that nociceptive stimuli activate parietal lobe posterior of SI (Schlereth, T. et al., 2003; Forss, N. et al., 2005). Few fMRI studies have assessed this region (Kulkarni, B. et al., 2005; Schmahl, C. et al., 2006).

5.45.3.4 The Cingulate Cortex

The cingulate cortex is located above the corpus callosum and around its anterior knee (Figure 6). The anterior cingulate cortex (ACC) comprises Brodmann areas 24 and 32, whereas the posterior cingulate cortex (PCC) contains areas 23 and 31 (Vogt, B. A. et al., 1995). ACC receives nociceptive thalamocortical input from the mediodorsal (MD) and parafascicular (Pf) nuclei (Vogt, B. A. et al., 1979). ACC has been further subdivided into midcingulate cortex, which is associated with response selection and motor efferent functions, and ACC proper that is related to emotion and autonomic efferent functions (Vogt, B. A., 2005). Nociceptive

input to human cingulate cortex has been confirmed by subdural recordings and by intracortical recordings (Lenz, F. A. et al., 1998b; Hutchison, W. D. et al., 1999). About 87% of the PET and fMRI studies reported activation of the cingulate cortex (Apkarian, A. V. et al., 2005), but no region of the cingulate cortex is considered to be nociceptive specific (Vogt, B. A., 2005).

Nociceptive neurons in ACC have large or even whole-body receptive fields (Figure 7, Sikes, R. W. and Vogt, B. A., 1992; Yamamura, H. et al., 1996). For this reason it is unlikely that they contribute to the sensory dimension of pain. Monkey ACC neurons activate during pain avoidance behavior, reflecting anticipation, and response selection (Koyama, T. et al., 1998; 2001). The cingulate cortex is supposed to participate in the affective-motivational dimension of pain. This conclusion has been confirmed by a PET study of hypnotic modulation of perceived pain affect that also modulated perfusion of ACC (Hofbauer, R. K. et al., 2001) and by correlation analysis (Tölle, T. R. et al., 1999).
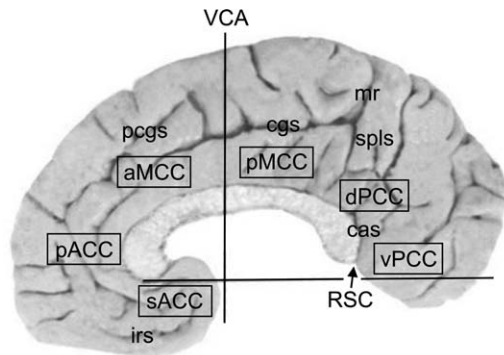
Figure 6 Distribution of cingulate cortex regions and subregions. Region borders are marked with arrows. Cross-hair shows vertical plane at the anterior commissure (VCA) and the anterior–posterior commissural line. A functional overview, derived from the analysis of a large volume of literature illustrates general regional function. aMCC, anterior mid-cingulate cortex; cas, callosal sulcus; cgs, cingulate sulcus; dPCC, dorsal posterior cingulate cortex; irs, inferior rostral sulcus; mr, marginal ramus of cgs; pACC, pregenual anterior cingulate cortex; pcgs, paracingulate sulcus; pMCC, posterior mid-cingulate cortex; RSC, retrosplenial cortex; sACC, subgenual anterior cingulate cortex; spls, splenial sulci; vPCC, ventral posterior cingulate cortex. Reproduced from Vogt, B. A. 2005. Pain and emotion interactions in subregions of the cingulate gyrus. Nat. Rev. Neurosci. 6, 533–544.

5.45.3.5 The Prefrontal Cortex

The PFC (including Brodmann areas 9, 10, 46) comprises the major part of the frontal lobe and is located anterior of the motor cortical areas. There is no evidence that it would receive a direct nociceptive thalamo-cortical input, but the PFC receives cortico-cortical input from the cingulate gyrus that may convey nociceptive information. About 55% of the PET and fMRI studies reported activation of the PRC in healthy subjects, and 81% of the studies in chronic pain patients (Apkarian, A. V. et al., 2005). The PRC is assumed to participate in the cognitive-evaluative dimension of pain and in endogenous pain control (Lorenz, J. et al., 2003; Schmahl, C. et al., 2006).

5.45.4 Functional Roles of Cortical Nociceptive Signal Processing

Pain perception has been conceived to consist of sensory-discriminative, affective-motivational and cognitive-evaluative dimensions (Melzack, R. and Casey, K. L. 1968). The sensory-discriminative dimension includes intensity discrimination, pain qualities, stimulus localization and timing discrimination; this dimension is traditionally thought to involve lateral thalamic nuclei and the somatosensory cortices SI and SII. The affective-motivational dimension includes perception of the negative hedonic quality of pain, autonomic nervous system manifestations of emotions, and motivated behavioral responses; this dimension is traditionally thought to involve medial thalamic nuclei and the limbic cortices ACC and MCC. The insula has an intermediate position in that concept, receiving input from lateral thalamus but projecting into the limbic system. The cognitive-evaluative dimension includes interaction with previous experience, cognitive influence on perceived pain intensity and an overall evaluation of its salience; this dimension is traditionally thought to involve the PRC. Numerous neuroimaging studies have assessed various experimental paradigms derived from several psychological concepts that do not easily fit into the traditional three dimensions of pain. Therefore, we here report imaging evidence for involvement of cortical areas in specific functions instead of the dimensions of pain.

5.45.4.1 Location and Quality of Phasic Pain

Neuroimaging studies have examined brain regions activated by many types of painful stimulation, including noxious heat and cold, muscle stimulation using electric shock or hypertonic saline, topical and intradermal capsaicin, colonic distention, rectal distension, gastric distension, esophageal distension, ischemia, cutaneous electric shock, ascorbic acid, laser heat, as well as an illusion of pain evoked by combinations of innocuous temperatures (Apkarian, A. V. et al., 2005; Bushnell, M. C. and Apkarian, A. V., 2005). Despite the differences in sensation, emotion and behavioral responses provoked by these different types of pain, individuals can easily identify each as being painful. Thus, there appears to be a common construct of pain with an underlying network of brain activity in the areas described above. Nevertheless, despite the similarities in pain experiences and similarities in neural activation patterns, each pain experience is unique. Subjects can usually differentiate noxious heat from noxious cold from noxious pressure. This ability to differentiate pains is particularly puzzling, since there is ubiquitous convergence of information from cutaneous, visceral and muscle tissue throughout the
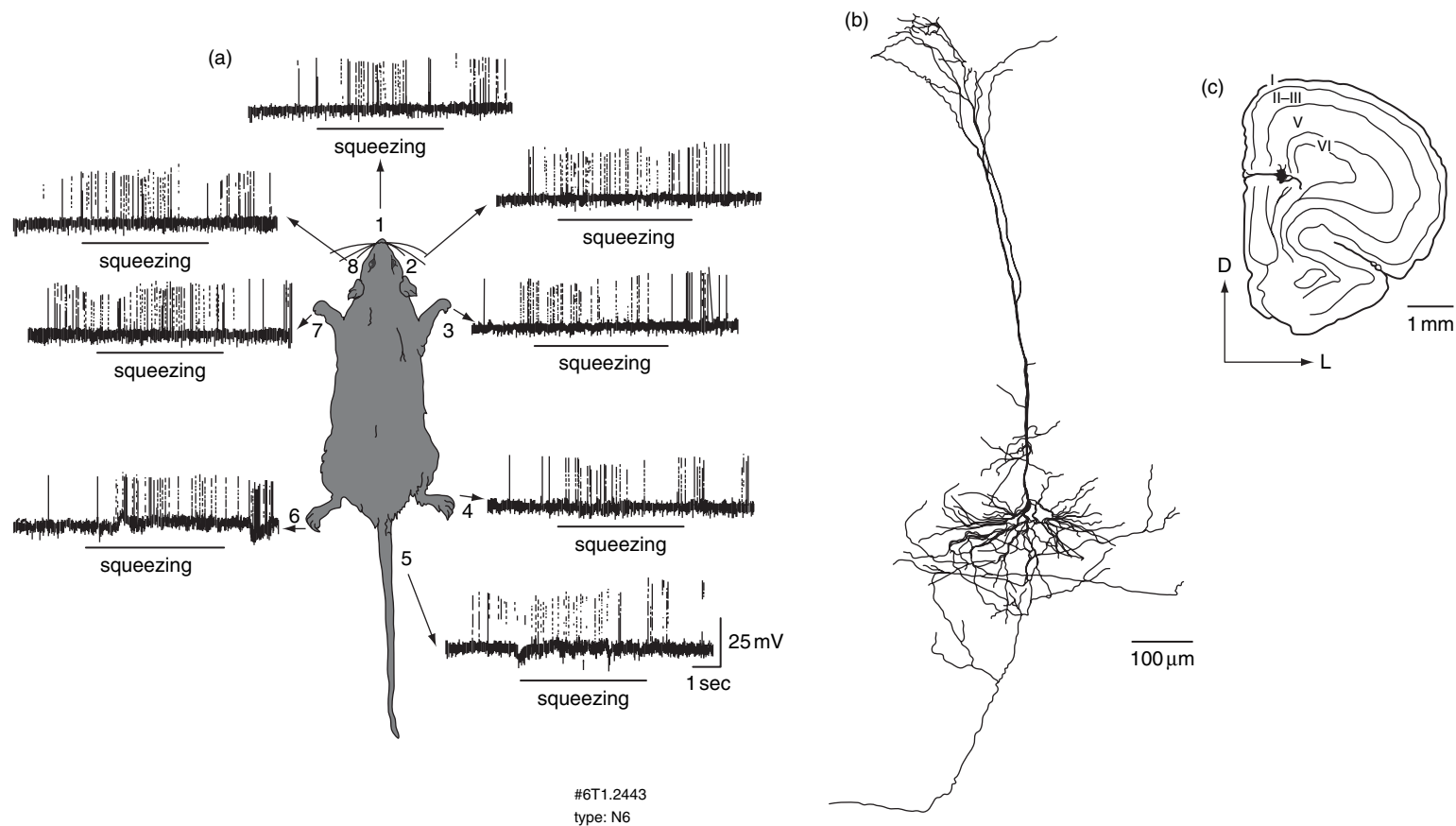
Figure 7 Nociceptive neuron in the anterior cingulate gyrus. (a) Responses to painful mechanical stimuli show a whole-body receptive field for this neuron. (b) Intracellular dye injection reveals a lamina V pyramidal neuron. (c) Location of the recorded neuron in the rat cingulate cortex. Reproduced from Yamamura, H., Iwata, K., Tsuboi, Y., Toda, K., Kitajima, K., Shimizu, N., Nomura, H., Hibiya, J., Fujita, S. and Sumino, R. 1996. Morphological and electrophysiological properties of ACCx nociceptive neurons in rats. Brain Res. 735, 83–92.

afferent nociceptive system (Willis, W. D. and Coggeshall, R. E., 2004). The convergence and the similarities in brain regions activated by different types of pain are consistent with phenomena such as referred pain, but cannot explain either the ability to identify the origin of pain or with contrasting behavioral reactions to cutaneous and visceral pain (withdrawal versus quiescence).

There is evidence from single neuron recordings, MEG, PET, and fMRI that neural activity in SI cortex could underlie the identification of the locus of cutaneous pain. Kenshalo and colleagues (Kenshalo, D. R. et al., 1988; Kenshalo, D. R. and Isensee, O., 1983) showed that SI nociceptive neurons have discrete receptive fields, so that different neurons respond to painful stimulation in different skin areas. Correspondingly, EEG, PET, and fMRI studies have shown a topographic organization of nociceptive responses in SI cortex similar to the organization of tactile responses, i.e., a medio-lateral organization of foot, hand, face, and intra-abdominal areas (Tarkka, I. M. and Treede, R. D., 1993; Andersson, J. L. R. et al., 1997; DaSilva, A. F. M. et al., 2002; Strigo, I. A. et al., 2003; Vogel, H. et al., 2003). Most imaging studies find little somatotopic organization of pain in other cortical areas (Tarkka, I. M. and Treede, R. D., 1993; Xu, X. P. et al., 1997), thus suggesting that responses in SI cortex may be most important for pain localization. More recently, a somatotopic organization has also been documented for operculo-insular cortex (Vogel, H. et al., 2003; Baumgärtner, U. et al., 2006a). A left hemisphere dominance has been reported for the sensory dimension of pain (Schlereth, T. et al., 2003), whereas right hemisphere dominance was observed for the affective dimension (Pauli, P. et al., 1999; Brooks, J. C. W. et al., 2002).

Strigo I. A. and colleagues (2003) directly compared brain activations produced by esophageal distension and cutaneous heat on the chest that were matched for pain intensity. They found that the two qualitatively different pains produced different primary loci of activation with insula, SI, motor and prefrontal cortices. Such local differences in responses within the nociceptive network might subserve our ability to distinguish visceral and cutaneous pain as well as the differential emotional, autonomic, and motor responses associated with these different sensations.

5.45.4.2   The Time Domain

Most information about the temporal sequence of pain-evoked brain activation comes from EEG or MEG studies. The dual pain sensation elicited by a single brief painful stimulus that is due to the different conduction times in nociceptive A- and C-fibers (about 1 s difference) is reflected in two sequential brain activations in EEG and MEG recordings from SI, SII, and MCC (Bromm, B. et al., 1983; Bragard, D. et al., 1996; Magerl, W. et al., 1999; Opsommer, E. et al., 2001; Iannetti, G. D. et al., 2003). EEG mapping studies (Kunde, V. and Treede, R. D., 1993; Miyazaki, M. et al., 1994), source analysis (Tarkka, I. M. and Treede, R. D., 1993; Valeriani, M. et al., 1996; Ploner, M. et al., 1999), and intracranial recordings (Lenz, F. A. et al., 1998a; Frot, M. et al., 1999) show that the earliest pain-induced brain activity originates in the vicinity of SII. In contrast, tactile stimuli activate this region only after processing in the primary somatosensory cortex (Ploner, M. et al., 2000). The adjacent dorsal insula is activated slightly but significantly later than the operculum (Frot, M. and Mauguière, F., 2003). These observations support the suggestion derived from anatomical studies that the SII region and adjacent insula are primary receiving areas for nociceptive input to the brain (Apkarian, A. V. and Shi, T., 1994; Craig, A. D., 2002).

5.45.4.3   Attention and Distraction Effects on Pain-Evoked Cortical Activity

Early human brain imaging studies examining the effects of attention and distraction show modulation of pain-evoked activity in a number of cortical regions, including sensory and limbic structures, as well as prefrontal areas (Bushnell, M. C. et al., 1999; Longe, S. E. et al., 2001; Bantick, S. J. et al., 2002; Schlereth, T. et al., 2003). These results generally show reduced activations in sensory regions of the cortex and some increased activity in more frontal regions, suggesting that attentional modulation is mediated through the latter structures resulting in reduced sensory processing, where the attentional distraction is usually reported resulting in reduced perceived magnitude of pain. A more recent study extends these notions by showing that during distraction there is a functional interaction between pregenual ACC and frontal cortex exerting a top-down modulation on periaqueductal gray (PAG) and thalamus to in turn reduce activity in cortical sensory regions and correspondingly decrease perception of pain (Petrovic, P. et al., 2000; Tracey, I. et al., 2002; Valet, M. et al., 2004). Given that ACC is implicated in attentional modulation as well as pain perception, a distraction study indicates that some portions of the

pregenual ACC region are decreased with distraction while others are increased, consistent with these two different functions (Frankenstein, U. N. *et al.*, 2001).

5.45.4.4   Anticipation and Expectation

Anticipation or expectation of pain can activate many of the cortical areas related to perception of pain in the absence of a physical pain stimulus (Ploghaus, A. *et al.*, 1999; Hsieh, J. C. *et al.*, 1999b; Sawamoto, N. *et al.*, 2000; Porro, C. A. *et al.*, 2002). Two studies have attempted to identify the circuitry for modulation of pain by expectation. In one study MCC, caudate nucleus, cerebellum, and nucleus cuneiformis were modulated by systematic manipulation of pain intensity expectation by two different cues (Keltner, J. R. *et al.*, 2006), whereas pain intensity itself modulated somatosensory cortex, insula, and rostral ACC. In the second study expectancy was modulated by a placebo procedure, resulting mainly in modulation including MCC, PRC, cerebellum, pons, and parahippocampal gyrus (Kong, J. *et al.*, 2006). The latter study is complicated by the fact that the procedure is a combination of manipulation of expectancy and placebo acupuncture treatment. Generally, there remains a strong need for systematic studies to identify brain elements that modulate pain responses due to expectation.

5.45.4.5   Empathy

A provocative study opened the field regarding the interaction between pain and empathy, where the authors defined empathy as the ability to have an experience of another's pain. Using this definition and comparing brain activity for experiencing pain or knowing that their loved one, present in the same room, was experiencing the same pain, the authors showed many cortical regions similarly activated for both conditions, especially bilateral operculo-insular cortex and MCC (Singer, T. *et al.*, 2004). These results were interpreted as evidence for the affective component of pain being active in both empathy and pain, and thus concluded that empathy for pain involves the affective component, but not the sensory component, of pain. The study induced a flurry of activity in attempting to understand the relationship between empathy and pain. Multiple groups have replicated the main finding and proposed different underlying mechanisms (Morrison, I. *et al.*, 2004; Botvinick, M. *et al.*, 2005; Jackson, P. L. *et al.*, 2005), with multiple studies showing that at least MCC

activity reflects the pain experienced by others and that multiple cortical areas involved in sensory processing of pain are also activated.

The overall notion that empathy involves assessment of the pain experienced by others – pain mirroring – was tested directly in subjects with alexithymia, a cognitive and emotional deficit leading to difficulty in identifying one's own emotional state and also other people's emotional state. The study showed in fact reduced activity in PRC and MCC during a pain empathy condition in this patient population (Moriguchi, Y. *et al.*, 2006). Even though these results are internally consistent, their interpretation remains problematic. Simple introspection casts doubt on the notion that empathy means actually experiencing another person's pain. Instead, what is called empathy may be the assessment of the magnitude of negative emotion that the other person may be experiencing, i.e., a cognitive function of interpersonal communication. According to that concept, empathy may be defined as a complex form of psychological inference that enables us to understand the personal experience of another person through cognitive/evaluative and affective processes. A study in patients with congenital insensitivity to pain (Danziger, N. *et al.*, 2006) reported a deficit in rating pain-inducing events, but normal inference of pain from facial expressions (empathy), indicating that empathy for pain does not require an intact pain percept.

5.45.5   Pain Modulation

5.45.5.1   Psychological Modulation of Pain

The psychological modulation of pain has been observed very early on and studied in the clinical and laboratory settings (Beydoun, A. *et al.*, 1993; Villemure, C. and Bushnell, M. C., 2002). Modern brain imaging techniques now provide powerful tools with which mechanisms of these modulations can be documented and dissected. Given that these are cognitive/attentional modulations their effects should be observed at the cortical level.

5.45.5.1.1   Hypnosis and pain-evoked cortical activity
Hypnosis can alter pain perception. It has been used to differentially modulate sensory and affective dimensions of pain and thus distinguish the cortical regions involved in these dimensions. Such studies indicate that SI activity is preferentially modulated

when the hypnotic instructions are directed to the intensity of pain, while MCC activity is preferentially modulated when hypnosis is directed to the unpleasantness of pain (Rainville, P. *et al.*, 1997, Hofbauer, R. K. *et al.*, 2001). Brain activity for hypnotically induced pain perception seem to be different from activity for imagined pain in sensory, limbic, and prefrontal activation patterns (Derbyshire, S. W. *et al.*, 2004). The sensory and limbic cortical activations for hypnotically induced and stimulation-induced pain seem relatively similar, the only region that may be differentiating them seems to be the medial PRC (Raij, T. T. *et al.*, 2005).

5.45.5.1.2   Mood and emotional states and pain-evoked cortical activity

Studies show that experimental procedures that improve mood generally reduce pain, while those that have a negative effect on mood increase pain (Zelman, D. C. *et al.*, 1991; Marchand, S. and Arsenault, P., 2002). One study showed that looking at fearful faces increased their level of anxiety and discomfort, which also resulted in enhanced esophageal stimulation-evoked activity in limbic regions like ACC and insula (Phillips, M. L. *et al.*, 2003).

5.45.5.1.3   Placebo and pain-evoked cortical activity

Placebo is a potent modulator of pain; it afflicts all clinical studies of pain pharmacology. Placebo effects have also been seen in depression and in Parkinson's disease and recent brain imaging studies show a robust brain and subcortical reward circuitry's involvement in these (Lidstone, S. C. and Stoessl, A. J., 2007). The first neurochemical evidence for opiate involvement of placebo was demonstrated about 30 years ago by showing that placebo analgesia can be blocked by naloxone (Levine, J. D. *et al.*, 1978). Consistent with this notion, changes in endogenous opiate release are shown to be involved in placebo-induced analgesia, where PRC (medial and lateral) as well as insula and ventral striatum seem to be involved, where high placebo responders increased opiate release in ventral striatum was positively correlated with pain ratings (Zubieta, J. K. *et al.*, 2005). Results generally consistent with this brain response pattern have been demonstrated by a number of other groups (Wager, T. D. *et al.*, 2004; Benedetti, F. *et al.*, 2005; Kong, J. *et al.*, 2006); the medial prefrontal/rostral ACC responses for placebo seem to recruit PAG and amygdala (Bingel, U. *et al.*, 2006); and involvement of PAG in placebo-induced analgesia

is observed in the above studies as well, which links opiate descending modulation with prefrontal cortical control of placebo analgesia. The correspondence between placebo analgesia and reward was directly studied and the results show a strong correspondence between brain regions involved in each (Petrovic, P. *et al.*, 2005).

5.45.5.2   Pharmacological Modulation of Pain

A league table of analgesic efficacy has been generated based on pain-related evoked potentials (Scharein, E. and Bromm, B., 1998). Since these studies used electrical stimuli that circumvent peripheral nociceptive transduction mechanisms, this table reflects central rather than peripheral analgesic actions, as evidenced, e.g., by the higher efficacy of the antidepressant imipramine than the nonsteroidal anti-inflammatory drug (NSAID) acetylsalicylic acid. Since dipole source analysis has not been applied in these EEG studies, possible cortical sites of actions were not differentiated. Combining fMRI and pharmacology promises to provide that type of information (Tracey, I., 2001; Borsook, D. *et al.*, 2006). In addition, PET techniques can be used for direct tracing of cortical distribution of a given drug, when it has been labeled with the positron emitting ^{11}C isotope.

5.45.5.2.1   Opiates

There is a vast literature regarding opiate-mediated descending modulation through the PAG and a similarly large literature on its effects on inhibitory interneurons in the spinal cord. At the cortical level, it has been noted that opiate receptors are present in many parts of the nociceptive system, with high specific binding in ACC, insula, and frontal operculum, and with moderate specific binding in MCC, SII, and SI (Jones, A. K. P. *et al.*, 1991b; Baumgärtner, U. *et al.*, 2006a).

Recent studies of opiate-mediated responses in the brain have used two approaches, examination of metabolic function in response to pharmacological agents and direct measurement of opiate receptor binding potential. Exogenous administration of μ-opioid receptor agonist drugs show dose-dependent increased metabolic activity in regions rich with μ-opioid receptors, which in the cortex are mainly localized to PRC and ACC (Firestone, L. L. *et al.*, 1996; Schlaepfer, T. E. *et al.*, 1998; Wagner, K. J. *et al.*, 2001). Also, μ-opioid agonist fentanyl on brain responses to painful stimuli

have been explored, showing that most cortical responses to pain are reduced or eliminated, confirming analgesic effects of the opiate (Casey, K. L. *et al.*, 2000; Petrovic, P. *et al.*, 2002). Changes in endogenous opioid system is studied using a selective μ-opioid radiotracer, showing activation of opiate neurotransmission in rostral ACC, PRC, and insula during a tonic muscle pain (Zubieta, J. K. *et al.*, 2001).

5.45.5.2.2 Dopamine

Dopamine is best known for its role in motor, motivation, and pleasure control. There is accumulating evidence to suggest that dopamine acting at the level of the basal ganglia may also be involved in pain modulation. Human brain imaging studies document increased pain sensitivity to be associated with lower levels of endogenous dopamine (Pertovaara, A. *et al.*, 2004; Martikainen, I. K. *et al.*, 2005; Scott, D. J. *et al.*, 2006); and sustained experimental pain results in release of dopamine in the basal ganglia (Scott, D. J. *et al.*, 2006), and indicate an interaction between opiate activity and dopamine where alfentanil administration results in decreased mechanical pain and decreased release of dopamine in the basal ganglia (Hagelberg, N. *et al.*, 2002). Moreover, abnormal levels of dopamine in the basal ganglia have been associated with chronic pain in burning mouth syndrome and atypical facial pain (Jaaskelainen, S. K. *et al.*, 2001; Hagelberg, N. *et al.*, 2003a; 2003b), and perhaps in fibromyalgia (Wood, P. B. *et al.*, 2007). Patients with restless legs syndrome display a pronounced mechanical hyperalgesia to pinprick stimuli that is slowly reversed by dopaminergic agonists (Stiasny-Kolster, K. *et al.*, 2004), but this action is probably mediated by extrastriatal dopamine receptors.

5.45.5.2.3 Estrogen

Gender is one of the most important determinants of human health. Women far outnumber men in susceptibility to many autoimmune disorders, fibromyalgia, and chronic pain, differences in physiological responses to stress may potentially be an important risk factor for these disorders as physiologic responses to stress seem to differ according to gender, with phase of menstrual cycle, menopausal status and with pregnancy (Kajantie, E. and Phillips, D. I., 2006). Consistent with this idea recent fMRI study shows that brain activity in premenopausal women as studied for negative valence/high arousal in contrast to neutral visual stimuli show differences when the task is performed during early follicular menstrual cycle phase compared to late follicular/mid-cycle; with greater activity found during early follicular phase in amygdala, hypothalamus, hippocampus, orbital frontal cortex, and ACC, suggesting that estrogen may attenuate arousal in women through cortical-subcortical control of hypothalamic–pituitary–adrenal circuitry (Goldstein, J. M. *et al.*, 2005). There is also growing evidence of gender differences in the anatomy of the brain, its connectivity, and in cognitive abilities (Hampson, E., 2002; Becker, J. B. *et al.*, 2005). Multiple studies have documented that threshold and tolerance for pain is lower for women (Wiesenfeld-Hallin, Z., 2005; Rolke, R. *et al.*, 2006; Wilson, J. F., 2006).

Gender differences in cortical activity for acute pain has been observed in early studies (Paulson, P. E. *et al.*, 1998). The association of sex hormones with pain perception and pain memory was studied by Zubieta J. K. and colleagues (Zubieta, J. K. *et al.*, 2002; Smith, Y. R. *et al.*, 2006). They scanned healthy women during their early follicular phase when estrogen levels are low and then repeated the scan during that same phase in another month after they had worn for a week an estrogen-releasing skin patch which increased their estrogen to levels normally seen in the menstrual cycle. These studies showed that more μ-opioid receptors were available in the presence of high estrogen levels, and women reported less pain in response to acute painful stimuli than when their estrogen levels were low. Moreover, estrogen-associated variations in the activity of μ-opioid neurotransmission correlated with individual ratings of the sensory and affective perceptions of pain and the subsequent recall of that experience. These data demonstrate a significant role of estrogen in modulating endogenous opioid neurotransmission and associated psychophysical responses to an acute pain stressor in humans. Approximately similar results have been reported by another group (De Leeuw, R. *et al.*, 2006).

5.45.6 Overview Regarding the Role of the Cortex in Acute Pain Perception

The above sections describe the contribution of modern imaging studies to our understanding of the involvement of the cortex in pain perception. Cortical activity is demonstrated to possess properties necessary for involvement in pain perception, like somatotopic representation of painful stimuli,

correlation with stimulus intensity, modulation with attention, modulation with expectation and other psychological variables, and distinct brain regions showing differential activity for sensory and affective dimensions of pain, as well as attenuation of responses with analgesic drugs (Apkarian, A. V. *et al.*, 2005). Thus, human brain imaging studies have asserted the role of the cortex in acute pain.

However, because imaging studies identify brain responses in a correlative manner, they may all reflect secondary processes. Perception of pain automatically directs attention to the source of pain, results in autonomic responses, motor reflexes to escape from the pain, and other emotional and cognitive responses that undoubtedly are at least partially mediated through cortical processes. Therefore, the role of the cortex in pain perception in contrast to its activity as a consequence of these secondary responses remains unclear and needs to be properly addressed in future studies (Apkarian, A. V., 2004).

In fact, unpublished data from Apkarian's laboratory suggest that a large proportion of the brain network activated with acute pain may be responses that are commonly involved in general magnitude estimation for any sensory modality, and as a result are not specific for nociception (abstract Society for Neuroscience 2006), suggesting that the majority of cortical activity for acute pain are instead sensory, cognitive, emotional, and attentional responses to nociceptive inputs. Careful clinical and neuropsychological examination of patients with small brain lesions, combined with high-resolution structural and neuropharmacological neuroimaging in the same patients, will be needed to address the question what brain structures are necessary for acute pain perception. Anatomical tracing studies and single unit recordings should address the question, to what extent nociceptive specific neurons exist in these brain structures. For most parts of the nociceptive cortical network, as illustrated above, it is likely that they participate only partly in pain perception, by providing certain feature extraction functions, but they also participate in other functions in different contexts.

5.45.7   Clinical Applications

It should be emphasized that although the subjective phenomenon of being in pain can be considered an emergent phenomenon of cortical activity (Treede, R. D., 2001), there is currently no measure of brain activity that would objectively show whether or not a person is in pain. Therefore, neither EEG/MEG nor imaging with fMRI or PET can be used to verify the presence of ongoing spontaneous pain.

EEG and MEG recordings of evoked potentials, however, are sensitive enough to verify whether the ascending nociceptive pathways are intact in a given individual patient (Bromm, B. and Lorenz, J., 1998; Treede, R. D. *et al.*, 2003; Cruccu, G. *et al.*, 2004). A prerequisite for this use of EEG and MEG technology is a phasic adequate stimulus for nociceptor activation. Radiant heat pulses of a few milliseconds duration, as generated by infrared lasers, have been validated for this purpose (Plaghki, L. and Mouraux, A., 2003), and LEPs can thus be used to verify the presence of negative sensory signs of nociception (hypoalgesia).

Neither fMRI nor PET are sensitive enough to allow clinical assessment of nociceptive pathways in individual cases, since so far no activation paradigm has been developed that would reliably induce a particular cortical activation pattern in each and every healthy subject. Thus, negative findings with these techniques are inconclusive.

For the study of pathological nociceptive processing at the group level, however, fMRI and PET techniques are extremely powerful. These techniques have broadened our understanding of the pathophysiology of conditions with decreased pain perception such as afferent pathway lesions or borderline personality disorder, and conditions with increased pain perception such as neuropathic pain or fibromyalgia (Gracely, R. H. *et al.*, 2004; Maihöfner, C. *et al.*, 2005; Garcia-Larrea, L. *et al.*, 2006; Schmahl, C. *et al.*, 2006; Schweinhardt, P. *et al.*, 2006). In addition, PET allows direct estimation of pharmacological and biochemical processes in the brain, such as alterations in dopamine or opioid receptor availability (Hagelberg, N. *et al.*, 2003a; Willoch, F. *et al.*, 2004).

5.45.8   Chronic Pain

5.45.8.1   Studying Brain Activity in Chronic Pain with Nonspecific Painful Stimuli

Chronic pain might result from cortical processing of chronic nociceptive spinothalamic input according to the same mechanisms as in acute pain, or there might be specific changes in cortical processing of nociceptive input in patients with chronic pain. Such changes

could then either be a causal factor for or a consequence of the chronicity of the pain condition.

A recent meta-analysis in fact shows that across some 100 studies one can establish statistically significant differences in incidence of different brain areas activated by experimental painful stimuli between acute and chronic pain conditions: PRC shows a stronger activation in chronic pain patients, whereas other nociceptive cortical areas and the thalamus show a weaker response (Table 2). A simple interpretation of these findings would be that nociceptive signal processing for experimental painful stimuli in chronic pain patients involves a reduced sensory discriminative component and an increased affective-motivational or cognitive-evaluational component. That interpretation would also be consistent with the stronger affective component of clinical pain as compared to experimental pain (Chen, A. C. N. and Treede, R. D., 1985). But there are further implications: Is the result a consequence of some trivial confounds or does it signify changes in the physiology of pain? One could construct a long list of confounds that may underlie the observation, from attentional shifts, to coping mechanisms, to effects of drug use, and heightened anxiety and depression.

The standard approach for studying brain activity for acute pain is to induce pain by a mechanical or thermal stimulus and determine brain regions modulated with the stimulus period and even with the various intensities used. Therefore, it is natural to carry the same technology to the clinical arena and apply it to chronic pain patients. As an example, we discuss one study which attempted to identify brain activity in complex regional pain syndrome (CRPS) patients using fMRI (Apkarian, A. V. et al., 2001a; 2001b).

The design of the study was to examine brain activity for thermal stimuli applied to the body part where CRPS pain was present, and compare brain responses to this stimulus between CRPS and healthy subjects. Moreover, as the pain in CRPS patients with sympathetically maintained pain (SMP) may be modulated by a sympathetic block, it was reasoned that one could decrease the patients' ongoing pain and then re-examine brain activity responses to the same stimulus. The study was done in a small group of patients and this by itself is an important weakness. The main observation was that thermal stimuli in CRPS evoked more prefrontal cortical activity than usually seen in healthy subjects, and this was reversed (became more similar in pattern to normal subjects' brain activity to thermal stimuli) following sympathetic blocks. The introduction of sympathetic blocks necessitated the use of the same procedure in healthy subjects as well, where its effects were minimal. The study also observed that when a placebo block resulted in decreased pain perception then the cortical response pattern changed similarly to that of effective blocks. These results show that brain activity may be distinct between CRPS and healthy subjects for thermal stimuli.

5.45.8.2   Clinical Pain Conditions Studied by Stimulation and the Role of the Cortex

A direct approach to studying clinical pain states is to provoke it and examine brain activity. This is doable by drugs in headaches and in cardiac pain. As a result there is growing literature in both fields. There is also now good evidence that migraine with aura is accompanied with decreased blood flow and decreased activity in the occipital cortex, and migraine with or

Table 2   Frequency of brain areas active during pain in normal subjects as compared to patients with clinical pain conditions

	ACC	SI	SII	IC	Th	PFC
Pain in normal subjects in 68 studies	47/54 (87%)	39/52 (75%)	38/51 (75%)	45/48 (94%)	28/35 (80%)	23/42 (55%)
Clinical pain conditions in 30 studies	13/29 (45%)	7/25 (28%)	5/25 (20%)	15/26 (58%)	16/27 (59%)	21/26 (81%)
Comparison between pain in normal subjects and in clinical conditions	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P = 0.095$	$P = 0.038$

Incidence values are based on positron emission tomography, single photon emission-computed tomography, and functional magnetic resonance imaging studies. For details see Apkarian et al., 2005. P values are based on Fisher's exact statistics contrasting incidence for each area. ACC, anterior cingulate cortex; IC, insular cortex; PFC, prefrontal cortex; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; Th, thalamus.

without aura is associated with increased cortical thickness in visual cortical regions involved in motion detection (Granziera, C. *et al.*, 2006).

5.45.8.2.1　Migraine

Migraine attacks are characterized by unilateral severe headache often accompanied by nausea, phonophobia and photophobia. Activation of the trigeminovascular system is thought to be responsible for the pain itself, and cortical spreading depression (CSD) seems to underlie the aura symptoms. This view has been greatly advanced and substantiated by brain imaging studies. fMRI studies show CSD-typical cerebrovascular changes in the cortex of migraineurs while experiencing a visual aura (Hadjikhani, N. *et al.*, 2001). The subsequent decrease in fMRI signal is temporally correlated with the scotoma that follows the scintillations. These fMRI signal changes develop first in the extrastriate cortex, contralateral to the visual changes. It then slowly migrated towards more anterior regions of the visual cortex, representing peripheral visual fields, in agreement with the progressive movement of the scintillations and scotoma from the centre of vision towards the periphery. A recent study that analyzed visually triggered attacks showed hyperemia in the occipital cortex, independently of whether the headache was preceded by visual symptoms (Cao, Y. *et al.*, 1999). An alternative view considers migraine aura and headache as parallel rather than sequential processes, and proposes that the primary cause of migraine headache is an episodic dysfunction in brainstem nuclei that are involved in the central control of nociception (Goadsby, P. J. *et al.*, 2002).

5.45.8.2.2　Cluster headache

The pathophysiology of cluster headache is thought to involve multiple brain regions. Brain imaging studies imply that the associated excruciatingly severe unilateral pain is likely mediated by activation of the first (ophthalmic) division of the trigeminal nerve, while the autonomic symptoms are due to activation of the cranial parasympathetic out-flow from the VIIth cranial nerve. The circadian rhythmicity of cluster headache has led to the concept of a central origin for its initiation (Strittmatter, M. *et al.*, 1996).

Using PET in cluster headache patients, significant activations ascribable to the acute cluster headache were observed in the ipsilateral hypothalamic gray matter and in multiple cortical areas including cingulate and PRC. When compared to the headache-free state only hypothalamic activity was distinct (May, A. *et al.*, 2000). This highly significant activation was not seen in cluster headache patients out of the bout when compared to the patients experiencing an acute cluster headache attack. In contrast to migraine, no brainstem activation was found during the acute attack compared to the resting state. Newer MRS results further substantiate this idea by showing reduced metabolites within the hypothalamus of cluster headache patients in contrast to healthy or migraine headache controls (Wang, S. J. *et al.*, 2006). These data suggest that while primary headaches such as migraine and cluster headache may share a common pain pathway, the trigeminovascular innervation, and activate similar cortical regions, the underlying pathogenesis may be quite different.

5.45.8.2.3　Cardiac pain

Cardiac pain and its variants have been studied by brain imaging using various drugs that bring about these symptoms (Rosen, S. D. *et al.*, 1996; 2002). In patients with myocardial ischemia the perception of angina is associated with activity in the hypothalamus, PAG, thalami, rostral ACC, and bilateral PRC. In patients with silent myocardial ischemia it seems that the silence is not due to impaired afferent signaling, but rather it is associated with a failure of transmission of signals from the thalamus to the frontal cortex. In contrast, in patients with syndrome X, a condition of chest pain with ischemiclike stress electrocardiography but entirely normal coronary angiogram, activity in the right anterior insula distinguished these patients from patients with known coronary disease. These patients appear to have a deficit in central pain habituation (Valeriani, M. *et al.*, 2005). Overall, these studies imply that difference between different cardiac pain conditions are due to central processing, e.g., syndrome X is interpreted as a cortical pain syndrome, a top-down process, in contrast with the bottom-up generation of a pain percept caused by myocardial ischemia in coronary artery disease.

5.45.8.2.4　Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a disorder of abdominal pain or discomfort associated with bowel dysfunction. Hypersensitivity to visceral, but not somatic, stimuli has been demonstrated in IBS. A number of groups have examined brain activity in this condition mainly by monitoring responses to

painful and nonpainful rectal distensions, as well as responses to the anticipation of painful distensions. Two studies are interesting since both show in normal subjects a significant positive correlation between cingulate cortex activity and subjective rating of rectal distension pain, and in both studies this relationship completely disappears in IBS patients (Silverman, D. H. et al., 1997; Mertz, H. et al., 2000). IBS is more prevalent in women than in men. Brain imaging studies have now shown gender differences in brain activity in IBS (Berman, S. M. et al., 2000; Naliboff et al., 2001; Berman, S. M. et al., 2002b; Nakai, A. et al., 2003). There are large differences between the studies, making their synthesis difficult (see Ringel, Y., 2006).

More recent studies show a hint for sensitization in IBS patients because subliminal and supraliminal distensions of rectal distension seem to indicate small differences between IBS and healthy controls in the total cortical volume activated or in regional activity as a function of distention volume (Andresen, V. et al., 2005; Lawal, A. et al., 2006). A study of IBS in contrast to healthy subjects examined thermal and visceral hyperalgesia and related brain activity (Verne, G. N. et al., 2003). This seems the only study where besides pain intensity and unpleasantness measures, the authors also document fear and anxiety and show that all are rated higher by IBS for both heat and rectal distention, and not surprisingly these increased sensations and emotions give rise to larger cortical activations in IBS. The latter is most likely a reflection of a perceptual magnitude mismatch between the groups and says little as to the IBS cortical activity abnormalities. Such mismatches at least for fear and anxiety most likely are common in the majority of studies of IBS. One assumes that the simple introduction of a rectal balloon in IBS would result in increased anxiety, which undoubtedly effects cortical activity to visceral and somatic pain, yet its specific contribution has remained unexplored.

In a more elegant study the authors use perception-related ratings during rectal distention to evoke either urge to defecate or pain, and compared brain activity related to the ratings between IBS patients and healthy subjects. (Kwan, C. L. et al., 2005). The approach is similar to the technique used in mapping brain activity for spontaneous pain in chronic back pain (CBP) and in postherpetic neuralgia (PHN; Baliki, M. N. et al., 2006; Geha, P. Y. et al., 2007). The results show large differences between the two groups contrasted, with far more extensive brain activations in the healthy subjects. The results are complicated by the fact that the authors do not take into consideration the influence of spontaneous pain. Still, this is perhaps one of the best-controlled IBS studies, and indicates distinct cortical areas involved in the urge and pain perceptions in each group.

There is now evidence that serotonin (5-HT) may be involved in IBS. One study (Nakai, A. et al., 2003) examined serotonin synthesis in the brain and indicated greater brain regional serotonin synthesis in female IBS. There is also evidence that alosetron, a 5-HT$_3$ receptor antagonist, is clinically effective in treating some subtypes of IBS. Berman S. M. et al. (2002a) examined brain activity in a large population of IBS, before and after a randomized, placebo-controlled, 3-week use of alosetron. Treatment improved IBS symptoms and regional cerebral blood flow in brain regions rich with 5-HT$_3$ receptor and involved in emotional and aversive functions: amygdala, ventral striatum, and dorsal pons, implying that the therapeutic effects are due to central actions and not peripheral. Thus, generally the IBS studies show that brain responses are different to rectal stimuli in patients, and that these central events may be critical to IBS.

5.45.8.3 Spontaneous Pain as a Confound in Assessing Brain Activity

A person who has lived for years in the presence of pain, must have developed some coping mechanisms that aid in pursuing other everyday life interests in spite of the presence of the pain. How does this impact the brain? Can one consider the patient in chronic pain as composed of a brain-signaling pain together with a brain undertaking other tasks as in healthy subjects? Or, does the presence of ongoing pain interact and impact other processes as well? Certainly our cognitive and anatomic studies suggest that the latter is more likely. We have now direct evidence of the modulation that ongoing pain imposes on brain activity in general.

A recent study reported brain activity for spontaneous pain in PHN patients before and after topical lidocaine treatment (Geha, P. Y. et al., 2007). The PHN patients were imaged before, after 6-hours and 2-weeks treatment with lidocaine. Behaviorally and based on questionnaires most participants showed a modest but significant decrease in their ongoing pain. The patients were scanned while they were either rating their ongoing pain or rating a visual bar that varied in time in a pattern that mimicked their ratings of pain (Figure 8). Thus, the
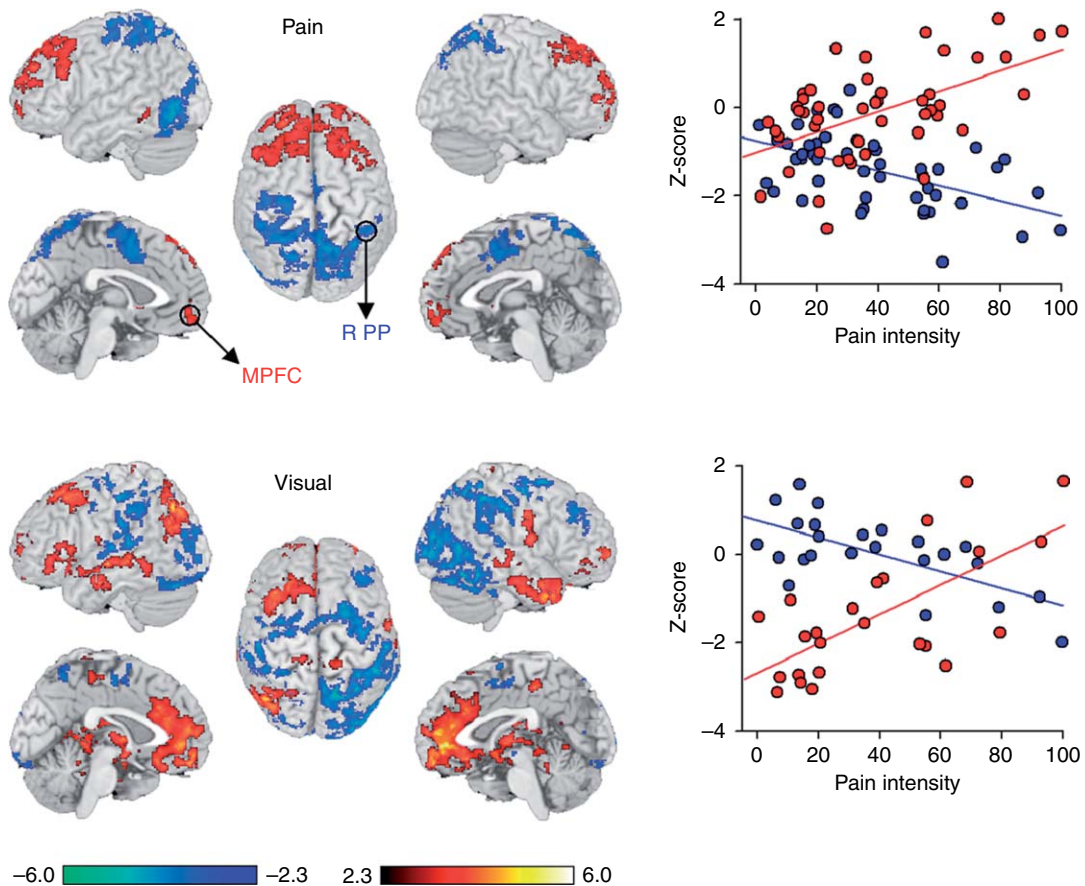
Figure 8 Intensity of ongoing pain changes brain activity and thus cognitive processing. Eleven postherpetic neuralgia patients were studied by functional magnetic resonance imaging (fMRI) once before and twice after lidocaine application on the painful skin. In all sessions, patients performed two different tasks: in the Pain task they continuously rated the fluctuations of their spontaneous pain, and brain activity related to this was identified using methods. In the Visual task they rated fluctuations of a bar varying in time, brain activity was determined with the same approach as for the pain task. The relationship between brain activity and intensity of ongoing pain was determined by using a covariate analysis, where for each fMRI scan its related pain intensity was used to determine the effect of this parameter on brain responses. Across-subject and across all scans average variation of brain activity is displayed for both tasks in the left. Red are brain regions that are positively correlated and blue regions that are negatively correlated with intensity of ongoing pain (normalized to z-values). The right scatter-grams show this effect for two brain regions (right posterior parietal cortex, R PP, $x = 33$ $y = -45$ $z = 50$; and medial prefrontal cortex, MPFC, $x = 9$ $y = 50$ $z = -40$, as respectively circled). Each dot represents a single patient's activity at a single time. Top scatter-gram is for Pain task; bottom for Visual task, red symbols and regression line are for MPFC; blue for R PP. MPFC exhibited significant positive correlations with pain intensity for pain ($r = 0.49$, $P < 0.05$) and visual ($r = 58$, $P < 0.01$) task, while R PP showed negative correlation for pain ($r = -0.48$, $P < 0.05$) and visual ($r = -0.64$, $P < 0.01$) task. Brain areas that show increased correlation with ongoing pain are interpreted as a functional compensation for the decreased attentional resources. Reproduced from Geha, P. Y., Baliki, M. N., Chialvo, D. R., Harden, R. N., Paice, J. A., and Apkarian, A. V. 2007. Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy. Pain 128, 88–100.

latter is a control task that captures motor and cognitive parts of the task but, of course, it does not reflect the pain. Brain activity for both tasks was increasing from first to third session. This observation is similar to earlier reports that decrease in clinical pain in many cases results in increased brain activity. In this case, however, the internal control was also changing in a manner parallel to the pain condition, hinting that the effects of decreased pain was modulating more than just pain-related circuitry.

To identify the role of spontaneous pain on brain activity in general, a correlation analysis was done for both tasks with mean spontaneous pain. Figure 8 shows the influence of pain intensity on across-sessions averaged brain activity for both tasks.

The resultant map is generally similar for both tasks: activity in medial and lateral prefrontal regions was positively correlated, while posterior parietal attentional areas were negatively correlated with mean pain intensity. This result shows that brain activity for both tasks is influenced by the level of spontaneous pain, implying that pain intensity influences task performance in general. This is in line with previous studies showing that ongoing pain may interfere with cognitive functions (Lorenz, J. et al., 1997).

This result reinforces the need for correcting brain activity by a control condition performed at the same pain level that is the necessity of subtracting the visual task from spontaneous pain rating task, at each treatment session. For both tasks, the fact that posterior parietal cortical activity was negatively correlated with mean ongoing pain suggests that the attentional abilities of patients are directly related to the intensity of their pain, which would in turn impact their abilities in performing anything that would demand concentration.

Moreover, multiple prefrontal regions were positively correlated to the mean pain, suggesting that the patients' brain regions underlying higher cognitive functions become more active as the pain intensity increases. The exact cognitive implications for these brain activity patterns remain unclear. In contrast, the finding indicates that the intensity of spontaneous pain impacts brain activity for any task that the subject attempts to perform, enhancing some aspects and inhibiting others. Therefore, the decreased brain activity reported for pain tasks in many clinical pain conditions (Peyron, R. et al., 2000; Derbyshire, S. W., 2003; Apkarian, A. V. et al., 2005; Kupers, R. and Kehlet, H., 2006) is most likely a reflection of the presence of the spontaneous pain, and is not specific to the task being investigated.

The fact that pain intensity seems to modulate brain activity in general has another powerful consequence. It suggests that simply studying brain activity, in tasks unrelated to pain, one should be able to identify the presence of pain and study its effects on sensory/cognitive/motor/attentional processing, an exciting prospect that remains to be pursued.

5.45.8.4 Functional Magnetic Resonance Imaging of Spontaneous Pain

Spontaneous pain is highly prevalent in clinical pain conditions, and is usually the primary drive for patients seeking medical care. Thus, understanding its related brain circuitry is both scientifically and therapeutically imperative. Cortical responses to standard mechanical or thermal stimulation are of limited value for understanding these clinical pain conditions. Spontaneous pain fluctuates unpredictably in the time scale of seconds to minutes, and these fluctuations have characteristic properties that differentiate between different chronic pain conditions such as PHN and CBP (Foss, J. M. et al., 2006). This variability (specific fractal dimension) can also be observed in fMRI signals when such patients rate their spontaneous pain. Therefore, this technique was applied to study brain activity in CBP (Baliki, M. N. et al., 2006) and PHN patients (Geha, P. Y. et al., 2007) in relation to their subjective report of fluctuations of spontaneous pain.

The combination of relating brain activity to spontaneous pain and correcting for confounds by subtracting brain activity for visual bar lengths, provides a robust approach with which clinical pain may be studied directly. Note that in this case the brain activity is related to exactly the event that the patient complains about. With this approach, in CBP patients (Baliki, M. N. et al., 2006) it was shown that the brain regions activated when the pain was increasing correspond to brain regions seen for acute pain in normal subjects. In contrast, for time periods when the pain was high and sustained, the brain activity was mainly limited to medial PRC, a region usually not activated for acute pain. The resultant brain activity was strongly correlated to the patients' reported pain intensity at the time of the scan, specifically with medial prefrontal activity. Also, the duration or chronicity of the pain was captured in the insular activity, a region activated only during increases in spontaneous pain. Thus, two fundamental properties of CBP its intensity and duration were directly reflected in the brain activity identified in these patients. By applying a thermal painful stimulus in the same patients (as well as in healthy subjects) the same study showed that brain regions reflecting the stimulus intensity were not related to that reflecting the intensity of spontaneous pain. In turn, the brain region that reflected spontaneous pain intensity was only activated for the latter and did not reflect thermal painful stimulus intensity. Therefore, at least in the patient group studied spontaneous pain involved a different brain activity pattern than acute pain.

5.45.8.5 Neuropathic Pain

Patients with neuropathic pain show decreased responses in the thalamus to experimental painful

stimuli (Peyron, R. *et al.*, 2000). A MRS study showed a decrease in the level of *N*-acetyl-aspartate, a neuronal marker, in the thalami of patients with chronic neuropathic pain after spinal cord injury (SCI), when compared to patients with SCI but without pain (Pattany, P. M. *et al.*, 2002). Thus, neurochemical brain imaging provides evidence for the occurrence of long-term changes in the brain chemistry and morphology of chronic neuropathic pain patients. Thalamic activity in neuropathic patients was also reported to increase after pain relief (Hsieh, J. C. *et al.*, 1995), and to be significantly negatively correlated with the duration of the condition in CRPS patients (Fukumoto, M. *et al.*, 1999). Thus, the reduced activation of the thalamus may also be an altered functional state rather than an irreversible degeneration. Neuropathic pain patients in addition show a reduced availability of opioid receptor binding sites (Maarrawi, J. *et al.*, 2007). This reduction was symmetric in peripheral neuropathic pain, suggesting a possible release of endogenous opioids, but lateralized to the hemisphere contralateral to the pain in central pain patients, consistent with a loss of receptors (Jones, A. K. P. *et al.*, 2004, Willoch, F. *et al.*, 2004).

Brain activity differences between healthy subjects and patients in activation paradigms are difficult to interpret since they do not distinguish between brain activity specifically related to the clinical condition and abnormalities in sensory processing secondarily associated with the clinical state. Particularly in neuropathic pain, the accompanying sensory deficit may be reflected in the imaging results and not the pain. Reduced relevance of the acute stimulus to subjects who are already in pain may also account for much of the decreased regional brain activity in neuropathic pain. To overcome such nonspecific brain activity differences one needs to compare brain activity for stimuli where perceptual evaluation has been equated between patients and normal healthy subjects.

Three studies (Hsieh, J. C. *et al.*, 1995; 1999a; Apkarian, A. V. *et al.*, 2001b) have looked at the regions of the brain modulated by relief of chronic neuropathic pain: CRPS, peripheral neuropathy, and trigeminal neuropathy. Two of these studies show that the PRC activity is decreased, and all three studies report decreased rostral ACC activity, after successful pain relief. It is to be noted that in addition to those regions some areas were also less activated with pain relief such as the insula (Hsieh, J. C. *et al.*, 1995) and the anterior limbic thalamus (Hsieh, J. C. *et al.*, 1999a), whereas others were more activated

after pain relief like the medial PRC (Hsieh, J. C. *et al.*, 1999a). This heterogeneity is not surprising because pattern of brain activity may be specific to each neuropathic pain condition.

5.45.8.6   Low Back Pain and Fibromyalgia

As mentioned above, brain activity of healthy subjects and patients with increased pain sensitivity should be compared in such a way that perceived intensity has been matched across the two groups. A recent study used such a design and showed generally heightened brain activity for painful stimuli of equivalent perceptual intensity both in fibromyalgia and CBP patients as compared to healthy subjects (Gracely, R. H. *et al.*, 2002; Giesecke, T. *et al.*, 2004). Morphometric and neurochemical brain imaging studies provide evidence for the occurrence of long-term changes in the brain chemistry and morphology of chronic pain patients. The level of *N*-acetyl-aspartate, a neuronal marker, was decreased in the medial and lateral PRC of CBP patients compared to an age- and gender-matched control group (Grachev, I. D. *et al.*, 2000). A morphometric study in chronic pain showed also a decrease in gray matter density in the dorsolateral PRC and the thalamus of CBP patients when compared to matched controls (Apkarian, A. V. *et al.*, 2004). Furthermore, these long-term chemical and morphological changes are significantly correlated with different characteristics of pain such as pain duration (Apkarian, A. V. *et al.*, 2004), pain intensity (Pattany, P. M. *et al.*, 2002; Grachev, I. D. *et al.*, 2002; Apkarian, A. V. *et al.*, 2004), and sensory-affective components (Grachev, I. D. *et al.*, 2002). The morphometric and neurochemical studies imply an active role of the central nervous system in chronic pain, suggesting that supraspinal reorganization may be critical for chronic pain.

5.45.8.7   Overview Regarding the Role of the Cortex in Chronic Pain Perception

In spite of a plethora of data there remains a host of uncertainties about their significance. Overall, the clinical brain imaging studies indicate reduced information transmission through the thalamus to the cortex, and increased activity in PFC, mostly in medial PFC coupled with atrophy in dorsolateral PFC. The number of studies remain very small and hence our confidence as to the reproducibility of these changes remain minimal. Still, the observations

regarding cortical and thalamic activity changes in chronic pain are in general consistent with the notion that chronic pain conditions preferentially engage brain areas involved in cognition/emotion and decreases activity in regions involved in sensory evaluation of nociceptive inputs.

Evidence has been presented that brain activity, chemistry, and morphology may be reorganized in chronic pain conditions. Does this evidence imply that there is supraspinal reorganization, above and beyond what is established in the periphery and spinal cord? That is, even if we establish a brain pattern of activity for some chronic pain condition, does this reflect some unique contribution of the brain to this state or is it simply a reflection of lower level reorganization? The answer is not straightforward. However, only by answering such questions will brain imaging be able to provide new information to the myriad mechanisms described for peripheral and spinal cord reorganization in chronic pain.

5.45.9 Conclusions and Outlook

The study of nociceptive processing in the cerebral cortex has come a long way. In contrast to earlier assumptions, the classical somatosensory cortex areas are not the only ones activated by painful stimuli. In addition, limbic areas such as the anterior and mid-cingulate cortex and the insula have also been recognized as part of the nociceptive network, and more recently also cognitive areas in the PRC. Limbic areas are usually considered to mediate emotional processes, but they are also involved in autonomic and motor functions. In this way, progress in understanding the cortical nociceptive network mirrors that in understanding the subcortical networks, which also include many connections to autonomic and motor nuclei as well as hypothalamus, cerebellum, and basal ganglia. Images of brain activation by painful stimuli leave the impression that at least half of the brain participates in processing nociceptive information. At other times, many of the same areas participate in visual, motor, emotional, cognitive, or other signal processing. In that sense, our current understanding of the nociceptive network in the brain is consistent with our current understanding of how the brain uses distributed processing for its many functions. It is not clear, however, to what extent any part of the cerebral cortex is specific for nociception. The best candidate region for such a function lies in the parasylvian cortex, in the vicinity of SII and the dorsal insula. In chronic pain, nociceptive processing in the cerebral cortex is partly preserved and partly altered, in particular with respect to PRC functions. This reorganization may be a neuroplastic response to the chronicity of pain, it may reflect activation of antinociceptive processes, or it may even represent a predisposing factor for the development of chronic pain. The methods available for the study of nociceptive processing in the brain allow to address many of these open questions in the near future, and this part of pain research is bound to remain a very productive one.

References

Andersson, J. L. R., Lilja, A., Hartvig, P., Långström, B., Gordh, T., Handwerker, H., and Torebjörk, E. 1997. Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography. Exp. Brain Res. 117, 192–199.

Andresen, V., Bach, D. R., Poellinger, A., Tsrouya, C., Stroh, A., Foerschler, A., Georgiewa, P., Zimmer, C., and Monnikes, H. 2005. Brain activation responses to subliminal or supraliminal rectal stimuli and to auditory stimuli in irritable bowel syndrome. Neurogastroenterol. Motil. 17, 827–837.

Apkarian, A. V. 2004. Cortical pathophysiology of chronic pain. Novartis Found. Symp. 261, 239–245.

Apkarian, A. V. and Shi, T. 1994. Squirrel monkey lateral thalamus. I. Somatic nociresponsive neurons and their relation to spinothalamic terminals. J. Neurosci. 14, 6779–6795.

Apkarian, A. V., Bushnell, C., Treede, R. D., and Zubieta, J. K. 2005. Human brain mechanisms of pain perception and regulation in health and disease. Eur. J. Pain 9, 463–484.

Apkarian, A. V., Grachev, I. D., and Krauss, B. R. 2001a. Imaging brain pathophysiology of chronic CRPS pain. In: Complex Regional Pain Syndrome (eds. R. Harden, W. Janig, and J. C. Baron), pp. 209–227. IASP Press.

Apkarian, A. V., Sosa, Y., Sonty, S., Levy, R. E., Harden, R., Parrish, T., and Gitelman, D. 2004. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J. Neurosci. 24, 10410–10415.

Apkarian, A. V., Stea, R. A., Manglos, S. H., Szeverenyi, N. M., King, R. B., and Thomas, F. D. 1992. Persistent pain inhibits contralateral somatosensory cortical activity in humans. Neurosci. Lett. 140, 141–147.

Apkarian, A. V., Thomas, P. S., Krauss, B. R., and Szeverenyi, N. M. 2001b. Prefrontal cortical hyperactivity in patients with sympathetically mediated chronic pain. Neurosci. Lett. 311, 193–197.

Baliki, M. N., Chialvo, D. R., Geha, P. Y., Levy, R. M., Harden, R. N., Parrish, T. B., and Apkarian, A. V. 2006. Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain. J. Neurosci. 26, 12165–12173.

Bantick, S. J., Wise, R. G., Ploghaus, A., Clare, S., Smith, S. M., and Tracey, I. 2002. Imaging how attention modulates pain in humans using functional MRI. Brain 125, 310–319.

Baumgärtner, U., Buchholz, H. G., Bellosevich, A., Magerl, W., Siessmeier, T., Rolke, R., Höhnemann, S., Piel, M., Rösch, F., Wester, H. J., Henriksen, G., Stoeter, P., Bartenstein, P., Treede, R. D., and Schreckenberger, M. 2006a. High opiate receptor binding potential in the human lateral pain system. Neuroimage 30, 692–699.

Baumgärtner, U., Tiede, W., Treede, R. D., and Craig, A. D. 2006b. Laser-evoked potentials are graded and somatotopically organized anteroposteriorly in the operculoinsular cortex of anesthetized monkeys. J. Neurophysiol. 96, 2802–2808.

Becker, J. B., Arnold, A. P., Berkley, K. J., Blaustein, J. D., Eckel, L. A., Hampson, E., Herman, J. P., Marts, S., Sadee, W., Steiner, M., Taylor, J., and Young, E. 2005. Strategies and methods for research on sex differences in brain and behavior. Endocrinology 146, 1650–1673.

Benedetti, F., Mayberg, H. S., Wager, T. D., Stohler, C. S., and Zubieta, J. K. 2005. Neurobiological mechanisms of the placebo effect. J. Neurosci. 25, 10390–10402.

Berman, S. M., Chang, L., Suyenobu, B., Derbyshire, S. W., Stains, J., Fitzgerald, L., Mandelkern, M., Hamm, L., Vogt, B., Naliboff, B. D., and Mayer, E. A. 2002a. Condition-specific deactivation of brain regions by 5-HT3 receptor antagonist Alosetron. Gastroenterology 123, 969–977.

Berman, S., Munakata, J., Naliboff, B. D., Chang, L., Mandelkern, M., Silverman, D., Kovalik, E., and Mayer, E. A. 2000. Gender differences in regional brain response to visceral pressure in IBS patients. Eur. J. Pain 4, 157–172.

Berman, S. M., Naliboff, B. D., Chang, L., Fitzgerald, L., Antolin, T., Camplone, A., and Mayer, E. A. 2002b. Enhanced preattentive central nervous system reactivity in irritable bowel syndrome. Am. J. Gastroenterol. 97, 2791–2797.

Beydoun, A., Morrow, T. J., Shen, J. F., and Casey, K. L. 1993. Variability of laser-evoked potentials: attention, arousal and lateralized differences. Electroencephalogr. Clin. Neurophysiol. 88, 173–181.

Bingel, U., Lorenz, J., Schoell, E., Weiller, C., and Büchel, C. 2006. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. Pain 120, 8–15.

Borsook, D., Becerra, L., and Hargreaves, R. 2006. A role for fMRI in optimizing CNS drug development. Nat. Rev. Drug Discov. 5, 411–424.

Biemond, A. 1956. The conduction of pain above the level of the thalamus opticus. Arch. Neurol. Psychiat. 75, 231–244.

Botvinick, M., Jha, A. P., Bylsma, L. M., Fabian, S. A., Solomon, P. E., and Prkachin, K. M. 2005. Viewing facial expressions of pain engages cortical areas involved in the direct experience of pain. Neuroimage 25, 312–319.

Bragard, D., Chen, A. C. N., and Plaghki, L. 1996. Direct isolation of ultra-late (C-fibre) evoked brain potentials by CO2 laser stimulation of tiny cutaneous surface areas in man. Neurosci. Lett. 209, 81–84.

Bromm, B. and Lorenz, J. 1998. Neurophysiological evaluation of pain. Electroenceph. Clin. Neurophysiol. 107, 227–253.

Bromm, B. and Treede, R. D. 1984. Nerve fibre discharges, cerebral potentials and sensations induced by CO_2 laser stimulation. Human Neurobiol. 3, 33–40.

Bromm, B., Neitzel, H., Tecklenburg, A., and Treede, R. D. 1983. Evoked cerebral potential correlates of C-fibre activity in man. Neurosci. Lett. 43, 109–114.

Brooks, J. C. W., Nurmikko, T. J., Bimson, W. E., Singh, K. D., and Roberts, N. 2002. fMRI of thermal pain: effects of stimulus laterality and attention. Neuroimage 15, 293–301.

Buchsbaum, M. S., Kessler, R., King, A., Johnson, J., and Cappelletti, J. 1984. Simultaneous cerebral glucography with positron emission tomography and topographic electroencephalography. Prog. Brain Res. 62, 263–269.

Bushnell, M. C. and Apkarian, A. V. 2005. Representation of Pain in the Brains. In: Wall and Melzack's Textbook of Pain, Chapter 6, 5th Edition (eds. S. B. McMahon and M. Koltzenburg), pp. 107–124. Elsevier.

Bushnell, M. C., Duncan, G. H., Hofbauer, R. K., Ha, B., Chen, J. I., and Carrier, B. 1999. Pain perception: is there a role for primary somatosensory cortex? Proc. Natl. Acad. Sci. U. S. A. 96, 7705–7709.

Cao, Y., Welch, K. M. A., Aurora, S., and Vikingstad, E. M. 1999. Functional MRI-BOLD of visually triggered headache in patients with migraine. Arch. Neurol. 56, 548–554.

Carmon, A., Mor, J., and Goldberg, J. 1976. Evoked cerebral responses to noxious thermal stimuli in humans. Exp. Brain Res. 25, 103–107.

Casey, K. L., Svensson, P., Morrow, T. J., Raz, J., Jone, C., and Minoshima, S. 2000. Selective opiate modulation of nociceptive processing in the human brain. J. Neurophysiol. 84, 525–533.

Chen, A. C. N. 1993. Human brain measures of clinical pain: a review. I. Topographic mappings. Pain 54, 115–132.

Chen, A. C. N. and Treede, R. D. 1985. The McGill pain questionnaire in the assessment of phasic and tonic experimental pain: behavioral evaluation of the 'pain inhibiting pain' effect. Pain 22, 67–69.

Chen, A. C. N., Chapman, C. R., and Harkins, S. W. 1979. Brain evoked potentials are functional correlates of induced pain in man. Pain 6, 365–374.

Craig, A. D. 1995. Supraspinal Projections of Lamina I Neurons. In: Forebrain Areas Involved in Pain Processing (eds. J. M. Besson, G. Guilbaud, and H. Ollat), pp. 13–25. John Libbey Eurotext.

Craig, A. D. 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat. Rev. 3, 655–666.

Craig, A. D., Bushnell, M. C., Zhang, E. T., and Blomqvist, A. 1994. A thalamic nucleus specific for pain and temperature sensation. Nature 372, 770–773.

Cruccu, G., Anand, P., Attal, N., Garcia-Larrea, L., Haanpää, M., Jørum, E., Serra, J., and Jensen, T. S. 2004. EFNS guidelines on neuropathic pain assessment. Eur. J. Neurol. 11, 153–162.

DaSilva, A. F. M., Becerra, L., Makris, N., Strassman, A. M., Gonzalez, R. G., Geatrakis, N., and Borsook, D. 2002. Somatotopic activation in the human trigeminal pain pathway. J. Neurosci. 22, 8183–8192.

Danziger, N., Prkachin, K. M., and Willer, J. C. 2006. Is pain the price of empathy? The perception of others' pain in patients with congenital insensitivity to pain. Brain 129, 2494–2507.

Davis, K. D. 2003. Neurophysiological and anatomical considerations in functional imaging of pain. Pain 105, 1–3.

Davis, K. D., Wood, M. L., Crawley, A. P., and Mikulis, D. J. 1995. fMRI of human somatosensory and cingulated cortex during painful electrical nerve stimulation. Neuroreport 7, 321–325.

De Leeuw, R., Albuquerque, R. J., Andersen, A. H., and Carlson, C. R. 2006. Influence of estrogen on brain activation during stimulation with painful heat. J. Oral Maxillofac. Surg. 64, 158–166.

Derbyshire, S. W. 2003. A systematic review of neuroimaging data during visceral stimulation. Am. J. Gastroenterol. 98, 12–20.

Derbyshire, S. W., Whalley, M. G., Stenger, V. A., and Oakley, D. A. 2004. Cerebral activation during hypnotically induced and imagined pain. Neuroimage 23, 392–401.

Dieterich, M., Bense, S., Lutz, S., Drzezga, A., Stephan, T., Bartenstein, P., and Brandt, T. 2003. Dominance for vestibular cortical function in the non-dominant hemisphere. Cereb. Cortex 13, 994–1007.

Disbrow, E., Roberts, T., and Krubitzer, L. 2000. Somatotopic organization of cortical fields in the lateral sulcus of homo sapiens: evidence for SII and PV. J. Comp. Neurol. 418, 1–21.

Dong, W. K., Chudler, E. H., Sugiyama, K., Roberts, V. J., and Hayashi, T. 1994. Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. J. Neurophysiol. 72, 542–564.

Duclaux, R., Franzen, O., Chatt, A. B., Kenshalo, D. R., and Stowell, H. 1974. Responses recorded from human scalp evoked by cutaneous thermal stimulation. Brain Res. 78, 279–290.

Eickhoff, S. B., Schleicher, A., Zilles, K., and Amunts, K. 2006. The human parietal operculum. I. Cytoarchitectonic mapping of subdivisions. Cereb. Cortex 16, 254–267.

Firestone, L. L., Gyulai, F., Mintun, M., Adler, L. J., Urso, K., and Winter, P. M. 1996. Human brain activity response to fentanyl imaged by positron emission tomography. Anesth. Analg. 82, 1247–1251.

Fitzgerald, P. J., Lane, J. W., Thakur, P. H., and Hsiao, S. S. 2004. Receptive field properties of the macaque second somatosensory cortex: evidence for multiple functional representations. J. Neurosci. 24, 11193–11204.

Fitzgerald, P. J., Lane, J. W., Thakur, P. H., and Hsiao, S. S. 2006. Receptive field (RF) properties of the macaque second somatosensory cortex: RF size, shape, and somatotopic organization. J. Neurosci. 26, 6485–6495.

Foss, J. M., Apkarian, A. V., and Chialvo, D. R. 2006. Dynamics of pain: fractal dimension of temporal variability of spontaneous pain differentiates between pain States. J. Neurophysiol. 95, 730–736.

Forss, N., Raij, T. T., Seppa, M., and Hari, R. 2005. Common cortical network for first and second pain. Neuroimage 24, 132–142.

Frankenstein, U. N., Richter, W., McIntyre, M. C., and Remy, F. 2001. Distraction modulates anterior cingulate gyrus activations during the cold pressor test. Neuroimage 14, 827–836.

Frot, M. and Mauguière, F. 1999. Operculo-insular responses to nociceptive skin stimulation in humans (A review). Neurophysiol. Clin. 29, 401–410.

Frot, M. and Mauguière, F. 2003. Dual representation of pain in the operculo-insular cortex in humans. Brain 126, 438–450.

Frot, M., Rambaud, L., Guénot, M., and Mauguière, F. 1999. Intracortical recordings of early pain-related CO2-laser evoked potentials in the human second somatosensory (SII) area. Clin. Neurophysiol. 110, 133–145.

Fukumoto, M., Ushida, T., Zinchuk, V. S., Yamamoto, H., and Yoshida, S. 1999. Contralateral thalamic perfusion in patients with reflex sympathetic dystrophy syndrome. Lancet 354, 1790–1791.

Garcia-Larrea, L., Maarrawi, J., Peyron, R., Costes, N., Mertens, P., Magnin, M., and Laurent, B. 2006. On the relation between sensory deafferentation, pain and thalamic activity in Wallenberg's syndrome: a PET-scan study before and after motor cortex stimulation. Eur. J. Pain 10, 677–688.

Geha, P. Y., Baliki, M. N., Chialvo, D. R., Harden, R. N., Paice, J. A., and Apkarian, A. V. 2007. Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy. Pain 128, 88–100.

Giesecke, T., Gracely, R. H., Grant, M. A., Nachemson, A., Petzke, F., Williams, D. A., and Clauw, D. J. 2004. Evidence of augmented central pain processing in idiopathic chronic low back pain. Arthritis Rheum. 50, 613–623.

Gingold, S. I., Greenspan, J. D., and Apkarian, A. V. 1991. Anatomic evidence of nociceptive inputs to primary somatosensory cortex: relationship between spinothalamic terminals and thalamocortical cells in squirrel monkeys. J. Comp. Neurol. 308, 467–490.

Goadsby, P. J., Lipton, R. B., and Ferrari, M. D. 2002. Migraine – current understanding and treatment. N. Engl. J. Med. 346, 257–270.

Goldstein, J. M., Jerram, M., Poldrack, R., Ahern, T., Kennedy, D. N., Seidman, L. J., and Makris, N. 2005. Hormonal cycle modulates arousal circuitry in women using functional magnetic resonance imaging. J. Neurosci. 25, 9309–9316.

Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A., Petzke, F., Williams, D. A., and Clauw, D. J. 2004. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. Brain 127, 835–843.

Gracely, R. H., Petzke, F., Wolf, J. M., and Clauw, D. J. 2002. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum. 46, 1333–1343.

Grachev, I. D., Fredrickson, B. E., and Apkarian, A. V. 2000. Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. Pain 89, 7–18.

Grachev, I. D., Fredrickson, B. E., and Apkarian, A. V. 2002. Brain chemistry reflects dual states of pain and anxiety in chronic low back pain. J. Neural Transm. 109, 1309–1334.

Granziera, C., DaSilva, A. F., Snyder, J., Tuch, D. S., and Hadjikhani, N. 2006. Anatomical alterations of the visual motion processing network in migraine with and without aura. PLoS Med. 3, e402.

Greenspan, J. D., Lee, R. R., and Lenz, F. A. 1999. Pain sensitivity alterations as a function of lesion location in the parasylvian cortex. Pain 81, 273–282.

Hadjikhani, N., Sanchez, d. R., Wu, O., Schwartz, D., Bakker, D., Fischl, B., Kwong, K. K., Cutrer, F. M., Rosen, B. R., Tootell, R. B., Sorensen, A. G., and Moskowitz, M. A. 2001. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. Proc. Natl. Acad. Sci. U. S. A. 98, 4687–4692.

Hagelberg, N., Forssell, H., Aalto, S., Rinne, J. O., Scheinin, H., Taiminen, T., Nagren, K., Eskola, O., and Jaaskelainen, S. K. 2003a. Altered dopamine D2 receptor binding in atypical facial pain. Pain 106, 43–48.

Hagelberg, N., Forssell, H., Rinne, J. O., Scheinin, H., Taiminen, T., Aalto, S., Luutonen, S., Nagren, K., and Jaaskelainen, S. 2003b. Striatal dopamine D1 and D2 receptors in burning mouth syndrome. Pain 101, 149–154.

Hagelberg, N., Kajander, J. K., Nagren, K., Hinkka, S., Hietala, J., and Scheinin, H. 2002. Mu-receptor agonism with alfentanil increases striatal dopamine D2 receptor binding in man. Synapse 45, 25–30.

Hampson, E. 2002. Sex Differences in Human Brain and Cognition: the Influence of Sex Steroids in Early and Adult Life. In: Behavioral endocrinology, 2nd edn. (eds. J. B. Becker, S. M. Breedlove, D. Crews, and M. M. McCarthy) pp. 579–628. MIT Press.

Hari, R. and Forss, N. 1999. Magnetoencephalography in the study of human somatosensory cortical processing. Phil. Trans. R. Soc. Lond. B 354, 1145–1154.

Head, H. and Holmes, G. 1911. Sensory disturbances from cerebral lesions. Brain 34, 102–254.

Hofbauer, R. K., Rainville, P., Duncan, G. H., and Bushnell, M. C. 2001. Cortical representation of the sensory dimension of pain. J. Neurophysiol. 86, 402–411.

Hsieh, J. C., Belfrage, M., Stoneelander, S., Hansson, P., and Ingvar, M. 1995. Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 63, 225–236.

Hsieh, J. C., Meyerson, B. A., and Ingvar, M. 1999a. PET study on central processing of pain in trigeminal neuropathy. Eur. J. Pain 3, 51–65.

Hsieh, J. C., Stone-Elander, S., and Ingvar, M. 1999b. Anticipatory coping of pain expressed in the human anterior

cingulate cortex: a positron emission tomography study. Neurosci. Lett. 262, 61–64.

Hutchison, W. D., Davis, K. D., Lozano, A. M., Tasker, R. R., and Dostrovsky, J. O. 1999. Pain-related neurons in the human cingulate cortex. Nature Neurosci. 2, 403–405.

Iannetti, G. D., Truini, A., Romaniello, A., Galeotti, F., Rizzo, C., Manfredi, M., and Cruccu, G. 2003. Evidence of a specific spinal pathway for the sense of warmth in humans. J. Neurophysiol. 89, 562–570.

Jaaskelainen, S. K., Rinne, J. O., Forssell, H., Tenovuo, O., Kaasinen, V., Sonninen, P., and Bergman, J. 2001. Role of the dopaminergic system in chronic pain – a fluorodopa-PET study. Pain 90, 257–260.

Jackson, P. L., Meltzoff, A. N., and Decety, J. 2005. How do we perceive the pain of others? A window into the neural processes involved in empathy. Neuroimage 24, 771–779.

Jones, A. K. P., Brown, W. D., Friston, K. J., Qi, L. Y., and Frackowiak, R. S. J. 1991a. Cortical and subcortical localization of response to pain in man using positron emission tomography. Proc. R. Soc. Lond. B 244, 39–44.

Jones, A. K. P., Qi, L. Y., Fujirawa, T., Luthra, S. K., Ashburner, J., Bloomfield, P., Cunningham, V. J., Itoh, M., Fukuda, H., and Jones, T. 1991b. In vivo distribution of opioid receptors in man in relation to the cortical projections of the medial and lateral pain systems measured with positron emission tomography. Neurosci. Lett. 126, 25–28.

Jones, A. K. P., Watabe, H., Cunningham, V. J., and Jones, T. 2004. Cerebral decreases in opioid receptor binding in patients with central neuropathic pain measured by [11C]diprenorphine binding and PET. Eur. J. Pain 8, 479–485.

Kajantie, E. and Phillips, D. I. 2006. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology 31, 151–178.

Kanda, M., Nagamine, T., Ikeda, A., Ohara, S., Kunieda, T., Fujiwara, N., Yazawa, S., Sawamoto, N., Matsumoto, R., Taki, W., and Shibasaki, H. 2000. Primary somatosensory cortex is actively involved in pain processing in human. Brain Res. 853, 282–289.

Keltner, J. R., Furst, A., Fan, C., Redfern, R., Inglis, B., and Fields, H. L. 2006. Isolating the modulatory effect of expectation on pain transmission: a functional magnetic resonance imaging study. J. Neurosci. 26, 4437–4443.

Kenshalo, D. R. and Isensee, O. 1983. Responses of primate SI cortical neurons to noxious stimuli. J. Neurophysiol. 50, 1479–1496.

Kenshalo, D. R. and Willis, W. D. 1991. The Role of the Cerebral Cortex in Pain Sensation. In: Cerebral Cortex, Vol. 9 (ed. A. Peters), pp. 153–212. Plenum Press.

Kenshalo, D. R., Chudler, E. H., Anton, F., and Dubner, R. 1988. SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. Brain Res. 454, 378–382.

Kenshalo, D. R., Iwata, K., Sholas, M., and Thomas, D. A. 2000. Response properties and organization of nociceptive neurons in area 1 of monkey primary somatosensory cortex. J. Neurophysiol. 84, 719–729.

Kong, J., Gollub, R. L., Rosman, I. S., Webb, J. M., Vangel, M. G., Kirsch, I., and Kaptchuk, T. J. 2006. Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging. J. Neurosci. 26, 381–388.

Koyama, T., Kato, K., Tanaka, Y. Z., and Mikami, A. 2001. Anterior cingulate activity during pain-avoidance and reward tasks in monkeys. Neurosci. Res. 39, 421–430.

Koyama, T., Tanaka, Y. Z., and Mikami, A. 1998. Nociceptive neurons in the macaque anterior cingulate activate during anticipation of pain. Neuroreport 9, 2663–2667.

Kunde, V. and Treede, R. D. 1993. Topography of middle-latency somatosensory evoked potentials following painful laser stimuli and non-painful electrical stimuli. Electroenceph. Clin. Neurophysiol. 88, 280–289.

Kulkarni, B., Bentley, D. E., Elliott, R., Youell, P., Watson, A., Derbyshire, S. W., Frackowiak, R. S., Friston, K. J., and Jones, A. K. 2005. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. Eur. J. Neurosci. 21, 3133–3142.

Kupers, R. and Kehlet, H. 2006. Brain imaging of clinical pain states: a critical review and strategies for future studies. Lancet Neurol. 5, 1033–1044.

Kwan, C. L., Diamant, N. E., Pope, G., Mikula, K., Mikulis, D. J., and Davis, K. D. 2005. Abnormal forebrain activity in functional bowel disorder patients with chronic pain. Neurology 65, 1268–1277.

Lamour, Y., Guilbaud, G., and Willer, J. C. 1983. Rat somatosensory (SmI) cortex: II. Laminar and columnar organization of noxious and non-noxious inputs. Exp. Brain Res. 49, 46–54.

Lamour, Y., Willer, J. C., and Guilbaud, G. 1982. Neuronal responses to noxious stimulation in rat somatosensory cortex. Neurosci. Lett. 29, 35–40.

Lawal, A., Kern, M., Sidhu, H., Hofmann, C., and Shaker, R. 2006. Novel evidence for hypersensitivity of visceral sensory neural circuitry in irritable bowel syndrome patients. Gastroenterology 130, 26–33.

Lenz, F. A., Rios, M., Chau, D., Krauss, G. L., Zirh, T. A., and Lesser, R. P. 1998a. Painful stimuli evoke potentials recorded from the parasylvian cortex in humans. J. Neurophysiol. 80, 2077–2088.

Lenz, F. A., Seike, M., Richardson, R. T., Lin, Y. C., Baker, F. H., Khoja, I., Jaeger, C. J., and Gracely, R. H. 1993. Thermal and pain sensations evoked by microstimulation in the area of human ventrocaudal nucleus. J. Neurophysiol. 70, 200–212.

Lenz, F. A., Rios, M., Zirh, A., Chau, D., Krauss, G., and Lesser, R. P. 1998b. Painful stimuli evoke potentials recorded over the human anterior cingulate gyrus. J. Neurophysiol. 79, 2231–2234.

Levine, J. D., Gordon, N. C., and Fields, H. L. 1978. The mechanism of placebo analgesia. Lancet 2, 654–657.

Lidstone, S. C. and Stoessl, A. J. 2007. Understanding the placebo effect: contributions from neuroimaging. Mol. Imaging Biol. 9, 176–185.

Longe, S. E., Wise, R., Bantick, S., Lloyd, D., Johansen-Berg, H., McGlone, F., and Tracey, I. 2001. Counter-stimulatory effects on pain perception and processing are significantly altered by attention: an fMRI study. Neuroreport 12, 2021–2025.

Lorenz, J., Beck, H., and Bromm, B. 1997. Cognitive performance, mood and experimental pain before and during morphine-induced analgesia in patients with chronic non-malignant pain. Pain 73, 369–375.

Lorenz, J., Minoshima, S., and Casey, K. L. 2003. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 126, 1079–1091.

Maarrawi, J., Peyron, R., Mertens, P., Costes, N., Magnin, M., Sindou, M., Laurent, B., and Garcia-Larrea, L. 2007. Differential brain opioid receptor availability in central and peripheral neuropathic pain. Pain 127, 183–194.

Magerl, W., Ali, Z., Ellrich, J., Meyer, R. A., and Treede, R. D. 1999. C- and Ad-fiber components of heat-evoked cerebral potentials in healthy human subjects. Pain 82, 127–137.

Maihöfner, C., Forster, C., Birklein, F., Neundörfer, B., and Handwerker, H. O. 2005. Brain processing during

mechanical hyperalgesia in complex regional pain syndrome: a functional MRI study. Pain 114, 93–103.

Marchand, S. and Arsenault, P. 2002. Odors modulate pain perception: a gender-specific effect. Physiol. Behav. 76, 251–256.

Martikainen, I. K., Hagelberg, N., Mansikka, H., Hietala, J., Nagren, K., Scheinin, H., and Pertovaara, A. 2005. Association of striatal dopamine D2/D3 receptor binding potential with pain but not tactile sensitivity or placebo analgesia. Neurosci. Lett. 376, 149–153.

Marshall, J. 1951. Sensory disturbances in cortical wounds with special reference to pain. J. Neurol. Neurosurg. Psychiatry 14, 187–204.

May, A., Ashburner, J., Büchel, C., McGonigle, D. J., Friston, K. J., Frackowiak, R. S., and Goadsby, P. J. 1999. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat. Med. 5, 836–838.

May, A., Bahra, A., Buchel, C., Frackowiak, R. S., and Goadsby, P. J. 2000. PET and MRA findings in cluster headache and MRA in experimental pain. Neurology 55, 1328–1335.

Melzack, R. and Casey, K. L. 1968. Sensory, Motivational, and Central Control Determinants of Pain. A New Conceptual Model. In: The Skin Senses. (eds. D. R Kenshalo and C. Charles), pp. 423–443. Thomas.

Mertz, H., Morgan, V., Tanner, G., Pickens, D., Price, R., Shyr, Y., and Kessler, R. 2000. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. Gastroenterology 118, 842–848.

Miyazaki, M., Shibasaki, H., Kanda, M., Xu, X., Shindo, K., Honda, M., Ikeda, A., Nagamine, T., Kaji, R., and Kimura, J. 1994. Generator mechanism of pain-related evoked potentials following CO2 laser stimulation of the hand: scalp topography and effect of predictive warning signal. J. Clin. Neurophysiol. 11, 242–254.

Moriguchi, Y., Decety, J., Ohnishi, T., Maeda, M., Mori, T., Nemoto, K., Matsuda, H., and Komaki, G. 2006. Empathy and judging other's pain: an fMRI study of alexithymia. Cereb. Cortex doi: 10.1093/cercor/bh1130.

Morrison, I., Lloyd, D., di Pellegrino, G., and Roberts, N. 2004. Vicarious responses to pain in anterior cingulate cortex: is empathy a multisensory issue? Cogn. Affect. Behav. Neurosci. 4, 270–278.

Nakai, A., Kumakura, Y., Boivin, M., Rosa, P., Diksic, M., D'Souza, D., and Kersey, K. 2003. Sex differences of brain serotonin synthesis in patients with irritable bowel syndrome using a [^{11}C]methyl-l-tryptophan, positron emission tomography and statistical parametric mapping. Can. J. Gastroenterol. 17, 191–196.

Özcan, M., Baumgärtner, U., Vucurevic, G., Stoeter, P., and Treede, R. D. 2005. Spatial resolution of fMRI in the human parasylvian cortex: comparison of somatosensory and auditory activation. Neuroimage 25, 877–887.

Ohara, S., Crone, N. E., Weiss, N., and Lenz, F. A. 2006. Analysis of synchrony demonstrates 'pain networks' defined by rapidly switching, task-specific, functional connectivity between pain-related cortical structures. Pain 123, 244–253.

Ohara, S., Crone, N. E., Weiss, N., Treede, R. D., and Lenz, F. A. 2004. Cutaneous painful laser stimuli evoke responses recorded directly from primary somatosensory cortex in awake humans. J. Neurophysiol. 91, 2734–2746.

Opsommer, E., Weiss, T., Plaghki, L., and Miltner, W. H. R. 2001. Dipole analysis of ultralate (C-fibres) evoked potentials after laser stimulation of tiny cutaneous surface areas in humans. Neurosci. Lett. 298, 41–44.

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M., and Mauguière, F. 2002. Representation of

pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cereb. Cortex 12, 376–385.

Pascual-Marqui, R. D., Michel, C. M., and Lehmann, D. 1994. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int. J. Psychophysiol. 18, 49–65.

Pattany, P. M., Yezierski, R. P., Widerstrom-Noga, E. G., Bowen, B. C., Martinez-Arizala, A., Garcia, B. R., and Quencer, R. M. 2002. Proton magnetic resonance spectroscopy of the thalamus in patients with chronic neuropathic pain after spinal cord injury. AJNR Am. J. Neuroradiol. 23, 901–905.

Pauli, P., Wiedemann, G., and Nickola, M. 1999. Pain sensitivity, cerebral laterality, and negative affect. Pain 80, 359–364.

Paulson, P. E., Minoshima, S., Morrow, T. J., and Casey, K. L. 1998. Gender differences in pain perception and patterns of cerebral activation during noxious heat stimulation in humans. Pain 76, 223–229.

Pertovaara, A., Martikainen, I. K., Hagelberg, N., Mansikka, H., Nagren, K., Hietala, J., and Scheinin, H. 2004. Striatal dopamine D2/D3 receptor availability correlates with individual response characteristics to pain. Eur. J. Neurosci. 20, 1587–1592.

Petrovic, P., Dietrich, T., Fransson, P., Andersson, J., Carlsson, K., and Ingvar, M. 2005. Placebo in emotional processing-induced expectations of anxiety relief activate a generalized modulatory network. Neuron 46, 957–969.

Petrovic, P., Kalso, E., Petersson, K. M., and Ingvar, M. 2002. Placebo and opioid analgesia- imaging a shared neuronal network. Science 295, 1737–1740.

Petrovic, P., Petersson, K. M., Ghatan, P. H., Stone-Elander, S., and Ingvar, M. 2000. Pain-related cerebral activation is altered by a distracting cognitive task. Pain 85, 19–30.

Peyron, R., Laurent, B., and García-Larrea, L. 2000. Functional imaging of brain responses to pain. A review and meta-analysis 2000. Neurophysiol. Clin. 30, 263–288.

Phillips, M. L., Gregory, L. J., Cullen, S., Cohen, S., Ng, V., Andrew, C., Giampietro, V., Bullmore, E., Zelaya, F., Amaro, E., Thompson, D. G., Hobson, A. R., Williams, S. C., Brammer, M., and Aziz, Q. 2003. The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. Brain 126, 669–684.

Plaghki, L. and Mouraux, A. 2003. How do we selectively activate skin nociceptors with a high power infrared laser? Physiology and biophysics of laser stimulation. Neurophysiol. Clin. 33, 269–277.

Ploghaus, A., Tracey, I., Gati, J. S., Clare, S., Menon, R. S., Matthews, P. M., and Rawlins, J. N. 1999. Dissociating pain from its anticipation in the human brain. Science 284, 1979–1981.

Ploner, M., Schmitz, F., Freund, H. J., and Schnitzler, A. 1999. Parallel activation of primary and secondary somatosensory cortices in human pain processing. J. Neurophysiol. 81, 3100–3104.

Ploner, M., Schmitz, F., Freund, H. J., and Schnitzler, A. 2000. Differential organization of touch and pain in human primary somatosensory cortex. J. Neurophysiol. 83, 1770–1776.

Porro, C. A., Baraldi, P., Pagnoni, G., Serafini, M., Facchin, P., Maieron, M., and Nichelli, P. 2002. Does anticipation of pain affect cortical nociceptive systems? J. Neurosci. 22, 3206–3214.

Price, D. D. 2000. Psychological and neural mechanisms of the affective dimension of pain. Science 288, 1769–1772.

Raij, T. T., Numminen, J., Narvanen, S., Hiltunen, J., and Hari, R. 2005. Brain correlates of subjective reality of physically and

psychologically induced pain. Proc. Natl. Acad. Sci. U. S. A. 102, 2147–2151.

Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., and Bushnell, M. C. 1997. Pain affect encoded in human anterior cingulate but not somatosensory cortex. Science 277, 968–971.

Ringel, Y. 2006. New directions in brain imaging research in functional gastrointestinal disorders. Dig. Dis. 24, 278–285.

Robinson, C. J. and Burton, H. 1980. Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory, and granular insular cortical areas of M. fascicularis. J. Comp. Neurol. 192, 93–108.

Rolke, R., Baron, R., Maier, C., Tölle, T. R., Treede, R. D., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Botefur, I. C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G. B., Magerl, W., Maihofner, C., Rolko, C., Schaub, C., Scherens, A., Sprenger, T., Valet, M., and Wasserka, B. 2006. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 123, 231–243.

Rosen, S. D., Paulesu, E., Nihoyannopoulos, P., Tousoulis, D., Frackowiak, R. S., Frith, C. D., Jones, T., and Camici, P. G. 1996. Silent ischemia as a central problem: regional brain activation compared in silent and painful myocardial ischemia. Ann. Intern. Med. 124, 939–949.

Rosen, S. D., Paulesu, E., Wise, R. J., and Camici, P. G. 2002. Central neural contribution to the perception of chest pain in cardiac syndrome X. Heart 87, 513–519.

Sawamoto, N., Honda, M., Okada, T., Hanakawa, T., Kanda, M., Fukuyama, H., Konishi, J., and Shibasaki, H. 2000. Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. J. Neurosci. 20, 7438–7445.

Scharein, E. and Bromm, B. 1998. The intracutaneous pain model in the assessment of analgesic efficacy. Pain Rev. 5, 216–246.

Scherg, M. 1992. Functional imaging and localization of electromagnetic brain activity. Brain Topogr. 5, 103–111.

Schlaepfer, T. E., Strain, E. C., Greenberg, B. D., Preston, K. L., Lancaster, E., Bigelow, G. E., Barta, P. E., and Pearlson, G. D. 1998. Site of opioid action in the human brain: mu and kappa agonists' subjective and cerebral blood flow effects. Am. J. Psychiatry 155, 470–473.

Schlereth, T., Baumgärtner, U., Magerl, W., Stoeter, P., and Treede, R. D. 2003. Left-hemisphere dominance in early nociceptive processing in the human parasylvian cortex. Neuroimage 20, 441–454.

Schmahl, C., Bohus, M., Esposito, F., Treede, R. D., Di Salle, F., Greffrath, W., Ludaescher, P., Jochims, A., Lieb, K., Scheffler, K., Hennig, J., and Seifritz, E. 2006. Neural correlates of antinociception in borderline personality disorder. Arch. Gen. Psychiatry 63, 659–667.

Schweinhardt, P., Glynn, C., Brooks, J., McQuay, H., Jack, T., Chessell, I., Bountra, C., and Tracey, I. 2006. An fMRI study of cerebral processing of brush-evoked allodynia in neuropathic pain patients. Neuroimage 32, 256–265.

Scott, D. J., Heitzeg, M. M., Koeppe, R. A., Stohler, C. S., and Zubieta, J. K. 2006. Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity. J. Neurosci. 26, 10789–10795.

Seitz, R. J., Roland, P. E., Bohm, C., Greitz, T., and Stone-Elander, S. 1991. Somatosensory discrimination of shape: tactile exploration and cerebral activation. Eur. J. Neurosci. 3, 481–492.

Sikes, R. W. and Vogt, B. A. 1992. Nociceptive neurons in area 24 of rabbit cingulate cortex. J. Neurophysiol. 68, 1720–1732.

Silverman, D. H., Munakata, J. A., Ennes, H., Mandelkern, M. A., Hoh, C. K., and Mayer, E. A. 1997. Regional cerebral activity in normal and pathological perception of visceral pain. Gastroenterology 112, 64–72.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R. J., and Frith, C. D. 2004. Empathy for pain involves the affective but not sensory components of pain. Science 303, 1157–1162.

Smith, Y. R., Stohler, C. S., Nichols, T. E., Bueller, J. A., Koeppe, R. A., and Zubieta, J. K. 2006. Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. J. Neurosci. 26, 5777–5785.

Spreng, M. and Ichioka, M. 1964. Langsame Rindenpotentiale bei Schmerzreizung am Menschen. Pflügers Arch. 279, 121–132.

Stevens, R. T., London, S. M., and Apkarian, A. V. 1993. Spinothalamocortical projections to the secondary somatosensory cortex (SII) in squirrel monkey. Brain Res. 631, 241–246.

Stiasny-Kolster, K., Magerl, W., Oertel, W. H., Möller, J. C., and Treede, R. D. 2004. Static mechanical hyperalgesia without dynamic tactile allodynia in patients with restless legs syndrome. Brain 127, 773–782.

Strigo, I. A., Duncan, G. H., Boivin, M., and Bushnell, M. C. 2003. Differentiation of visceral and cutaneous pain in the human brain. J. Neurophysiol. 89, 3294–3303.

Strittmatter, M., Hamann, G. F., Grauer, M., Fischer, C., Blaes, F., Hoffmann, K. H., and Schimrigk, K. 1996. Altered activity of the sympathetic nervous system and changes in the balance of hypophyseal, pituitary and adrenal hormones in patients with cluster headache. Neuroreport 7, 1229–1234.

Talbot, J. D., Marrett, S., Evans, A. C., Meyer, E., Bushnell, M. C., and Duncan, G. H. 1991. Multiple representations of pain in human cerebral cortex. Science 251, 1355–1358.

Tarkka, I. M. and Treede, R. D. 1993. Equivalent electrical source analysis of pain-related somatosensory evoked potentials elicited by a CO_2 laser. J. Clin. Neurophysiol. 10, 513–519.

Timmermann, L., Ploner, M., Haucke, K., Schmitz, F., Baltissen, R., and Schnitzler, A. 2001. Differential coding of pain intensity in the human primary and secondary somatosensory cortex. J. Neurophysiol. 86, 1499–1503.

Tölle, T. R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., Zieglgänsberger, W., Willoch, F., Schwaiger, M., Conrad, B., and Bartenstein, P. 1999. Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. Ann. Neurol. 45, 40–47.

Tommerdahl, M., Delemos, K. A., Vierck, C. J., Favorov, O. V., and Whitsel, B. L. 1996. Anterior parietal cortical response to tactile and skin-heating stimuli applied to the same skin site. J. Neurophysiol. 75, 2662–2670.

Tracey, I. 2001. Prospects for human pharmacological functional magnetic resonance imaging (phMRI). J. Clin. Pharmacol. Suppl. 21S–28S.

Tracey, I., Ploghaus, A., Gati, J. S., Clare, S., Smith, S., Menon, R. S., and Matthews, P. M. 2002. Imaging attentional modulation of pain in the periaqueductal gray in humans. J. Neurosci. 22, 2748–2752.

Treede, R. D. 2001. Neural Basis of Pain. In: International Encyclopedia of the Social & Behavioral Sciences (eds. N. J. Smelser and P. B. Baltes), pp. 11000–11005. Elsevier.

Treede, R. D., Apkarian, A. V., Bromm, B., Greenspan, J. D., and Lenz, F. A. 2000. Cortical representation of pain: functional characterization of nociceptive areas near the lateral sulcus. Pain 87, 113–119.

Treede, R. D., Baumgärtner, U., and Lenz, F. A. 2007. Nociceptive Processing in the Secondary Somatosensory Cortex. In: Encyclopedia of Pain (eds. R. F. Schmidt and W. D. Willis), pp. 1376–1379. Springer.

Treede, R. D., Kenshalo, D. R., Gracely, R. H., and Jones, A. K. P. 1999. The cortical representation of pain. Pain 79, 105–111.

Treede, R. D., Meyer, R. A., and Campbell, J. N. 1998. Myelinated mechanically insensitive afferents from monkey hairy skin: heat response properties. J. Neurophysiol. 80, 1082–1093.

Treede, R. D., Lorenz, J., and Baumgärtner, U. 2003. Clinical usefulness of laser-evoked potentials. Neurophysiol. Clin. 33, 303–314.

Valeriani, M., Rambaud, L., and Mauguière, F. 1996. Scalp topography and dipolar source modelling of potentials evoked by CO_2 laser stimulation of the hand. Electroenceph. Clin. Neurophysiol. 100, 343–353.

Valeriani, M., Sestito, A., Le Pera, D., De Armas, L., Infusino, F., Maiese, T., Sgueglia, G. A., Tonali, P. A., Crea, F., Restuccia, D., and Lanza, G. A. 2005. Abnormal cortical pain processing in patients with cardiac syndrome X. Eur. Heart J. 26, 975–982.

Valet, M., Sprenger, T., Boecker, H., Willoch, F., Rummeny, E., Conrad, B., Erhard, P., and Tölle, T. R. 2004. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain – an fMRI analysis. Pain 109, 399–408.

Verne, G. N., Himes, N. C., Robinson, M. E., Gopinath, K. S., Briggs, R. W., Crosson, B., and Price, D. D. 2003. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. Pain 103, 99–110.

Villemure, C. and Bushnell, M. C. 2002. Cognitive modulation of pain: how do attention and emotion influence pain processing? Pain 95, 195–199.

Vogel, H., Port, J. D., Lenz, F. A., Solaiyappan, M., Krauss, G., and Treede, R. D. 2003. Dipole source analysis of laser-evoked subdural potentials recorded from parasylvian cortex in humans. J. Neurophysiol. 89, 3051–3060.

Vogt, B. A. 2005. Pain and emotion interactions in subregions of the cingulate gyrus. Nat. Rev. Neurosci. 6, 533–544.

Vogt, B. A., Nimchinsky, E. A., Vogt, L. J., and Hof, P. R. 1995. Human cingulate cortex: surface features, flat maps, and cytoarchitecture. J. Comp. Neurol. 359, 490–506.

Vogt, B. A., Rosene, D. L., and Pandya, D. N. 1979. Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. Science 204, 205–207.

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., and Cohen, J. D. 2004. Placebo-induced changes in fMRI in the anticipation and experience of pain. Science 303, 1162–1167.

Wagner, K. J., Willoch, F., Kochs, E. F., Siessmeier, T., Tölle, T. R., Schwaiger, M., and Bartenstein, P. 2001. Dose-dependent regional cerebral blood flow changes during remifentanil infusion in humans: a positron emission tomography study. Anesthesiology 94, 732–739.

Wang, S. J., Lirng, J. F., Fuh, J. L., and Chen, J. J. 2006. Reduction in hypothalamic 1H-MRS metabolite ratios in patients with cluster headache. J. Neurol. Neurosurg. Psychiatry 77, 622–625.

Wiesenfeld-Hallin, Z. 2005. Sex differences in pain perception. Gend. Med. 2, 137–145.

Willis, W. D. and Coggeshall, R. E. 2004. Sensory Mechanisms of the Spinal Cord: Primary Afferent Neurons and the Spinal Dorsal Horn, Vol. 1. Kluwer Academic/ Plenum Publishers.

Willoch, F., Schindler, F., Wester, H. E., Empl, M., Straube, A., Schwaiger, M., Conrad, B., and Tölle, T. R. 2004. Central poststroke pain and reduced opioid receptor binding within pain processing circuitries: a [C-11]diprenorphine PET study. Pain 108, 213–220.

Wilson, J. F. 2006. The pain divide between men and women. Ann. Intern. Med 144, 461–464.

Wood, P. B., Patterson, J. C., Sunderland, J. J., Tainter, K. H., Glabus, M. F., and Lilien, D. L. 2007. Reduced presynaptic dopamine activity in fibromyalgia syndrome demonstrated with positron emission tomography: a pilot study. J. Pain 8, 51–58.

Yamamura, H., Iwata, K., Tsuboi, Y., Toda, K., Kitajima, K., Shimizu, N., Nomura, H., Hibiya, J., Fujita, S., and Sumino, R. 1996. Morphological and electrophysiological properties of ACCx nociceptive neurons in rats. Brain Res. 735, 83–92.

Xu, X. P., Fukuyama, H., Yazawa, S., Mima, T., Hanakawa, T., Magata, Y., Kanda, M., Fujiwara, N., Shindo, K., Nagamine, T., and Shibasaki, H. 1997. Functional localization of pain perception in the human brain studied by PET. Neuroreport 8, 555–559.

Zelman, D. C., Howland, E. W., Nichols, S. N., and Cleeland, C. S. 1991. The effects of induced mood on laboratory pain. Pain 46, 105–111.

Zubieta, J. K., Smith, Y. R., Bueller, J. A., Xu, Y., Kilbourn, M. R., Jewett, D. M., Meyer, C. R., Koeppe, R. A., and Stohler, C. S. 2001. Regional mu opioid receptor regulation of sensory and affective dimensions of pain. Science 293, 311–315.

Zubieta, J. K., Bueller, J. A., Jackson, L. R., Scott, D. J., Xu, Y., Koeppe, R. A., Nichols, T. E., and Stohler, C. S. 2005. Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. J. Neurosci. 25, 7754–7762.

Zubieta, J. K., Smith, Y. R., Bueller, J. A., Xu, Y., Kilbourn, M. R., Jewett, D. M., Meyer, C. R., Koeppe, R. A., and Stohler, C. S. 2002. μ-Opioid receptor-mediated antinociceptive responses differ in men and women. J. Neurosci. 22, 5100–5107.