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Deconstructing Central Pain with Psychophysical and Neuroimaging Studies

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1. Introduction

The IASP has defined central pain as initiated or caused by a primary lesion or dysfunction of the central nervous system (CNS)" (Merskey, 1986). A more recent and specific definition describes central pain as "pain arising as a direct consequence of a lesion or disease affecting the central somatosensory system" (Treede et al., 2008). This definition recognizes that a disturbance of the central somatosensory system is the essential feature of central pain. A disturbance of this system applies to all central pain conditions, although they exhibit great variability across different etiologies. This chapter includes structural and functional imaging results, as well as the results of psychophysical studies, as they complement the imaging results. There is some overlap between the content of this chapter and our previous reviews of this topic (Veldhuijzen et al., 2007;Greenspan et al., 2008;Veldhuijzen et al., 2011).

2. Prevalence of sensory abnormalities in central pain?

Patients with central pain (CP) inevitably show stimulus-evoked sensory abnormalities which include negative symptoms such as hypoesthesia and hypoalgesia, as well as positive symptoms such as hyperalgesia Hyperalgesia is increased pain evoked by a stimulus which can be painful, such as deep pressure over a muscle which has been injured or bruised. Another positive symptom is allodynia which is pain evoked by a stimulus which is not normally painful, such as pain evoked by light touch following a sunburn.
When studied by quantitative sensory testing (QST, Table 1), patients with central post-stroke pain (CPSP) exhibit hypoesthesia for cold in 85-91% of patients, for warmth in 85-100%. Decreased sensation for pain (hypoalgesia) is found for cold pain in roughly 45% of patients, and for heat pain in 7-91% (Boivie et al., 1989;Leijon et al., 1989;Andersen et al., 1995;Vestergaard et al., 1995;Greenspan et al., 2004). As shown in Table 1, CPSP patients show decreased tactile sensibility in 27-52% of cases. These results demonstrate that decreased sensation or negative sensory signs vary widely across the CPSP patient population. Overall, these patients do not show sensory deficits for all types of thermal and

	(Ohara et al., 2004)	(Boivie et al., 1989;Leijon et al., 1989)	Clinic (Vestergaard et al., 1995) QST (Andersen et al., 1995).
Burning cold/cold pain	53% overall; 38%, burning & cold; 15%, hot and cold;	59%, 16/27	38%, 6/16 (freezing 3/16)
Mechanical pain	77% overall 33%, sharp/stab; 23%, pressure heavy; tight/ squeezing 7% each	Aching 30%, Pricking 30%, lacerating 26%.	86%, 23/27.
Pain rating	7.1 mean, 2.0 SD	2.5-7.9 mean by stroke location	3.3 median (0-7)
Touch – method	**Von Frey for threshold; brushes for allodynia**	**V Frey for threshold; Pin prick for hyperalgesia**	**V Frey hair, V Frey.**
Normal threshold	50%, 5/10	48%, 13/27.	54%, 6/11.
Hypoesthesia	50%, 5/10	52%, 14/27	27%, 3/11.
Allodynia/ hyperalgesia	54% 7/13.	16/27, 59% - hyperalgesia	1/11-hyperalgesia to rotating von Frey hair
Cool – method	**Peltier Medoc**	**Peltier Somedic, warm minus cool threshold**	**Peltier Somedic**
Normal threshold	15%, 2/13	0/27	9%, 1/11.
	85%, 11/13, 3 with equal bilateral hypoesthesia	Diff in cool-warm thresholds 17/27; larger change in cool 2/27	91%, 10/11.
Cold pain – method	**As above**		
Normal threshold	31%, 4/13	7% normal difference between cold & heat pain threshold	18%, 2/11-unaffected side lower
Hypoalgesia	46%, 6/13 (2 indeterminate)	93% abnormal difference between cold & heat pain threshold	45%, 5/11 (4/11-bilateral)
Allodynia	23%, 3/13	No abnormally sensitive thresholds, but 5/22 (23%) reported discomfort to metal at room temperature	0/11
Warm – method	**As above**		
Normal threshold	15%, 2/13	-	-
Hypoesthesia	85%, 11/13	Diff in cool-warm thresholds, 17/27; larger change in warm threshold 8/27	11/11

Heat pain – method	**As above**		
Normal	93%, 12/13	7% normal difference between cold & heat pain threshold	9%, 1/11.
Hypoalgesia	7%, 1/13 (2 indeterminate)	93% abnormal difference between cold & heat pain threshold	91%, 10/11.
Allodynia	0/13 (2 borderline)	No abnormally sensitive thresholds.	0/11

Table 1. Summary of QST and descriptors of CPSP. The fourth column included both clinical findings (n=16) (Vestergaard et al., 1995) and quantitative sensory testing (n=11) (Andersen et al., 1995). Similarly, the third column included both clinical (Leijon et al., 1989) and sensory testing results (both N=27) (Boivie et al., 1989). Another very large series could not included because quantitative sensory testing results were not described as population statistics, (Bowsher, 1997).

painful stimuli, but they do show decreased sensitivity to at least some submodality of thermal or noxious stimuli.

Another important observation is that some patients with injuries or disease of the central nervous system (CNS) may experience thermal hypoesthesia or hypoalgesia as a result of a CNS lesion without developing central pain. This has been demonstrated for patients with lesions of the spinal cord (Ducreux et al., 2006;Finnerup et al., 2003), and brain (Andersen et al., 1995;Garcia-Larrea et al., 2010).

In the case of cortical lesions, the results of a recent study demonstrate warm and cold hypoesthesia based on QST thresholds in all subjects with lesions of parietal or insular cortex or both (Veldhuijzen et al., 2009). The largest degree of thermal hypoesthesia by threshold measures was found in the subject with the largest lesion, which involved extensive parietal and insular lobar lesions (see also (Greenspan et al., 1999). Suprathreshold measures demonstrated that sensory loss for painful and nonpainful hot and cold modalities was maximal for the largest parietal lesions.

Subjects with relatively small lesions restricted to the posterior insula and retroinsula showed central pain and cold allodynia, based on thresholds and clinical assessment. Cold allodynia based on thresholds but not on clinical assessment were observed in patients with parietal lesions sparing the insula. Similarly, a study of two patients with lesions of the insula and adjacent cortical lobes confirmed normal heat pain thresholds but increased ratings of heat pain compared to controls (Starr et al., 2009). These results suggest that non-painful cold and heat sensations are jointly mediated by parietal and insular cortical structures, while thermal pain sensation is more robust, requiring larger cortical lesions of these same structures to produce hypoalgesia. In addition, these studies dramatically demonstrate that neither the presence nor the extent of abnormal thermal sensation nor cold allodynia following a CNS lesion predicts the presence or the characteristics of central pain syndromes.

The variability of negative and positive symptoms and signs in patients with central pain raises the possibility that the level of spontaneous pain is correlated with the extent of sensory loss in patients with central pain. Such a relationship has been reported among patients with central pain resulting from spinal cord injury (SCI) (Ducreux et al., 2006). Specifically, two differences were observed between syringomyelia patients with or without allodynia. Those with allodynia tended to have 1) lesser thermosensory deficits and 2) more

asymmetrical thermosensory deficits than those without allodynia. The intensity of the spontaneous burning pain was correlated with the degree of thermal sensory loss. Additionally, thermal deficits were less severe in patients with cold allodynia compared to those with tactile allodynia. Therefore, the pattern of thermal sensory loss may differentially influence different features of central pain.

Another study of SCI secondary to syringomyelia compared diffusion tensor imaging (DTI) and electrophysiological potentials between patients with and without neuropathic pain and healthy controls (Hatem et al., 2010). Among those SCI patients with neuropathic pain, higher average daily pain intensity correlated with the extent of structural damage to the spinal cord tracts. Additionally, the number of intact nerve axons within the whole spinal cord was inversely correlated with deep spontaneous pain and dysaesthesias. Patients with both spontaneous and evoked pain had less structural spinal cord damage by morphological and electrophysiological criteria compared to patients with only spontaneous pain. Therefore, in patients with SCI there was strong evidence that the extent of structural lesions is strongly correlated with the expression of spontaneous and evoked pain, or hypersensitivity (Hatem et al., 2010).

Based on the sample of 30 central pain patients (mostly CPSP) evaluated with QST at our research center, we found no relationship between the extent of thermosensory loss (based on cool or warm thresholds), and the level of ongoing pain. Therefore, thermal hypoesthesia may manifest differently in patients with different etiologies of central pain.

3. Central pain and cold allodynia

Cold allodynia is often associated with central pain even though it is not found in the majority of patients with CPSP (Table 1). The expression of cold allodynia is variable, which suggests that there is more than one mechanism for cold allodynia in different patients. In our recent study of seven patients with isolated parietal and/or insular lesions, 4/7 patients had cold allodynia based on thresholds, but only two of these had central pain and clinical cold hyperalgesia based on increased ratings of a painful cold waterbath stimulus (Veldhuijzen et al., 2009). Overall, these results suggest that posterior insular/retroinsular lesions in isolation can lead to cold allodynia as assessed by clinical, threshold and suprathreshold measures.

The matter is further complicated by differences in cold allodynia measured by different QST techniques. Cold allodynia can be evoked by touching the patient with a cool object, such as metal, at room temperature. In this case, the obligatory tactile stimulus may contribute to allodynia sensation, particularly in subjects with tactile allodynia. During QST, cold allodynia is often measured by thresholds for cold pain using a probe which is held on the skin while the temperature decreases until the patient reports pain perception. Surprisingly, the pain with a cold object contact often does not correspond to the pain evoked by the contact probe at the same temperature.

These phenomena have been observed in an early study which reported that 5/22 central pain patients had clinical cold allodynia but none had cold allodynia as measured with a contact temperature probe (Boivie et al., 1989). A similar observation was made in a more recent study (see Table 1). In the same study, 2 patients showed increased sensitivity to cold pain by thresholds, which met experimental criteria for cold allodynia, but the patients did not exhibit cold allodynia during clinical exams.

3.1 Ongoing pain

No relation between the size or location of a lesion and the presence or intensity of central pain has been found, although CP requires an impairment of thermosensory pathways or nociceptive pathways or both (see Table 1) (Boivie et al., 1989;Leijon et al., 1989;Andersen et al., 1995;Vestergaard et al., 1995;Greenspan et al., 2004;Lewis-Jones et al., 1990). In addition, studies of patients with central pain secondary to SCI show that the spinothalamic tract is not differentially affected in pain-free patients as opposed to patients with ongoing central pain (Ducreux et al., 2006;Finnerup et al., 2003). Therefore, lesions involving the spinothalamic pathway and its cortical connections, while necessary, are not sufficient to explain the development of central pain.

In a large series of patients (n=270) investigated for somatosensory abnormalities following stroke, five subjects were identified that presented with central pain and pure thermoalgesic sensory loss contralateral to the cortical stroke. All of these patients had involvement of the posterior insula and inner parietal operculum. Lemniscal sensory modalities and somatosensory evoked potentials to non-noxious inputs were preserved, while thermal and pain sensations were profoundly altered, and laser-evoked potentials were abnormal in all (Garcia-Larrea et al., 2010).

The nature of neural abnormalities in central pain is poorly understood. It has been proposed that thalamic bursting (low-threshold spike or LTS pattern) occurs at a higher rate among neurons in the region of the Ventral caudal (Vc) nucleus in patients with central pain as opposed to those with movement disorders (Jeanmonod et al., 1996;Lenz et al., 1989;Lenz et al., 1994). Another report found no difference in the thalamic burst rate between patients with chronic pain as opposed to those with movement disorder (Radhakrishnan et al., 1999). In the latter report, most of the neuronal recordings were made outside Vc in patients with peripheral neuropathic pain rather than central pain. Thus, this latter report does not speak directly to the mechanism of central pain. Electrical stimulation in the area of Vc evoked pain more commonly in central pain patients with allodynia, versus those without allodynia (Lenz et al., 1998;Davis et al., 1996). Overall, these studies suggest that reorganization of the region of Vc contributes to the symptoms of central pain.

In a study of MR spectroscopy, concentrations of markers for neurons (N-acetyl aspartate, NA) and glial cells (myo-inositol, Ins) in the thalamus were significantly different between patients with versus without central pain after SCI (Pattany et al., 2002;Stanwell et al., 2010). NA concentrations and NA/Ins ratios were lower in patients with pain versus those without, while Ins concentrations were higher for pain patients. In addition, NA concentrations were inversely correlated with VAS pain intensity, and Ins was directly correlated with pain intensity in the pain group. These results suggest that in SCI patients, dysfunction or loss of thalamic neurons is greater among SCI patients with central pain than among those without.

A recent study of SCI patients used a sophisticated wavelet-based analysis of the entire MRS signal to identify differences between SCI patients and intact controls, and between SCI patients with versus without central pain (DiPiero et al., 1991;Hsieh et al., 1995;Iadarola et al., 1995). Signals from the thalamus best discriminated between SCI patients and intact controls, yet signals from regions of the anterior cingulate and prefrontal cortex, but not the thalamus, highly discriminated between SCI patients with versus without central pain. While such an approach cannot identify the specific molecular differences, it does reveal which brain regions exhibit neurochemical differences that relate specifically to neuropathic central pain.

Neuroimaging studies of CP patients have most often reported thalamic hypoactivity, but some have observed thalamic hyperactivity. PET (positron emission tomography) studies

have found a decrease in thalamic cerebral blood flow (CBF) on the same side as the lesion in patients with central pain patients at rest (Ness et al., 1998). The spatial resolution of these studies does not permit identification of the specific thalamic nuclei which were involved. This decrease in activity could be reversed by stimulation of the motor cortex (Peyron et al., 1995), or therapeutic intravenous infusion of lidocaine (Cahana et al., 2004). A similar decrease in thalamic bloodflow has been reported in patients with central and peripheral neuropathic pain combined. Specifically, the thalamus opposite the affected body region had lower bloodflow than the thalamus on the same side as the affected region in patients with SCI and central pain (Lenz et al., 2010). However, a single photon emission CT (SPECT) study found bilateral increased thalamic metabolism associated with pain of high intensity, but decreased blood flow associated with pain of low intensity (Cesaro et al., 1991).

Finally, PET results from CP patients show decreased thalamic bloodflow in both medial and lateral thalamus. Both SPECT and PET studies demonstrate increased thalamic activity contralateral to stimulation of the allodynic sites compared to non-allodynic sites in CPSP patients with or without unilateral allodynia (Lenz et al., 2010). The brain metabolic and bloodflow differences estimated by PET or SPECT reflect both inhibitory and excitatory synaptic activity. Therefore, decreased thalamic bloodflow in patients with CP might reflect decreased inhibitory synaptic activity, which may be related to loss of neurons, as suggested by the MR spectroscopy study reviewed above (Fukumoto et al., 1999). This decrease in bloodflow could occur despite the increased spontaneous thalamic firing rates, since spontaneous activity may not be reflected in metabolic or bloodflow imaging studies of the brain.

It is also possible these results are due to adaptive changes in the thalamus following the inciting lesion. For example, in patients with complex regional pain syndrome a SPECT study found increased thalamic bloodflow in patients with symptoms at 3 to 7 months after the injury, while decreased bloodflow occurred with long-term symptoms (24–36 months after) (Fukumoto et al., 1999).

Finally, ongoing pain in patients with CP might be related to changes in the opiodergic intrinsic modulatory system. These patients show decreased binding of the non-selective opioid binding ligand, diprenorphine, versus healthy controls, which indicate higher levels of binding sites occupied by opioids originating in the brain's intrinsic opioid system (Willoch et al., 2004). These reductions in opioid receptor binding within the "medial nociceptive system" were most pronounced in the dorsolateral prefrontal cortex (Brodmann area 10), anterior cingulate cortex (Brodmann area 24), insular cortex, and the medial thalamus. There were also reductions in binding in the lateral nociceptive system including the inferior parietal cortex (Brodmann area 40). Similar but more extensive decreases in binding were found in a study which included parietal cortex, cingulate and midbrain gray matter; these decreases were independent of the lesion locus which caused CP (Head and Holmes, 1911).

3.2 Mechanisms of cold allodynia in patients with central pain

An often cited hypothesis of cold allodynia suggests that it is the result of disinhibition of the medial nociceptive system following disruption of the lateral nociceptive system (Lenz et al., 2010). An approximate version of this hypothesis was proposed long ago (Head and Holmes, 1911), but the more recent version proposes that the medial system (ACC and medial thalamus) is critical to the mechanism of both central pain and cold allodynia.

This hypothesis was tested by a PET study which reported the bloodflow activity resulting from cutaneous stimulation with a cool, tactile stimulus (ice in a plastic container) in patients with central pain due to lateral medullary stroke (Wallenberg) syndrome (Peyron et al., 1998). This stimulus produced differential activation of structures contralateral to the

affected side but not when it was applied to the unaffected side. These structures included: the primary sensory and motor cortex (contralateral to stimulation), the lateral thalamus (contralateral to stimulation), inferior parietal lobule (bilateral), and the frontal inferior gyrus. Notably, allodynic stimulation failed to evoke responses in medial thalamus or the portion of the ACC associated with pain. This study, then, did not support the model of disinhibition of the medial nociceptive processing system, but rather supported an amplification of the lateral nociceptive processing system as a basis for central pain allodynia.

A single subject PET study of a patient with central pain resulting from an infarct of the thalamus revealed a dramatic increase in sensory and motor cortical activation contralateral to allodynic cold stimulation of the affected hand (Kim et al., 2007). These increases may indicate disruption of a modulatory effect of the insula upon sensorimotor cortex which occurs in the normal brain. A study of two patients with large insular lesions but without central pain found that activation of S1 cortex ipsilateral to the lesioned insula was dramatically increased in response to painful heat stimulation (Starr et al., 2009).

Cold allodynia was associated with BOLD (blood oxygen level dependent) activation in the posterior insula, ACC, bilateral anterior insula, inferior parietal cortex, and supplementary motor cortex contralateral to the stimulus, and in the ipsilateral frontal gyrus of patients with syringomyelia (Ducreux et al., 2006). Brain activation in response to cold allodynic stimulation was much greater than usually evoked by the normally innocuous stimulus, and was comparable to the activation evoked by painful stimuli in controls without sensory abnormality. As noted above, a PET study of patients with Wallenburg strokes did not find activation of the ACC in response to stimuli which produced allodynia (Peyron et al., 1998), although such activation is often found in response to acute pain stimuli in healthy controls (Apkarian et al., 2005;Lenz et al., 2010). A combined PET and fMRI study of a unique patient with strokes of both the ACC and parietal cortex demonstrated cold allodynia, in the absence of hyperactivity in the remaining ACC (Peyron et al., 2000).

In contrast, one fMRI study of a patient with CPSP resulting from a stroke of the postero-lateral thalamus and adjacent internal capsule found activation of the ACC, the posterior parietal cortex, and the putamen during allodynia evoked by a cool stimulus (Seghier et al., 2005). Another fMRI study examined cold allodynia in normal controls evoked by cutaneous application of menthol, which rendered the skin hypersensitive to normally non-painful cold stimuli (Seifert and Maihofner, 2007). Stimulation of the sensitized skin was compared with the same intensity evoked by a normal cold pain stimulus. The pain evoked during allodynia resulted in more activation in dorso-lateral prefrontal cortex, bilateral anterior insula, and in parts of the brainstem. This range of results limits our ability to understand the mechanism of cold allodynia in terms of structures in the brain, particularly the ACC.

3.3 Mechanisms of tactile allodynia in patients with central pain

Tactile hypoesthesia and allodynia are common features of central pain as measured by use of von Frey hairs and camel hair brushes. Hypoesthesia for tactile sensation are associated with lesions of the dorsal columns, while such sensory loss is not found with lesions of the STT which spare the dorsal columns (Finnerup et al., 2007).

One recent study provided the first evidence that A-beta fibers are involved in dynamic mechanical allodynia (Landerholm and Hansson, 2010) In a portion of the central pain patients, dynamic allodynia occurred during a compression nerve block transitioning to a sensation of dysethesia. The remaining patients transitioned directly to the absence of allydynia following the block. In a subset of patients with central pain, concurrent changes in cold, but not warm, perception were found indicating A-delta involvement as well.

In contrast, tactile allodynia was more often associated with normal tactile thresholds than with tactile hypoesthesia in a study of CPSP patients (Hofbauer et al., 2006). Therefore, tactile allodynia may be the result of abnormal forebrain processing of signals transmitted through a relatively intact dorsal column – medial lemniscal system. This is consistent with reports of dysesthesias, which can be evoked by activation of afferents projecting through the dorsal column – medial lemniscal pathway in patients with post-stroke dysesthesias, a variation of CPSP (Triggs and Beric, 1994).

Cortical activation associated with tactile allodynia has been examined in experimental allodynia and peripheral neuropathic pain. A study of experimental allodynia resulting from application of capsaicin treatment in normal volunteers found that S1 and S2 activation occurred during nonpainful stimulation using von Frey filaments (Lorenz et al., 2002). When stimulating the area with mechanical allodynia, significant activation was found in the prefrontal cortex, as well as middle and inferior frontal gyri. There was no activation of the ACC.

In a patient with peripheral neuropathic pain after a peroneal nerve injury ongoing burning pain and tactile allodynia were observed; tactile stimuli evoked a deep pain, despite decreased tactile sensation (Hofbauer et al., 2006). Tactile allodynic sensations of the involved foot were compared with brush stimulation of the non-involved foot, and were associated with higher BOLD signals in S2, ipsilateral anterior insula, and ACC. Increased BOLD signals in S1 or ipsilateral posterior insula were not associated with stimulation of the involved foot, although such increased signals were observed after stimulation of the non-involved foot.

In a group of patients with complex regional pain syndrome, mechanical stimulation of the involved side evoked hyperalgesia and larger than control BOLD signals in several pain-related brain regions, including contralateral S1, bilateral S2, bilateral insula, inferior parietal lobule, and widespread ACC (Maihofner and Handwerker, 2005). Allodynia to a moving brush stimulus has also been studied in patients with traumatic peripheral nerve injury of the extremities, who suffered from ongoing pain and tactile allodynia (Witting et al., 2006). In these patients, allodynia in the affected limb yielded higher bloodflow than in the non-affected limb in contralateral orbitofrontal cortex and ipsilateral anterior insular cortex. Brushing of normal skin in the mirror image of the allodynic area produced a distinctly different pattern with increased bloodflow in contralateral S1 and posterior parietal cortex.

One imaging study has examined BOLD activation by tactile allodynia in patients with central pain secondary to syringomyelia (Ducreux et al., 2006). Tactile allodynia evoked by repeated brushing with a soft brush produced a pattern of brain activation distinct from that produced in normal controls with the same brushing, or with cold allodynic stimulation in these same patients. In all groups, activation was observed in the contralateral S1 and S2, and in parietal association areas. Tactile allodynia specific BOLD activation was elicited in the contralateral thalamus, bilateral middle frontal gyrus, and supplementary motor area, but was not observed in the insula or in the anterior and middle cingulate cortexes.

4. Conclusions

Based upon the data available today, it is not possible to draw any more than tentative conclusions. A frequent observation from PET and SPECT studies is that of thalamic hypometabolism in the painful resting state. At the same time, allodynic stimulation can evoke a stronger thalamic signal than normal. Both observations can be explained by a partially denervated thalamus and by a major disruption of GABA-mediated inhibition (Rausell et al., 1992). There is also some evidence that dysfunction of the thalamic nucleus Vc is involved in the mechanism of central pain (Montes et al., 2005;Kim et al., 2007).

The cortical regions associated with central pain can vary considerably among studies and symptoms of central pain. A recent study has suggested that CPSP occurred only in individuals with lesions including posterior insula/retroinsula, which spare the anterior and posterior parietal cortex (Veldhuijzen et al., 2009). Evidence from neuroimaging studies suggests that the parietal lobe is involved in the mechanism of CPSP and CPSP-associated allodynia in subjects with strokes of the lateral medulla (Wallenberg syndrome)(Peyron et al., 1998), and the thalamic nucleus Vc which projects to the parietal cortex (Kim et al., 2007). In both studies, a combined cold and mechanical cutaneous stimulus produced allodynia, and was associated with intense bloodflow activation of contralateral sensorimotor (frontal and parietal) cortex. In addition, pain sensations are evoked in subjects with CPSP by electrical stimulation of S1 cortex (Katayama et al., 1994;Nguyen et al., 2000;Brown and Barbaro, 2003) or of thalamic nucleus Vc, which projects to it (Lenz et al., 1998;Davis et al., 1996). Lesions of parietal cortex can dramatically relieve pain in subjects with CPSP resulting from thalamic lesions (Soria and Fine, 1991;Helmchen et al., 2002;Canavero and Bonicalzi, 2007). Consideration of these observations suggests the hypothesis that a network of insular and sensorimotor cortex is specifically disrupted in central pain, leading to increased activity in sensorimotor cortex, particularly with respect to the expression of allodynia.

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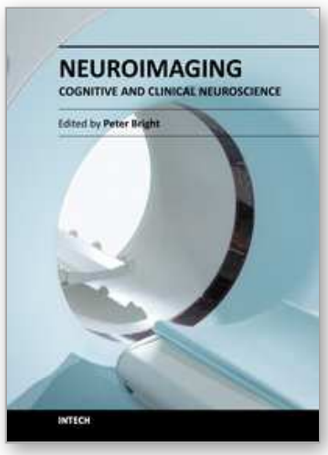
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The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive theory have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address how cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function - the where question).

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