15

Understanding Central Pain: New Insights from Forebrain Imaging Studies of Patients and of Animals with Central Lesions

Thomas J. Morrow and Kenneth L. Casey

Neurology Research Laboratories, Veterans Affairs Hospital, and Departments of Neurology and Physiology, University of Michigan, Ann Arbor, Michigan, USA

Functional imaging of pain-related central nervous system (CNS) activity provides a powerful method for exploring the complex neural mechanisms that support the pain experience. Over the last decade, major advances in brain imaging techniques in humans using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have expanded our knowledge of the neurophysiology of pain and enhanced our understanding of the central mechanisms of pain processing far beyond the limits of traditional electrophysiological and lesion studies. Functional imaging, by allowing us to examine the responses of multiple CNS regions simultaneously in awake, behaving subjects during acute and chronic pain states, provides clear evidence that there is no common “center” or pathway for the generation of pain. Instead, the evidence points to a distributed parallel network or matrix of cortical and subcortical structures that receives afferent input via distinct anatomical pathways (see Apkarian 1995; Casey and Minoshima 1997).

Although most functional imaging studies of pain have used PET or fMRI to examine human subjects, the number of imaging studies performed on animal models of pain is increasing due to recent advances in methodology. Human studies have an obvious advantage in being able to simultaneously assess both experiential/cognitive aspects of pain and brain activation. However, both PET and fMRI have relatively limited spatial resolutions,
whereas film-based animal imaging studies boast spatial resolutions on the order of 20–50 μm. This fine spatial resolution, coupled with the availability of tissue sections, allows us to correlate activation with very small, histologically defined CNS regions. Human functional imaging studies of chronic pain states are subject to significant variability arising from inter-individual differences in the chronic pain syndrome itself. In contrast, inter-individual variation in animal models of chronic pain is considerably reduced by the fact that the pain syndrome can be produced in a carefully controlled fashion. For these reasons our laboratory has employed regional cerebral blood flow (rCBF) imaging in animal models of chronic pain to complement our related human studies using PET. These imaging approaches combine to provide a powerful platform for the investigation of CNS mechanisms of pain. This chapter presents data from these complementary human and animal imaging studies.

STUDIES OF NORMAL HUMANS

We have just begun to identify the sources of variation in the normal pain activation of the human forebrain. However, the results reviewed elsewhere (Casey 1999; Derbyshire 1999) provide a background of information that is sufficiently consistent, even across genders (Paulson et al. 1998), to support studies of the physiological variables that determine the patterns of brain activation during normal pain. For example, Derbyshire and Coghill, with colleagues, used correlation analyses to investigate the inter-regional distribution of information about heat pain intensity (Derbyshire et al. 1997; Coghill et al. 1999). Both groups found that such information is widely distributed among pain-activated regions. In related investigations, Rainville and colleagues (1997) used hypnotic suggestion to uncouple the perception of heat pain unpleasantness from heat pain intensity in normal subjects. They were able to show a positive correlation of pain unpleasantness with the intensity of rCBF response in a far-anterior (dorsal perigenual) region of the anterior cingulate cortex; this correlation was not found in a specific examination of the primary somatosensory (S1) cortex. In differentiating the perception of pain from the anticipation of pain, Ploghaus and colleagues (1999) used fMRI to show that the activation of some regions, previously identified in PET studies of heat pain, is better correlated with the anticipation of pain than with pain perception. Thus, the anticipation of heat pain was related to activity in the far frontal cingulate cortex, anterior insula, and anterior cerebellar vermis, while the perception of pain was related to activity in adjacent regions (mid-anterior cingulate, mid-insula, and paravermian
Finally, we have recently shown the importance of the duration of the heat pain experience in determining the pattern of forebrain activation (Casey et al. 2001). This PET study of normal subjects showed that the pattern of brain activation and the perception of heat pain both change during repetitive noxious heat stimulation. The perceived intensity and unpleasantness of pain both increase with greater duration of the repetitive stimulation. These psychophysical changes could be mediated by brain structures that show increased activity with longer periods of stimulation; these structures include the contralateral M1/S1 cortex, bilateral S2 and mid-insular cortex, contralateral ventral posterior thalamus, medial ipsilateral thalamus, and the vermis and paravermis of the cerebellum. Structures that are equally active throughout stimulation (the contralateral mid-anterior cingulate cortex and premotor cortex) are less likely to mediate these psychophysical changes. Structures showing significant or borderline activation only during the early scans (ipsilateral premotor cortex, contralateral perigenual anterior cingulate cortex, lateral prefrontal cortex, and anterior insular cortex) could mediate pain-related attentive or anticipatory functions, but this hypothesis remains to be tested.

Other forms of pain have been studied less intensively. We have compared the pattern of brain activation produced by cutaneous mechanical contact heat pain with the pain produced by infrared laser stimulation, by ice water immersion, and by deep electrical stimulation of muscle (Casey et al. 1996; Svensson et al. 1997). Cutaneous heat pain and deep immersion cold pain produce similar, but not identical, patterns of brain response. Five regions that are responsive during both heat and cold pain (the cerebellar vermis, ipsilateral thalamus, contralateral premotor cortex, contralateral anterior cingulate cortex, and the confluent activation of contralateral anterior and lenticular nucleus) each show a greater response during cold pain than during heat pain. However, the extensive spatial overlap of responses suggests a pattern common to these different types of pain (Casey et al. 1996). Similarly, when perceived pain intensity is similar, direct statistical comparisons between cutaneous laser and intramuscular stimulation show no reliable differences between these two forms of noxious stimulation, indicating a substantial overlap in the pattern of brain activation (Svensson et al. 1997).

Imaging studies of visceral pain are also at an early stage of development, but evidence indicates that these studies will reveal important CNS abnormalities in patients with myocardial and visceral disease (Rosen and Camici 2000). A review of imaging studies of normal visceral pain shows again that similar cerebral structures are activated during visceral and somatic pain (Ladabaum et al. 2000). We used voxelwise correlations with
each stimulus temperature compared to the resting rCBF. Preliminary results show that each patient has abnormal thalamic and/or cortical asymmetry at rest and increased thalamic and/or cortical responsiveness to contralateral stimulation at HPT and above. At rest, three patients have hemithalamic hypoactivity, and one patient has hemithalamic hyperactivity in the hemisphere contralateral to the pathological pain. In contrast, a patient with global left arm hypoesthesia due to a nerve root lesion has contralateral resting hemithalamic hypoactivity but no evidence for thalamic hyper-responsiveness.

One advantage of PET, as compared with fMRI, for these studies is that it provides the opportunity to determine the excitability of cerebral structures as determined by the rCBF response compared to the resting (no stimulation) level. Fig. 1 shows an example taken from the analysis of a patient with a lacunar infarction adjacent to the right ventral posterior lateral thalamus (yellow arrow, left image, top panel). This patient, a hypertensive 67-year-old man, has painful dysesthesia of the left hemibody at rest, while his right thalamus is hypoactive compared to the left thalamus (Fig. 1, “rest” image). This patient has an elevated HPT (49°C) and high HPTol on both sides, so we tested his thalamic responses to contralateral stimulation at the three temperatures shown. As shown in the images and accompanying bar graph, his right hemithalamus, which is hypoactive at rest, is significantly more responsive to contralateral noxious heat than the left. Whether the left hemithalamus is also abnormally hyporesponsive remains to be determined in this sample case. It is clear, however, that in this patient, as in others we have studied thus far, the thalamus contralateral to the central pain may be hypoactive at rest but hyper-responsive during contralateral heat stimulation. This observation could not be made without information about regional activity during the resting, unstimulated state as determined by PET. In addition, both the psychophysical and cerebral responses in patients can be compared quantitatively with those of our sample of normal men in the same age range.

These results suggest that the pathological hypoactivity in the resting hemithalamus masks an underlying hyper-responsiveness to noxious stimulation. This phenomenon may be due to a loss of resting inhibitory activity within the thalamus, leading to bilateral and widespread cortical abnormalities. Other imaging studies have shown reduced thalamic activity during ongoing peripheral (Hsieh et al. 1995; Iadarola et al. 1995) or central (Pagni and Canavero 1995) neuropathic pain without stimulation. Cesaro and colleagues (1991) used single photon emission computed tomography (SPECT) to investigate the cerebral responses to pain in four patients with central post-stroke pain (CPSP). They found thalamic hyperactivity exclusively in
Fig. 1. Top: Anatomical MRI scan shows lacunar infarction adjacent to the right thalamus (arrow) in a patient with bilaterally elevated heat pain threshold (49°C) and central pain syndrome involving the left side of the body. Sequential PET regional cerebral blood flow (rCBF) images show hypoactivity of the right thalamus at rest with increasing hemodynamic activity at increasing intensities of contralateral (left arm) contact heat stimulation (49°C, 52°C, and 55°C; 5 seconds). Flame bar at right shows the difference (Z score) from normalized global cerebral blood flow. Bottom: Volume of interest analysis of right and left thalamic hemodynamic responses (percentage change from resting normalized rCBF) to contact heat stimulation of the contralateral arm at the highest stimulus intensity. The right thalamus, which was relatively hypoactive at rest, shows increased responsiveness compared to the left (t test; P < 0.029), which shows a tendency for reduced responsiveness.
two patients with hyperpathia when the abnormal, but not the normal, side was stimulated. Peyron and colleagues (1998) also reported increased contralateral thalamic responsiveness during cold allodynia in patients with lateral medullary infarction (Wallenberg syndrome). Sensory stimulation evokes considerable inhibitory activity in the mammalian thalamus (Salt 1989; Roberts et al. 1992). Inhibitory interneurons and synaptic profiles comprise a significant population of primate thalamic neurons (Ohara et al. 1989; Williamson et al. 1994), and these are highly susceptible to pathological changes following spinal cord injury (SCI) (Ralston et al. 1996). It seems likely that further analyses of clinical cases such as those presented here will reveal the complexity of physiological and anatomical changes that are triggered by injury to the central or peripheral nervous system (Pons et al. 1991; Kaas et al. 1997; Jones and Pons 1998).

SUPRASPINAL CONSEQUENCES OF EXCITOTOXIC SCI: ANIMAL IMAGING STUDIES

Spinal cord injury in humans and animals often results not only in variable motor deficits but also in the development of chronic central pain syndromes. It is also clear from the scholarly clinical and basic science reports presented in the chapters of this book that our understanding of the neural mechanisms of central pain in SCI is incomplete. These abnormal pain states frequently include spontaneous chronic pain as well as an increased responsiveness to previously innocuous (allodynia) and noxious (hyperalgesia) somatic stimuli. One area of research that has been largely ignored with respect to the varied consequences of spinal injury comprises the pathophysiological and neurochemical changes at sites remote to the site of injury, specifically cortical and subcortical supraspinal regions. Because spinal injury leads to partial or complete deafferentation of supraspinal structures, it is likely that, secondary to the disruption of spinal pathways, these supraspinal regions may undergo significant reorganization. It is therefore reasonable to conclude that SCI-induced changes in the activation pattern of supraspinal structures may be partly responsible for the development or maintenance of some aspects of a central pain state. However, few studies have looked at changes in supraspinal processing following spinal injury.

Animal studies employing metabolic or regional blood flow mapping techniques allow the simultaneous study of changes in neuronal activation induced by nociceptive input in large populations of neurons in different CNS structures of the same animal (Coghill and Morrow 2001). Some 2-deoxyglucose (2-DG) studies have shown a functional correlation of acute
and chronic pain nociception with activation of a large array of spinal and supraspinal regions including the spinal cord, brainstem, and thalamic, cortical, and limbic regions (Coghill et al. 1991; Porro et al. 1991a,b; Price et al. 1991; Mao et al. 1992; Porro and Cavazzuti 1996; Neto et al. 1999; Schadrack et al. 1999). Recent studies in our laboratory have demonstrated that autoradiographic estimates of rCBF can be used to simultaneously identify acute and chronic pain-specific alterations in the activation of multiple forebrain structures (Morrow et al. 1998, 2000; Paulson et al. 2000). At present, autoradiographic 2-DG or rCBF imaging in animals allows considerably greater resolution of CNS structures than can be achieved with either PET or fMRI in humans, making imaging in animals an ideal platform for investigating the CNS mechanisms of SCI-induced central pain syndromes. Accordingly, we conducted several studies using the Yezierski model of excitotoxic SCI (Yezierski 1996; Yezierski et al. 1998) to determine the extent and nature of SCI-triggered supraspinal changes in rats, using rCBF as an indicator of neuronal activity. For this model, a spinal lesion is produced by a microinjection of quisqualic acid into the dorsal horn on one side of the spinal cord in rats. We computed a mean index of activation for each of 25 sampled regions of interest across all animals in an experimental group (for detailed methods see Morrow et al. 1998).

**SCI-INDUCED CHANGES IN BASELINE (UNSTIMULATED) FOREBRAIN ACTIVATION**

We found increases in activation in unstimulated Long Evans SCI rats that suggest that pathophysiological changes may have occurred not only at spinal levels but also in supraspinal structures. As compared to controls, Long Evans SCI rats exhibited bilateral increases in the baseline (unstimulated) activation of both cortical and subcortical structures traditionally associated with the processing of somatosensory information (Morrow et al. 2000), including the S1 and S2 cortex and the thalamic posterior group (PO), ventral lateral thalamus (VL), ventral posterior lateral thalamus (VPL), and ventral posterior medial thalamus (VPM) (see Fig. 2). A role in nociceptive processing for many of the thalamic, cortical, and adjacent brain regions activated in the present study is well documented (for review see Willis and Westlund 1997). Ness et al. (1998) also described increased activation in the thalamus and cortex using PET in SCI patients during the perception of chronic pain. Nociceptive activation of the S1 and S2 cortex also has been reported in animal and human studies of acute pain (Willis 1985; Price 1988; Talbot et al. 1991; Casey et al. 1994; Coghill et al. 1994).
CENTRAL PAIN MECHANISMS

Fig. 2. Regions of interest showing significant baseline (unstimulated) increases in activation because of excitotoxic SCI in Long Evans rats ($P \leq 0.05$, ANOVA), Arc = arcuate nucleus; SI = primary somatosensory cortex; SII = secondary somatosensory cortex; PO = posterior group; VL = ventral lateral thalamus; VPL = ventral posterior lateral thalamus; VPM = ventral posterior medial thalamus.

INFLUENCE OF GENETIC STRAIN ON THE PATTERN OF FOREBRAIN ACTIVATION AFTER SCI

In another study, we found that SCI-induced changes in the basal (unstimulated) pattern of forebrain activation can vary significantly with the strain of rat used. Fig. 3 shows that in contrast to the Long Evans strain, excitotoxic SCI in Sprague-Dawley rats produced robust bilateral increases in rCBF primarily within limbic forebrain structures, although the S1 and S2 cortex also showed an increase in activation above control levels similar to Long Evans rats. Such strain differences in cerebral activation should not be unexpected and may account in part for reported variations in the development neuropathic pain behaviors when different strains of rats or mice are used. Strain-related differences in the onset of neuropathic pain behaviors have been reported after nerve injury (Panerai et al. 1987; Cohn and Seltzer 1991; Defrin et al. 1996; Mogil 1999) and SCI (Popovich et al. 1997; Gorman et al. 2001). In addition, the development of both allodynia and hyperalgesia in rats or mice with partial nerve injury are also strain-dependent (Mogil and Adhikari 1999; Mogil et al. 1999a,b,c; Yoon et al. 1999). Such behavioral data, coupled with our findings of strain-related variations in the SCI-induced pattern of forebrain activation, highlight the importance of genetic factors when using animal models of central pain either to investigate neural mechanisms or to evaluate potential interventions.
Fig. 3. Effect of genetic strain on SCI-induced differences from control in baseline (unstimulated) brain activation. Long Evans rats showed increases in activation primarily in somatosensory structures, whereas Sprague Dawley rats exhibited SCI-induced increases in activation primarily in limbic forebrain structures. Asterisks (*) denote a significant difference between Long Evans and Sprague Dawley rats ($P \leq 0.05$, ANOVA). SI = primary somatosensory cortex; SII = secondary somatosensory cortex; VL = ventral lateral thalamus; VM = ventral medial thalamus; VPL = ventral posterior lateral thalamus; VPM = ventral posterior medial thalamus; PO = posterior group; AD = anterior dorsal thalamic group; BLA = basolateral amygdala; CC = cingulate cortex; HBC = habenular complex; IPN = interpeduncular nucleus; PVN = periventricular nucleus; RS = retrosplenial cortex.

**STIMULUS-EVOKED FOREBRAIN ACTIVATION IN SCI RATS**

Excitotoxic SCI is known to produce abnormal behavioral responses to thermal stimuli in the innocuous range (thermal allodynia) as well as the noxious range (thermal hyperalgesia) (Yezierski et al. 1998). As compared to preoperative baseline values and the responses of control subjects, SCI Sprague-Dawley rats exhibited enhanced behavioral responses to noxious 47°C stimuli (thermal hyperalgesia) applied to the hindfoot on the side of the spinal lesion (see Fig. 4) that were paralleled by increases in the stimulus-evoked activation

Fig. 4. Bar graph shows the hyperalgesic behavioral response to a noxious 47°C stimulus applied to the hindfoot on the same side as the spinal cord lesion. Color-enhanced brain images are single brain sections from one stimulated control and one stimulated SCI rat. Note the significantly increased activation to the same 47°C stimulus in thalamic and cortical structures of the SCI rat. ROD = relative optical density.
CENTRAL PAIN MECHANISMS

Control 47°C Stimulus

SCI 47°C Stimulus

IPSI

CONTRA

Withdrawal Latency (seconds)

47°C Stimulus

*
in several forebrain somatosensory structures. Although Fig. 4 shows only single brain images of a coronal section from one stimulated control and one stimulated SCI rat, it clearly highlights the hyperactivation by noxious thermal stimuli in thalamic and cortical structures of the SCI rat as compared to the control. Such increases in the activation of cortical and thalamic structures has also been reported in patients with SCI pain (Ness et al. 1998). Electrophysiological investigations have described spontaneous and evoked hyperactivity in the VPL nucleus of the cat following an ipsilateral transection of the spinothalamic tract (Koyama et al. 1993). Lenz et al. (1994) reported similar findings in a study examining thalamic neuronal activity in patients with SCI. Faggin et al. (1997) also showed that deafferentation produces an immediate and simultaneous change in neuronal activity in rat thalamus and cortex. Furthermore, a recent case report using PET in a patient experiencing central pain due to a supraspinal lesion (Casey et al. 1999; see also human studies described earlier in this chapter) identified hyperactivation in the thalamus on the involved side during noxious thermal stimulation on a background of thalamic hypoactivation.

The changes in forebrain activation described here constitute remote responses to injury and suggest that widespread functional alterations occur within cortical and subcortical regions following injury to the spinal cord. Based on the data presented here and evidence from other studies, it is reasonable to speculate that following SCI, the onset and especially the maintenance of chronic pain-related behaviors is in part the result of alterations in the pattern of neuronal activation in these supraspinal structures. Contributing to this elevated state of activation would be the relay of discharges from spinal generators of abnormal activity as well as the effects produced secondary to deafferentation of supraspinal structures. To address this hypothesis it will be important to record neuronal activity from different brain regions areas identified as having elevated levels of rCBF in these animal imaging studies. Future studies will be necessary to gain a better understanding of the extent of “remote” supraspinal changes and specifically the functional reorganization in the somatotopic map secondary to spinal injury.

In conclusion, the results presented here show that brain imaging can be a powerful tool for investigating the neural mechanisms of central pain syndromes in human patients as well as animal models. Finally, the combined evidence from human and animal studies suggests that one common feature in the development of a central pain syndrome involves thalamic and possibly cortical hyperexcitability.
REFERENCES


Faggin BM, Nguyen KT, Nicolelis MA. Immediate and simultaneous sensory reorganization at cortical and subcortical levels of the somatosensory system. *Proc Natl Acad Sci USA* 1997; 94:9428–9433.


Correspondence to: Thomas J. Morrow, PhD, Neurology Research Laboratories, Veterans Affairs Hospital, Research 11R, 2215 Fuller Road, Ann Arbor, MI 48105, USA. Tel: 734-761-7956; Fax: 734-761-7693; email: ruscat@umich.edu.