Cortical Pathophysiology of Neuropathic Pain: Human Brain Imaging Studies and Theories of Neuropathic Pain

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Research over the last two decades has revolutionized our understanding of mechanisms underlying neuropathic pain conditions, especially for processes in the periphery and the spinal cord. Both in the periphery and in the spinal cord a neuropathic injury causes drastic reorganization of nociceptive coding. Many of these changes are directly relevant to spinal cord injury (SCI) pain conditions, as elaborated in many chapters in this book. This reorganization includes changes in the phenotype of large-fiber afferents, in the responsiveness of silent nociceptors, in the receptor and neurotransmitter expression of different afferents and of spinal cord cells, and in the response properties of spinal cord cells. Such changes will clearly affect spinocephalad information transmission and result in changes in cortical representation of pain. SCI pain, which often is due to a complete severance of the cord and is accompanied by chronic pain in body sites below the site of the injury, must be considered a major subcategory of phantom pain. This consideration implies that at least some forms of SCI pain must be primarily due to supraspinal networks, involving the cortex not merely as a final transmission site of spinal cord inputs, but rather as a source of the perception per se. This chapter deals with the issue of the relative importance of cortical circuitry as opposed to spinal cord reorganization and transmission of the reorganized spinal information in neuropathic chronic pain conditions. Work in my laboratory over multiple years has concentrated on identifying the cortical networks underlying chronic neuropathic pain conditions in humans. We have not studied SCI pain patients,
and to our knowledge no studies have directly examined the human brain network engaged in SCI pain. This chapter reviews progress in our laboratory in identifying cortical regions involved in chronic pain, emphasizing the results from ongoing work. I argue that ongoing steady pain is a sine qua non of chronic neuropathic conditions. As a result, the identification of cortical circuitry underlying such conditions provides direct insight into the mechanisms—e.g., reorganization of nociceptive pathways and of changes in cortical dynamics and cortical biochemistry—that may be critical for the ongoing pain. Moreover, information about brain regions engaged in ongoing pain should be similar across multiple neuropathic pain conditions. Thus, these results should also shed light on the brain circuitry in ongoing SCI pain. Our studies using functional magnetic resonance imaging (fMRI) and hydrogen spectroscopy (^H-MRS) provide a consistent picture of the cortical elements critical for such conditions. Overall, we observe that the prefrontal cortex is involved in two distinct clinical chronic pain conditions. The details of the specific prefrontal regions engaged in each condition seem distinct, which has important consequences regarding the subjectivity of various clinical pain conditions. Biochemical analysis of chronic pain patients in comparison to age- and sex-matched normal subjects indicates that the prefrontal cortical neurons undergo use-dependent atrophy in a pattern that reflects the specifics of the dimensions of pain experienced by these patients. I will review current theories of neuropathic pain to determine their consistency with the experimental results and to outline a plausible mechanism of chronic pain, bearing in mind the limited number of clinical conditions that have been studied so far.

A main emphasis of research in our laboratory has been the search for noninvasive brain imaging techniques that can be used to study clinical pain conditions. I will outline two separate approaches, fMRI and ^H-MRS, and describe their properties in measuring human brain activity and human brain biochemistry, especially from the viewpoint of understanding the cortical circuitry of clinical chronic pain conditions.

MEASURING FUNCTIONAL BRAIN ACTIVITY

Functional MRI is becoming the main method for measuring brain activity in humans. Functional MRI is a noninvasive method with which scientists can indirectly monitor brain activity in awake humans while the participants are subjected to some stimulus or are instructed to perform some task. Functional MRI detects small fluctuations in tissue magnetization properties
secondary to neuronal activity. Because fMRI is noninvasive and, as far as we know, harmless, there is no limit to the number of fMRI tests that can be performed. Changes in neuronal activity are accompanied by changes in cerebral blood flow, blood volume, level of oxygenation, and tissue metabolic rate. Transient changes in these parameters alter the balance between paramagnetic deoxyhemoglobin and diamagnetic oxyhemoglobin in red cells. Changes in this balance result in transient local magnetization changes, which can be monitored directly by fMRI (Kwong et al. 1992). This method has been used to visualize brain activations in a large set of stimulus and task conditions, including thermal painful stimuli (e.g., Davis et al. 1995, 1998, 2000; Gelain et al. 1998, 1999; Apkarian et al. 1999, 2000). In such studies the participant is subjected to a stimulus-control condition, repeated many times. By assuming that the stimulus and control situations are reproducible and represent different brain states, researchers can determine the brain regions where local magnetization differs between the two states and infer that these regions participate in the perceptual change accompanying stimulus-control sequences. This type of analysis is also used in positron emission tomography (PET), where radionucleotide-tagged metabolic markers are injected into participants. The differential distribution of these radioactive markers between the two states indicates the distinctive brain regions involved.

Several laboratories have determined the temporal properties of brain hemodynamics (Cohen et al. 1997; Bandettini and Cox 2000). These studies indicate that the brain hemodynamic response has a characteristic time course and generally can be viewed as a typical response to a transient input, which in linear systems theory is equivalent to the impulse response function. This characterization in turn has led to new experimental designs that present very brief stimuli and look for related hemodynamic responses in the MR images; this approach is called event-related fMRI design and analysis. A main advantage of event-related design is its ability to present short stimuli with randomly varying intervals between events, which reduces predictability and expectation by the volunteers. The main assumption in functional brain imaging is that subjects’ responses to a given stimulus are reproducible and time-locked with the application of the stimulus, but in chronic pain this assumption usually does not hold true, which necessitates alternative designs. fMRI is a noninvasive tool that can readily identify cortical networks involved in certain tasks or stimuli. It delineates the brain network difference between the stimulus and control conditions examined. The longer-term organization of these networks may be examined by fMRI, although such designs are complicated and rarely used.
TEMPORAL PROFILE OF PAIN CONSCIOUSNESS

Unlike touch, vision, or audition, neural systems underlying pain perception are slow. As a result, pain perception can often be dissociated from the stimulus. There is a complex relationship between the intensity of pain experienced and its temporal properties. Hardy et al. (1968) showed that when a thermal painful stimulus is mild, the reported pain may be delayed by several seconds from the start of the stimulus and may be transient. These authors also showed individual variability in temporal changes in pain perception as well as differences in temporal properties of pain as a function of intensity. As the intensity of the thermal painful stimulus is increased, its perception becomes more constant and outlasts the stimulus. However, this temporal pattern seems to differ among individuals. Such temporal dissociations between stimulus and perception may become far more dramatic in pain abnormalities, as shown by Gracely et al. (1996). Neuropathic pain patients show a long delay between the start of a painful stimulus and their perceived pain, as well as a strong sensitization that far outlasts the stimulus when the same stimulus is repeated a few seconds later.

We have taken advantage of this temporal dissociation between a painful stimulus and the subjective perception of pain to analyze the brain circuitry of pain (Apkarian 1999). Within the parietal cortex, spanning from the anterior commissure to just behind the posterior commissure, a monotonic change occurs in the brain response to painful thermal stimulation such that the more anterior regions are better related to the stimulus itself while the more posterior portions of the region are better related to the perception of the pain. We extended the method to directly image brain regions involved in the ongoing spontaneous pain of clinical neuropathic pain conditions (Apkarian et al. 2001b).

The conceptual novelty of our fMRI studies is the notion that we can take advantage of the unique temporal properties of pain to identify cortical regions specifically involved in the subjective, conscious perception of pain and to be able to apply this to directly study cortical regions involved in clinical pain syndromes.

MEASURING THE SUBJECTIVE EXPERIENCE OF PAIN

The need to study the subjective experience of pain was eloquently stated years ago by Donald D. Price. In the first chapter of his book (1988), he states:
The definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage..." (Merskey 1986) leaves us in a very interesting philosophical position with regard to the study of pain. If pain is defined subjectively as an experience, then the scientific study of pain ultimately has to study and even measure that experience. [italsics are my emphasis]

This challenge is exactly what we have achieved. It should first be stated that all prior brain-imaging studies of pain have examined brain activity patterns between two states. By comparing a painful state to a nonpainful state, researchers have defined brain regions involved in pain perception in PET and fMRI studies. This approach does not distinguish between stimulus coding and pain perception in the brain.

In our earlier fMRI study of cortical regions activated by a thermal painful stimulus, we simply compared the brain areas significantly activated during the painful state as compared to the nonpainful warm control state (Gelnar et al. 1999). This cortical pattern was compared to that seen when subjects performed a vibrotactile or motor task. The study showed that multiple brain regions are activated in an experimental painful task, including the primary and secondary somatosensory cortices, the primary and supplementary motor cortices, the posterior parietal cortex, the insula, and the anterior cingulate cortex. This pattern of brain activity has been demonstrated by many brain imaging studies (for details see Apkarian et al. 1995; Bushnell et al. 1999; Treede et al. 1999, 2000). Because fMRI has a higher spatial resolution than PET, it enables researchers to further subdivide these activated regions with respect to specific Brodmann's areas and in relation to activations seen in the vibrotactile or motor tasks. These comparisons point to the conclusion that thermal painful stimulation activates brain regions uniquely responding to this stimulus, such as the secondary somatosensory cortex, the anterior cingulate cortex, and portions of the primary somatosensory and motor cortices, as well as regions that overlap with vibrotactile sensation and motor performance.

Subsequently, we analyzed the fMRI thermal painful stimulus results in relation to the time course of the stimulus and pain perception (Apkarian et al. 1999). We determined the time course of pain perception in another group of subjects who were required to continuously rate the intensity of subjectively perceived pain when they were presented with the same thermal painful stimulus as used in the fMRI study. These ratings showed that although the thermal painful stimulus was constant, the subjectively perceived pain varied. Painful heat was applied for 35 seconds (with 35-second controls) and was constant through the stimulus period. The subjective pain
reports, however, continuously increased during each stimulus period, over 35 seconds. Moreover, the time variation was greater in the peak pain perceived. By taking advantage of this temporal dissociation between stimulus characteristics and pain perception, we analyzed brain activity with both time curves and identified cortical regions more closely related to either the stimulus or the perception (Apkarian et al. 1999). This analysis showed a gradual transition of information processing anteroposteriorly in the parietal cortex. Within this region, activity in the anterior areas more closely reflected thermal stimulus parameters, while activity more posteriorly was better related to the temporal properties of pain perception. Within the brain region analyzed, the posterior parietal cortex best reflects the time-varying conscious subjective report of pain. We tentatively conclude that this area may be critical in pain consciousness. The region is clinically significant because lesions of this part of the brain, especially in the right hemisphere, lead to hemi-neglect. Therefore, the normal conscious awareness of pain may be critically linked to the normal awareness of body image. Overall, these results indicate that we have developed an approach with which we can differentiate and relate cortical regions to the subjective conscious perception of pain, fulfilling Price’s wish.

AN OBJECTIVE MEASURE OF PAIN

In an article published on the occasion of the 25th anniversary of the International Association for the Study of Pain, Allan Basbaum (1998), writing on “New techniques, targets and treatments for pain: what promise does the future hold?” stated that “a better objective measure of a patient’s pain will have enormous value.”

Seemingly paradoxically, our results indicate that the examination of brain activity by correlating subjective reports of pain perception to the fMRI signal provides an objective measure of the presence of pain. The relevant parameter, especially in patients suffering from pain, is not stimulus representation in the brain but rather the extent to which their consciousness is preoccupied by pain. The latter can only be known by first determining which brain regions are specifically involved in the subjective knowledge of pain and then examining the extent to which these areas are active when the patients indicate a high level of pain. Our methodology directly targets the latter, and as a result it has the potential of becoming an objective measure of pain.

An example may better illustrate why our approach is objective. We have been studying a patient with syringomyelia who psychophysically
performs thermal discrimination at chance level. However, she thinks that she can feel warm and cold stimuli. During the fMRI study of cortical activity, she did rate the stimulus as warm some of the time (the stimulus is accompanied by a tactile cue). When her brain activity was examined in relation to the stimulus, contralateral somatosensory regions were activated. When the brain activity was examined in relation to the ratings, only motor regions were active ipsilateral to the stimulus and contralateral to the hand with which the ratings were performed. Thus, the perception-related activity simply shows rating of related finger movements. The subject is attempting to perform a task that she cannot do, and the perception-related activity indicates this fact. Therefore, although the method uses subjective ratings of perception, if these ratings do not match the subject’s conscious state the resultant brain activity pattern will show the discrepancy.

SO M ATOTO P Y FOR ACUTE/EXPERIMENTAL PAIN

Several groups have used fMRI to examine cortical circuitry underlying experimental and acute pain conditions. These studies show close similarity to results reported by PET studies, where similar thermal painful stimuli were used to map cortical activations (e.g., Jones et al. 1991; Talbot et al. 1991; Casey et al. 1994; Coghill et al. 1994; Hsieh et al. 1996; Derbyshire et al. 1997). Multiple reviews have discussed these results and compared them between tasks and among laboratories (Apkarian 1995; Bushnell et al. 1999; Ingvar 1999; Treede et al. 1999, 2000). In a recent study we examined the cortical somatotopy of thermal pain (Darbar et al. 1999). We examined segregation of cortical activity to painful thermal stimuli when the stimulus was applied to either the hand or the foot, as compared to vibrotactile stimuli applied to the hand. We observed somatotopic activations within the primary somatosensory cortex. Within the superior operculum of the lateral sulcus we observed multiple topographic maps for thermal pain, some of which were bilaterally activated. More anteriorly, at the junction of the insula and the inferior frontal gyrus, we observed bilateral activity that clearly lacked somatotopy. A weak somatotopy was observed in the anterior cingulate cortex; this portion of the midline cortex is most consistently activated across pain tasks and laboratories and seems to be involved in the perception of pain unpleasantness (Rainville et al. 1997), yet its specific role in pain perception remains uncertain (see Davis et al. 2000). Below I will compare these thermal pain activations with the cortical networks we have identified in chronic pain patients.
APPLICATION OF fMRI TO CLINICAL CHRONIC PAIN STATES

COMPLEX REGIONAL PAIN SYNDROME

An important distinction between chronic and acute pain conditions is the general inability of researchers to control and manipulate chronic pain conditions. Thus it is more complicated to apply brain imaging methods to the delineation of cortical networks underlying such states. In standard fMRI methods the primary assumption is that the stimulus and control conditions are well defined and clearly separate. However, chronic pain interacts with any painful stimulus applied in chronic pain patients. An fMRI study of patients with complex regional pain syndrome type I (CRPS-I) was designed specifically to isolate the brain network involved in the ongoing chronic pain from that of a painful stimulus (Apkarian et al. 2001a). This study recruited patients with CRPS-I with clear evidence for sympathetically mediated pain (SMP) because sympathetic blocks can be used to decrease chronic SMP (Ribbers et al. 1997), and the effects of thermal painful stimuli can be tested before and after the block.

Temporary relief of SMP by peripheral sympathetic blockade also permits us to study related neural activity without perturbing sensory inputs. We used fMRI in examining thermal painful stimuli applied to the chronically painful body site, both before and after sympathetic blockade, to determine the cortical network of chronic pain. We began with the assumption that the dual states of chronic pain and pain due to thermal painful stimuli can be additively present in the brain, such that cortical activity represents both conditions together. Moreover, when the same thermal stimulus is applied after a sympathetic block that significantly reduces or abolishes the chronic spontaneous pain, brain activity now represents the thermal pain network alone. Therefore, the residual brain activity, after subtracting the brain activation before the block from that obtained after the block, reflects the brain network responsible for chronic pain perception. The result of this subtraction across the patients and multiple trials indicated that chronic CRPS-I with SMP was associated with a widely spread prefrontal hyperactivity, as well as activity in the anterior cingulate and decreased activity in the thalamus contralateral to the affected body side. The parietal and insular regions that were activated in control subjects for thermal stimuli and that were also activated prior to sympathetic block in the CRPS patients did not survive the subtraction.

Ineffective sympathetic blocks that did not diminish SMP did not change the cortical responses to the painful thermal stimulus, while effective placebo resulted in similar responses to those of effective blocks. Several groups
of normal volunteers were used as a comparison to the activations in the
CRPS patients. In one group of normal volunteers, thermal painful stimuli
were applied before and after sympathetic blocks. In this group the sympa-
thetic block decreased sensorimotor activity and had no effect on prefrontal
activations. Thus, sympathetic blocks have disparate effects in CRPS and
normal subjects, implying a reorganization in the relationship between the
central nervous system and autonomic responses.

The pattern of brain activation in CRPS patients is relevant to that of
SCI pain patients in multiple ways. First, the classification of SCI pain in-
cludes CRPS-type pain. It is unclear whether this is limited to pain at the site
of injury, or if it may also extend to pain at levels below the injury. In any
case, CRPS-type brain activity is at least directly related to the brain activa-
tions one expects in the subset of SCI pain patients with clear CRPS symp-
toms. It remains unknown what portion of SCI pain patients belong to this
subcategory. The second link between SCI pain and CRPS pain is more im-
portant: because in both cases the main debilitating pain is the ongoing
pain. In the study described above (Apkarian et al. 2001a), we attempted to
isolate the brain circuitry underlying sympathetically mediated ongoing pain.
The results imply that the brain region most commonly involved in ongoing
pain across multiple patients and across a large number of scans is the
prefrontal cortex. This finding does not imply that other brain regions are
not involved in the spontaneous pain perception, but rather that this is the
most consistent region on average. Variability among patients may be sig-
nificant as to the specific cortical areas involved in the spontaneous pain,
which one would expect given different patients’ variability in pain behav-
ior and pain affect. We hope that fMRI will allow us to delineate and iden-
tify this variability in the near future. Also, the frontal cortex is implicated
in a large number of cognitive functions, and different portions of the pre-
frontal cortex are implicated in multiple diverse functions. The relationship
between these cognitive functions and neuropathic pain activations are dis-
ussed below. In CRPS patients, prefrontal activity was concentrated in the
most frontal pole and in the lateral portions of the prefrontal cortex.

The results obtained in the CRPS patients also carry important implica-
tions regarding nociceptive transmission pathways. The overall thalamic ac-
tivity in the CRPS patients was similar between the thalamus contralateral to
the painful body and the ipsilateral side when the comparison was made for
thermal painful stimuli averaged over all stimulus and pre- and post-sympa-
thetic block conditions. However, this comparison was very different in the
subtraction of the pre- from post-sympathetic block conditions. In this case
there was a large asymmetry, with the thalamus contralateral to the CRPS-
affected hand showing a significant decrease in activity as compared to the
ipsilateral thalamus. The first comparison simply shows that during thermal painful stimulation the overall thalamic activity is not different between its two sides. This result may simply reflect the small amount of change in a small portion of the thalamus during thermal stimulation, which is not detected in the average of the whole thalamus. The second comparison implies an overall decrease in the thalamus on the side where the spontaneous CRPS pain is experienced, in the condition where this is specifically isolated. Several groups have reported thalamic hypoactivity in chronic pain conditions (Di Piero 1991; Hsieh et al. 1995; Iadarola et al. 1995). This finding seems to be the most consistent result in brain imaging studies of chronic pain conditions. It has been interpreted by multiple diverse viewpoints, all of which attempt to preserve the notion that the pain condition must involve nociceptive transmission through the spinothalamic pathway. However, the simplest interpretation of thalamic hypoactivity is that the thalamus is disengaged from the chronic pain state. In turn, this view implies that the spinothalamic pathway is not critical and may in fact be actively inhibited in the spontaneous chronic pain state. Such inhibition is neither surprising nor contradictory to the behavioral manifestations of chronic pain conditions and may in fact be a mode of coping with the pain. Suppressed spinothalamic transmission may be a sign that the brain is actively attempting to block sensory information about the intensity, location, and modality of pain. In fact, a large body of clinical data shows that chronic pain is often accompanied by decreased sensory perception of both painful and nonpainful stimuli, especially at the site where the ongoing chronic pain is experienced (see, e.g., Casey 1991). This interpretation implies that the amount of suffering in chronic pain does not relate to the sensory information per se but rather to the negative affect as reflected in the frontal activations.

These results shed new insight on nociceptive transmission through spinocephalad pathways versus dynamic brain states for neuropathic pain perception. Given that the prefrontal cortex is the most consistently active brain region during spontaneous neuropathic pain and considering our conclusion that the spinothalamic pathway is inhibited in this condition, what are the options for interpreting these results regarding the coding and representation of chronic pain? The most simplistic interpretation would be that nociceptive information is transmitted to the prefrontal cortex through pathways outside the spinothalamic projections, i.e., pathways bypassing the thalamus and gaining access to the cortex directly. A number of pathways are candidates for these projections, which may be reinforced by the persistence of the pain. This interpretation is most consistent with the ideas proposed by Cassinari and Pagni (1969), although it also harks back to Cartesian "labeled line" notions of information coding, which we do not favor.
HUMAN BRAIN IMAGING STUDIES

An alternative explanation takes into account the general role of the prefrontal cortex in cognitive control. As Miller and Cohen (2001) state, "the prefrontal cortex is important when 'top-down' processing is needed; that is, when behavior must be guided by internal states or intentions." Thus, the prefrontal cortex determines the relative salience that the brain attaches to external events relative to internal intentions. Therefore, the prefrontal hyperactivity during neuropathic pain may simply be the signature of this heightened salience that the prefrontal cortex attaches to pain, and particularly to the pain's affective or emotional salience. From this viewpoint the chronic pain state becomes a central sensitization state, where the sensitization is at the level of the cortex, and does not involve transmission from spinal sensitized pathways. Another interpretation would be that the change in salience is the establishment of a long-term memory trace that engages the whole consciousness of the organism. These lines of thought lead to specific hypotheses regarding cortical synchronization and changes in the dynamics of synchronization across cortical regions with the change from acute pain perception to chronic neuropathic pain perception. We are testing these ideas directly in animal models of acute and chronic pain conditions. Another aspect of these lines of thought is the link between chronic pain behavior and addictive behavior. Recent studies implicate the prefrontal cortex in addictive behavior in a manner very similar to our interpretation of its role in neuropathic pain behavior, namely as the site where salience to external inputs is modified (Volkow et al. 2000). Therefore, the mechanisms of neuropathic pain may share important characteristics with those of addiction, and therapy strategies for addiction may be useful in chronic pain as well.

CHRONIC BACK PAIN

It is not clear to what extent the assumption regarding linear additivity of chronic and acute pain conditions is tenable. Most likely the interaction between acute and chronic pain is nonlinear, and the subtractive analysis used above for identifying the ongoing pain of CRPS ignores the multiplicative term between the two states and only identifies the linear component. To improve on this approach we developed an alternative fMRI method that directly examines brain activity of chronic pain (Apkarian et al. 2001b). Subjects are equipped with a finger-spanning device to continuously rate and log their perceived pain during fMRI data collection. These ratings are convolved with a canonical hemodynamic response function to generate predictor waveforms with which related brain activity can be identified. The approach uses continuous logging of ongoing subjective pain reports and
relates these ratings back to objective measures of brain activity. We studied patients with chronic low back pain. In one series of fMRI scans the patient simply lies in the scanner and indicates spontaneous fluctuations of the subjective pain. In another series of scans, the patient performs a straight-leg-raising procedure to exacerbate the back pain. In both conditions the patient continuously rates the pain, and in the second condition he or she is asked to ignore the leg movements. The results indicate the feasibility of differentiating between different pain states. We have argued that this approach can be generalized to identify brain circuitry underlying diverse clinical pain conditions (for details, see Apkarian et al. 2001b). The group average for spontaneous ratings of ongoing back pain in five patients was averaged across multiple repetitions of fMRI scans (Krauss et al. 1999). The preliminary results indicate activations primarily in the prefrontal cortex, similar to the chronic pain-related activity in CRPS, as well as in the insula ipsilateral to the painful leg.

COMPARING THE BRAIN PAIN NETWORK BETWEEN NORMAL VOLUNTEERS AND CHRONIC PAIN GROUPS

We recently described the extent of overlap in brain activations between the three groups of studies described above, evaluating the similarity of the cortical network of activity in normal subjects subjected to a thermal stimulus in comparison to the activity during spontaneous pain in CRPS patients, and to that in chronic back pain patients who are asked to continuously rate their ongoing pain (Apkarian et al. 2001c). This comparison questions the extent to which chronic and acute pain conditions depend on the same cortical circuitry, and as a result how much cortical reorganization underlies chronic pain conditions, as well as the extent to which diverse chronic pain conditions depend on the same cortical circuitry. Results indicated that the anterior cingulate cortex was the only region of overlap among the three groups. Thus, we concluded that in both chronic pain conditions cortical activity engages more prefrontal regions. Moreover, we argued that the details of the regions activated in the chronic pain conditions are unique to each condition.

These results imply that the subjective experiences of acute and chronic pain are significantly different because they engage different cortical circuitry. Moreover, although the two chronic pain conditions activate mainly prefrontal areas, they too differ from each other in their subjectivity. It is unlikely that this diversity is due to differences in the spinocephalad transmission lines. Rather, it must be attributed to the salience of the two chronic pain conditions. Once again, this argument implies that the cortical sensitization
details give rise to a prefrontal cortex-driven network that in turn governs the subjectivity of the chronic pain.

MEASURING HUMAN BRAIN BIOCHEMISTRY

Nuclear magnetic resonance spectroscopy (MRS) is a method used in chemistry and physics laboratories to analyze molecular interactions and identify chemical compounds. Recently this approach was adapted for in vivo analysis of brain chemistry. The key to this method is to localize MR signals to a specific volume, an approach commonly used in anatomical MRI. In all biological tissues including the brain, water is the predominant chemical, so observation of weak signals from metabolites with concentrations thousands of times smaller than that of water requires methods for suppressing the water signal. Advances in MR technology in automating voxel positioning and suppressing the water signal have made MRS a relatively simple noninvasive approach for studying brain chemistry (see Sibilli and Brown 1998). Proton spectra (1H-MRS) enable the measurement of concentrations of various metabolites and excitatory and inhibitory neurotransmitters. 1H-MRS has been used to examine the brain biochemistry of various neurological patient populations, such as patients suffering from stroke, various types of brain tumors, multiple sclerosis, Alzheimer’s disease, and epilepsy.

1H-MRS can be used to measure the chemical concentrations (i.e., peaks or intensities) of up to nine different compounds in the living brain: N-acetyl aspartate (NAA), choline (Cho), glutamate (Glu), glutamine (Gln), \(^\gamma\)aminobutyric acid (GABA) (Glu + Gln + GABA is often measured as Glx due to overlap between the peaks of these compounds), myo- and scyllo-inositol complex (Ins), glucose (Glc), lactate (Lac), and creatine (Cr). These measurements are performed as relative ratios among peaks (most commonly relative to Cr) or as absolute concentrations. Absolute concentration measurement requires an external or internal standard, which remains difficult to perform routinely, especially because the external standard method is sensitive to magnetic field inhomogeneities due to separation of the standard and the measured volume.

The 1H-MRS spectra are usually characterized by three major peaks: NAA at 2.02 parts per million (ppm), Cr at 3.0 ppm, and Cho at 3.2 ppm. NAA is the dominant peak in normal adult brain spectra. The Cr spectrum is a combination of creatine and phosphocreatine (Michaelis et al. 1993). The proton Cho signal is a combination of Cho and Cho-containing compounds: choline plasmogen, glycerophosphorylcholine, phosphorylcholine, cytidine-diphosphate-choline, acetylcholine, and phosphatidylcholine (Michaelis et al. 1993).
Growing literature shows a depletion of brain NAA in neurodegenerative diseases (reviewed in Salibi and Brown 1998), suggesting that it is a neuronal marker (this chemical is present only in living, mature neurons and not in glia). Subsequent breakdown of NAA leads to aspartate, an excitatory amino acid neurotransmitter. Recent reports suggest that NAA is also required for brain lipid biosynthesis (for further details, see Faull et al. 1999). Cr resonance is considered to be more stable than the NAA peak and is commonly used as a reference. However, this peak is abnormal with hypoxia, trauma, stroke, and tumor (Salibi and Brown 1998). The Cr level is involved in energy metabolism in the brain.

Brain chemistry varies regionally and with sex and age (Grachev and Apkarian 2000a), with an overall increase in regional chemical concentration from childhood to young adult (up to 25 years old) and then a decrease with further aging (Grachev and Apkarian 2000b). The age- and sex-dependent changes highlight an important difference between MRS and fMRI. MRS is usually measured in subjects while the subject simply lies in the scanner. We have tested whether MRS can detect task-dependent changes, but we failed to observe any consistent changes in MRS signal in the sensorimotor cortex during a finger apposition task or during a thermal painful task. It is thought that $^1$H-MRS spectra remain unchanged under anesthesia. The only chemical measured by $^1$H-MRS that would be expected to change with a cognitive task is glucose (this change may be detected if large data sets are collected). All other chemicals should be independent of the instantaneous changes in cognitive states. These observations imply that when $^1$H-MRS spectra do show change they must reflect the long-term reorganization of brain circuitry.

**BRAIN BIOCHEMISTRY REFLECTS SUBJECTIVE PROPERTIES OF CHRONIC PAIN**

We used $^1$H-MRS to study brain chemistry in chronic back pain patients compared to age- and sex-matched normal subjects. We made six separate single-voxel measurements in six different left-brain regions (Grachev et al. 2000). The hypothesis we tested was that, in chronic pain patients, brain areas that show hyperactivity in fMRI studies should also show abnormal brain chemistry. We tested three brain regions, the thalamus, cingulate cortex, and dorsolateral prefrontal cortex, where we quantified the concentrations of NAA, Cho, Glu, Gln, GABA, Ins, Glc, and Lac relative to the concentration for the creatine/phosphocreatine complex (Cr), which is commonly used as an internal standard. All chronic back pain subjects received clinical
evaluation and completed perceptual measures of pain and anxiety. The results show that chronic back pain alters human brain chemistry: NAA and Glc were reduced in the dorsolateral prefrontal cortex, whereas the cingulate and sensorimotor cortices and other brain regions showed no chemical concentration differences. Given that decreases in NAA are documented in various conditions involving neuronal cell damage and loss (Salibi and Brown 1998), our results provide evidence for a link between chronic pain and neuronal degeneration, specifically in the prefrontal cortex. These results also show the concordance between the fMRI studies and the MRS measures, both pointing to the prefrontal cortex as an important brain site for chronic pain.

The chronic back pain subjects in the MRS study completed perceptual measures of pain (the short form of the McGill Pain Questionnaire; Melzack 1987) and anxiety (the State-Trait Anxiety Inventory; Spielberger et al. 1983) minutes before brain imaging. These measures were correlated with brain regional chemical concentrations. There was a specific relationship between regional chemicals and perceptual measures of pain and anxiety. Chemicals in the prefrontal cortex of these patients showed the strongest relationship with the affective components of back pain. Therefore, this study indicates not only that brain chemistry is different in chronic pain patients but also that the abnormal changes reflect the specific perceptual parameters that define the details of the suffering that constitutes chronic back pain. This study also demonstrates that the relationship among various chemicals across the different brain regions was abnormal in the back pain patients as compared to normal subjects, indicating regional reorganization of brain biochemistry with chronic pain.

PREFRONTAL CORTEX AND CHRONIC PAIN

The above results highlight the importance of the engagement of the prefrontal cortex in chronic pain conditions. We observed prefrontal activation in chronic CRPS and back pain patients in functional imaging studies that concentrated on identifying the ongoing component of chronic pain. Also, the biochemical analysis of the chronic back pain patients shows the main shift in brain biochemistry to be localized to the prefrontal cortex. Thus, using disparate brain imaging methods and examining different clinical populations, we repeatedly observed the involvement of the prefrontal cortex in chronic pain. A cursory review of the literature indicates that most functional imaging studies of acute and experimental pain show substantial activity in the prefrontal cortex, although the significance of this activity has been usually ignored.
The prefrontal cortex is the neocortical region that is most elaborated in primates. It comprises a collection of interconnected neocortical areas that sends and receives projections from virtually all cortical sensory, motor, and subcortical structures (Miller and Cohen 2001). Tasks that uniquely require an intact prefrontal cortex, such as the Stroop task or the Wisconsin Card Sorting Task, are described as tapping cognitive functions of either selective attention, behavioral inhibition, working memory, or rule-based or goal-directed behavior. Miller and Cohen (2001) argue that all these functions depend on representation of rules or goals in the form of prefrontal cortical activity patterns, which configure processing in other parts of the brain in accordance with current task demands. Different pathways in the prefrontal system, carrying different sources of information, compete for expression in behavior, and the winners are those with the strongest sources of support. Therefore, central reorganization in chronic pain simply becomes a manifestation of the change in representation rules specifically for nociceptive signals, where a long-term winner pattern enhances the affective significance of nociceptive processing. Consistent with these ideas, we have collected preliminary data in studies that evaluated chronic pain patients as to their ability in long-term planning—a task that is critically dependent on ventral orbital circuitry of the prefrontal cortex. The results indicate decreased ability of chronic pain patients in long-term planning, as compared to normal subjects (Kunar et al. 2000).

Different portions of the prefrontal cortex have been associated with distinct functional organizations. For example, orbital and medial areas are associated with behavioral inhibition, whereas ventrolateral and dorsal regions are associated with memory or attentional functions (Furster 1989). Moreover, both deficits and activation of the orbital prefrontal cortex have been mostly associated with tasks involving social, emotional, and appetitive stimuli (Swedo et al. 1989; Price 1999; O’Doherty et al. 2000), while more dorsal regions are reported to be activated in cognitive tasks. The differential extent of the involvement of these regions in distinct chronic pain conditions and in acute pain indicates that the salience of pain may vary subjectively along these dimensions. These relationships imply that the extent to which different types of chronic pain impinge on attentional-cognitive tasks as compared to social-emotional tasks may be unique in different clinical conditions.
COMPARISON OF THE CURRENT MODEL WITH OTHER PROPOSED MECHANISMS

In this chapter we have presented the experimental data underlying the simple model we propose for chronic neuropathic pain conditions, including SCI pain. We propose that chronic neuropathic pain is associated with prefrontal activity and with prefrontal biochemical abnormalities. This is interpreted as a change in the "top-down" control of behavior where the salience of pain is increased at the cost of other cognitive and emotional behavioral abilities. This change most likely comes about by the establishment of new connectivity strengths, for example by changes in across brain synchronizations, where chronic pain may be viewed as a long-term memory that cannot be turned off, and thus it constantly interferes with attention to other tasks. Clearly this cortical network reorganization is driven, at least initially, by changes in the peripheral nervous system and spinal cord. However, the chronicity of the pain may simply reflect the extent of the change in "top-down" control of pain transmission circuitry. The details of the interaction between "top-down" and "bottom-up" control of pain perception remain to be studied.

In the only previous conference organized on the topic of central pain syndromes, Tasker et al. (1991) reviewed the historical literature as well as their clinical experience of the condition. They concluded that the most common property of central pain (i.e., neuropathic pain of central origin, which certainly includes SCI pain) is its steadiness. They estimated that 98.6% of their patients exhibit steady pain of various types: burning pain in 64.6%, aching in 38.6%, and dysesthesia in 31.6% (Tasker et al. 1991). Therefore, in this chapter we emphasize the brain imaging experiments that specifically aim to define the brain circuitry underlying the steady pain of chronic neuropathic conditions.

Since the first descriptions of central pain syndromes, many scientists have emphasized that the central underlying process involves the most direct nociceptive information pathway, the spinothalamic tract (see Chapters X, X). Lesions along this pathway either cause or, less frequently, relieve, pain conditions. Neurosurgeons have used deep brain stimulation along this pathway to relieve pain (see Chapter X). Occasionally, stimulation within the lateral thalamus, at termination sites for the spinothalamic pathway, can replicate the pain. Our viewpoint is that differentiating between transmission pathways might be an altogether erroneous concept regarding chronic pain conditions. Instead, we emphasize changes in dynamic cortical network
strength. Our model for chronic pain provides a new viewpoint regarding the success of deep brain stimulation procedures. Pain relief by such procedures may be a consequence of reestablishing inputs from this pathway to the cortex and thus counterbalancing the prefrontal network. In time this barrage of activity can reset the connectivity strengths of the cortical prefrontal “top-down” control to more normal levels.

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