

Functional imaging of pain: new insights regarding the role of the cerebral cortex in human pain perception

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There has been a large increase in the use of brain imaging technologies to study pain. Most likely this trend will accelerate even more in the near future. Comparing among the studies that have examined the brain physiology of human pain perception the general impression is confusing. It seems that depending on the laboratory, the specifics of the technology used and the details of stimulus delivery, different results are obtained regarding the brain sites and their type of involvement (increased or decreased activity) in pain perception. This review is an attempt to allay some of this confusion by proposing a set of hypotheses that can explain most of the differences more coherently. The main conclusion of this review is rather surprising, because the arguments lead to the notion that the spinothalamic pathway may not be the major system involved in clinically relevant pain states.

Key words: acute, chronic, clinical pain / PET / SPECT / fMRI / cortex

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TRADITIONALLY, FUNCTIONAL IMAGING TECHNOLOGY as applied to the human brain has been extremely expensive and cumbersome. As a result these tools were only available to a small group of scientists. However, it is foreseen that the recent technical advances, especially in functional magnetic resonance imaging, will make such tools universally available in the very near future. Within the next few years virtually all academic institutions in the United States will have the capability of doing functional human brain imaging studies (using Echo Planar functional

“The typical concerns of the Philosopher of Mind might be represented by three questions: (1) How do we know that other people have pains? (2) Are pains brain states? (3) What is the analysis of the concept pain?”

From: *The Philosophy of Mind*, ch. 10, 1992. Hilary Putnam

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Magnetic Resonance Imaging, fMRI). In this sense, the age of human brain physiology has dawned yet again. Therefore, the number of studies examining the human brain anatomy/physiology of pain will expand very rapidly, in parallel with the expansion of all human brain imaging studies. The scientific challenge will be to translate this enormous technologic advance into concrete gains in the understanding of the brain in pain, and in transforming the technology into a clinical diagnostic and prognostic tool. Electrophysiologic tools, such as electroencephalography and brain evoked potentials, have been available to the scientific and clinical community for over 50 years and have been used extensively to study many pain states (for review see ref 1). Unfortunately, the impact of these studies on our understanding of mechanisms underlying pain remain minimal, although more recent advances in laser stimulation evoked potentials²⁻⁴ seem more promising. A cursory look at the functional imaging literature suggests that we are heading in the same ambiguous direction, i.e. the findings from one laboratory to the next, and from one experimental paradigm to the other seem inconsistent and not interpretable. This is the negative synopsis of the imaging studies of the human brain during pain perception. The alternate, positive interpretation is that these studies, although still small in number, have very quickly shown that our current understanding of human pain is very limited, and that the studies actually point toward the new directions that need to be pursued. In the following this positive interpretation will be reviewed, outlining the new directions as hypotheses to be tested.

Techniques and terminology

This section is a quick overview of the current state of brain imaging technology. It is by no means comprehensive. A large number of excellent reviews and books have been recently published on the subject; for more details see refs 5-8. Brain electrical activity

can be monitored by single unit recordings, intra- or extracellular techniques, or by monitoring large populational activity by electroencephalography or magnetencephalography. Brain activity can also be studied by tracking metabolic or blood flow changes. The coupling between blood flow and brain activity was discovered by Roy and Sherrington.⁹ The generation of action potentials and synaptic transmission deplete cellular energy stores and require cerebral glucose metabolism to re-establish these stores. Metabolic brain activity in humans can now be imaged using several different techniques: non-tomographic ¹³³Xenon method with gamma emission detectors, single photon computed emission tomography (SPECT), positron emission tomography (PET), and fMRI. The ¹³³Xenon and SPECT methods monitor regional cerebral blood flow. PET can monitor regional blood flow, glucose utilization, or regional metabolic oxygen consumption, depending on the radiotracer used. fMRI measures local changes in magnetic field as a function of both blood flow and blood oxygenation. Most authors reporting cerebral activity are careful in specifying the actual metabolic signal being monitored. This becomes important especially in studies of the damaged brain where different metabolic events may become decoupled from each other. Since this review is concerned mainly with imaging studies in the normal brain, and since decoupling between metabolic pathways has not been studied in pain states, it will be assumed that there are no significant differences between the different metabolic signals, and the term 'cerebral activity' will be used for all functional metabolic imaging signals throughout the review.

The duration over which cerebral activity is integrated varies with imaging technique and radiotracer used. The fMRI provides the fastest integration times (1–5 s), and actually enables determining the time constants underlying cerebral blood flow and oxygenation changes. Integration times for PET studies range from 5–10s for H₂¹⁵O studies of oxygenation, to 20–30 min for glucose utilization studies. The ¹³³Xenon and SPECT methods require integration times larger than 3 min. The spatial resolution of these techniques varies greatly as well. The ¹³³Xenon and SPECT methods have the worst spatial resolutions, larger than 10 mm. The spatial resolution of the PET techniques has greatly improved in time, with a concomitant increase in sensitivity, such that the new generation PET machines are able to determine cerebral activity in individual subjects. Thus, when comparing among different brain imaging studies it

becomes imperative to keep in mind the spatial and temporal resolution differences between studies. Unfortunately many authors do not bother reporting the spatial and temporal resolution of the specific PET machine employed in their studies. The spatial resolution of fMRI remains better than the other metabolic brain imaging techniques. However, it remains uncertain as to whether the sensitivity of fMRI in detecting changes in cerebral activity matches that of PET. The main advantage of fMRI over PET is its complete non-invasiveness. This enables repeated multiple imaging studies in the same person with minimal worry regarding health hazards. The main difficulty of fMRI is its sensitivity to electrical and magnetic fields interference, which imposes severe limitations on experimental designs.

Increases in blood flow or blood oxygenation or glucose consumption are all directly attributed to be secondary to increased neuronal activity. This electrical activity is generally thought to reflect increases in synaptic activity and in spiking in the excitatory neurons that receive, process and transmit information, especially in the neocortex. An ideal completely consistent with the correspondence between regional cerebral activity increases in humans, in many diverse tasks, and with the single unit physiology carried out in other animals. As detailed below, brain imaging studies of pain states have revealed a large number of regions where decreases in cerebral activity are observed regardless of which metabolic marker is used. Many scientists have been reluctant to ascribe decreased cerebral activity to inhibition in electrical activity. The main argument advanced is that inhibition requires activation of local inhibitory neurons, which consumes energy and translates into increased metabolic demand or increased cerebral activity. However, at least in the neocortex, the inhibitory interneurons make up only about 10% of the total pool and their soma sizes, axon lengths and diameters are much smaller than the excitatory projecting pyramidal neurons. Thus, relative to the projecting cells, the metabolic demands of interneurons are probably much less. When a cortical region is inhibited, one can hypothesize that the relative increase in metabolic demand by local interneurons is dwarfed by the overall decrease in demand by projecting cells. These hypotheses remain to be directly demonstrated, but for this review it is assumed that decreased cerebral activity reflects inhibition of electrical activity in the excitatory projecting cells both in the cortex and in the thalamus.

Brain imaging of headache

Brain imaging has been used most extensively in the past in headache research. Most of these studies were carried out in Denmark, where over 5,000 patients were studied up to 1991.¹⁰ The majority of these studies were performed using either ¹³³Xenon or SPECT. The main conclusion of these studies is the detection of hyperperfusion of the brain during a migraine or cluster headache attack, which may persist for days after the headache, and a hypoperfusion during migraine aura. However, since the major brain arteries can function independent of brain blood flow, it remains unclear whether the vascular blood flow increase translates into a global increase of brain blood flow.¹¹ The blood flow increases are bilateral primarily involving the frontal and temporal cortices, include subcortical structures such as the striatum and the thalamus, as well as white matter structures. Moreover, these increases are not correlated with the side of the head where pain is reported (see e.g. ref 12). Therefore, these studies indicate that the hyperperfusion is more than likely not a functional increase due to the head pain alone and it probably is not even the primary cause of the head pain. Thus the mechanisms underlying the vascular hypothesis of migraine headaches remain to be established.

Everyday experience indicates that headaches are certainly associated with strong discriminative and affective somatosensory percepts. The brain regions involved in these perceptions must be similar to regions activated with other pain perceptions, although the detailed affective components and the associated brain regions involved may be unique. The brain regions involved in headache perception have not been reported probably because of the low resolution of the imaging techniques used. Moreover, the changes in cerebral perfusion complicate subtractive studies by the need for proper normalizations between brain images obtained during headache and baseline conditions.

Early imaging studies of pain

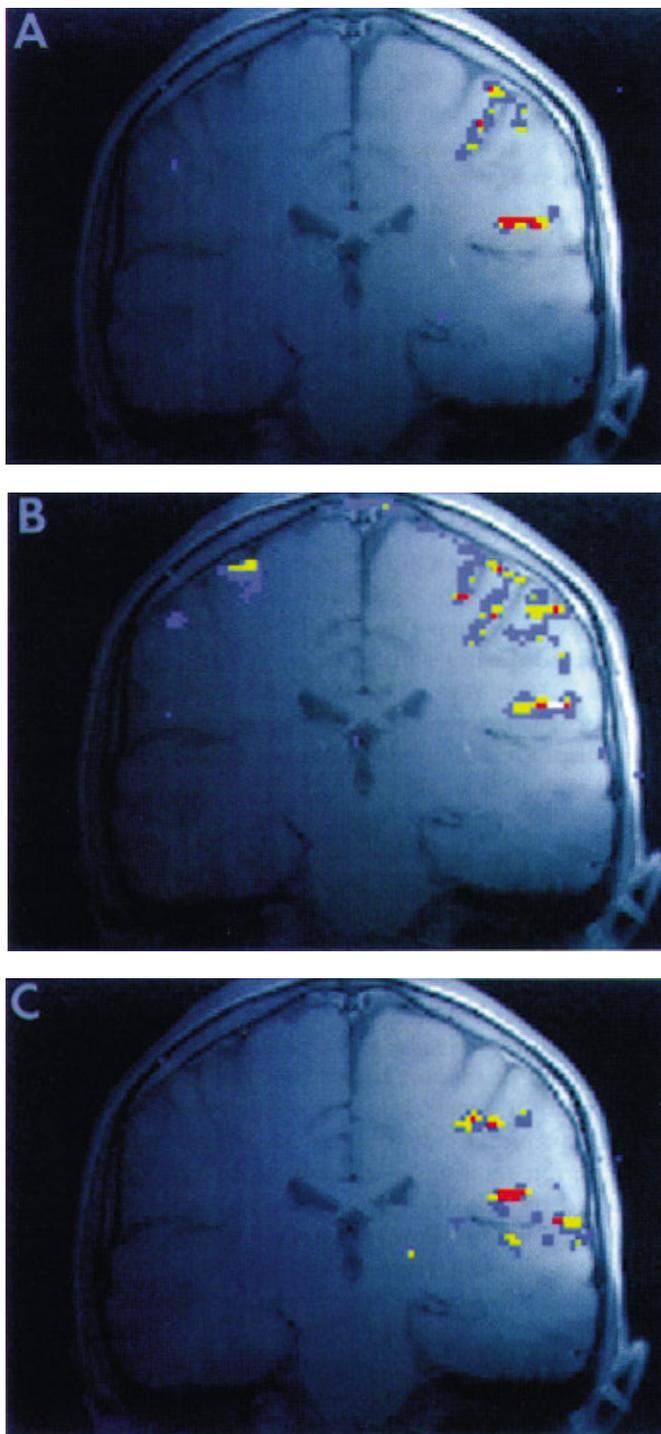
Ingvar, D.H., and colleagues^{13,14} performed the first human brain imaging studies of pain. Pain was induced by electrical stimulation of the thumb. Intra-arterial ¹³³Xenon injections and 32 gamma emission detectors, placed lateral to the hemisphere contralateral to the stimulated thumb, measured regional

cerebral blood flow. Stimulating the thumb at painful intensities increased the mean blood flow to this hemisphere. Blood flow increases were seen in the frontal lobe, and when compared to the rest state in postcentral regions. Interestingly, the authors comment in the discussion: 'Occasionally we observed a diminution of the flow during high intensity skin stimulation.... The flow diminution was general and there were no respiratory changes which could have explained it' (ref 14, p. 556). Therefore, even in this first study, cortical blood flow decreased during pain in some situations. What specific conditions give rise to increases versus decreases in cortical activity in pain states? Recent studies have specifically addressed this question, and its interpretation is a major focus in this review. The first PET study of pain perception in humans was carried out by Buchsbaum *et al.*¹⁵ using the ¹⁸F-2-deoxyglucose PET technique with in plane resolution of 17.5 mm, and electrical stimulation of the forearm, activating both nociceptive and non-nociceptive afferents. Glucose use was highest in the contralateral postcentral gyrus region, as compared to ipsi- and contra- precentral and postcentral gyral regions. These authors, in agreement with the earlier study, point out that during rest and electrical stimulation there is an anteroposterior gradient of activity — 'hyperfrontality', which is more pronounced during pain.

In a later report Ingvar and colleagues¹⁶ studied cortical activity in both ipsilateral and contralateral hemispheres in subjects trained with a painful thermal stimulation paradigm. Here the authors present more information regarding their data from the earlier study.¹⁴ In Figure 1 they review the individual blood flow changes for non-painful and painful electrical stimulation as compared to rest. The data show increased contralateral hemispheric blood flow in five cases and decreased blood flow in three cases for painful electrical stimulation, as compared to the non-painful state. In five trained subjects they apply intermittent radiant heat stimuli on the right thenar region of the hand for 10 minutes, at intensities giving rise to either warmth or pain perceptions. The ¹³³Xenon technique with two arrays of 31 detectors placed on both sides of the head was used to detect cerebral blood flow. Excluding the activity in one subject who experienced high levels of anxiety during the task, the mean hemispheric blood flows were increased during the non-painful stimulus, and decreased back to rest levels during the painful stimulus. The regional warm-rest changes in blood flow were increased in most cortical areas, most

significantly in the left temporal region. In contrast, pain-warm changes in blood flow were negative in most regions, most significantly decreased in the contralateral temporal region, but were significantly elevated in both parietal regions. Based on these

results and the activity observed in the one subject with high anxiety, the authors interpret their earlier observations of increased blood flow during noxious stimulation as due to anxiety resulting from their subjects' lack of training.



Imaging studies of experimental pain: phasic stimuli

Jones *et al*¹⁷ and Talbot *et al*¹⁸ reported the first PET studies of brain activations for experimentally induced thermal pain. Both studies indicated the involvement of the cortex in pain perception. They both used very similar scanning (5–8.5 mm transaxial resolution) and stimulation techniques: phasic 5 s duration heat pulses delivered through a contact thermode. These two reports had a number of differences regarding brain activation sites with thermal pain, although in subsequent reports the two laboratories have tended to agree with the main findings. Jones *et al*¹⁷ emphasized activation of the contralateral anterior cingulate cortex, thalamus and basal ganglion, when non-painful heat (mean = 41.3 °C) was compared to painful heat (mean = 46.4 °C), averaged over six subjects. They reported no significant changes in cerebral activity when baseline (mean = 36.3 °C) was compared to the non-painful heat stimulus. In contrast, Talbot *et al*¹⁸ observed activations in the anterior cingulate, secondary somatosensory cortex (SII), and primary somatosensory cortex (SI), when the PET images were compared

Figure 1. Cerebral activations in MI, SI, and SII in one subject during a noxious thermal (A), motor (B), and vibrotactile (C) tasks. A single coronal slice is shown, although eight slices were studied. High resolution anatomic MR images are overlaid with significant increases in fMRI intensity for the three tasks. Sixty control images are compared with 60 stimulus images, and individual voxel *t*-statistics computed. Only voxel clusters of size greater than 4 that exceed a *t*-value of 2.002 ($P < 0.05$) are shown. The color code in A is: *t*-values 2.002–4.00 are shown in blue, 4.01–6.00 are yellow, and 6.01–8.00 are red. The color code in B is: *t*-values 2.002–7.50 are shown in blue, 7.51–13.00 are yellow, 13.01–18.50 are red, and 18.51–24 are white. The color code in C is: *t*-values 2.002–4.30 are shown in blue, 4.31–6.60 are yellow, and 6.61–9.00 are red. In A the highest active region is the region above the lateral sulcus, area SII. The activity surrounding the central sulcus is the only other significantly active area. The activity just medial and superior to the central sulcus is MI, while the lateral and inferior gyrus is SI and shows a smaller active area. In the motor task (B) activity is more prominent in MI and MII, and a larger portion of SI is active. During vibrotactile stimulation (C) the activity in MI is much less.

between non-painful heat (41–42 °C) and painful heat (48–49 °C), averaged over eight subjects. The thalamus and basal ganglia were not scanned in this study. Therefore, the main difference between the two studies was the parietal somatosensory cortical activity, which may have been due to the smaller number of subjects and lower temperatures used by Jones *et al.*¹⁷ In fact, in a subsequent study where the number of subjects was increased, the group reported both SI and SII activation and deactivation depending on the perceived pain, where somatosensory cortical deactivation was observed at higher pain perception levels.¹⁹ The initial studies by both groups did not examine cerebral regions that may have shown decreased activity with pain. In a subsequent more extensive study, these investigators again examined brain regions involved in thermal pain perception and compared these sites with areas involved in vibrotactile perception.²⁰ The same regions as mentioned above were observed for the pain task. The subtraction was done between baseline and painful heat. Moreover, a number of other regions with changes in cerebral activity were also observed. Cerebral activations with pain were seen in the anterior insula bilaterally, and in two foci in the supplementary motor area. Cerebral deactivations were seen in the posterior cingulate and the orbital gyrus, contralaterally. The authors note that the volunteers significantly increased their heart rates just prior to the painful stimulus, implying a heightened anxiety state which may have contributed to the additional areas observed. The vibratory stimulus activated: the contralateral SI — an area coincident to that observed for pain, the SII bilaterally — an area more posterior and medial than for pain, the posterior insula bilaterally, the contralateral thalamus, anterior cingulate and supplementary motor area just below the threshold for statistical significance, and the vibratory stimulus deactivated the middle frontal gyrus and the orbital gyrus. Thus, most areas activated and deactivated, outside of SI, thalamus and orbital gyrus, for the vibrotaction task were distinct from those for the painful thermal task.

Casey *et al.*²¹ essentially replicated the studies done in Talbot *et al.*¹⁸ in a larger group of subjects ($n=18$). They used 5-s thermal heat pulses delivered to six different sites on the forearm for the duration of the scan, using PET with $H_2^{15}O$. The interstimulus interval, the thermal probe size, and the shape of the heat pulse were slightly different between the two studies. These authors were able to scan a larger span of the brain than in the other studies. Their results in

general confirm the earlier studies. New areas that they observe to be activated with thermal pain are the medial dorsal midbrain and the cerebellar vermis. This study did not analyze cerebral areas deactivated with the painful task. Similar to the earlier results by Jones *et al.*¹⁷ Casey *et al.*²¹ also report no significant changes in cerebral activity when the thermal stimulus is not noxious.

Overall, these studies indicate that parietal, insular and cingulate cortical regions, and at least the thalamus and striatum as well, are involved in the perception of thermal pain. Whether these different cortical and subcortical areas process distinct aspects associated with the perception of the painful stimulus remains to be determined. Not surprisingly, increases in the number of subjects per study and the use of more sensitive PET scanning techniques have increased the number of areas identified in the pain task. The latter points to a common pitfall in brain imaging studies, i.e. the lack of significant changes in a particular brain region does not imply that the region is not involved in the task. It should be emphasized that all of these studies used a very similar stimulation paradigm, very short duration tonic thermal stimulus, applied intermittently on the skin for the duration of the scan. Because of this strong similarity between the paradigms, it is impossible to determine how robust are the reported results. The main worry is that cerebral activity in such phasic stimuli may have very little to do with pain perception but rather with the detection of the initial shock of high intensity stimulus, which may induce changes in wakefulness and startle, or may induce a strong desire to consciously remove the hand from the stimulus. Such an effect may still change cerebral activity but the change would be very brief and strongly coupled to the start of the painful thermal stimulation. PET studies are unable to distinguish between such changes in activations from a sustained change in cerebral activity maintained for the duration of the stimulus. Recently, Casey *et al.*²² using PET with $H_2^{15}O$, analysed the cerebral activation patterns in repetitive painful heat stimuli between the start of the stimulus and at a later phase (15 s from the start). The early phase activations were similar to those reported above, in the later phase the same activations persisted, but ipsilaterally, the insula, thalamus and cerebellum were also active. The authors interpret these results by pointing out that the subjects' pain and unpleasantness perceptions were higher at the later phase. Alternatively, these results can be construed as evidence for a non-specific arousal or

attentional state change because it can be argued that the stimulus is perceived on the same location in early as well as late phases of stimulation, yet the brain activity has become more bilateral.

Imaging studies of experimental pain: tonic stimuli

Apkarian *et al*²³ delivered thermal stimuli by immersing volunteers' hands (three subjects each scanned three times) in a heated water bath to assess cortical activity during sustained pain. Cortical activity was studied to non-painful stimuli and painful thermal stimuli using SPECT with Tc99m-HMPAO as the radiotracer. MRI scans were used for anatomic localization of the changes. Contralateral somatosensory cortical activity was decreased in four SPECT scans, in all subjects, when the digits of the hand were in moderately painful hot water for 3 minutes (radiotracer injection started 30 s after hand immersion). No significant changes were seen when the hand was in tepid water. In contrast, cortical activity increased in sensorimotor regions during vibratory and palpation tasks. Since the spatial resolution of SPECT is low (about 17–20 mm), exact localization of the cerebral changes could not be ascertained, although the center of decreased cerebral activity was in the precentral gyrus — approximating hand representation area and also seemed to extend into SII. The main contribution of the study was to indicate that sustained, tonic painful stimulation results in cerebral activity patterns very different from the phasic painful stimuli. It is possible that the decreased activity masked a smaller, more-focused increased activity in the digit area of SI.

Obviously, there are a large number of technical differences between this study and the PET studies described above, and one can ascribe the differences in the obtained results to various technical quirks. However, a more fruitful interpretation is that the differences in the results are due to the types of painful stimuli. Accepting the latter implies that the increased cortical activity observed in phasic stimuli, at least in SI and perhaps in SII, is more related to the decision, conscious, or reflective, or both, of keeping the stimulated body part in place and subjecting it to the threatening environment. This process requires access to discriminative information, i.e. where and how intense the pain will be. Past this initial motoric, or motivational, state one can still perceive pain. However, this perception may not depend on activa-

tion of SI or SII and might in fact require their inhibition by modulatory systems. Thus, the PET studies above may be viewed as outlining the cortical areas involved in the motoric motivational process, while the SPECT study may be viewed as tapping into the later perceptual processes. It must be emphasized again that the lack of significant changes outside of SI or SII in the Apkarian *et al*²³ study say nothing regarding the involvement of other regions in the different phases of pain perception.

A number of observations are consistent with this biphasic notion of cortical activity during pain perception, most importantly recent PET and fMRI studies of chronic pain reviewed below. Electroencephalographic studies by Backonja *et al*²⁴ provide further support to this notion. Their study indicates that immersion of the hand in painfully cold water results in an initial decrease, followed by a sustained increase in alpha power (biphasic response). These results imply an early somatosensory activation in response to the tonic pain progressing to eventual somatosensory inhibition, after the first minute of pain. Such inhibition is not observed when the painful stimulus is more phasic (usually much shorter than 1 min). A recent PET study of tonic pain by Duncan *et al*²⁵ is also consistent with the biphasic hypothesis. In this PET study, the authors point out that if the thermal stimulus is tonic, and maintained at fixed temperature for 60 s, then the cortical activations do not reach significance. To obtain significant activations only the first 40 s of the scans are used, and the scans need to be regressed with subjects' reports of unpleasantness. Using these procedures, the activated regions tend to be more motoric than somatosensory, including: basal ganglia, red nucleus and cerebellum (personal communication).

We reasoned that if the inhibition in the somatosensory cortical response to sustained painful stimulation is functionally significant then it must alter vibrotactile perception. Apkarian *et al*²⁶ tested vibrotaction during tonic painful thermal stimulation, in 10 subjects where the pain and vibratory stimuli were coincident. The painful heat was delivered through an annulus placed on the thenar eminence and vibrotaction tested inside this annulus. Increases in vibrotactile thresholds (tested at 1, 10 and 100 Hz) and decreases in sensitivity of suprathreshold magnitude estimation were consistently observed when the subjects were in pain. In a subsequent study we have observed that the decreased sensitivity in vibrotactile perception is limited to the dermatome where the painful stimulus is presented (manuscript in prepara-

tion). These psychophysical studies confirm that tonic pain inhibits somatosensory vibrotactile information processing. Nathan²⁷ observed that in patients with chronic pain, pain relief by a variety of interventions: nerve block, nerve section, intrathecal anesthesia, results in sharpening touch perception for the duration of the relief. Therefore, both chronic and acute, sustained tonic pain inhibits touch perception and the relief from the pain results in improved touch or vibrotactile percepts. A number of recent imaging studies of clinical pain states agree with these notions (see later).

A recent PET study, using [¹⁵O]butanol (in five subjects), by Hsieh *et al*²⁸ further extends the observations of Apkarian *et al*²³ by showing decreased cortical activity in limbic and sensory regions of the cortex during both anticipation and endurance of sustained painful stimuli. Pain was induced by electrical stimulation of the wrist, delivered at 80% of pain tolerance. This pain task activated the same somatosensory regions reported by others for phasic painful stimuli, and regions related to motor programming and execution: bilateral premotor areas, contralateral supplementary, primary, and cingulate motor areas, and ipsilateral cerebellum. The authors note the lack of correlation between SI activation and pain ratings or stimulus intensity. Since the painful stimulus used was electrical, both non-nociceptive and nociceptive afferents were activated, thus the activations especially in SI and SII may be due to either or both groups of afferents. Extensive decreases in cerebral activity were observed during pain, including bilateral auditory, visual, and somatosensory areas, and limbic and paralimbic areas: prefrontal, cingulate, and temporopolar regions. In the anticipation task the painful stimulus was presented only after the PET scans were terminated. There were no changes in SI or SII, but increased activity was seen in the ipsilateral thalamus and contralateral caudate. Decreases were observed in many of the same structures as in the pain task, although the amount of decrease was less for pain anticipation. The SI decreases were bilateral, but contralaterally outside of the area activated with painful stimulation. The authors conclude that the decreased activity represents a central coping mechanism in response to the sustained pain or in anticipation of the pain, and suggest that the cause is extrathalamic. Perhaps the main difference between this study and Apkarian *et al*²³ is the perceived magnitude of the painful stimulation. In both the psychophysical and SPECT imaging studies, we attempted to keep the painful thermal stimulus at a

moderate pain level, and in the psychophysical study we ascertained that auditory thresholds were unchanged but vibrotactile thresholds were increased during pain.²⁶ The latter indicates that the pain intensity was not high enough to interfere with all attentional abilities of the subjects. Therefore, the results of Hsieh *et al*²⁹ may reflect a further expansion of the decreases in cerebral activity when the painful stimulus is—or is anticipated to be—at a higher intensity, resulting in inhibitions in many regions outside the somatosensory cortex. A recent PET study of attention very closely agrees with these results.³⁰ Drevets *et al* examined human cerebral activity in SI and SII in anticipation of either focal innocuous touching or painful electric shocks, or in subjects with simple animal phobias during studies in which the subjects feared an animal might touch their faces. In all three conditions cerebral activity decreased in SI and SII, bilaterally. At least within SI, the decreases were in regions outside the representation of the body part where a stimulus was expected. The magnitude of the decrease in SI correlated with anxiety levels during pain anticipation. Increased cerebral activity was reported only in premotor areas. The authors argue that the decreases are part of a gating mechanism for sharpening differences between sites where a stimulus is anticipated, and other skin areas. Two earlier PET studies have indicated opposite results.^{31,32} When subjects directed their attention to a fingertip expecting stimulation by von Frey hair at threshold intensities, cerebral activity was increased by 25% in the SI finger area.³¹ Also, when subjects attended a vibrotactile stimulus on the finger, SI activation was 13% higher, compared to when they were engaged in a distraction task.³² Neither study reports on decreased cerebral activity, which presumably was not tested. The studies by Apkarian *et al*,²³ Hsieh *et al*²⁸ and Drevets *et al*³⁰ suggest that inhibitory mechanisms are an essential component of cortical processing, and that the specific cortical areas inhibited are a function of the details of the task and the stimulus intensity, actual or anticipated.

Di Piero *et al*³³ reported a ¹³³xenon SPECT study of cerebral activity for the cold pressor test, which the authors indicate is mediated through C-fiber afferents. Volunteers were scanned in the rest state and after the immersion of the hand in 0 °C water for 4 minutes. The results show activation in the contralateral sensorimotor cortex, and in the frontal and temporal regions of the cortex. Casey and colleagues are currently conducting similar studies using PET

and less-intense cold stimuli (personal communication). They, too, see cortical activations with this task. These results seem contradictory to the biphasic notion of pain perception, i.e. the sustained C-fiber mediated pain seems to exhibit sustained cortical activations. However, to what extent the activated patterns are motoric, versus somatosensory, remains unclear. Perceptually, the cold pressor test, especially at 0 °C, induces a very strong urge to withdraw the hand from the water bath. If a person can withstand the pain for more than 1 minute, then the withdrawal urge becomes relatively less intense (most people are unable to keep their hand in 0 °C water for over 1 min). Whether such differences in the motoric motivational components of various pain inducing stimuli explain the differences in the observed cerebral activity remains to be systematically studied.

Over the last year, we have been studying cerebral activity in humans using fMRI with echo planar imaging. fMRI studies of pain are underway in a number of other laboratories: refs 34-36 and A.K.P. Jones (personal communication). In our studies the subjects move their hand digits 2-5 between two surfaces: a neural temperature surface (35 °C), and a surface heated 0.5-1.0 °C above the subject's pain threshold (45-47 °C). During a functional MRI scan the hand is held on each surface for 36 s, cycled for six times. Eight coronal slices are imaged, 10 times during each stimulus or control state, spanning the parietal temporal cortex (manuscript in preparation). The results show activations in MI, SII and SI, as well as in anterior cingulate, supplementary motor and anterior insular regions, contralateral to the stimulated hand (Figure 1). No consistent deactivations were observed with this task. Since these studies use a surface coil placed on the head opposite to the stimulated hand, the ipsilateral activity was not studied. The activation sites closely correspond to those described in the PET studies using phasic pain tasks. The fMRI results showed large differences between subjects regarding the exact location and magnitude of the activations. The most consistent activation was in MI. This MI signal persisted in thermal pain tasks where the stimulus was delivered while keeping the hand immobilized. The fMRI activation sites were determined for each subject based on their anatomic MR images, in contrast to the PET results are usually the average cross brains normalized to a standard atlas. Moreover, the spatial resolution of fMRI is higher than current PET technology. Therefore, for phasic painful stimuli, the PET activations reported

localized to SI are probably a reflection of averaging between activations in MI as well as SI.

The fMRI activations observed were sustained for the duration of the stimulus (Figure 2). Earlier fMRI studies have shown that the blood flow/oxygenation activation time constant is 3-4 s. Thus, if the cortical responses to painful heat were a startle or arousal effect linked to the initial fast rise in skin temperature, then the cortical activations should have returned to baseline within 10-15 s. The time profiles of the activations in MI, SI and SII all show an early partial adaptation followed by a sustained activation that briefly outlasts the duration of the stimulation. Whether these activation profiles might in a longer sustained painful stimulation return to, or decrease below (result in inhibition) baseline is currently under study in our laboratory.

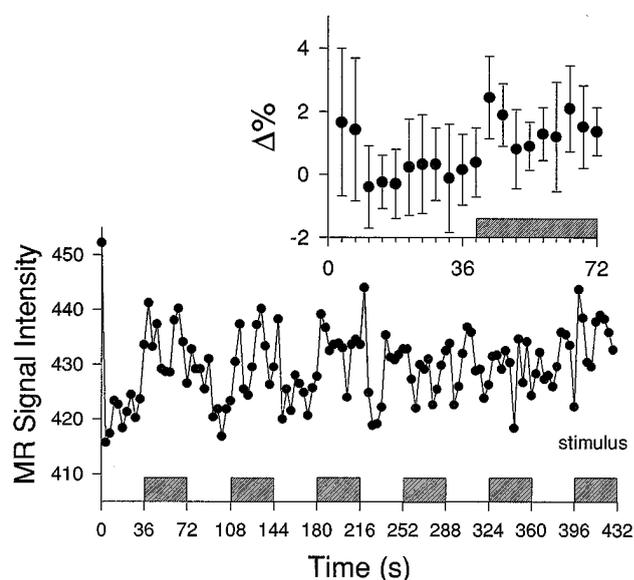


Figure 2. The temporal pattern of MR signal intensity changes are shown in one subject during noxious thermal stimulation in a region of interest located in SI. Six cycles of stimulus and control pairs were carried out continuously, 10 images were acquired in each stimulus or control state (lasting 36 s). The inset figure shows the MR signal in percent change after averaging across the six cycles (error bars = standard deviation). The activity in SI has a t -value of 3.84, which corresponds to $P < 0.0002$. The average response shows that in the stimulus phase there is a slight initial adaptation and a sustained activation for the duration of the stimulus. The averaged response also has elevated activity during the first few control images. This is most likely due to the time constant of recovery of fMRI signal at the end of the stimulus cycle because the task was performed continuously. Similar activation profiles were observed in MI and SII.

In addition to the thermal pain task, the fMRI scan sessions included a finger apposition and a vibrotactile task. The cortical activations observed in these two tasks in MI, SI and SII partially overlapped with the pain activation sites in about 90% of the pain activated regions (Figure 1). The strong overlap between MI, SI and SII activation sites across all three tasks reinforces the notion that the early activation of these areas during pain are part of a motoric decision making process. The maintained activation for the stimulus duration implies that the time constant of the early motoric phase of pain perception is longer than the stimulus duration used (36 s), at least for this task.

Imaging studies of clinical pain

A small number of brain imaging studies have examined clinically relevant pain states. However, the results of these studies are relatively consistent between laboratories and between different pain states. The surprising observation is that somatosensory cortical and the contralateral thalamic activity generally remain either unchanged or show decreased cerebral activity during sustained clinical, or chronic, pain.

Tran Dinh *et al*⁶⁷ performed ¹³³xenon emission studies in 14 trigeminal neuralgia patients. The authors observed bilateral increases in cerebral blood flow in the internal carotid, anterior cerebral, and middle cerebral arterial territories 1 hour after glycerol injection in the trigeminal cistern, as compared to the rest scans performed 24 hours pre glycerol injections. The investigators ascribe these changes to trigeminal-vascular connectivity and do not take into consideration the effects of relief from the trigeminal pain. Hosobuchi³⁸ reported on three patients with cerebral ischemia treated with electrical stimulation of the cervical spinal cord. In two of the patients ¹³³xenon emission or SPECT studies indicated cerebral blood flow increases and alleviation of ischemia symptoms (in all cases) with the spinal cord stimulation. The blood flow response was not ascribed to afferent inputs because, the author points out that in cats, the blood flow increase with spinal cord stimulation occurs only after a long time delay (120–180 min) and that it outlasts the stimulation (by 30–60min).

Cerebral activity in patients with central pain has been investigated by a variety of laboratories. Katayama *et al*⁶⁹ studied cerebral activity changes with

electrical stimulation of the thalamus in five pain patients, using PET with ¹⁵O₂. All patients had intractable deafferentation pain, which was adequately controlled by electrical stimulation of the ventral posterior lateral nucleus of the thalamus. At high intensity thalamic stimulation—giving rise to half body dysesthesias—cerebral activity was increased bilaterally in the thalamus, postcentral gyrus and middle frontal gyrus. At lower stimulation intensities—dysesthesias localized to the painful body site—there were still bilateral increases in these areas but the ipsilateral increases were more pronounced. With no thalamic stimulation, presumably during pain, cerebral activity was not different from normal. This study is the earliest brain imaging study of clinical pain. However, the results do not contribute to understanding pain states. In a PET study, with [¹⁸F]FDG as radiotracer, LaTerre *et al*⁴⁰ reported unilaterally decreased thalamic activity and no cortical changes in a thalamic pain patient with an infarct confined to the putamen and parts of the internal capsule. Larger thalamic lesions led to decreased cerebral activity in the cortex.⁴¹ Lee *et al*⁴² studied cerebral activity in six patients with thalamic infarcts and central pain, using SPECT and Tc99m-HMPAO as radiotracer. In three of the subjects the infarct was localized to the thalamus, and there was ipsilateral cortical decreased cerebral activity in all three subjects. In the other three patients the infarct was outside the thalamus and cortical activity was symmetrical. A study by Cesaro *et al*⁴³ compared thalamic activity in central pain patients, using SPECT with IMP-I¹²³ radiotracer (PET studies in a similar patient population were carried out by Hirato *et al*⁴⁴). In two patients the authors observed thalamic hyperactivity opposite to the body site in pain. In one patient the SPECT scan was repeated during pain relief by antidepressants, and showed no thalamic asymmetry. One year later, the treatment was discontinued and pain returned. A SPECT scan again showed thalamic asymmetry. In the other three patients thalamic activity was symmetric in spite of unilateral pain. No clear conclusions can be drawn regarding cerebral sites involved in central pain because both increases and decreases in thalamic activity are observed and no other consistent changes in cerebral activity have been reported. Most of these studies were done with low spatial resolution imaging technology, and the authors acknowledge the need for more extensive cerebral activation studies of central pain. A significant confounding factor in such studies is the presence of the lesion, the location and size of which

affects cerebral activity patterns, at least partially independent of the painful syndrome.

Di Piero *et al*⁴⁵ studied changes in cerebral activity in five patients with severe chronic pain due to cancer. This PET study using $C^{15}O_2$ as the radiotracer, compared cerebral activity during pain to the cortical activity one week after an anterolateral cordotomy for pain relief, and to resting cerebral activity in five normal subjects. The authors observed decreased thalamic activity in the pre-cordotomy scans as compared to normal subjects' thalamic activity, especially in the thalamus contralateral to the body side in pain. Decreased activity in the thalamus contralateral to the pain was also significant when the patients' brain scans were compared before and after cordotomy. The prefrontal and SI cerebral activity were unchanged with pain relief. A recent study by Iadarola *et al*⁴⁶ closely agrees with the results of Di Piero *et al*.⁴⁵ Cerebral activity was studied in four patients with post-traumatic neuropathic pain and one patient with post-herpetic neuralgia, using PET scan with $H_2^{15}O$ (Iadarola *et al*⁴⁶). Cerebral activity was decreased in the thalamus with inputs from the body side in pain in all five patients, relative to the other thalamus (with inputs from the unaffected body), and in comparison to thalamic activity in 13 normal subjects. These authors consider a number of alternatives to pain relief as the explanation for the decrease in thalamic activity. (1) Neurodegenerative processes may accompany the pain pathology, but they consider this unlikely since Di Piero *et al*⁴⁵ show the decrease is reversible. (2) A local interneuronal overcompensatory inhibition in an attempt to control the hyper-excited neurons mediating the pain. However, they point out, this is not consistent with persistent pain. (3) Overlearning of the pain requiring less thalamic activity for the perception. (4) Blood flow and neural activity uncoupled during chronic pain. Iadarola *et al*⁴⁶ do not comment regarding changes in the cerebral cortex in these patients. Derbyshire *et al*⁴⁷ studied responses to phasic thermal stimulation on the hand in women with atypical facial pain and compared the activity to normal women performing the same task, in PET scans with $H_2^{15}O$. The activation patterns were essentially the same as those reported for phasic stimulation earlier. The only difference was a decrease in activation in prefrontal cortex and larger activations of the anterior cingulate in the pain patients.

Clinical visceral pain was studied by Rosen *et al*⁴⁸ by monitoring cerebral activity in patients with angina pectoris. In 12 patients with angina and coronary

artery disease cerebral activity was imaged by PET with $H_2^{15}O$. In each patient, scans were done under different conditions: Various baseline conditions, during infusion of low dose dobutamine, which did not cause myocardial ischemia or angina, and during infusion of high dose dobutamine, which resulted in angina and increased heart rate and systolic blood pressure in all patients. During angina compared to baseline, increased cerebral activity was observed in the hypothalamus, periaqueductal gray, thalamus and prefrontal cortex bilaterally, and left anterior cingulate. Cerebral activity was reduced bilaterally in the mid-rostrocaudal cingulate cortex, and fusiform gyrus, right posterior cingulate and left parietal cortices. In the baseline scans just after induction of angina, thalamic, but not cortical, activity remained high. The latter observation is interpreted as evidence for the thalamus receiving inputs from the heart after cessation of the angina percept, which may be relevant to silent myocardial ischemia. The activity in the anterior cingulate was in a region distinct from that seen for phasic somatic pain.^{17,18} The periaqueductal gray activity observed by Rosen *et al*⁴⁸ is probably the same region reported activated in the midbrain for phasic somatic pain by Casey *et al*.²¹ The hypothalamic activity observed by Rosen *et al* is at the same rostrocaudal level as that of the periaqueductal gray activity. Thus, hypothalamic activity could have been observed in at least the study by Casey *et al*,²¹ but was not. Therefore, the hypothalamic activation may be unique to the anginal visceral pain. The bilateral thalamic activations with no changes, or decreases, in somatosensory cortical activity strongly imply that the thalamic activity must be confined to medial thalamic regions, which have connections with the cingulate and prefrontal cortical areas. This is the only convincing clinical pain study showing consistent increased thalamic activity, which may be unique to the type of pain or to the duration of the pain induced. The lack of activation in the insular cortex is curious because animal experiments emphasize this area as a prime cortical target for visceral inputs.

Another recent study by Hsieh *et al*⁴⁸ investigated cerebral activity changes in eight patients with unilateral painful mononeuropathies before and following pain relief by a regional nerve block. PET scans with [^{15}O]butanol were used to obtain three PET image sets in the pain state and another three images after pain relief (30 min after nerve block). Two statistical comparisons were performed on the data: a conservative general comparison between the two states that showed increased cerebral activity in the

pain state bilaterally, in the anterior insula, the posterior parietal cortices, the inferior prefrontal cortices, the cerebellar vermis, and unilaterally in the right anterior cingulate. When the data was tested for laterality, in addition to the above changes cerebral activity was observed decreased in the contralateral thalamus for the pain state. No alterations in cerebral activity were seen in SI and SII. Therefore, the authors state that 'it is conceivable that the brain may recruit different operational mechanisms in processing a long-lasting pain state with persisting emotional distress versus phasic perceptual challenges with a low tone of affection'. They also emphasize the observation that the anterior cingulate was active in the right brain despite the sidedness of pain, consistent with the idea that this hemisphere is more important in emotional and autonomic responses. Hsieh *et al.*²⁸ provide a summary figure (Figure 3, Hsieh *et al.*²⁸) of a large number of studies where anterior cingulate activity was reported, noting that the area activated with pain is distinct from regions involved in attentional and motor control and motor intentional tasks, and closely corresponds to the region activated with itch perception.²⁹ They conclude that recruitment of limbic networks is essential to the experience of chronic pain, and that this activation pattern emphasizes the affective dimension of chronic pain.

We have been studying cerebral activation in patients suffering from upper extremity unilateral sympathetic pain (reflex sympathetic dystrophy, RSD, manuscript in preparation). In three such patients, fMRI scans examined the parietal-temporal cortex with either thermal or air puff painful stimuli. The thermal pain paradigm was the same as we have used in normal subjects (see previously). The air puff stimulus was used in one patient who had severe allodynia. In all subjects, noxious stimulation of the hand with chronic pain resulted in large decreases in cerebral activation in contralateral SI and SII. The same stimulus when presented on the unaffected hand resulted in activations in contralateral SI and SII. The patients were placed in the MRI scanner with an axillary catheter placed on the painful side through which a local anesthetic could be administered. After the fMRI scans in the chronic pain state were completed, the anesthetic was administered at a volume and concentration sufficient to block the sympathetic fibers, but not the sensory or motor fibers. Sensory fiber intactness was ascertained by measuring thermal and vibratory thresholds just before and after termination of the imaging study. Ten to 15 minutes after blocking the sympathetic

outflow, another set of fMRI scans with noxious stimulation was carried out. The block significantly reduced the chronic pain and resulted in reversing the cerebral activity in the parietal cortex. Post-block parietal cortical activity contralateral to the chronically painful side was now increased, and was similar in pattern to that observed with stimulation of the unaffected side, both before and after blocking, and was similar to the increased activity we have observed in normal subjects. In one of these patients, we have observed this reversal in activation pattern in two separate sessions, carried out one month apart. These results show that the same noxious stimulus gives rise to opposite patterns of somatosensory cortical activation, depending on the background state of the subject's perception. Moreover, this pattern is immediately reversed when the underlying chronic pain perception is eliminated or diminished. Preliminary observations in the frontal cortex indicate a reverse pattern, i.e. prefrontal areas are mainly activated when the noxious stimulus is superimposed on a chronically painful site, and inhibited or unchanged during noxious stimulation without chronic pain. The implications of these observations are very similar to those reached by Hsieh *et al.*²⁸ It seems that the affective state of the subject controls the type of somatosensory processing of painful inputs. It is proposed that: Although the stimulus is perceived of similar magnitude, both during and in the absence of the chronic pain, during chronic pain the noxious stimulus acts mainly as an extra-exacerbation of the chronic pain. In contradistinction to this, in the absence of the chronic pain, the noxious stimulus induces a motor decisional component that increases the activity in the somatosensory areas that feed into the motor system.

Conclusions

The main conclusion of this review is that the cortical areas activated by short duration thermal pulses (in the order of seconds) do not reflect the clinical pain states. Most clinical pain states seem to correspond to decreased thalamic activity, accompanied with either no changes, or decreases during noxious stimulation, of somatosensory cortical activity. The clinical pain states seem to activate mainly anterior cingulate and prefrontal cortical activity, and in different cases insular cortex, hypothalamus and periaqueductal gray.

The anterior cingulate, and probably some prefrontal regions, seem active in both clinical and experimental pain states. In contrast, the thalamus, SI and SII seem most robustly activated with phasic noxious stimuli. These results have novel and profound implications regarding the roles of different cortical and subcortical areas in processing painful information. The decrease in thalamic activity, together with increased cingulate activity, as shown by Hsieh *et al.*,²⁸ implies that cingulate activity cannot be from the thalamus. Therefore, pathways outside the spinothalamic tract need to be considered, especially in the chronic pain state. Direct projections from the spinal cord to multiple limbic and striatal areas were first described by Giesler and colleagues in the rat (previous chapter). We have confirmed the existence of these pathways in both the rat and the monkey (manuscript submitted, Newman *et al.*⁴⁹). Therefore, nociceptive neurons in the spinal cord can directly influence multiple limbic regions, like the hypothalamus, amygdala, septal nuclei, anterior midline nuclei, and striatal regions, like the ventral pallidum and the globus pallidus. Many of these regions are strongly interconnected, as well as connected with cingulate and prefrontal cortices. Many of the limbic regions also receive inputs from the brainstem where the spinoreticular pathways massively terminate. The brain imaging studies of pain, therefore, point to a very different emphasis in research regarding the central processing of pain. There is a large body of literature regarding thalamic and somatosensory coding of nociceptive stimuli.⁵⁰ Only recent animal studies have indicated the existence of nociceptive responsive cells in limbic regions, e.g. in the amygdala,⁵¹ cingulate cortex,⁵² and prefrontal cortex.⁵³ Unfortunately, virtually nothing is known about the responses of cells in these areas to sustained nociceptive stimuli, the clinically more relevant stimulus.

The above studies also indicate that systems outside of the spinothalamic system may control the type of processing taking place in the spinothalamic system. Painful conditions relevant to the clinical setting and to sustained pain seem to activate cortical areas outside the spinothalamic domain, which in turn inhibit the spinothalamic inputs to the cortex. Mostly due to technical limitations, electrophysiologic studies of nociception in animals have been done with short duration noxious stimuli. As a result, these studies, including those in our laboratory (e.g. ref 54), have been primarily concentrated on cells of origin and target of the spinothalamic pathway.⁵⁰ Therefore, very little is known regarding the responses of

spinothalamic cells to sustained painful stimuli and the modulation of the nociceptive responses by limbic systems during sustained pain.

Classically, the role of the cerebral cortex in pain perception, especially the somatosensory cortex, was thought to be minimal. The main observations refuting a role for the cortex in pain being: stimulation of the surface of the cortex, in and around SI, very rarely elicits reports of pain in awake humans;⁵⁵ ablation of SI or SII rarely results in pain relief, and when it does, the effects are short lasting.⁵⁶ These results agree with Head and Holmes's position, who in 1911⁵⁷ wrote that 'pure cortical lesions cause no increase or decrease of sensibility to measured painful stimuli'. The recent imaging studies, therefore, agree with this classic position and also imply that the thalamus, especially the lateral thalamus, and SI and SII, are minimally involved in clinical pain states. Their importance in a fight or flight situation, however, is reinforced by the brain imaging studies where phasic noxious stimuli was used. Parrent *et al.*⁸ reported two patients with central pain who had no functional thalami on the affected side, as determined by CT and by electrophysiologic exploration of the thalamus. The authors attribute the central pain perception to either subthalamic activity or to the ipsilateral spinothalamic pathway. Given the above imaging studies, the ipsilateral spinothalamic activation is not likely to be the pathway mediating the pain perception. More importantly, the results which had surprised the authors are entirely consistent with the brain activations seen for the clinical pain-imaging studies. The imaging studies also closely agree with the clinical literature regarding cortical lesions. Cingulotomy, leucotomy and different variations of such lesions seem to be the only cortical lesions that may result in lasting pain relief for intractable pain patients.⁵⁹ This is not an endorsement of ablative procedures for pain relief, but rather that the reported results of these procedures agree with the notion that prefrontal and limbic regions of the cortex are importantly involved in sustained pain perception.

The conclusion that the spinothalamic targets in the thalamus and the cortex may not be important in clinical pain states is surprising, given the animal physiologic studies. In rat models of arthritic pain or neuropathic pain, single unit recordings in the lateral thalamus and in SI show profound changes in response properties. A larger incidence of nociceptive neurons are found in these preparations, and the neuron discharges outlast the stimulus duration.⁶⁰⁻⁶²

Either these results are unique to the experimental situation, type of species, and physiologic conditions, i.e. anesthetized preparation, or they are involved in activating inhibitory circuits. The brain imaging results strongly rule out a significant role for lateral thalamic somatosensory regions involvement in clinical pain states. However, the intralaminar and medial thalamic regions may still be necessary in clinical pain perceptions. The spinothalamic inputs to these regions are more focused⁶³ and it is possible that decreased activity in the lateral thalamus may mask the simultaneous increased activity in more medial thalamic areas, especially since the spinothalamic regions in the medial thalamus are connected with the limbic cortical areas that are active in clinical pain states. Paradoxically, the rat studies of medial thalamic nociceptive responsive cells do not show any significant changes in their response properties between normal animals and arthritic rats.⁶⁴ The majority of the physiologic studies of nociresponsive cells in animal models of chronic pain have concentrated on the thalamus and somatosensory cortex. Melzack and colleagues have been studying brain areas important in the perception of sustained pain by using formalin injections in rats. Since formalin injection induces sustained pain for over an hour, it may be viewed as a short-term model of chronic pain. These studies show that the pain perception is induced by spinal cord mechanisms, but maintained by more central mechanisms.⁶⁵ Moreover, these studies implicate the cingulate cortex, hippocampus, fornix, and the medial thalamus, and refute a role for the lateral thalamus in formalin-induced pain perception.⁶⁶⁻⁶⁹

Brain imaging studies indicate that we can reliably identify patients in chronic pain states. Perhaps we may even be able to differentiate between various pain states. There is some evidence of the latter in the reviewed literature. Therefore, although we are at a very early stage in understanding the human brain physiology of pain, there is every indication that the approach will soon become of significant diagnostic and even prognostic value.

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