Functional Magnetic Resonance Imaging of Pain Consciousness: Cortical Networks of Pain Critically Depend on What is Implied by "Pain"

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Current Review of Pain 1998, **3:**308–315
Current Science Inc. ISSN 1069–5850

Brain imaging studies, using primarily functional magnetic resonance imaging (fMRI), are reviewed. These studies are aimed at developing imaging approaches that can be used in the clinical setting to investigate clinically relevant pain states. To this end, our recent studies indicate that by taking advantage of the temporal variations in pain perception, we are able to identify cortical regions that may be uniquely involved in pain consciousness. This procedure in turn becomes a general approach with which clinical pain states can be studied. Preliminary results are shown in patients suffering from chronic reflex sympathetic dystrophy (RSD) and chronic back pain. The review emphasizes that different experimental pain states, and chronic and acute clinical pain states, seem to involve dramatically different networks, the details of which remain to be worked out. It is concluded that these procedures need to be applied in the larger clinical setting in which multicentered studies may be conducted to begin building the brain pain network atlas.

In this article, the ongoing research in my laboratory, regarding human pain perception and its representation in the brain, is briefly reviewed. Most of our current studies use fMRI to study the physiology and pathophysiology of experimental and clinical pain states. Three main ideas are introduced: 1) examining the temporal properties of pain perception creates the opportunity to investigate and identify brain regions specifically involved in pain consciousness; 2) this approach also leads to examining clinically significant pain states; and 3) the brain networks activated during different stimulus conditions can be dramatically different, and depend on stimulus parameters, perception parameters, and the history of pain (chronic vs acute pains of different durations and types).

Temporal Properties of Pain

Unlike touch, vision, or audition, neural systems underlying pain perception are slow. As a result, pain perception can often be dissociated from the stimulus. Figure 1 illustrates this point, using data from published studies.

Figure 1*A* illustrates that when a thermal painful stimulus is mild, pain perception can be delayed by seconds from the onset of the stimulus, and its intensity profile does not accurately reflect the stimulus profile. Moreover, that the perceived pain is transient, because the stimulus ceases being painful after a given duration. The measured and calculated skin temperature is shown, together with calculated temperatures at different depths within the skin. The numeric pain rating in time is shown in gray.

Figure 1*B* shows the time course of pain ratings in four normal subjects, following the immersion of the hand in hot water of different temperatures. Even though the temperature on the skin is constant, the perceived pain fluctuates in time and is different across subjects. Mild painful stimuli are transient in all four subjects. Fo more intense stimuli, the perception of pain is preserved throughout the stimulus duration but its temporal intensity profile is distinct in each subject. Such stimulus and perception dissociations become more pronounced in pain patients.

Figure 1*C* is from a patient with peripheral neuropathy. The pain perception begins seconds after the stimulus, far outlasts the stimulus, and during repeat application there is long lasting sensitization. The major conceptual novelty of our recent fMRI studies is the notion that we can take advantage of these unique temporal properties of pain to identify cortical regions specifically involved in the subjective, conscious percept of pain and to use this approach to directly study cortical regions involved in clinical pain syndromes.

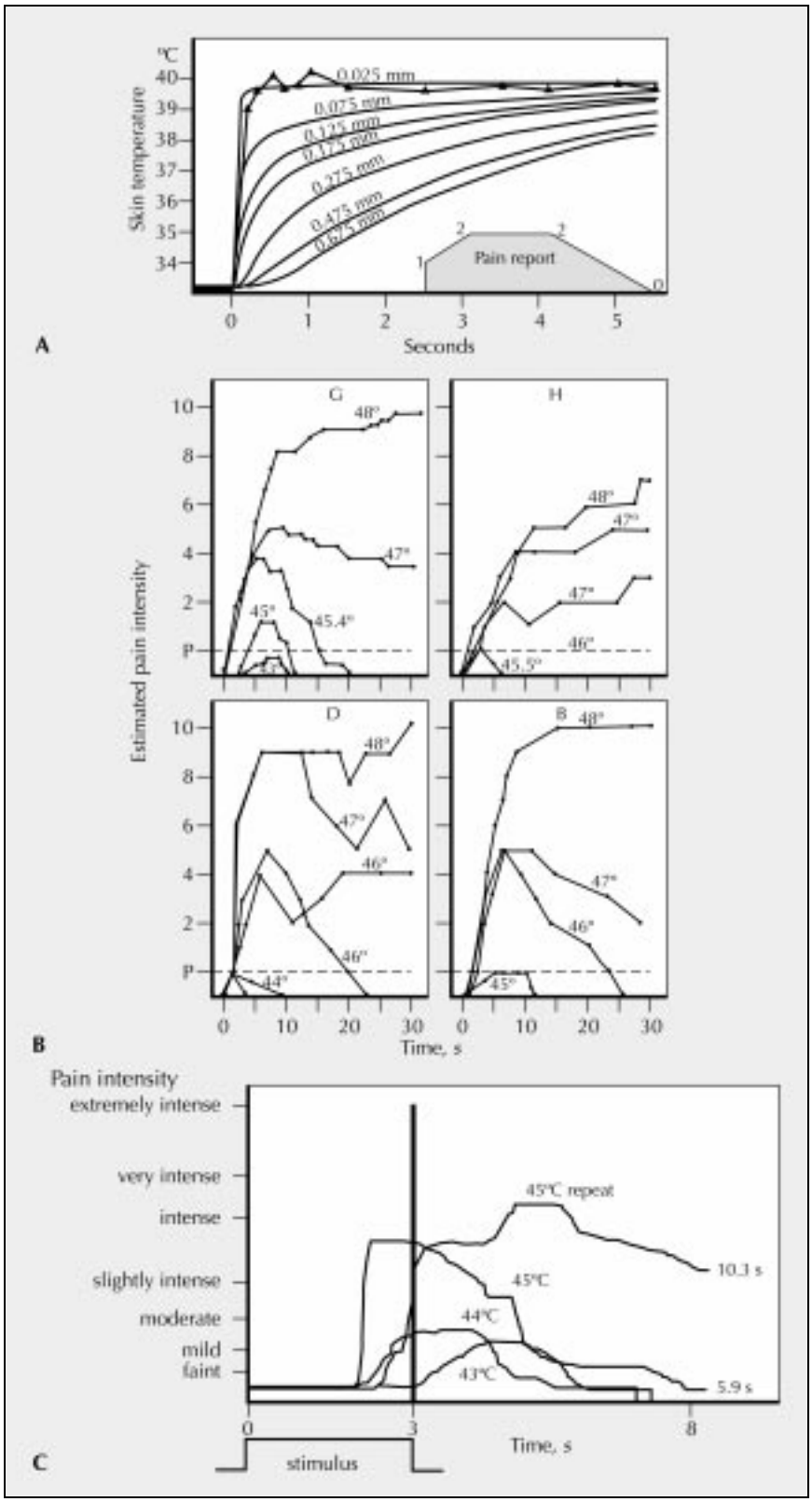

Figure 1. A, Demonstrates the dissociation between a thermal stimulus and its perception when the stimulus is mild. (*Adapted from* Hardy *et al*. [1].) **B,** Demonstrates temporal differences in pain perception for different temperature thermal painful stimuli and between different subjects. (*Adapted from* Hardy *et al*. [1].) **C,** Abnormal pain perception patterns in time in a neuropathic pain patient. (*Adapted from* Gracely *et al*. [2].)

Dimensions of Pain

Three distinct dimensions have been defined for pain [3,4]: 1) sensory-discriminative dimension, which signals spatial and intensity characteristics of the stimulus; 2) cognitive-evaluative dimension, which extracts a perceptio and an evaluation of the meaning of the stimulus; and 3) affective-motivational dimension, which is the desire t avoid the damage. There is a vast literature regarding the anatomic, physiologic, and more recently human brain imaging studies that differentiate between brain region involved in the sensory-discriminative versus affective-motivational dimensions of pain.

In the cortex, the early somatosensory stages, with inputs from the lateral thalamus, are classified as coding the discriminative dimension, whereas cortical areas, with inputs from the medial thalamus and belonging to the limbic structures, are thought to be coding the affective dimension [5,6]. The analogy in the visual system would be to the dimensions of contrast, color, and motion, which are processed in different portions of the visual cortical system

In this article we examine pain along a different dimension, namely the transformation of stimulus properties to subjective conscious perception properties. The analogous example in vision would be the transformation from edge detection to face recognition. Edge detection occurs within the earliest stages of the visual cortex (V1/V2), whereas face recognition happens in very late stages of the visual stream (temporal and frontal cortex).

Measuring the Subjective Experience of Pain

The need for studying the subjective experience of pain has been eloquently stated years ago by Donald D. Price [7]. In the first chapter of his book, he states:

"The definition of pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage…' [8] leaves us in a very interesting philosophic position with regard to the study of pain. If pain is defined **subjectively** as an experience, then the scientifi study of pain ultimately has to study and even measur that experience." (underline and bold is our emphasis

This is exactly what we have been able to achieve in our recent fMRI studies. It should first be stated that all prior brain-imaging studies of pain have examined brain activity patterns between two states (block design or state-related design). By comparing a painful state to a nonpainful state, brain regions involved in pain processing have been defined in positron emission tomography (PET) and fMRI studies. This approach does not distinguish between stimulus coding and pain perception in the brain.

In our first fMRI study of cortical regions activated by a thermal painful stimulus, we simply compared the brain areas significantly activated during the painful state with the nonpainful warm control-state [9]. This cortical pattern was compared with that seen when the subjects performed a vibrotactile task or a motor task. The results of 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, insula, and anterior cingulate. Such a pattern of brain activity has now been demonstrated by a large number of other brain imaging studies [9].

Because fMRI has a higher spatial resolution than PET, it enables further subdividing of these activated regions, with respect to specific Brodmann's areas (BA) 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, and portions of the primary somatosensory and motor cortices, as well as regions that overlap with vibrotaction and motor performance.

Subsequently, we analyzed the fMRI thermal painful stimulus results in relation to the time course of the stimulus and pain perception [10••]. The time course of the pain perception was determined in another group of subjects, who were required to continuously rate the intensity of the subjectively perceived pain when they were presented with the exact same thermal painful stimulus as used in the fMRI study.

Figure 2 illustrates these ratings, and shows that although the thermal painful stimulus is constant the subjectively perceived pain varies. The painful heat is applied for 35 seconds (with 35-second controls) and is constant through the stimulus period. The subjective pain reports, however, continuously increase during each stimulus period, over 35 seconds. Moreover, as the average response indicates, there is a longer time variation in the peak pain perceived. Between the first and second painful stimulus cycles, there is a slight habituation, whereas in each subsequent cycle the peak pain further increases indicating the presence of a long-term sensitization. By taking advantage of this temporal dissociation between stimulus characteristics and pain perception, we interrogated the brain activity with both time curves and identified cortical regions more closely related to either the stimulus or the perception [10••].

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, whereas activity more posteriorly was better related to the temporal properties of pain perception. Insular cortex at the level of the anterior commissure was the region best related to the thermal stimulus, and the posterior parietal cortex was the region best related to the pain perception. The posterior parietal cortex, therefore, seems to be a region that 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 leads to hemi-neglect. Therefore, the nor-

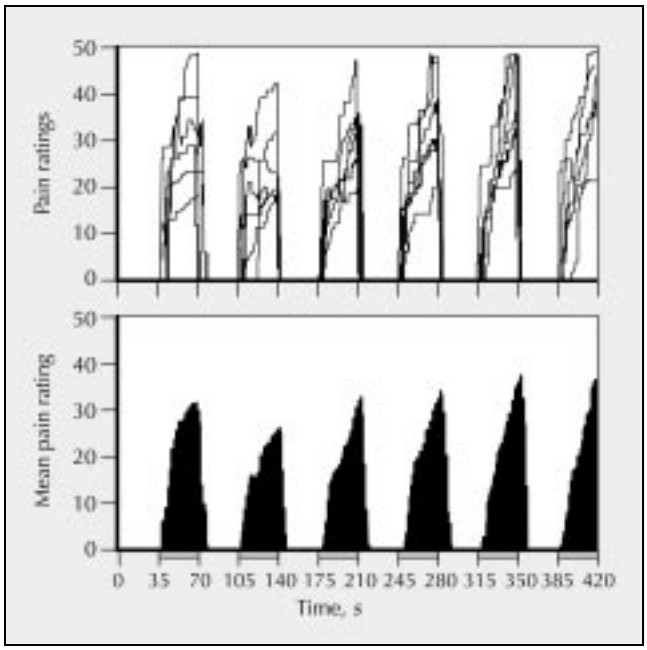

Figure 2. The temporal properties of pain perception for a standard thermal stimulus applied for 35 seconds, every 35 seconds, six repetitions. The *top panel* shows individual ratings. The *bottom panel* is the group average pain ratings. The gray boxes under the bottom panel show the thermal stimulus presentation times. (*Adapted from* Apkarian *et al*. [10].)

mal conscious awareness of pain may be critically linked to the normal awareness of body image. In more recent studies we have used individual subject temporal ratings of pain as a means with which we have started examining various clinical pain states.

Different Brain Networks for Different Pains

Dependence on stimulus parameters

Our first brain-imaging study for pain was conducted using single photon emission computed tomography. In this study subjects immersed their hand in hot water for 3 minutes, and brain metabolic changes were determined using a radio-labeled nucleotide [11]. The study indicated that the sensorimotor regions contralateral to the stimulated hand showed decreased metabolic activity. We interpreted this result as indicating that a large portion of this cortex was inhibited during such a task. Because this region of th brain subserves primarily vibrotaction, we reasoned tha the observed inhibition must impact touch perception. In a psychophysical study we were able to demonstrate that indeed touch perception is decreased in sensitivity during a painful stimulus [12].

In a more recent fMRI study, we examined the cortical activity pattern when painful thermal stimuli were applied either to just one fingertip (small body region) o to all four fingers of the hand (larger body region subjected to pain). The intensities of the stimuli were adjusted to lead to equal magnitude pain ratings. The results indicate that the same cortical regions identified to be active in our earlier fMRI study [9] were also active in these situations [13]. Moreover, as expected when the painful stimulus covered a large body part, then most of these regions showed more extensive activity. Surprisingly, there was also an inverse relationship when brain areas with decreased activity were examined. With the smaller body part in pain, much larger areas of the brain showed decreased activity as compared to the larger stimulus. This result was again confirmed psychophysically.

These results illustrate that small subtle changes in stimulus parameters can give rise in large dynamic reorganization in the cortical network that results in the perception. The single photon emission computed tomography study indicates that long-duration sustained painful stimuli give rise to cortical inhibition, which impacts touch perceptions; whereas the fMRI study shows that the spatial properties of painful stimuli can also inhibit the cortical activity. In the latter case, the smaller the surface area in pain, the larger is the cortical inhibition, and hence als the decrease in touch sensitivity.

Dependence on clinical pain states

We have now examined patients suffering from RSD and from chronic back pain. Figure 3 illustrates cortical activity on an equivalent region of the brain in such patients as compared with acute and experimental pain states. All six panels (Figures 3*A–F)* are taken from the same superior-inferior plane, following transforming brain anatomy and superimposed regions of activity of individual or group subject data into standard anatomic atlas coordinates [14] (see Krauss and Apkarian [15] for details of the transformation). For further details regarding data analysis see the original studies (Gelnar [9,16], Apkarian[10••,12,13]).

Figure 3*A* illustrates cortical activity in one normal volunteer when a thermal painful stimulus was applied to the palm of the right hand. The activity illustrated in color is primarily in the contralateral hemisphere to the stimulated hand, where multiple subdivisions of the insula are active.

In Figure 3*B* the average brain activity in patients suffering from RSD is shown when brain activity to a thermal stimulus is determined, both before and after sympathetic blocks administered to the axilla of the arm that has RSD. When such blocks are successful they, temporarily, relieve the RSD pain and the decrease the perceived stimulus pain. Figure 3*B* is the result of subtracting brain activity postblock from preblock, in cases in which the block succeeded in relieving the pain. The figure illustrates that the main brain region modulated by changes in the chronic pain state is the prefrontal cortex (including orbital and dorsolateral portions).

Figures 3*C* and 3*D* show brain activity in a patient with chronic back pain. Figure 3*C* is the case when the patient is experiencing ongoing spontaneous back pain. Figure *D* shows brain activity when the back pain is further exacerbated by invoking radicular pain. The activity in Figure 3*C*

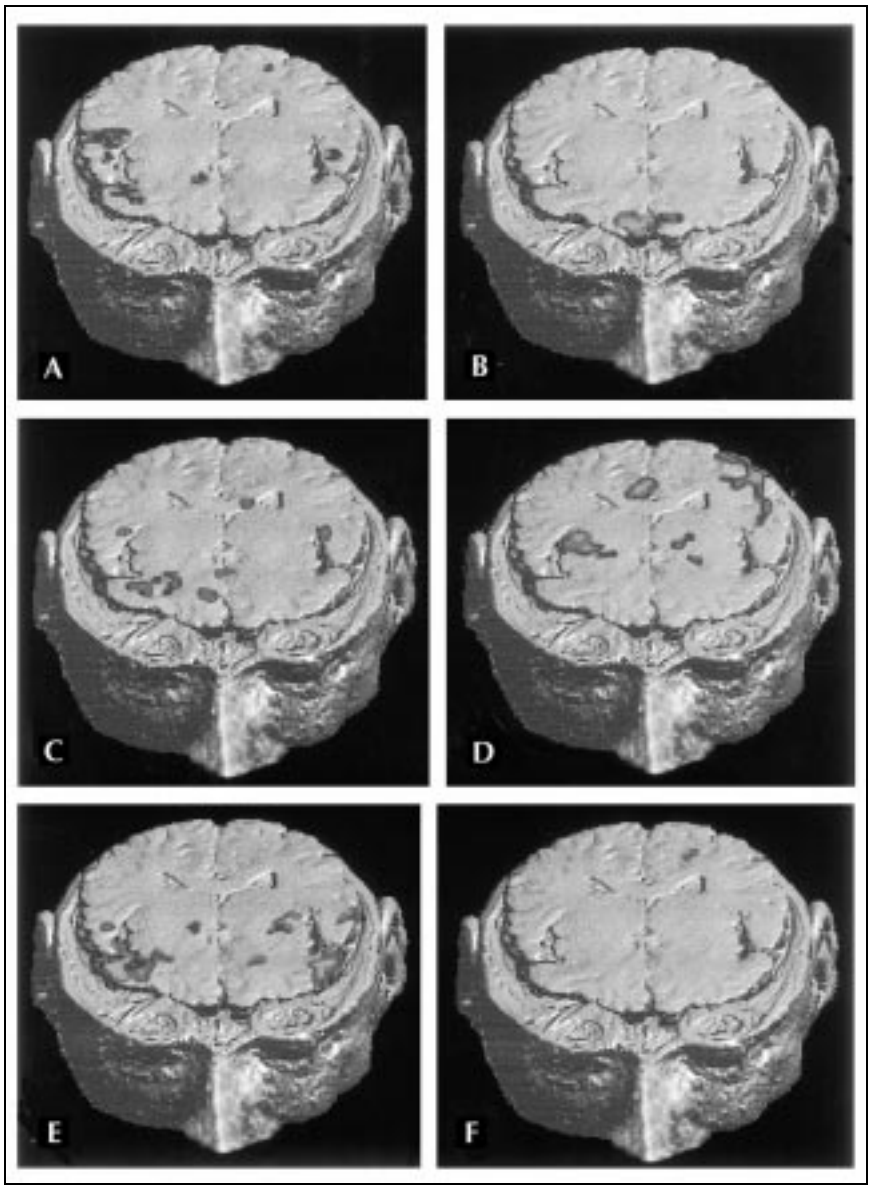

Figure 3. Differences in brain activity to pain in different clinical and experimental settings, taken from various ongoing studies in Apkarian's laboratory. **A,** Shows cortical activity in a normal volunteer for thermal painful stimuli applied to the hand. **B,** Cortical regions, which are affected by changes in chronic pain, are shown for patients suffering from reflex sympathetic dystrophy. **C,** Cortical activity during spontaneous chronic back pain. **D,** Cortical activity in the same subject as in *C*, in which the back pain is exacerbated by radicular pain. **E,** Cortical activity in a normal subject, in which the radicular pain is mimicked acutely. **F,** Cortical activity in the same subject as in *E*, in which the leg is still manipulated as in *E* but without causing pain. The *gray* image shows the underlying anatomy of the brain region shown. The colored pixels indicate the extent of brain activations: dark brown is at $P < 0.05$, medium brown at $P < 0.01$, brown at $P < 0.001$, and light brown at $P < 0.0001$ significance level.

is mainly contralateral and frontal, whereas in Figure 3*D* it is more bilateral and includes posterior insula and ipsilateral posterior parietal cortex.

Figure 3*E* shows brain activity in a normal volunteer when the subject acutely experiences leg extension pain, acutely mimicking the radicular pain of the chronic back pain patient. Some of the brain regions activated closely approximate the activity seen in Figure 3*C*. When the leg extension is reduced to a level where pain is not experienced, most of the brain activity disappears (Fig. 3*F*).

Overall, Figure 3 illustrates the range of changes that the cortical network may undergo for different pain states. A number of brain regions are shared between these diverse types of pain experience, whereas others seem unique to each state. Understanding these organizational principles for pain representation in the brain is the major challenge that brain-imaging studies must tackle in the next decade. The results shown in the chronic RSD and back pain patients have been reported in abstracts only. The manuscripts of these studies are forthcoming.

Evidence That Chronic Pain Involves Cortical Reorganization

Based on animal physiologic studies, chronic pain should be accompanied by cortical reorganization. This hypothesis is based on the role ascribed to spinal cor *N*-methyl-*D*-aspartate receptors in central sensitization [17], excitotoxic changes observed in the spinal cord of rat models of chronic pain [18], as well as on the experience-dependent changes seen in awake monkeys [19]. This has now been confirmed by a series of elegant studies by Flor *et al.* [20].

The first study by Flor *et al.* [20] showed a $r = 0.93$ correlation between the amount of cortical reorganization and the amount of phantom-limb pain experienced after arm

amputation. In a follow-up study the authors showed a causal relationship between cortical reorganization and phantom-limb pain, by demonstrating that when a local anesthetic block of the stump eliminated the phantom pain it was mirrored by a very rapid reversal of cortical reorganization in somatosensory cortex [21••]. In patients in which the pain was not eliminated, the reorganization did not change either. In another study the authors show similar reorganization in chronic low back pain patients [22••].

The reorganization reported by Flor *et al.* [20] is primarily for innocuous, and in some cases noxious, stimulation of the skin, and it was determined for responses in the primary somatosensory cortex. Their results imply similar reorganizational principles for very different types of chronic pain. The cortical responses we have seen in patients with RSD with hyperalgesia are very different from the preliminary results we have obtained in patients with low back pain (see above). However, we do not know whether this difference is due to examining stimulus-responses versus perception-responses, or if they are actually indicative of distinct cortical reorganizations for different chronic pain states, even though the reorganization in the primary somatosensory cortex may still be similar between them.

Studies by Ramachandran *et al.* [23] on the effects of vision on phantom sensations showed that in 50% of patients with phantom pains, the pain immediately disappears when patients stared at a mirror causing the illusion of opening both hands simultaneously. This latter observation, which has now been observed in a larger population, is perhaps the most convincing evidence for centralization of chronic pain states. A recent report presents a patient with refractory RSD with ongoing pain, allodynia, hyperhydrosis, and temperature abnormalities that were constant for over 10 years [24]. All of these symptoms resolved o dramatically diminished after the patient suffered a traumatic cerebral contusion. The case shares similarities to the study by Ramachandran [23], and reinforces the notion that understanding the mechanisms underlying chronic pain states necessitates understanding the dynamics of the underlying neural networks at the level of the cortex.

Relationship Between Our Studies and Other Brain Imaging Studies of Pain

We have reviewed the brain imaging studies of pain in two papers [5,9]. A number of other investigators have also reviewed the topic. The most recent review was published by Treede *et al.* [25]. The majority of studies have been done in normal subjects and by using PET. These studies generally show that the cortical network associated with pain includes primary and secondary somatosensory regions, motor regions, posterior parietal cortex, cingulate, insula, and prefrontal cortex. Recently number of groups have started using fMRI to study the cortical network for pain.

Davis *et a*l. [26,27,28] have now published a number of fMRI studies of pain (see also Porro *et al.* [29]), showing good correspondence with the PET results regarding the cortical regions activated during pain. An fMRI study b Davis *et al.* [26] and by Derbyshire *et al*. [30] show that the anterior cingulate activity during pain is distinct from anterior cingulate activity in attentional tasks. The fMRI studies are usually poorer in quality than the PET studies, because they tend to study a more limited region of the brain, the data analysis methods used are less rigorous, and the individual subject data are not transformed into standard coordinates. It should be mentioned that PET studies do no have the time resolution to distinguish stimulus-relate activity from perception, and all previous studies have made the tacit assumption that studying stimulus responses, *ie*, subtracting one state from the other, identifies the cortical circuitry underlying pain perception.

Generally our fMRI results agree with the earlier studies regarding painful stimulus-related activity in the cortex. The main difference between our results and the earlier studies relate to the perception-related activity. Our results show that activity in the cingulate, somatosensory regions, motor regions, and insular cortex are more related to the stimulus than the perception. Of those, insula seems to reflect the thermal stimulus best, which is consistent with the study by Craig *et al*. [31], which similarly shows that this region may be uniquely involved in monitoring skin temperature.

Perhaps the most influential recent paper in the field is the study by Rainville *et al.* [32], in which pain unpleasantness was selectively manipulated by hypnosis. The study showed that the anterior cingulate was the only region showing a significant correlation to this manipulation. A number of other studies also emphasize that portions of the cingulate cortex are uniquely involved in coding the affective dimension of pain [28,33–35]. In our recent fMRI study of pain sensitization [36], we observe a large activation in the cingulate when activity is examined in relation to the stimulus, but this signal completely disappears when cortical activity is probed in relation to pain sensitization. Because the intensity of pain during sensitization most likely also reflects the magnitude of the associate unpleasantness, we deduce that the affective component of pain is more likely a reflection of prefrontal cortical activity (the only limbic region that is active in sensitization), which is modulated or conditioned by the cingulate. On the other hand, our study of patients with RSD indicates that the only other region outside the prefrontal cortex that seems to participate in changes in chronic pain state is the anterior cingulate, at coordinates that closely approximate the region reported in the hypnosis study [32].

The pain patient groups studied by functional imaging have been reviewed earlier. Generally the observation i that somatosensory cortical and thalamic activity remain either unchanged or show decreased cerebral activity during sustained clinical, or chronic, pain affecting the con-

tralateral body. A number of these studies and newer studies also show that chronic or sustained pain state involve increased prefrontal activity, *eg*, mimicking ischemic pain in angina patients [37]; mononeuropathy pain before and after nerve blocks [35]; ethanol injection in the skin [38]; and capsaicin-evoked allodynia [39]. In a study of visceral noxious stimuli [40], it was shown that anterior cingulate activity is related to noxious or simulated noxious rectal distention in normal subjects; in contrast patients with irritable bowel syndrome showed prefrontal cortical activity to noxious rectal distensions. The study again implies that the relative activation of the prefrontal cortex versus cingulate cortex may depend o the patient's pain state.

Conclusions

In this article we demonstrate that attending to the temporal variations in pain perception can be used to delineate brain regions, which may be uniquely involved in giving rise to pain consciousness. This approach naturally lends itself to delineate brain activity in chronic and acute clinical pain states. We have recently patented this approach. A corporation has been formed to expedite carrying this procedure into clinical application as soon as possible. Th preliminary results that we have regarding clinical pain illustrates the complexity of the brain networks involved in pain, and indicates the need for performing large multicentered studies to generate the brain atlas of the cortical networks, which we suspect are uniquely involved in different clinical pain conditions.

Acknowledgements

I would like to thank all the collaborators that made these studies possible. The contributions of N.M. Szeverenyi, B.R. Krauss, andP.A. Gelnar have been critical to the success of these studies. The contributions ofP.S. Thomas, B. Frederickson, G. Tillapaugh-Fay,S. Huckins, A. Darbar, and M. Fonte are also appreciated. This research was funded by National Institute of Health/National Institute of Neurological Disease and Stroke grant NS 35115 and by the Department of Neurosurgery at SUNY Health Science Center.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of special interest
- •• Of outstanding interest

1. Hardy JD, Stolwijk AJ, Hoffman D: **Pain following step increase in skin temperature.** In *The Skin Senses.* Edited by Kenshalo DR. Springfield, IL: Charles C. Thomas; 1968:444–456.
2. Gracely RH, Price DD, Roberts WJ, Bennett GJ: **Quantitative sensory testing in patients with complex regional pain syndrome (CRPS) I and II.** In *Reflex Sympathetic Dystrophy: A Reappraisal.* Edited by Jänig W, Stanton-Hicks M. Seattle: IASP Press; 1996:151–172.
3. Melzack R, Casey KL: **Sensory, motivational, and central control determinants of pain.** In *The Skin Senses.* Edited by Kenshalo DR. Springfield, IL: Charles C. Thomas; 1968:423–439.
4. Price DD: **Physiological mechanisms of pain inhibition.** In *Psychological and Neural Mechanisms of Pain.* New York: Raven Press; 1988:181–210.
5. Apkarian AV: **Functional imaging of pain: new insights regarding the role of the cerebral cortex in human pain perception.** *Semin Neurosci* 1995, **7:**279–293.
6. Willis WD: *The Pain System: The Neural Basis of Nociceptive Transmission in the Mammalian Nervous System.*Basal, Switzerland: S. Karger AG;1985.
7. Price DD: **Physiological mechanisms of pain inhibition.** In *Psychological and Neural Mechanisms of Pain.* New York: Raven Press; 1988:1–17.
8. Merskey H: **Classification of chronic pain by the International Association for the Study of Pain subcommittee on taxonomy.** *Pain* 1986, **3(suppl):**217–219.
9. Gelnar PA, Krauss BR, Sheehe PR, *et al.*: **A comparative fMRI study of cortical representations for thermal painful, vibrotactile, and motor performance tasks.** *Neuroimage* 1999, **in press.**
10. •• Apkarian AV, Darbar A, Krauss BR, *et al.*: **Differentiating cortical areas related to pain perception from stimulus identification: temporal analysis of fMRI activations in a painful thermal task.** *J Neurophysiol* 1999, **8:**2956–2963.

This review is based on the results reported in this paper. The study shows the methodology necessary for distinguishing brain regions related to conscious perception of pain in distinction from regions more related to the painful stimulus.

11. Apkarian AV, Stea RA, Manglos SH, *et al.*: **Persistent pain inhibits contralateral somatosensory cortical activity in humans.** *Neurosci Lett* 1992, **140:**141–147.
12. Apkarian AV, Stea RA, Bolanowski SJ: **Heat-induced pain diminishes vibrotactile perception: a touch gate.** *Somatosens Mot Res* 1994, **11:**259–267.
13. Apkarian AV, Gelnar PA, Krauss BR, Szeverenyi NM: **Cortical response patterns to thermal pain depend upon stimulus size: A functional MRI study.** *Pain* 1999, **in press.**
14. Talairach J, Tourneaux P: *Co-planar Stereotaxic Atlas of the Human Brain. 3-Dimensional Proportional System:* An Approach to Cerebral Imaging. New York: Thieme Medical; 1988.
15. Krauss B,Apkarian AV: **Group average activation maps of functional MRI: methodology of identifying group brain areas activated during painful thermal stimuli, motor and vibrotactile tasks in humans.** *Rivista di Neuroradiologia* 1998, **11(suppl 2):**135–138.
16. Gelnar PA, Krauss BR, Szeverenyi NM, Apkarian AV: **Fingertip representation in the human somatosensory cortex: an fMRI study.** *Neuroimage* 1998, **7:**261–283.
17. Price DD: **Psychophysical measurement of normal and abnormal pain processing.** In *Touch, Temperature, and Pain in Health and Disease: Mechanisms and Assessments.* Edited by Boivie J, HanssonP, Lindblom U. Seattle: IASP Press; 1994:3–26.
18. Bennett GJ, Xie Y-K: **A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man.** *Pain* 1988, **33:**87–107.
19. Merzenich MM, Jenkins WM: **Reorganization of cortical representations of the hand following alterations of skin inputs induced by nerve injury, skin island transfers and experience.** *J Hand Ther* 1993, **6:**89–104.
20. Flor H, Elbert T, Knecht S, *et al.*: **Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation.** *Nature* 1995, **375:**482–484.

21.•• Birbaumer N, Lutzenberger W, Montoya P, *et al.*: **Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization.** *J Neurosci* 1997, **17:**5503–5508.

To the author's knowledge this is the first study that establishes a causal relationship between pain and cortical reorganiztion. The study also points to the notion that reorganization in this case may be the culprit for the chronic pain.

22.•• Flor H, Braun C, Elbert T, Birbaumer N: **Extensive reorganization of primary somatosensory cortex in chronic back pain patients.** *Neurosci Lett* 1997, **224:**5–8.

This study demonstrates that chronic pain that patients suffer from for multiple years may be relieved by visual illusion in which the subject sees the phantom body in motion. It emphasizes the importance of multisensory interaction and is a clear demonstration that clinical pain states involve the cortex.

23. Ramachandran VS, Rogers-Ramachandran D, Cobb S: **Touching the phantom limb.** *Nature* 1995, **377:**489–490.
24. Shibata M, Nakao K, Galer BS, *et al.*: **A case of reflex sympathetic dystrophy (complex regional pain syndrome type I) resolved by cerebral contusion.** *Pain* 1999, **79:**313–315.
25. Treede RD, Kenshalo DR, Gracely RH, Jones AKP: **The cortical representation of pain.** *Pain* 1999, **79:**105–111.
26. Davis KD, Taylor SJ, Crawley AP, *et al.*: **Functional MRI of pain- and attention-related activations in the human cingulate cortex.** *J Neurophysiol* 1997, **77:**3370–3380.
27. Davis KD, Kwan CL, Crawley AP, *et al.*: **Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli.** *J Neurophysiol* 1998, **80:**1533–1546.
28. Davis KD, Wood ML, Crawley AP, Mikulis DJ: **fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation.** *Neuroreport* 1995, **7:**321–325.
29. Porro CA, Cettolo V, Francescato MP, Baraldi P: **Temporal and intensity coding of pain in human cortex.** *J Neurophysiol* 1998, **80:**3312–3320.
30. Derbyshire SW, Vogt BA, Jones AK: **Pain and Stroop interference tasks activate separate processing modules in anterior cingulate cortex.** *Exp Brain Res* 1998, **118:**52–60.
31. Craig AD, Reiman EM, Evans A, Bushnell MC: **Functional imaging of an illusion of pain.** *Nature* 1996, **384:**258–260.
32. Rainville P, Duncan GH, Price DD, *et al.*:**Pain affect encoded in human anterior cingulate but not somatosensory cortex.** *Science* 1997, **277:**968–971.
33. Derbyshire SWG, Jones AKP, Gyulai F, *et al.*: **Pain processing during three levels of noxious stimulation produces differential patterns of central activity.** *Pain* 1997, **73:**431–445.
34. Vogt BA, Derbyshire SWG, Jones AKP: **Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging.** *Euro J Neurosci* 1996, **8:**1461–1473.
35. Hsieh J-C, Belfrage M, Stone-Elander S, *et al.*: **Central representation of chronic ongoing neuropathic pain studied by positron emission tomography.** *Pain* 1995, **63:**225–236.
36. Krauss BR, Merola J, Szeverenyi NM, Apkarian AV: **fMRI study of cortical areas involved in pain sensitization.** *Soc Neurosci Abst* 1998, 24.
37. Rosen SD, Paulesu E, Frith CD, *et al.*: **Central nervous pathways mediating angina pectoris.** *Lancet* 1994, **344:**147–150.
38. Hsieh JC, Stahle-Backdahl M, Hagermark O, *et al.*: **Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study.** *Pain* 1996, **64:**303–314.
39. Iadarola MJ, Berman KF, Zeffiro TA, *et al.*: **Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET.** *Brain* 1998, **121:**931–947.
40. Silverman DHS, Munakata JA, Ennes H, *et al.*: **Regional cerebral activity in normal and pathological perception of visceral pain.** *Gastroenterology* 1997, **112:**64–72.