Cortical pathophysiology of chronic pain

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Abstract. Studies in my laboratory have been employing multiple non-invasive brain imaging techniques to study the characteristics of patients with chronic pain. Some of these results are briefly outlined in this communication. Our studies regarding brain activity in chronic pain are summarized, emphasizing the unique role of the prefrontal cortex in chronic, especially neuropathic pain states. I also review our work examining brain chemistry abnormalities in chronic pain. Given these results, we have examined chronic pain patients in a cognitive task, designed to probe brain regions that we think are specifically abnormal in chronic pain, these results are also summarized. An overview of the mechanisms that may be pertinent to the observed results is included.

The symposium that took place in Tsukuba, Japan, was organized to examine peripheral and central processes underlying chronic pain states. This chapter examines central pathophysiology of such conditions from the viewpoint of the human condition, and by taking into consideration cortical processes. A brief perusal of other chapters in this book should demonstrate that the largest portion of this symposium was dedicated to examining peripheral or spinal cord processes, which have been looked at in various animal models of chronic pain. Implicit in these studies is the notion that understanding and then reversing some of these processes should give rise to decreased pain-like behaviour in these animals. Thus, they are hinting at therapeutical approaches that one can then test in humans in clinical settings. This approach has been extensively tested over the last at least 15 years, i.e. since the advent of well-defined chronic pain-like behavioural models in animals (Bennett 1993). Unfortunately, outside of the example of cancer pain (see Mantyh 2004), we have yet to see a single new medication or therapeutic approach, developed specifically from data gathered from such animal models, that has had clinical impact.

One obvious question is the extent of correspondence between animal models and the human clinical chronic pain condition. This, although an important issue, will not be addressed here. A second, important assumption is the localizability of factors involved in chronic pain: meaning that the majority of the animal studies assume that mechanisms of chronic pain impact local processes be it in the periphery or the spinal cord. Many previous chapters deal with notions of peripheral vs. central sensitization, where the 'central' is localized, at least implicitly, to the spinal cord.

The studies outlined here are based on a different set of hypotheses:

- Since the extent of correspondence between human chronic pain conditions and animal models remains to be established, examining the human condition simply eliminates such ambiguities.
- Given that the brain is a highly interconnected dynamical network, and that chronic pain conditions are states that are maintained over years and even a whole lifetime, injury-induced reorganization in a given portion of the pain system must propagate throughout the network and impact the overall system.

Thus, we assume that chronic pain involves central sensitization that engages and restructures connectivity between the periphery, spinal cord, thalamus, and cortex. In fact, the data presented in this chapter point to a central re-organization at the highest level of the brain, i.e. the prefrontal cortex. The pain clinician is amply aware of the fact that chronic pain is more than increased excitability of peripheral afferents and spinal cord neurons, because chronic pain patients' behaviour is a combination of many interacting dimensions, including emotional, social, and environmental factors. In the presented studies we show that some of these factors can be objectively demonstrated.

A diversion to Tokyo

A second part of this meeting was held in Tokyo, where many Japanese pain clinicians attended the talks. For me this presented the opportunity to begin to learn how life goes on in a mega-metropolis, i.e. Tokyo. I cannot help myself but make the analogy between this city and the brain, and to compare the properties of this magnificent city to the brain in normal conditions and following acquisition of chronic pain-like behaviour.

Tokyo with its suburbs is home to more than 47 million people. A staggering size for a city and yet this would correspond to a few millimetres of cortical tissue, if we make the analogy of people to neurons. This analogy is not original and a number of physicists have suggested that understanding the self-organizational properties of a city should give profound insight to the dynamical properties of

the brain. I only spent a few days in Tokyo, so my impressions are limited and relatively superficial. Still, one cannot escape the organizational success of a city where people are bustling by — thousands in every major street intersection — and at the same time, there is limited traffic congestion. Major train stations like at Shinjuku, Ginza and Tokyo are a marvel to watch, and they are whole cities within themselves. Hundreds of trains, running on multiple platforms at the precision of seconds, transport millions of people all across the city. This enormous connectivity at a very high temporal resolution undoubtedly is a major contributor to the social and economic success of Tokyo. One can imagine the extent of havoc that failure in one of the stations, or even one of the lines, would generate locally, quickly propagating it throughout the whole city within a few hours. Alternatively, if the influx of people from a particular suburb suddenly increases by 10-fold, again the balance of the city would be immediately disrupted. If we assume, moreover, that this influx is composed of a specific minority group not welcomed by the society in general, then the reverberations would be more severe, especially if it is sustained over weeks, months, or years. The human history of treating unwanted minorities is very ugly, and yet it seems like a reasonable analogy for the brain in chronic pain. I do not want to belabour this line of thought; perhaps the reader can follow the thread between the analogy and our observations of the brain in chronic pain.

Examining the brain in chronic pain

Non-invasive brain imaging technologies provide the opportunity to directly study human clinical conditions. We have spent considerable time and effort in devising methodologies that would be applicable in studying clinical chronic pain conditions and used them to examine and compare between different chronic pain conditions. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have become standardized techniques with which human brain neuronal activity can be studied indirectly. A large number of studies have examined human brain activity, using fMRI or PET, to identify cortical circuitry for acute pain perception in normal subjects, see reviews by (Treede et al 2000, Bushnell et al 1999, Apkarian et al 2004a). There is now ample evidence that a well-defined cortical network participates in human perception of acute pain. The areas most consistently observed include: primary and secondary somatosensory cortices (SI and SII), anterior cingulate (ACC), insula (IC), prefrontal cortex (PFC), thalamus (Th), and cerebellum (CB). Our own studies of fMRI activity for acute pain is consistent with this pattern of brain activity (Apkarian et al 1999, Gelnar et al 1999, Apkarian et al 2000). When brain activity to acute thermal painful stimuli are examined in chronic pain patients, the resultant pattern is very similar to that seen for acute pain in normal subjects, independent of

the type of chronic pain, as seen in chronic back pain patients (Derbyshire et al 2002), and in complex regional pain syndrome (CRPS) patients (Apkarian et al 2001a). Thus, although chronic pain patients may have various cutaneous sensory abnormalities (e.g. Gracely et al 1992, Petzke et al 2003), mapping brain responses to acute pain does not distinguish them from normal subjects. On the other hand, when brain activity specifically related to the chronic pain is isolated then activity seems to be preferentially involving prefrontal cortical regions (Apkarian et al 2001a). We have preliminary data to indicate that this is also true in chronic back pain (CBP) patients (Baliki et al 2002), when brain activity in CBP patients is examined specifically in relation to the fluctuations of the subjective report of pain by the patients (Apkarian et al 2001b). To further examine the hypothesis that chronic pain preferentially involves PFC activity, in a large review article where brain imaging studies of pain were summarized over the last 15 years, a meta-analysis was performed examining the incidence of significant reports of brain activity in PFC as compared to SI, SII, IC, Th, and ACC (Apkarian et al 2004a). The results indicate that across almost 100 studies, incidence of PFC activity is significantly higher in chronic pain conditions as compared to acute pain states; the opposite is true for the other regions, namely their incidence is significantly decreased in chronic pain conditions in contrast to acute pain in normal subjects. Therefore, it seems there is now solid evidence for the idea that chronic pain conditions preferentially involve PFC. The PFC is a complicated large structure with many sub-specializations (Fuster 1997). The specific portions involved in chronic pain remains somewhat ambiguous, and thus the specific functional significance of this activity requires further studies.

The significance of preferential PFC activity needs to be commented on: the shift of activity from parietal and cingulate cortices to prefrontal regions implies that there is also a shift in perceptual characteristics in the experience of pain. The simplest explanation would be that perception has become dominated by cognitive evaluations of the condition, with decreased emphasis on its sensory properties. This interpretation is consistent with notions advanced recently regarding regional specialization of different brain regions in acute pain (Price 2000). Price (2000) subdivides pain unpleasantness to primary and secondary affective conditions, with the secondary component localized to PFC. Our fMRI data indicate that different subregions of PFC are involved in distinct chronic pain conditions, implying that they may be differentiated along the extent to which they are dominated by affective or cognitive-evaluative burdens. We think that the extent to which a given chronic pain condition may be dominantly affective or cognitive will depend on the type of chronic pain, and even on the individual patient's history of chronic pain.

The shift in brain activity pattern with chronic pain also implies reorganization of information flow in nociceptive pathways. To examine substrates of this

reorganization we turned to investigating brain biochemistry, using magnetic resonance spectroscopy (MRS). The methodology has the advantage that it can document long-term effects since instantaneous cognitive or perceptual states do not affect the measurements. In a series of MRS studies (Melzack 1987, Grachev et al 2000, 2001, 2002, Grachev 2001), we have now examined changes in brain regional chemistry in CBP patients, as compared to age- and gender-matched healthy control subjects. We observe decreased brain chemical concentrations for multiple chemicals in both dorsolateral prefrontal cortex (DLPFC) and orbital prefrontal cortex (OFC), with no detectable changes in SI-motor cortex, ACC, IC or Th. Moreover, we could demonstrate that across-region relationships between brain chemicals are disrupted in CBP, in a unique pattern in relation to pain, as compared to anxiety. We could also demonstrate that the specific dimensions of pain, as measured by the short-form McGill Pain Questionnaire (Melzack 1987), could be correlated with brain-regional chemistry changes. Thus, this directly links perceptual states of pain to brain chemistry.

N-acetyl-aspartate (NAA) was the main chemical that we observed to decrease regionally in CBP. NAA is localized mainly in neuronal cell bodies and has been observed to decrease in many neurodegenerative conditions; as a result, it is thought to be a marker for neuronal density. Therefore, we interpret the decrease in NAA as evidence for brain atrophy in these patients. Recently, we embarked on a study to compare brain grey-matter overall volume and regional grey-matter density in CBP patients as compared to age- and gender-matched normal subjects. Preliminary analysis of the data shows both global grey-matter volume decreases in CBP patients, beyond normal aging; as well as regional grey-matter density changes (Apkarian et al 2002), thus confirming the notion that the brain in chronic pain undergoes atrophy. The specific pattern of this atrophy remains to be determined.

Given the observed decreases in brain chemistry and brain grey matter and the fMRI evidence for preferential involvement of PFC in chronic pain conditions, we reasoned that cognitive tasks, especially ones that are emotionally driven, may be impaired in chronic pain patients. To this end we tested performance of CBP and CRPS patients, as compared to age-, gender-, and education-matched normal control volunteers, on an emotional decision making task (Apkarian et al 2004b). Both CBP and CRPS patients performed worse than controls on the gambling task. Moreover, gambling task outcomes in CBP were correlated with the intensity of back pain; while in CRPS patients when the pain was manipulated with sympathetic blocks (all CRPS were of sympathetically maintained type) performance could not be modulated. This cognitive deficit seems specific since CBP and CRPS patients tested normal for attention, language and short-term memory tasks. Moreover, when the gambling task was tested, in normal volunteers when one hand was immersed in painful hot water, and compared to a

second group where the hand was in warm non-painful water, there was no difference in performance between them. Thus, the deficit in gambling task performance seems unique to the chronic pain group and does not generalize to acute pain conditions.

In summary, our results indicate that cortical circuitry underlying chronic pain is distinct from that observed in acute pain, and preferentially involves OFC. In chronic back-pain patients brain chemistry is abnormal and there is a decreased cortical grey matter size, as well as decreased prefrontal cortical grey matter density. Moreover, chronic pain patients show a specific cognitive deficit which is consistent with the brain activity observed in such patients and with the observed chemical and morphological abnormalities as well. We, therefore, conclude that chronic pain is reflected at the cortical level, and is associated with cortical reorganization and perhaps even neurodegeneration.

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DISCUSSION

Mao: Can you tell for sure the area which lights up by fMRI actually represents neuronal excitation or inhibition?

Apkarian: This is a tough question that has been debated for a long time but I think the data nowadays are quite solid. A series of studies have shown that excitability of neurons is highly correlated with blood flow changes. Still, this is an indirect method. In the cortex at least, there is very little question that when there is decreased blood flow this represents inhibition and when there is increased flow this represents activation.

Mao: One of the issues that have been debated is whether neural inhibition also involves an energy requirement. It does.

Apkarian: But the overall net energy is the crucial factor, and at the cortical level the data are solid in that for the most part excitatory synaptic activity is the main drive for fMRI signal. Having said that, it should be added that proportionality between increases and decreases in neuronal activity and fMRI signal tend to be complicated and not linear except for a small range of stimulus intensities and durations.

Dray: I have a question relating to measuring the activity of areas that can induce neural inhibition. Have you ever asked a patient to imagine that they have less pain, so that areas that inhibit pain perception are highlighted? Would they be the same or different areas that light up when intense pain is felt?

Apkarian: In a sense this method includes these data. One could simply look at the opposite. I showed the map for activity when the pain is high versus when the

pain is low. If we do the opposite subtraction then we should observe brain regions that are inhibited when the pain is high. We have earlier reported on such regions in acute pain experiments (Apkarian et al 2000), where we report many regional decreases in fMRI signal. In the current study of chronic back pain we do not observe any significant decreased regional activity for the high-low comparison. I should add that the statistical analyses of such data are complicated and we constantly change, and hopefully improve, these methods. Thus I cannot rule out that the differences between our earlier results and the current are not based on technical differences. I prefer to think of these differences as reflecting distinct circuitry for chronic vs. acute pain. This data set is in patients with quite bad pain. If we do reverse the vectors we don't see anything activated. If we ask the question when the pain is low and compare this with when the pain is high, we don't see anything in the brain, whatever this means. On the other hand if we ask the question as to which brain areas are active when the pain perception transitions from a high to a low level, we get a complicated result that approximates the negative of the regions involved with high vs. low pain. Essentially implying that decreases in pain perception are probably involving similar but not exactly the same brain activity as for increases in pain perception.

Dray: Can such fMRI studies be done in animal models?

Apkarian: Of course.

Dray: You have highlighted an important role of prefrontal cortical areas: is there an equivalent in rodents?

Apkarian: Yes, I think so. In fact, we have an ongoing rodent study examining the role of the prefrontal cortex. We are showing similar effects in neuropathic pain models. When we do lesions in the prefrontal cortex in rodents we see changes in the neuropathic behaviour. By and large we are ignorant about the prefrontal cortex in rodents, but this doesn't mean that it does not have a functional equivalence to that observed in humans.

Perl: What is the resolution of the fMRI technique?

Apkarian: In human fMRI studies the usual voxel size that we currently use is around 3 mm^3. The actual spatial resolution would be three-to-four times larger than this value.

Perl: This doesn't give much detail over a rodent brain.

Apkarian: For rodents voxel size can be decreased to about 0.2 mm^3, which in turn results in a spatial resolution of three-to-four times this value. In rodents one can gain resolution by increasing scan time, especially since such experiments will most likely require scanning under anaesthesia.

McMahon: In your chronic pain patients, how certain can you be that a difference in brain activity when they are in a lot of pain versus less pain is really a measure of brain areas associated with pain processing? Might it be confounded by other

concurrent changes? Have you any ways of controlling for the non-painful things that co-vary with pain?

Apkarian: This is hard to do. Perhaps what we are seeing is not so much the pain, but the suffering of the pain. The regions that we are looking at may have to do with emotional evaluation, and specifically negative emotional evaluation. All this is saying is that this is the significant component of the pain that the patients have, as opposed to what the pain is. It is more like the 'flavour' of the pain that they have continuously. The fMRI scans that we do routinely include a variety of control scans that we use to subtract from the brain activity motoric responses, cognitive evaluative responses, as well as non-specific spurious correlations. Only after correcting for all of these can we make the claim that the remaining activity has a good chance of being related to the ongoing pain.

McMahon: The findings would perhaps be less interesting if patients were simply trying to move their leg to minimize their pain, for instance.

Apkarian: Fortunately those areas of the brain are not activated.

Devor: I think it is important to pursue the theme that Steve McMahon has just raised. You began with the statement, or at least the implication, that the cortex is the organ of pain. To challenge this would be like going to the Vatican to say that God doesn't exist. And yet there are difficulties. An implication of what you are saying is that the neuroactivity you showed us is directly related to the percept of pain. This seems logical and the correlates all fit. Who would challenge this conclusion? Yet, since the 1950s we have had the extensive work of Penfield and colleagues (Penfield & Rasmussen 1955) who electrically activated surface areas of cortex and only extremely rarely found any area where stimulation produced a percept of pain, including areas like S1 that routinely show 'activation' in modern imaging studies. This is not true of other senses: vision, smell and somatosensory percepts are readily evoked by cortical stimulation. Pain is not evoked, or rarely evoked. You could say that these authors only had access to the cortical surface and not deeper areas such as the medial temporal lobe and the insula. However, seizures happen there often, and it is extremely rare for seizures to be painful. I am thinking in the same general direction as Steve McMahon. Is it possible that what you are looking at is the cortex monitoring pain percepts that are happening in the brainstem or the cerebellum; and that the cortex is using this information to decide what to do next, but the actual activity you are seeing in the cortex is not the neural substrate of a pain percept?

Apkarian: If we go back to the early clinical studies that dispute the presence of pain in the cortex, there are also a number of opposite data sets. Whether they balance each other, I am not sure, but one could argue both ways. On the other hand, we now have fairly decent anatomical and physiological data from the cortex in animals, which demonstrate the presence of nociceptive neurons.

Devor: I don't deny that these cells are responding or changing their activity in response to a painful stimulus. This doesn't mean that their activity is generating a pain sensation.

Apkarian: Now you want me to discuss where the perception is happening; whether it is in or below the cortex. I don't know. The cortex has something to do with it. If there was something downstream that was the primary region of these events we should see it. Why isn't it there? Unfortunately, all current electrophysiological and brain imaging methods remain correlative in nature and there is no understanding of how perception comes about for any sensory modality, including pain.

Devor: Many subcortical modules show nice correlates to pain.

Apkarian: So do all of these cortical units.

Devor: But you prefer cortex to the cerebellum.

Apkarian: The data are clear. One can show intensity-dependent changes and unpleasantness-dependent changes. We don't have a way of knowing where consciousness is happening: we can only correlate simple parameters of perception to brain activity. With these tools it seems to work.

Devor: I've given you an alternative way of thinking about the correlation: it has nothing to do with perception, it only has to do with future planning, while the percept is happening in the brainstem or elsewhere. I am not disputing that the cortex is 'involved' in pain. I am just saying that the nature of its involvement might be quite different from what you are implying.

Perl: One must consider the human data on discrete cerebral cortical lesions. Certain cortical lesions are reported to abolish the ability to recognize pain selectively in parts of the body. Those who doubt the influence of the cerebral cortex on pain perception should carefully read John Marshall's 1951 article (Marshall 1951) reporting an analysis of missile wound injuries to the cortex that occurred in World War II. The cerebral cortex has something very particular to do with the recognition of painful stimuli and distinguishing them from other somatosensory events.

Devor: Cortical lesions have not been very useful in terms of clinical treatment for chronic pain.

Apkarian: Let me turn that upside down. We all agree that pain has many dimensions to it, and it has strong social, psychological and environmental influences. All of these are an integration of multiple functions. One assumes that they have to be integrated at a high level. The cortex has to be involved.

Devor: One could argue the same for the cerebellum.

Apkarian: There is no evidence anywhere for any perception at the level of the cerebellum.

Devor: There is plenty of evidence for the upper brainstem.

Apkarian: Now there are reports of deep insula cortex stimulation giving rise to pain perception.

Dray: I didn't think you were saying that the cortex can be singled out for being involved in pain signalling. I thought you were saying that there were several simultaneous regions that are either inhibited or activated, and the cortex is just one of them.

Devor: All the areas presented were in the cortex.

Apkarian: No. Sorry, I believe in the integration of information throughout the CNS. Saying perception happens in the cortex versus the cerebellum tends to diminish the network as a system within which perception happens. I am not going to deny the role of nociceptive neurons in the spinal cord. At the same time, the cortex has to be involved. The simple fact that the spinal cord neurons project, through a couple of synapses, to the cortex implies to me that changes in excitability of spinal cord cells has to be reflected also at the cortical level, and as such the perception of pain has to be the coordinated activity across the whole network, including spinal cord, brainstem, thalamus, and cortex. I have not seen any evidence that refutes this position.

Devor: Stimulation of the spinal cord does evoke pain, as does stimulation of the thalamus and many places in the brain stem. In the cortex it doesn't, basically.

Perl: That's not true. Stimulation of the cortex has been reported to cause pain. The areas involved are mainly hidden in sulci or folds.

Apkarian: The insular cortex does this beautifully.

Devor: There are very few cases reported. This is an area that is prominently involved in seizures. Seizures are common and very rarely painful.

Apkarian: Some of them are painful and the ones that are painful are in the right regions in the cortex.

Devor: I'm not sure we should base a whole theory of pain on these rare instances when most activity in the cortex does not evoke pain.

Apkarian: I think the new technology gives us a handle to move on, rather than being stuck with methodologies that were inadequate for the most part.

Baron: I was confused about your data that different chronic pain states have completely different networks in the brain.

Apkarian: It is not so much that they are very different but that they seem to be distinct subsets. The neuropathic patients seem to have very similar brain regions activated but the specific pattern seems different for complex regional pain syndrome patients as compared to chronic back pain patients, implying that the affective and cognitive perceptual properties of the pain may be unique for different chronic pain conditions.

Gintzler: How do you subtract out the element of distraction? When you are in chronic pain you are obviously going to be distracted: how do you eliminate this?

Apkarian: I can't. The only control for this is to test the attentional abilities of such patients, which we do. When we actually test for attentional abilities, these patients don't show any abnormality. On the other hand these patients are distracted specifically with their ongoing pain, and in our fMRI studies we ask them to ignore everything else and only evaluate the fluctuations of this pain. Thus, we are taking advantage of their distraction with their pain.

Gintzler: How do you assess attention?

Apkarian: It is a separate standard cognitive test looking for attentional abnormalities.

Dray: Do you have a hypothesis to account for the apparent loss of grey matter that you have measured?

Apkarian: Yes. There is a beautiful paper recently published from Dr Casey's lab (Lorenz et al 2003) which tried to subdivide the prefrontal cortical regions in a capsaicin thermal hyperalgesia test. It shows that there is antagonistic activity between the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex (OFC). It seems like the DLPFC is trying to control OFC activity, in essence trying to limit the amount of suffering. This would be exactly the kind of brain area that would be most stressed in a chronic pain patient where pain could not be controlled. In a sense the hypothesis would be that these are overstressed, over-active neurons that are slowly dying because of over-activity, given their functional role in pain perception control. Alternatively, if such patients already have a smaller DLPFC then they would be predisposed to develop chronic pain because of their inability to control OFC activity.

Perl: Another possibility is fluid accumulation in association with an interaction between active neurons and glial cells.

Apkarian: I haven't said what the specific mechanism for the atrophy is. There are many candidates. Is there a functional reason for it? This is my explanation for the specific site.

Mantyh: A similar argument has been made for depression. The idea was that a selective serotonin reuptake inhibitor (SSRI) or another agent that could alleviate the depression would reduce the atrophy. Have you looked at this also? In pain patients in which the pain is reduced, do you see a reduction in atrophy?

Apkarian: No, but we will. This is the first study that we have done in the subject. In a sense we would like to do a longitudinal study on this, with two populations: one with proper pain management and another without. These patients I have shown essentially have no management of their chronic pain.

Mantyh: One thing about depression studies is that they have been focusing on specific areas of the brain. If they didn't focus on these, they would lose all signal. Do you think that there are specific areas of the brain that are showing greater atrophy than others?

Apkarian: Yes, the main area is DLPFC, which is very consistent with our MR spectroscopy data, which shows decreased N-acetyl-aspartate (NAA) concentration in chronic back pain patients (Grachev et al 2000). Decreased NAA has been reported in all neurodegenerative conditions, as a result it is assumed to be a marker for neuronal atrophy. This initial finding prompted us to perform the morphometric study. Our starting hypothesis for the morphometric study was that the DLPFC would be one of the main areas that shows atrophy in chronic pain. The regional atrophy that we observe in these patients is distinct from that of depression or anxiety, for example.

Mao: I have a couple of comments. First is that you used a new pain rating scale?

Apkarian: That is actually an old pain scale, initially devised by S. S. Stevens back in the 1950s. In fact, he has shown that finger-span is a natural linear scale for magnitude estimation.

Mao: My other comment is that I am concerned that the population of chronic pain patients you have used may be selective because of the monetary compensation, which is rather common in clinical studies.

Apkarian: They may be motivated to get the money, but they have no clue what we are doing to them, especially when they are strapped into a scanner. They have no idea what to do to satisfy us.

Mao: I am just saying that they are collected in this systematic manner which might bias the outcome.

Wood: Have there been any fMRI studies of patients with phantom limb pain?

Apkarian: There is a whole series of studies examining brain responses and reorganization in subjects with phantom sensations as compared to subjects with painful phantom sensations. Herta Flor and colleagues have pioneered the work in this field (Flor et al 1995). Their reported results are quite relevant. Primarily these are magnetoencephalography studies where they show primary somatosensory cortex region reorganization. They show a correlation of the extent of the reorganization with the amount of pain that these patients have. Of course, they are correlating tactile reorganization with the amount of pain, so it is a little unclear how this correlation can have a causal relationship with pain perception. Still the data clearly indicates that phantom pain is very strongly related to changes that occur in the cortex.

Zhou: The idea of top-down descending facilitation is now getting more support. In addition to descending inhibitory or analgesic systems, descending facilitation systems are believed to be important, particularly in disease conditions. We have shown that this top-down system can facilitate responses of spinal dorsal horn neurons to various sensory stimuli (Zhuo & Gebhart 1992, 1997, 2002a,b, Zhuo et al 2002). From my reading of the literature on injuries and the cingulate cortex, there are two reports of particular relevance here. One recently showed that using placebo analgesic in humans also caused aberrations

in the cortex. They had previously shown that pain activates the cingulate cortex. My interpretation would be that imaging can show activation of neurons but cannot tell whether it is a pyramidal cell or an inhibitory interneuron in the cortex.

Apkarian: If placebo is a real effect and if the placebo perception is a decrease in activity in the cortical network for pain, one would expect that placebo would show the same sort of effect.

Zhou: No, pain increased the activity in imaging, and placebo which reduced the pain also showed the same increase.

Mantyh: If you compare results on your pain stimulation with your colleagues who are doing visual work, for example, are many more areas of the cortex activated in pain versus visual stimuli?

Apkarian: No, it is comparable. The only difference tends to be that the visual areas are much more contiguous with each other. In the field of visual experimentation, the science is much more sophisticated: one can look at colour discrimination versus motion detection versus face identification, and for these one can identify subsystems. This is what we have not yet been able to do in pain. What is the role of S1, S2, anterior cingulate, insular cortex or prefrontal cortex in the overall dimensions of the pain perception? As to the question of the number of areas, I think a strict comparison between sensory modalities is not very helpful. If for example one performs a brain imaging task where rest state is contrasted to a rich visual stimulus, like watching a silent colour movie, then a very large number of cortical regions will be activated. On the other hand, if the task is a contrast between objects and faces then most likely only the face region within the temporal cortex would be observed. The more specific the task the more localized and specific brain activity should be. So far, in the pain field the only comparable studies are those that have attempted to map intensity of pain with different brain regions (e.g. Coghill et al 1999).

Mantyh: When you look at the changes of blood flow for visual stimuli versus pain, are they similar?

Apkarian: Yes.

Mantyh: When I've looked at the data it has always struck me how with vision there are intense areas lit up, but with pain there are many more areas that light up and the areas are less precise. Do you think that pain is just activating many more areas of cortex?

Apkarian: It seems to be more distributed in the sense that there are more separate areas. Unfortunately, unlike vision where there are a lot of nice animal data on physiological functions to look for, we have essentially no animal data to guide us. As a result the experimental paradigms tend to be less specific in the kinds of questions we ask, which inevitably will give rise to a more distributed activity.

Dray: Why are there cognitive deficits in your patient population? Have you ever looked at the association between cognitive deficits and the intractability to pain therapy?

Apkarian: I showed you all the data I have. The only striking difference here is that between CRPS and back pain, there is a significant difference between the two populations in their cognitive performance. CRPS patients are much worse. I am not sure what this is due to. It is also important to keep in mind that the orbitofrontal cortex is an area that is tightly involved with autonomic regulation. If the task is specifically looking at orbitofrontal performance, then it is consistent with the CRPS patients doing worse on it.

Dray: Can you exclude things like previous drug histories that could have affected cognition?

Apkarian: I cannot exclude previous drug therapies in that study. I can exclude this factor in our morphometric study, where we actually quantified drug use but did not observe any significant relationship between drug use and brain atrophy. I should mention that we routinely exclude patients who are highly depressed, highly anxious, and who are on polypharmacy for their pain control. Thus, the general population of chronic pain patients that we are studying tend to be first highly chronic (which in the majority cases are people who have discovered that drugs are not helping and use them only occasionally), and second they are mostly engaged in normal lifestyle (that is, most of them work and lead a fairly routine life).

Oh: I was told that the somatosensory cortex has a column organizaton such that one column is fast adapting mechanosensory and the next column is slowly adapting mechanosensory. Is there any pain-specific column in the primary somatosensory cortex?

Apkarian: I think that Dan Kenshalo (Kenshalo et al 2000) would say that there is. When you find one nociceptive neuron in the cortex the chances of finding more are much higher.

Reeh: In the depth of the same sulcus. There are no pain-specific columns to my knowledge.

Apkarian: But once you find one neuron then finding more is likely. Dr Perl should comment on this.

Perl: The evidence is not striking. The problem, at least in part, seems to be that the nociceptive neurons in the primary cortex, somatosensory 1, are in the central sulcus. Therefore they are rarely approached by electrodes introduced from the surface. The central sulcus is deep and the nociceptive neuronal activity reported is from cells between the sensory and motor zones, not readily accessible by electrodes introduced from the surface. This is at least one explanation for the limited information about somatosensory neurons that specifically respond to noxious stimuli. Observations by Kenshalo on monkeys fit with the human

lesion data by Marshall (1951) which show that a loss of capacity to recognize painful stimuli is associated with limited lesions of the central sulcus region. Unfortunately, definitive studies require well focused studies on primates. Apparently cortical organization involves nests of cells. Whether they are columns or not is uncertain.

Devor: Returning to the cognitive matter, there is a substantial literature on cognitive deficits, and emotional deficits, in patients with chronic pain. Here, once again, the evidence suggests that if the peripheral cause of pain can be addressed and definitively removed, then the cognitive and emotional problems resolve themselves. It is not as if your pain burns out your cortex, so that you can't come back again. The one control that you offered is of normal people being submitted to an acute pain of equal intensity. But this has a very different meaning to your life than knowing that you are going to have pain for the next 20 years. I don't think that control really answers the question at all.

Apkarian: That control was only to show that this is not simply a distraction of the presence of pain. There is no way that I can come up with a control that equates the chronic pain with an acute one.

Devor: My point is that the change you are observing in the cortex isn't necessarily evidence of centralization. It may just be a reaction to a terrible life state. If we could make the pain go away, people might jump for joy.

Apkarian: That should show up as a more generalized cognitive deficit. It is not: it is a very specific deficit. The specificity gives us a clue that it is not a degenerate condition and nicely corresponds to the brain areas where we see the activity. Moreover, the evidence for brain atrophy taken together with the cognitive deficit, in fact is indicative of the likelihood that the chronic pain has burned out the brain and therapy may reinstate a happier personality but may not necessarily reinstate the ability of proper decision making.

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