Brain Imaging Findings in Neuropathic Pain

*Paul Y. Geha, MD and A. Vania Apkarian, PhD**

Address
*Northwestern University Feinberg School of Medicine, Department of Physiology, 303 East Chicago Avenue, Chicago, IL 60611, USA.
E-mail: a-apkarian@northwestern.edu

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The contribution of brain imaging technologies to the understanding of mechanisms underlying clinical neuropathic conditions is discussed in this article. Available technologies, their advantages, and contributions also are presented. The brain regions involved in acute pain are contrasted to chronic pain and the implications of these differences are discussed. Overall, the reasons for the limited contribution of these techniques to the science of chronic pain are presented in this article.

Introduction

Neuropathic pain remains an ill-defined condition. It is a clinical pain syndrome usually associated with a lesion to the nervous system [1,2•]. Such lesions can occur at many different levels, starting from peripheral nerves (postherpetic neuralgia), then the spinal cord (postspinal cord injury pain), to the brain itself (thalamic pain syndromes). However, only a small portion of people with such injuries develop chronic neuropathic pain. It is extensively studied in animal models and the work done thus far has uncovered multiple neurobiologic mechanisms involved. These include ectopic excitability of peripherally injured and neighboring nerve fibers, neuronal phenotypic switch and de novo production of pain neuromodulators, primary sensory fiber degeneration, and the loss of central inhibition partially caused by the selective loss of GABAergic neurons, all of which lead to central sensitization of nociceptive processing [2•]. These mechanisms can lead to the emergence of the symptoms of neuropathic pain and their understanding may lead to the discovery of new and more specific targets for pharmacotherapy, although successful clinical results have not yet been materialized. The animal studies have focused mainly on peripheral afferents and spinal cord mechanisms; hence, they assume implicitly or explicitly that the rest of the brain passively responds to these changes. Therefore, the extent to which these peripheral and spinal cord mechanisms, which have been unraveled in animal models, reflect the human clinical condition remains unknown. The advent of noninvasive brain imaging provides the opportunity to directly study chronic pain syndromes and identify the contribution of the cortex to human clinical neuropathic pain. The animal model studies, and various clinical investigations, provide ample evidence for the notion of reorganization of pain circuitry in the brain in neuropathic pain states [3,4]. The focus of this article is on identifying the site or sites of neuronal reorganization, pinpointing which if any of these modifications are critical for the condition, and whether human brain imaging studies can satisfactorily answer such questions.

A long list of noninvasive human brain imaging modalities are available. These range from electrical signal-monitoring techniques, such as electroencephalography and magnetoencephalography, to metabolic measures, such as positron-emission tomography (PET), functional magnetic resonance imaging (fMRI), and single photon emission computed tomography. These techniques provide monitoring of brain activity at different spatial and temporal resolutions [5••]. Other human brain imaging methods provide direct access to brain chemistry such as magnetic resonance spectroscopy and morphologic imaging methods, which can document changes in brain gray matter and white matter properties, such as voxel-based morphometry and diffusion tensor imaging. fMRI is the most widely used technique in human pain studies because of the possibility of online monitoring of brain activity in a wide variety of tasks. Despite all of these opportunities allowing direct access to the human brain, our understanding of chronic neuropathic pain remains in its infancy. Some of the reasons for this lack of progress are addressed in the following sections.

Discussion

The first question that needs to be answered is the contribution of human brain imaging studies regarding the role of the cortex in pain perception in healthy subjects. Before brain imaging, animal electrophysiology and human brain damage studies provided an ambiguous position on the issue. Very small numbers of nociceptive cells are described in electrophysiologic studies of the mammalian cortex [6] and brain lesion studies have been equivocal on the extent of pain perception deficits in humans; however, anatomic

studies show appropriate thalamocortical projections that can transmit nociceptive information directly from the thalamus to multiple cortical targets [7–9]. Throughout the past 15 years, a large number of PET and fMRI studies of acute pain in healthy subjects show a reproducible pattern of cortical activity for painful stimuli. This activity also is demonstrated to possess many properties necessary for involvement in pain perception, such as somatotopic representation of painful stimuli, correlation with stimulus intensity, modulation with attention, modulation with expectation and other psychologic variables, distinct brain regions showing differential activity for sensory and affective dimensions of pain, and attenuation of responses with analgesic drugs [5••]. At least six different brain areas are consistently activated with acute pain in healthy subjects: thalamus, primary somatosensory cortex (SI), secondary somatosensory cortex (SII), insular cortex (IC), anterior cingulate cortex (ACC), and prefrontal cortex (PFC). Incidence of activity recently was estimated for these regions to be between 75% and 94% for the first five structures and 55% for the PFC (incidence is percent of studies in which a given region was significantly activated from a total of 69 studies) [5••]. Thus, human brain imaging studies have asserted the role of the cortex in acute pain. However, despite this progress, the answer to the fundamental question 'is the cortex necessary for pain perception?' has remained elusive, primarily because all of the studies identify brain responses in a correlative manner. As a result, all of them may reflect secondary processes. Perception of pain automatically directs attention to the source of pain and results in autonomic responses, motor reflexes to escape from the pain, and other emotional and cognitive responses that undoubtedly are at least partially mediated through cortical processes. Therefore, the role of the cortex in pain perception in contrast to its activity as a consequence of these secondary responses remains unclear and needs to be properly addressed in future human imaging studies [10••].

Given the paucity of brain imaging studies specifically targeting neuropathic pain conditions, it is important to discuss the contribution of the technology in differentiating brain activity in healthy subjects in response to acute pain from brain activity in clinical pain conditions. The incidence of brain activity in clinical pain conditions was reported to be between 20% and 59% for the thalamus, SI, SII, ACC, and IC, which is statistically significantly lower than for acute pain in healthy subjects. In contrast, the incidence in PFC in clinical pain conditions increased to 81%, a statistically significant increase [5••]. Two earlier meta-analysis studies [11,12] also noted the regions with decreased incidence of activity. Despite the fact that the latest meta-analysis [5••] combined a highly heterogeneous population of patients, the observation shows first that the cortex is involved in clinical pain conditions and second that this involvement has a different brain-regional activity pattern. If one makes the simplistic assumption that pain-related brain activity in posterior cortical regions is more involved in the sensory discriminative processing of pain (based on spinothalamocortical termination patterns), and that the frontal cortical regions are more concerned with the affective and cognitive dimensions of pain, then a simple conclusion of the contrast of activity pattern between healthy subjects and clinical conditions would be that the latter have a stronger cognitive/emotional component.

A number of studies have examined brain activity and acute painful stimulation in clinical patient groups. Although most of these studies show activations in the SI, SII, thalamus, IC, and the ACC [13–15], overall brain activity differences in such paradigms remain un-interpretable because they do not distinguish between brain activity specifically related to the clinical condition and abnormalities in sensory processing secondarily associated with the clinical state. For example, reduced relevance of the acute stimulus to subjects who already are in pain may be sufficient to account for most of the decreased regional brain activity in clinical pain conditions. To overcome such nonspecific brain activity differences, one needs to compare brain activity for stimuli in which perceptual evaluation has been equated between patients and healthy subjects. A recent study used such a design and showed generally heightened brain activity for painful stimuli of equivalent perceptual intensity in patients with fibromyalgia and chronic back pain compared with healthy subjects [16,17].

Morphometric and neurochemical brain imaging studies provide evidence for the occurrence of long-term changes in the brain chemistry and morphology of patients with chronic neuropathic pain. Pattany *et al.* [18] showed a decrease in the level of *N*-acetyl-aspartate, a marker of neuronal degeneration and dysfunction, in the thalami of patients with chronic neuropathic pain after spinal cord injury compared with patients with a spinal cord injury, but no pain. Grachev *et al.* [19] showed that this same neuronal marker was decreased in the medial and lateral PFC of patients with chronic back pain compared with age- and sex-matched control subjects. The only morphometric study in chronic pain also showed a decrease in gray matter density in the dorsolateral PFC and the thalamus of patients with chronic back pain when compared with matched control subjects [20••]. Furthermore, these long-term chemical and morphologic changes are significantly correlated with different characteristics of pain such as pain duration [20••], pain intensity [18,20••,21], and sensory-affective components [21]. The morphometric and neurochemical studies imply an active role of the central nervous system in chronic pain, suggesting that supraspinal reorganization may be critical for chronic pain. However, the studies done with these techniques are very few and remain preliminary. Nevertheless, we suspect that work along these lines should be able to provide important clues regarding the mechanisms of supraspinal reorganizational in chronic pain.

On the other hand, functional brain imaging studies show that this change in brain chemistry and morphology is accompanied by a similar change in the pattern of brain activity, especially in the thalamus. Six different studies show that patients with chronic neuropathic pain, including peripheral neuropathic pain and complex regional pain syndrome, show a decrease in thalamic activity on the side receiving input from the diseased limb when compared with thalamic activity on the contralateral side [22–24] or with thalamic activity in healthy subjects [24]. Thalamic activity in patients with neuropathic pain is reported to increase after pain relief [25] and to be significantly negatively correlated with the duration of the condition in patients with complex regional pain syndrome [23]. The exact relationship between this decrease in the thalamic activity and the decreases observed in gray matter density and neurochemistry in this same region remains to be clarified, although all three techniques seem to be pointing in the same direction.

The picture becomes more complex when we examine cortical activity. As an example, activity in rostral ACC is significantly correlated with the perceived pain intensity during rectal distension in healthy subjects, but not in patients with irritable bowel syndrome [26]. Hence, the finding that rostral ACC is involved in the perception of pain unpleasantness in healthy subjects [27] may not apply to patients with chronic pain. Thus, we suspect that the functional roles of brain regions involved in pain perception in acute pain may shift and even reverse in chronic pain conditions. Few studies have examined brain activity related directly to the pain that the chronic pain condition is related to. The main difficulty being that such pain conditions are hard to control and modulate in the time frame necessary to examine brain activity.

Three studies [22,25,28] have looked at the regions of the brain modulated by relief of chronic neuropathic pain: complex regional pain syndrome, peripheral neuropathy, and trigeminal neuropathy. Two of these studies show that the PFC activity is decreased and all three studies report decreased rostral ACC activity after successful pain relief. In addition to those regions, some areas also were less activated with pain relief such as the IC [25] and the anterior limbic thalamus [28], whereas others were more activated after pain relief (*eg,* the medial PFC) [28]. This is not surprising because we believe that the pattern of brain activity should be specific to each chronic pain condition. In our recent study on chronic neuropathic back pain, we show that activity in the medial PFC and perigenual ACC (BA 32) correlate with spontaneous fluctuations of ongoing pain of chronic back pain in the absence of any external stimulation. This activity spreads to involve the extended amygdala if we use a less stringent statistical method [Baliki *et al.*, submitted]. These regions are known to be involved in emotional processing and reward circuitry [27,29,30], supporting the claim that cognitive/emotional dimensions of pain are more dominant in chronic neuropathic conditions. More recent studies are examining brain activity in patients with postherpetic neuropathy before and after treatment with lidocaine therapy [31] and in osteoarthritis and psoriatic patients before and after treatment with cyclooxygenase-2 inhibitors [Geha *et al.*, submitted]. Preliminary results indicate that the brain activity for different components of the conditions are associated with distinct brain activity, such as allodynia or hyperalgesia pain, in contrast to spontaneous pain in each condition.

Overall, the clinical brain imaging studies indicate reduced information transmission through the thalamus to the cortex and increased activity in the PFC, mostly in the medial PFC coupled with atrophy in the dorsolateral PFC. The number of studies remain very small; hence, our confidence regarding the reproducibility of these changes remain minimal. However, the observations regarding cortical and thalamic activity changes in chronic pain generally are consistent with the notion that chronic pain conditions preferentially engage brain areas involved in cognition/emotion and induce decreases in activity in regions involved in sensory evaluation of nociceptive inputs. This idea is consistent with the recent demonstration that patients with chronic back pain show impaired performance on a task that tests for ability in emotional decision-making [32]. More importantly, the studies suggest that the thalamus and cortex play a critical role that may need to be specifically determined for each and every clinical pain condition. Therefore, we think that to specifically examine the role of the cortex in different chronic pain conditions, brain imaging paradigms should be applied to those conditions directly and the painful condition itself should be studied specifically. Few researchers have adopted this concept since the advent of brain imaging techniques and this, in our opinion, is one of the major reasons why the potentials offered by human brain imaging techniques have not better impacted the science of neuropathic pain. Instead, a large number of acute pain studies claim that such studies shed light on clinical pain conditions with minimal evidence for this claim.

Conclusions

We have argued that brain activity, chemistry, and morphometry are uniquely reorganized in neuropathic pain conditions. Does this evidence imply that there is supraspinal reorganization above and beyond what is established in the periphery and spinal cord? That is, even if we establish a brain pattern of activity for some chronic pain conditions, does this reflect some unique contribution of the brain to this state or is it simply a reflection of lower level reorganization? How can one get out of this dilemma? Brain imaging studies usually provide a list of areas involved in a condition, together with a measure of the intensity of activity for these areas for different conditions, including acute and chronic pain. How can one

affirm that this pattern of brain activity is critical to the condition and reflects something beyond spinal cord processes? The answer is not straightforward. However, only by answering such questions will brain imaging be able to provide new information to the myriad of mechanisms described for peripheral and spinal cord reorganization. One approach is demonstrated in this review, namely the use of multimodal imaging techniques that complement each other and provide unique viewpoints to the condition. Beyond localizing activity in the brain for distinct chronic pain conditions, one also can describe the connectivity across these areas. Such an analysis was performed for chemical injury-induced hyperalgesia in healthy subjects in which the authors demonstrated that connectivity was different between two brain regions after the chemical injury [33]. Given the multiple changes observed in the brain of neuropathic pain conditions, it is highly likely that connectivity is distinct for acute and chronic pain, but remains to be demonstrated. It also is possible that global connectivity of brain activity, as recently described by Eguiluz *et al.* [34], may show properties uniquely associated with neuropathic pain.

In many ways, this review highlights that the technologies of noninvasive brain imaging are outpacing the rate at which these techniques have been applied to studying neuropathic pain. There is little doubt that proper application of these technologies will dramatically change our viewpoint regarding the etiology of chronic pain and hopefully even contribute to developing new therapies.

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