Spontaneous Pain and Brain Activity in Neuropathic Pain: Functional MRI and Pharmacologic Functional MRI Studies

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Functional brain imaging studies in chronic neuropathic pain patients have lagged far behind equivalent studies in acute pain. In the past few years, this trend has begun to shift. This article discusses the novel approach of studying brain activity for spontaneous pain and its modulation by pharmacologic manipulation. We argue that the approach provides a solid methodology for studying clinical (especially neuropathic) pain and patient populations, and moreover, that the latest results using this approach imply that distinct clinical chronic pain conditions seem to involve specific brain circuitry, which is also distinct from the brain activity commonly observed in acute pain.

Introduction

Recent reviews [1–7] emphasize the limited progress in understanding brain activity in clinical neuropathic pain conditions. In contrast, the literature regarding brain circuitry for acute or experimental pain is now firmly established and continues to generate new findings. Witness the recent excitement in unraveling the brain processes that may distinguish between physical pain, psychological pain, and pain empathy. More than a dozen papers have been published on the topic, and widely diverse explanations have been advanced for the observed results [8–10]. We think the proper explanation for the large overlap between pain- and pain empathy–related brain activity remains to be explained. Still, these observations provide a fresh outlook on the brain acute pain circuitry. Another new direction is the study of cortical mu-opiate neurotransmission, particularly its role regarding regulation of sensory and affective dimensions of pain [11]. A new venue in this field is also the study of the relationship of genetic polymorphism in brain mu-opiate transmission and acute pain [12]. The latter are research directions that have been ignored for much too long; instead, the emphasis over the past 30 or so years has concentrated on the role of opiate modulation of pain through brainstem and spinal cord circuitry.

This article only briefly reviews the main reasons why brain-imaging studies in clinical chronic pain conditions have lagged behind those for acute pain (the topic is more extensively covered in reviews cited earlier). The main issue is that the results remain inconsistent and inconclusive for the most part. Even the simple question as to whether clinical pain conditions involve the same or a distinct brain circuitry remains unsettled. There is a long list of methodologic, technical, and demographic difficulties that hamper studying clinical pain conditions. Mixing patients with various chronic pain etiologies together raises important issues regarding observed results. In fact, the problem that no two chronic pain patients can be absolutely equated is an issue that can only be overcome if large numbers of subjects are used, thus averaging out the noise that heterogeneity induces. However, a large part of the current pain studies have been done in very small groups in which the statistics are based on fixed effects models of variance, which increases the chance of observing false-positive results. Populational heterogeneity comes from lumping different chronic pain conditions together. Even when the group is limited to a specific condition, differences in location, intensity, duration, age, gender, and drug use, and interactions between these factors, dramatically complicate the picture. An important confounder in studying clinical pain conditions is the issue of adequate stimulus. Another is the effect of the presence of ongoing pain on brain activity. We have been battling these issues and present our solutions in this review.

Discussion

Differences in brain activity between acute/experimental pain and clinical/chronic/neuropathic pain conditions

There has been a long debate regarding the similarities and differences in brain activity between acute and

chronic pain conditions. The likelihood that the two conditions are equivalent is small given the vast number of animal studies indicating peripheral and spinal cord reorganization of nociceptive pathways occurring with sustained pain, with differential changes observed for inflammatory, neuropathic, and cancer-related pain conditions [13–15]. There is now convincing evidence for the reorganization of descending modulatory systems and their critical involvement in animal models of neuropathic pain [16]. Given these results, it is highly unlikely that supraspinal pain circuitry simply passively responds to these changes. Nevertheless, the extent of supraspinal reorganization and the factors driving the process remain mostly undiscovered. Our work over the past years has concentrated on the simplest aspects of this question from the human brain viewpoint.

When chronic back pain (CBP) and complex regional pain syndrome (CRPS) patients are assessed on an emotional decision-making task, both groups show impaired performance, with the CBP group showing that their deficit is directly correlated to the intensity of their back pain [17]. Chronic pain can also induce sensory/cognitive advantages. For example, CBP patients show decreased gustatory thresholds and heightened sensitivity for suprathreshold gustatory stimuli [18]. Moreover, CBP patients show brain atrophy localized to the lateral prefrontal cortex and the thalamus, in contrast with matched healthy subjects. The extent of the atrophy seems correlated to the duration of chronic pain, distinct for neuropathic versus non-neuropathic CBP, and also related to sensory and affective dimensions of CBP [19]. The three studies together imply that cognitive/sensory processing changes in chronic pain patients, some of which may be a direct consequence of the anatomic reorganization. The specific events and underlying mechanisms for these changes remain to be elucidated.

Studying brain activity in chronic pain with nonspecific painful stimuli

The sensory/cognitive and anatomic studies strongly suggest that chronic pain should have a distinct underlying brain activity pattern. In fact, a recent meta-analysis shows that across some 100 studies one can establish statistically significant differences in incidence of different brain areas activated between acute and chronic pain conditions [4]. The implications of this finding remain obscure. Is the result a consequence of some trivial confounds, or does it signify changes in the physiology of pain?

The standard approach for studying brain activity for acute pain is to induce pain by a mechanical or thermal stimulus and determine brain regions modulated with the stimulus period and even with the various intensities used. Therefore, it is natural to carry the same technology to the clinical arena and apply it to pain patients. This has been used extensively in the past, and we have commented on its shortcomings [4]. Here we discuss the issue based on one of our earliest studies in which we attempted to identify brain activity in CRPS patients using functional MRI (fMRI) [20,21].

The study was designed to examine brain activity for thermal stimuli applied to the body part where CRPS pain was present and compare brain responses to this stimulus between CRPS and healthy subjects. Moreover, because the pain in CRPS patients with sympathetically maintained pain can be modulated by sympathetic blocks, we reasoned that we could decrease the patients' ongoing pain and then re-examine brain activity responses to the same stimulus. The study was done in a small group of patients, and this by itself is an important weakness. The main observation was that thermal stimuli in CRPS evoked more prefrontal cortical activity than usually seen in healthy subjects, and this was reversed (became more similar in pattern to normal subjects' brain activity to thermal stimuli) after sympathetic blocks. The introduction of sympathetic blocks necessitated the use of the same procedure in healthy patients as well, in whom its effects were minimal. In this study, we also observed that when a placebo block resulted in decreased pain perception then the cortical response pattern changed similarly to that of effective blocks. The study did show that brain activity may be distinct between CRPS and healthy subjects for thermal stimuli but raised a number of unanswered questions, many of which challenge the validity of the approach. For example, the simple assumption that sympathetic blocks were only, or mainly, affecting the CRPS pain without interfering with afferent sensory transmission was unclear; the analysis was based on the idea that spontaneous pain per se would not affect subjects' ability to assess stimulus pain, which we now know is not true (see following text), and also that contrasting sympathetic block effects in CRPS and healthy subjects are valid.

Spontaneous pain as a confound in assessing brain activity

We were well aware of the limitations of our initial fMRI study of CRPS pain and have spent considerable energy attempting to improve on it. An important question that was ignored by us in that study, and by many other groups using stimuli to study brain activity in clinical pain conditions, is the effect of the presence of spontaneous pain on brain activity in general. A person who has lived for years in the presence of pain must have developed some coping mechanisms that aid in pursuing other everyday life interests in spite of the presence of the pain. How does this impact the brain? Can one consider the patient in chronic pain as composed of a brain signaling pain together with a brain undertaking other tasks as in healthy subjects? Or, does the presence of ongoing pain interact with and impact other processes as well?

In a recent study, we reported brain activity for spontaneous pain in postherpetic neuropathy (PHN) patients before and after local lidocaine treatment [22]. The

improvement that this design brings to studying clinical pain conditions is discussed in the following text. First, we expound on the effects of presence of pain on brain activity in general. The PHN patients were imaged before, after 6 hours, and 2 weeks after treatment with lidocaine. Behaviorally and based on questionnaires, most participants showed a modest but significant decrease in their ongoing pain. The patients were scanned while they were either rating their ongoing pain or rating a visual bar that varied in time in a pattern that mimicked their ratings of pain. Thus, the latter is a control task that captures motor and cognitive parts of the task, but of course, it does not reflect the pain. The group-averaged activity was determined for these two conditions, spontaneous pain ratings and visual bar length ratings, for all three sessions. We observed that brain activity for both tasks was increasing from first to third session. This observation is similar to earlier reports that decrease in clinical pain in many cases results in increased brain activity. However, in our case, the internal control was also changing in a manner parallel to the pain condition, hinting that the effects of decreased pain were modulating more than pain-related circuitry.

To identify the role of spontaneous pain on brain activity, we performed a correlation analysis for both tasks with mean spontaneous pain. We determined the modulation of brain activity with pain intensity by using mean pain intensity as a covariate. Figure 1 shows the influence of pain intensity on across-sessions averaged brain activity for both tasks. The resultant map is generally similar for both tasks: activity in medial and lateral prefrontal regions was positively correlated, whereas posterior parietal attentional areas were negatively correlated with mean pain intensity. This result shows that brain activity for both tasks is influenced by the level of spontaneous pain, implying that pain intensity influences task performance in general. This idea is further corroborated by the observation that in the visual task there was a trend in improvement in rating ability with sessions; that is, the patients followed the simple instruction of rating bar lengths and rated them more accurately after their spontaneous pain subsided.

This result reinforces the need for correcting brain activity by a control condition performed at the same pain level; that is, the necessity of subtracting the visual task from spontaneous pain rating task at each treatment session. For both tasks, the fact that posterior parietal cortical activity was negatively correlated with mean ongoing pain suggests that the attentional abilities of patients are directly related to the intensity of their pain, which would in turn impact their abilities in performing anything that would demand concentration. Moreover, multiple prefrontal regions were positively correlated to the mean pain, suggesting that the patients' brain regions underlying higher cognitive functions become more active as the pain intensity increases. The exact cognitive implications for these brain activity patterns remain unclear. However, the finding indicates that the intensity of spontaneous pain impacts brain activity for any task that the subject attempts to perform, enhancing some aspects and inhibiting others. Therefore, the decreased brain activity reported for pain tasks in many clinical pain conditions [4,5,23,24] is most likely a reflection of the presence of the spontaneous pain and is not specific to the task being investigated. Outside of our own studies, only one study used ongoing pain intensity as a covariate of no interest [25] when determining brain regions involved in traumatic nerve injury–related allodynia. The fact that pain intensity seems to modulate brain activity in general has another powerful consequence. It suggests that in simply studying brain activity, in tasks unrelated to pain, one should be able to identify the presence of pain and study its effects on sensory/cognitive/motor processing, a truly exciting prospect that needs to be pursued.

Spontaneous pain

If the standard mechanical or thermal stimulation has questionable value in assessing clinical pain conditions (and because clinical pain states are usually relatively refractory), what tools do we have to assess brain activity in relation to these clinical states? The approach we have taken is the study of spontaneous fluctuations of pain. Spontaneous pain is highly prevalent in clinical pain conditions and is usually the primary drive for patients seeking medical care. To our surprise, its temporal properties had not been studied in the past. We now have evidence that spontaneous pain fluctuates unpredictably in the time scale of seconds to minutes, and moreover that these fluctuations have characteristic properties that differentiate between chronic pain conditions [26•]. Our results demonstrate that variability of spontaneous pain fluctuations can distinguish between PHN and CBP patients, and also that this variability can be observed in fMRI signal when such subjects rate their spontaneous pain. Therefore, we have applied this technique to study brain activity in CBP [27•] and PHN patients [22] in relation to their subjective report of fluctuations of spontaneous pain.

fMRI of spontaneous pain

The combination of relating brain activity to spontaneous pain and correcting for confounds by subtracting brain activity for visual bar lengths provides a robust approach with which clinical pain may be studied directly. Note that in this case the brain activity is related exactly to the event that the patient complains about. This is an important point that needs emphasis. Most patients with pain complain of ongoing pain and not of allodynia or hyperalgesia. Certainly the latter two may be present and may be studied specifically, but by and large and especially for chronic pain, the spontaneous pain remains the primary source of discomfort and suffering. Thus, understanding its related brain circuitry is both scientifically and therapeutically imperative.

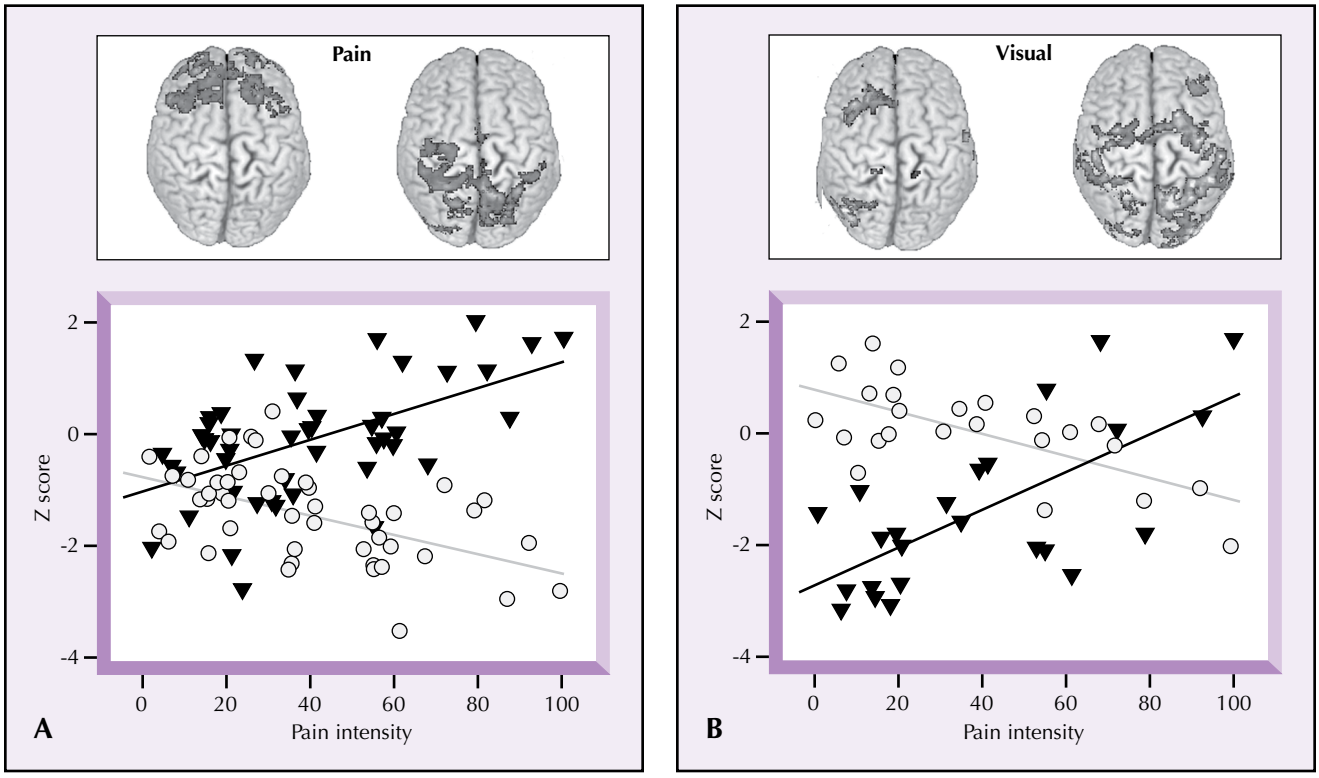

Figure 1. Intensity of ongoing pain changes brain activity and thus cognitive processing in a complex pattern, for pain and non-pain tasks. The figure is adapted from the study by Geha et al. [22], in which 11 postherpetic neuropathy patients were studied before and after lidocaine application on the painful skin. Each patient was scanned by functional MRI (fMRI) at three time points relative to the drug therapy. In all cases the patients performed two different tasks: in the pain task they continuously rated the fluctuations of their spontaneous pain (**A**), and in the visual task they rated fluctuations of a bar varying in time (**B**). Brain activity was identified using standard fMRI data analysis methods. The relationship between brain activity and intensity of ongoing pain was determined using a covariate analysis, in which the related pain intensity for each fMRI scan was used to determine the effect of this parameter on brain responses. Across subjects and across all scans, average variation of brain activity is displayed for both tasks as a top view. The left brain shows regions that were positively correlated with pain, whereas negatively correlated regions are shown on the right brain. Scatter-grams show this effect for two brain regions (right posterior parietal cortex [RPP], x = 33, y = -45, z = 50; and medial prefrontal cortex [MPFC], x = 9, y = 50, z = -40). Each symbol represents a single patient's activity at a single time; circles are for RPP and triangles for MPFC. Panel **A** scatter-gram is for pain task, panel **B** is for visual task. MPFC exhibited significant positive correlations with pain intensity for pain (r = 0.49, $P < 0.05$) and visual (r = 58, $P < 0.01$) task, whereas RPP showed negative correlation for pain (r = -0.48, $P < 0.05$) and visual (r = -0.64, $P < 0.01$) task. The negative correlation of PP with intensity of ongoing pain suggests that the engagement of this region in both tasks is reduced. Given that PP is the primary brain area involved in attention, the result identifies the fact that the larger the intensity of pain, the more the attentional resources are diverted away from the task at hand and toward the pain itself. As a result, we interpret that the brain areas that show increased correlation with ongoing pain are a functional compensation for the decreased attentional resources.

With this approach [27•], we have recently shown in CBP patients that the brain regions activated for periods when the pain is increasing correspond to brain regions seen for acute pain in normal subjects. In contrast, for time periods when the pain is high and sustained, the brain activity is mainly limited to the medial prefrontal cortex (mPFC), a region usually not activated for acute pain. Our confidence regarding these results stems from the fact that the resultant brain activity was strongly correlated to the patients' reported pain intensity at time of scan, specifically with medial prefrontal activity. Also, the duration or chronicity of the pain was captured in the insular activity, a region activated only during increases in spontaneous pain. Thus, two fundamental properties of CBP, its intensity and duration, can be directly recovered from the brain activity that we identify in these patients.

We were also able to demonstrate a double dissociation between brain activity for acute and spontaneous pain. By applying a thermal painful stimulus in the same patients (as well as in healthy subjects), we showed that brain regions reflecting the stimulus intensity are not related to that reflecting the intensity of spontaneous pain. In contrast, the brain region that reflected spontaneous pain intensity was only activated for the latter and did not reflect thermal painful stimulus intensity. Therefore, we can assert that at least in the patient group studied spontaneous pain involves a different brain activity pattern than acute pain.

Pharmacologic fMRI of pain

There is little question that fMRI offers a unique potential in the effort for developing new drug therapies, especially

for clinical pain conditions. This has been commented on in the past [6,7,28]. However, the application of the technique (dubbed pharmacologic fMRI [phfMRI]) remains at its infancy [29,30]. Important issues regarding the untangling of effects of a drug directly at its site of action (binding site) from those of secondary responses remain to be resolved.

The potential of integrating preclinical studies with human studies and using fMRI in both species has also been proposed, and some early results are now published [31,32]. The latter approach may become a very powerful tool in the development of new drug therapies, especially if standardized methods can be formulated that can be used in animal models and in humans concurrently. However, performing fMRI studies in rodents poses a long list of challenges, many of which remain unresolved.

An elegant first effort along this line is a study in which the effects of gabapentin were explored for acute pain and for sensitized skin pain [33]. The authors opted to study a pharmacologic manipulation for sensitization induced by application of capsaicin, arguing that this provides a model condition that may mimic clinical pain states. Whether acute thermal hyperalgesia really mimics any clinical pain condition is arguable and needs substantiation. Still, this is an excellent example of how drug effects can be studied in pain. It is also the first double-blind crossover fMRI study. Twelve healthy subjects were studied for either placebo or gabapentin, for mechanical stimulation either on the normal skin or on skin exhibiting secondary hyperalgesia after capsaicin administration. All subjects underwent all procedures in a random permutation. Gabapentin did not significantly reduce perceived pain intensity for either the normal skin stimulation or the sensitized skin, although its effect was stronger for the sensitized skin. In many ways, the lack of effects on perceived pain intensity actually simplifies the study and makes interpreting the results more straightforward because the observed brain activity changes cannot be simply attributed to changes in perception (which in turn would necessitate a correction factor to sort out the drug effects on central circuitry for nociception from its remote effects that in turn result in decreasing pain perception). The authors measured plasma levels of gabapentin and showed that it was detected only for the cases in which it was actually administered. The results show that gabapentin changes brain responses to nociceptive mechanical stimulation primarily when central sensitization is present. The most robust gabapentin effect during central sensitization was a reduction of stimulus-induced brain deactivations. Analysis of fMRI signal showed that the observed drug effects were not caused by global changes of brain activity. The study shows feasibility of studying drug effects with fMRI and raises intriguing questions regarding the central effects of gabapentin.

In a much simpler study, we tested the notion of phfMRI in a clinical setting. A patient with chronic psoriatic pain was studied for brain activity regarding joint pain before and after oral administration of a cyclooxygenase-2 (COX-2) inhibitor [34]. The patient refrained from using his COX-2 inhibitor for 24 hours before participating in the study. He was scanned 10 consecutive times, four before and six after drug ingestion. Within 1 hour after drug ingestion, the patient reported some decrease in joint pain, and this further decreased in the next 3 hours. We collected brain activity while stimulating various joints, and the patient continuously rated the magnitude of the pain using online continuous ratings (the same methodology as used for studying spontaneous pain, now used in relation to a stimulus that is specific to the clinical symptoms). The results showed that brain activity to the stimuli decreased after drug ingestion, and two specific brain regions were strongly correlated to the pain ratings. This study simply shows that one could identify brain activity modulation with a single dose of a drug administered in a single patient.

In a more comprehensive study, we examined the effects of lidocaine application on the skin in 11 PHN patients, studied at three time points (before, after 6 hours, and after 2 weeks of treatment) [22]. After correcting brain activity for rating spontaneous pain by appropriate visual rating controls (see earlier text), we observed decreased brain activity with treatment in parallel to the decrease in ratings of spontaneous pain, and also consistently with the changes in pain as reported by questionnaires. Although a long list of brain regions showed decreased activity with treatment, only a specific subset was modulated in relation to changes in pain ratings and relative to the questionnaire outcomes. We were also able to distinguish between brain areas that only transiently responded to treatment (decreased activity only after the 6-hour treatment) and regions that responded to the longer-term treatment. Generally, brain areas thought to be involved in sensory representation for pain were the regions that were modulated acutely, whereas regions involved in emotional and reward pathways responded to the longer-term treatment. Unlike the earlier study [33], this study did not have a placebo control arm. Therefore, we cannot rule out that some of the observed effects may be simply a result of the presence of treatment. Also, because the drug only affects skin sensory transduction by interfering with sodium channels, outside of the placebo response the observed results are interpreted in relation to nociceptive transmission.

Differences in brain activity between neuropathic conditions

In two studies, brain activity for spontaneous pain was studied in separate clinical pain groups [22,27•]. Both studies were done using the same technological approach and data collection and analysis techniques. Therefore, it is informative to compare the results. The PHN patients represent the most standard and accepted pain patient population representative of neuropathic pain. In

contrast, CBP is generally considered to be a consequence of various peripheral insults that may render the condition more musculoskeletal and/or neuropathic. The specific CBP patients studied all had some radiculopathy as part of their history. Thus, we considered them as having a neuropathic component to their pain. In the CBP patients, the primary brain site identified to be involved in coding the sustained spontaneous pain and strongly correlated with pain intensity was the mPFC. In contrast, in PHN the main regions that were activated and responded most robustly to long-term treatment were the amygdala and ventral striatum. Thus, at first glance these results suggest that different chronic pain conditions involve distinct brain activations, which are also distinct from brain regions commonly ascribed as being involved in acute pain. However, anatomically the ventral striatum, amygdala, and mPFC are strongly interconnected and are part of the hedonic and emotional evaluation system. Moreover, in the CBP patients, in addition to mPFC activity, both ventral striatum and amygdala were active but at a lower statistical significance. Therefore, the brain regions associated with spontaneous pain in both CBP and PHN show similarities and preferentially engage various components of the same circuitry.

Conclusions

We expounded on fMRI and phfMRI techniques that are especially apt in studying clinical chronic pain conditions. We argued that examining brain activity for spontaneous pain provides a novel, robust approach with which various clinical pain conditions can be directly investigated. Moreover, we provided examples of studies examining the modulation of fMRI responses to various drugs, in the context of human models of chronic pain and in actual clinical pain conditions. Therefore, we attempted to demonstrate the new directions that human brain imaging techniques are leading to, concentrating primarily in the work ongoing within our group.

There are other novel approaches being developed by other groups, especially in the laboratories of Borsook, Gracely, and Tracey, which we only touch upon mainly because they seem at an earlier developmental stage, at least as far as we are aware of their progress. Studies by Gracely et al. demonstrate that judicious use of mechanical stimulation in clinical pain conditions can reveal brain activity abnormalities in fibromyalgia and in CBP [35–38]. Also, several groups have been studying allodynia in various clinical conditions because its related activity should be readily demonstrable by appropriate stimuli as long as proper controls are included [25,39–44]. The extent to which these various studies have corrected resultant activity with appropriate controls is not discussed here. Suffice it to end with the proviso that there remains a long list of confounds that need to be more properly attended to before we make general conclusions regarding the brain responses we uncover in clinical pain conditions. We are hopeful that the outlined approaches will begin to make a difference in the clinical setting by actually aiding in the discovery of novel therapies for neuropathic pain conditions.

References and Recommended Reading

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

- • Of importance
- •• Of major importance

1. Baliki M, Apkarian AV: **The neurological effects of chronic pain.** *PainEurope* 2006, **2:**4–5.
2. Geha PY, Apkarian AV: **Brain imaging findings in neuropathic pain.** *Curr Pain Headache Rep* 2005, **9:**184–188.
3. Geha PY, Apkarian AV: **Pain and neuroanatomical effects: evidence for cortical reorganization.** *Psychiatric Times* 2006, **23:**22–24.
4. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK: **Human brain mechanisms of pain perception and regulation in health and disease.** *Eur J Pain* 2005, **9:**463–484.
5. Kupers R, Kehlet H: **Brain imaging of clinical pain states: a critical review and strategies for future studies.** *Lancet Neurol* 2006, **5:**1033–1044.
6. Schweinhardt P, Lee M, Tracey I: **Imaging pain in patients: is it meaningful?** *Curr Opin Neurol* 2006, **19:**392–400.
7. Schweinhardt P, Bountra C, Tracey I: **Pharmacological FMRI in the development of new analgesic compounds.** *NMR Biomed* 2006, **19:**702–711.
8. Jackson PL, Brunet E, Meltzoff AN, Decety J: **Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain.** *Neuropsychologia* 2006, **44:**752–761.
9. Moriguchi Y, Decety J, Ohnishi T, et al.: **Empathy and judging other's pain: an fMRI study of alexithymia.** *Cereb Cortex* 2006, [Epub ahead of print].
10. Singer T, Seymour B, O'Doherty J, Kaube H, et al.: **Empathy for pain involves the affective but not sensory components of pain.** *Science* 2004, **303:**1157–1162.
11. Zubieta JK, Smith YR, Bueller JA, et al.: **Regional mu opioid receptor regulation of sensory and affective dimensions of pain.** *Science* 2001, **293:**311–315.
12. Zubieta JK, Heitzeg MM, Smith YR, et al.: **COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor.** *Science* 2003, **299:**1240–1243.
13. Woolf CJ, Salter MW: **Neuronal plasticity: increasing the gain in pain.** *Science* 2000, **288:**1765–1769.
14. Julius D, Basbaum AI: **Molecular mechanisms of nociception.** *Nature* 2001, **413:**203–210.
15. Mantyh PW: **Cancer pain and its impact on diagnosis, survival and quality of life.** *Nat Rev Neurosci* 2006, **7:**797–809.
16. Gardell LR, Vanderah TW, Gardell SE, et al.: **Enhanced evoked excitatory transmitter release in experimental neuropathy requires descending facilitation.** *J Neurosci* 2003, **23:**8370–8379.
17. Apkarian AV, Sosa Y, Krauss BR, et al.: **Chronic pain patients are impaired on an emotional decision-making task.** *Pain* 2004, **108:**129–136.
18. Small DM, Apkarian AV: **Increased taste intensity perception exhibited by patients with chronic back pain.** *Pain* 2006, **120:**124–130.
19. Apkarian AV, Sosa Y, Sonty S, et al.: **Chronic back pain is associated with decreased prefrontal and thalamic gray matter density.** *J Neurosci* 2004, **24:**10410–10415.
20. Apkarian AV, Thomas PS, Krauss BR, Szeverenyi NM: **Prefrontal cortical hyperactivity in patients with sympathetically mediated chronic pain.** *Neurosci Lett* 2001, **311:**193–197.

21. Apkarian AV, Grachev ID, Krauss BR: **Imaging brain pathophysiology of chronic CRPS pain.** In *Complex Regional Pain Syndrome*. Edited by Harden R, Janig W, Baron JC. Seattle: IASP Press; 2001:209–227.
22. Geha PY, Baliki MN, Chialvo DR, et al.: **Brain activity for spontaneous pain of postherpetic neuralgia and its modulation by lidocaine patch therapy.** *Pain* 2006, **128:**88–100.
23. Derbyshire SW: **A systematic review of neuroimaging data during visceral stimulation.** *Am J Gastroenterol* 2003, **98:**12–20.
24. Peyron R, Laurent B, Garcia-Larrea L: **Functional imaging of brain responses to pain. A review and meta-analysis.** *Neurophysiol Clin* 2000, **30:**263–288.
25. Schweinhardt P, Glynn C, Brooks J, et al.: **An fMRI study of cerebral processing of brush-evoked allodynia in neuropathic pain patients.** *Neuroimage* 2006, **32:**256–265.
26.• Foss JM, Apkarian AV, Chialvo DR: **Dynamics of pain: fractal dimension of temporal variability of spontaneous pain differentiates between pain states.** *J Neurophysiol* 2006, **95:**730–736.

This is the first paper to show variability of chronic pain in timescale of minutes, and this variability is unique to different clinical pain conditions.

27.• Baliki MN, Chialvo DR, Geha PY, et al.: **Chronic pain and the emotional brain: specific brain activity associated with spontaneous fluctuations of intensity of chronic back pain.** *J Neurosci* 2006, **26:**12165–12173.

This is an important study because it is the first to show brain activity related to spontaneous pain of back pain patients without the application of an external (experimental) stimulus.

28. Borsook D, Becerra L, Hargreaves R: **A role for fMRI in optimizing CNS drug development.** *Nat Rev Drug Discov* 2006, **5:**411–424.
29. Rogers R, Wise RG, Painter DJ, et al.: **An investigation to dissociate the analgesic and anesthetic properties of ketamine using functional magnetic resonance imaging.** *Anesthesiology* 2004, **100:**292–301.
30. Wise RG, Rogers R, Painter D, et al.: **Combining fMRI with a pharmacokinetic model to determine which brain areas activated by painful stimulation are specifically modulated by remifentanil.** *Neuroimage* 2002, **16:**999–1014.
31. Borsook D, Becerra LR: **Breaking down the barriers: fMRI applications in pain, analgesia and analgesics.** *Mol Pain* 2006, **2:**30.
32. Negus SS, Vanderah TW, Brandt MR, et al.: **Preclinical assessment of candidate analgesic drugs: recent advances and future challenges.** *J Pharmacol Exp Ther* 2006, **319:**507–514.
33. Iannetti GD, Zambreanu L, Wise RG, et al.: **Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans.** *Proc Natl Acad Sci U S A* 2005, **102:**18195–18200.
34. Baliki M, Katz J, Chialvo DR, Apkarian AV: **Single subject pharmacological-MRI (phMRI) study: modulation of brain activity of psoriatic arthritis pain by cyclooxygenase-2 inhibitor.** *Mol Pain* 2005, **1:**32.
35. Giesecke T, Gracely RH, Grant MA, et al.: **Evidence of augmented central pain processing in idiopathic chronic low back pain.** *Arthritis Rheum* 2004, **50:**613–623.
36. Gracely RH, Petzke F, Wolf JM, Clauw DJ: **Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia.** *Arthritis Rheum* 2002, **46:**1333–1343.
37. Gracely RH, Grant MA, Giesecke T: **Evoked pain measures in fibromyalgia.** *Best Pract Res Clin Rheumatol* 2003, **17:**593–609.
38. Gracely RH, Geisser ME, Giesecke T, et al.: **Pain catastrophizing and neural responses to pain among persons with fibromyalgia.** *Brain* 2004, **127:**835–843.
39. Becerra L, Morris S, Bazes S, et al.: **Trigeminal neuropathic pain alters responses in CNS circuits to mechanical (brush) and thermal (cold and heat) stimuli.** *J Neurosci* 2006, **26:**10646–10657.
40. Ducreux D, Attal N, Parker F, Bouhassira D: **Mechanisms of central neuropathic pain: a combined psychophysical and fMRI study in syringomyelia.** *Brain* 2006, **129:**963–976.
41. Maihofner C, Handwerker HO, Birklein F: **Functional imaging of allodynia in complex regional pain syndrome.** *Neurology* 2006, **66:**711–717.
42. Peyron R, Schneider F, Faillenot I, et al.: **An fMRI study of cortical representation of mechanical allodynia in patients with neuropathic pain.** *Neurology* 2004, **63:**1838–1846.
43. Pukall CF, Strigo IA, Binik YM, et al.: **Neural correlates of painful genital touch in women with vulvar vestibulitis syndrome.** *Pain* 2005, **115:**118–127.
44. Witting N, Kupers RC, Svensson P, Jensen TS: **A PET activation study of brush-evoked allodynia in patients with nerve injury pain.** *Pain* 2006, **120:**145–154.