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The brain in chronic pain: clinical implications

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SUMMARY

This article examines the present, and potential future, impact of brain imaging on chronic pain. It is argued that novel theories of chronic pain are coming to the fore, specifically through brain imaging of the human brain in chronic pain. Such studies show that the brain reorganizes in relation to chronic pain, in a pattern specific to the type of clinical pain, and that brain networks and receptor targets are being identified and reverse translated to animal studies of their efficacy and mechanisms. Future studies need to integrate across human brain imaging techniques, as well as more intensive reverse translational methods.

Animal models of pain have been a major focus of pain research, especially regarding mechanisms of chronic pain, in the past few decades. Such models were increasingly acknowledged after evidence was shown that partial peripheral nerve injury seems to give rise to persistent behavior with features closely approximating human chronic pain condition. More than 20 years have passed since the first study describing such a model and related behavior [1]. Since then there has been a veritable explosion in variants of the approach for rodent models of persistent inflammatory pain and neuropathic pain, and newer models continue to be explored and developed. These persistent pain models have been explored as to peripheral and central cellular and molecular reorganization, especially regarding peripheral afferents, dorsal root ganglia, spinal cord circuitry, and brainstem descending modulation (e.g., see [2-4]). These advances were accompanied with great expectations as to the imminent novel therapeutics that were anticipated. Yet, after 20 years of extensive cellular and molecular studies of the physiology of animal models of pain very few novel drugs have been advanced for chronic pain. Here it is argued that the problem is not the models *per se* but more likely the level at which underlying mechanisms have been explored.

A total of 20 years have passed since the first modern noninvasive brain imaging techniques were introduced to the study of humans in pain [5-7]. This was historic, as it started the new field of studying the awake human brain in pain, and especially studying the properties of the human brain in chronic pain. We need to remember that until the advent of this technology the only tools available to study human chronic pain were clinical exams and psychological assessments. The current review attempts to provide an overview of what new understanding we have gained with human brain imaging technology specifically for chronic pain, to what extent these findings do or do not correspond to the studies in animal models

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for chronic pain, and what if any are the current and/or expected clinical benefits. The field is growing rapidly and new and surprising observations are accumulating in the topic. There are also a large number of reviews in the topic focusing on specific advances [8-17], therefore, here we present a more general overview regarding chronic pain, brain imaging, and clinical relevance.

Modern brain imaging techniques can now examine the human brain to extract information regarding anatomical, functional, metabolic and cognitive properties of the brain in pain. From a functional viewpoint, electrical signals can be monitored by EEG, or magnetoencephalography (MEG), recording techniques, which provide very accurate information about the timing of nociceptive information transmission to the brain albeit with poor spatial specificity. Blood and metabolism signals provided by functional MRI (fMRI) and PET are currently the most popular means of examining the human brain in general and also specifically for pain, yet they have lower temporal resolution than EEG, or MEG, but much better spatial information [10,13]. Currently fMRI remains the technique most commonly used to study the human brain. Given the large number of scientists involved with this technology, this field is rapidly advancing and continues to provide new methodologies and concepts about the organization of the brain in health and in disease, and these advances are beginning to be used to disentangle mechanisms of chronic pain at the brain level [11]. This noninvasive technology also provides powerful tools to study the anatomical properties of the brain regarding both gray matter and white matter abnormalities. Moreover, MRI affords techniques to investigate brain biochemistry and this approach has the potential of providing clues as to predisposition of the brain to chronic pain. In fact the latter technique (magnetic resonance spectroscopy) provided the first hints that brain gray matter density may decrease in chronic pain [18]. In addition, studying cognitive abilities within the context of brain function provides a strong tool with which we should be able to assess the cognitive cost of living with chronic pain. Very few such studies have been done in this context for chronic pain [19]. Finally, it should be emphasized that the multiplicity of tools with which the human brain can now be investigated are readily available to be combined with each other, which should provide complimentary and far more powerful information about the properties of the brain than when any one of the methods is used in isolation, and in fact it is clear that many brain imaging labs are following this path to study the human brain in chronic pain.

As we are primarily interested in the impact of brain imaging technology on chronic pain, its definition and determination in humans and animal models needs clarification. The official definition of chronic pain is pain that persists past the completion of injury-related healing processes [20]. Clinically, as one has no direct evidence of this healing process, chronic pain is defined operationally and arbitrarily, usually as pain that persists for more then 3-6 months from the initiating injury, with no scientific data to validate this definition. This may not be critical in the clinic, where most subjects have been suffering pain for years, but its relationship to initial injury and ideas regarding transition from acute to chronic pain require better precision. The issue becomes more complex when we extrapolate to animal models. In rodent models of chronic pain, pain and related mechanisms are studied within weeks after injury. Is this truly representative of human chronic pain? We do not know and we will not know until we methodically merge human and animal brain imaging studies and observe mechanistic correspondences between them. The good news is that the latter is already in the immediate horizon, as a number of groups are actively engaged in such studies (see below).

Animal studies of models of chronic pain traditionally have concentrated, and for the most part continue to concentrate, on peripheral and spinal cord mechanisms with the tacit assumption that these are the levels at which underlying mechanisms are critical for understanding pain and for discovering mechanisms and therapies for chronic pain. Human

brain imaging studies are primarily available for supraspinal, cortical and sub-cortical structures. Thus these studies were forced to look at the brain in pain. The early brain imaging work, in fact, was based on the position that brain measurements would provide signals that inform us of spinal cord and peripheral events. This viewpoint has been changing rapidly and instead the human brain imaging technology seems to point to the brain playing a critical role in pain, especially in chronic pain. Perhaps this view is not very surprising to the clinician who interacts daily with the peculiarities of the cognitive states of chronic pain. It still remains a contentious viewpoint within the community of pain researchers and the present overview is intended to highlight this viewpoint and pinpoint its clinical implications.

Acute pain & the 'neuromatrix'

Functional brain activity has now repeatedly demonstrated that acute painful stimuli in healthy subjects give rise to a consistent and reproducible activation of a set of brain regions [10]. This has been dubbed the pain 'neuro matrix,' with the associated notion that this network is necessary and sufficient for pain perception and that relative changes in extent of activity among these regions will be helpful in uncovering various pathological pain conditions. We prefer to label this activity pattern as acute nociceptive pain-related brain activity. Moreover, considerable effort has been made to unravel functional properties and distinctions between the activated areas: which of these areas are more lateralized relative to the stimulus, which better correlate with stimulus intensity, which better reflect sensory in contrast to affective properties of pain, and which are better modulated by various distracters such as attention, mood, or presence of other sensory inputs? There is modestly good evidence of differentiation of the acute pain-related areas along these dimensions [10,13], yet the notion of a specific and constant pain matrix remains unconvincing. In contrast to the assumptions underlying the pain matrix, the evidence for structural or functional brain organization in parallel or hierarchical pathways that specifically process nociceptive inputs (-as is the case for other kinds of sensory inputs such as somatosensory, auditory and visual) does not seem to generalize to clinical pain conditions, given that the bulk of the evidence for clinical pain conditions shows unique brain activity patterns with many brain regions identified outside of this neuromatrix [9,11].

Perhaps the most exciting new advances in mapping brain activity for acute pain is the demonstration that subjective ratings of painful stimuli can be individually identified for every stimulus in every subject in a specific part of the insular cortex, and that one can observe the spatiotemporal evolution of stimulus parameters into perception across multiple brain regions [11,21]. Thus we can now state that subjectivity of acute pain can be captured in the brain for each stimulus epoch, implying a causal relationship (i.e., simply affirming that pain is in the brain and this can be detected with fMRI every time it occurs). Given that fMRI seems to contain pain subjectivity one can then ask the question whether this is directly extractable from the brain. In fact, recent 'brain reading' algorithms are being developed and early findings show very powerful ability in identifying subjective responses to thermal pain from the whole brain fMRI signal that can be used for 'brain reading' [22]. In addition, there is now strong evidence that another part of the brain, the nucleus accumbens a region commonly assumed to be related to reward valuation, seems to calculate the salience of thermal stimuli and the reward of pain relief for every thermal painful stimulus in every subject [23]. This signal is likely involved in affective coloring of pain and as such it provides a motivational signal essential for learning and for behavior [8,24].

Overall, we can summarize by stating that brain activity for acute pain seems to be divisible to sensory processing regions, where a unique region encodes subjective perception of pain,

and a separate circuitry involved in salience and aversiveness evaluation, providing the opportunity of modulating these circuitry independently from each other.

Brain activity for chronic pain

Imaging the brain's physiological properties in chronic pain is more complicated than in acute pain. In contrast to acute pain, chronic pain is characterized by the presence of ongoing pain that by definition is difficult to experimentally manipulate, and chronic pain patient populations are by nature inhomogeneous, use diverse modes of drug and other types of therapy, and most chronic pains are comorbid with other conditions. Nevertheless important advances have been accomplished. We can now resolutely refute the simplistic notion that brain activity for chronic pain is enhanced activity of the 'neuromatrix' as identified for acute pain. Although common expectations have been that ongoing chronic pain would somehow interfere with acute pain and degrade its perception, our evidence is to the contrary. Chronic back pain patients rate thermal painful stimuli, applied at a site just overlying the body location where back pain is felt worst, very similarly to normal subjects [21,23]. The patients also show a double dissociation between brain regions signaling the perception of ongoing chronic pain from the perception of acute thermal pain [25]. Furthermore, the brain region signaling acute thermal pain in the patients is the same region as that identified in healthy subjects [25]. We have now studied multiple chronic pain-patient groups (chronic back pain, osteoarthritis, chronic pelvic pain, chronic post-herpetic neuralgia, chronic complex regional pain syndrome) regarding brain activity for either spontaneous pain, for allodynia, or for acute thermal or mechanical stimuli. This data can be summarized by stating that acute painful stimuli generally activate somatosensory, insular and cingulate cortical regions, while spontaneous pain and allodynia activate prefrontal cortex and limbic regions. In addition each of the chronic pain conditions evoke a brain activity pattern that seems unique to the condition [11,25-29]. The clinical implication of these findings is the important point that chronic pain seems to involve brain regions far more involved in emotions and self-evaluation and less involved in the activation of regions associated with acute nociception. This finding may not surprise the clinician, yet it is important in the determination of which therapies need to be directed more towards alleviating the suffering associated with chronic pain in contrast to nociception.

It should be pointed out that multiple labs have studied brain activity for acute painful stimuli in various chronic pain populations, and a number of them report enhanced brain activity. However, this data remains mostly unconvincing with small effect sizes that most likely would disappear with rigorous statistical testing and if examined in a larger population of subjects [10]. There are a number of groups studying visceral pain, both in health and in disease, and a large number of studies have been generated. Yet the results have often been contradictory, presumably in part due to the interaction between ongoing visceral pain, acute visceral pain and expectations (for a critical review and summary see [30]).

One can alternatively pose the question of the role of the brain in chronic pain as to how the presence of unremitting pain impacts brain physiology in relation to everyday (not pain related) tasks and with resting states (brain activity when subjects are not performing any specific task). It can readily be demonstrated that during different tasks the intensity of the ongoing pain modulates large areas of the brain that are unrelated to the performance of the task in either a positive or negative direction [27]. When this process is examined more systematically, we observe that during a trivial visual-motor attention task where performance is matched between healthy controls and chronic back pain patients and where brain activity positively related to the task is not different between the two groups, there is a large difference in brain regions negatively related with the task (i.e., regions that are more active during rest), and the general relationship between brain networks constituting the rest

state is abnormal [31]. This result has now been replicated for multiple chronic pain conditions by directly studying the resting state brain properties in diabetic neuropathy, fibromyalgia and nonspecific chronic pain [32-35]. These findings strongly suggest that the presence of ongoing pain can be identified in the brain of patients even when subjects are not required to do anything in particular. It remains to be determined whether this latter feature of chronic pain can help to distinguish between different types of chronic pain, either as a reflection of the pain itself, related coping mechanisms and/or associated cognitive and emotional changes. Still, it is important to emphasize the potential that resting state fMRI studies have in the field of chronic pain. The existing published studies of the impact of chronic pain on the brain remains limited, due to a long list of complications mentioned above. Therefore resting state studies provide a very simple alternative and will likely dominate the field in the near future. The field is new and evolving, yet a PubMed search indicates >1100 papers, and the first multicenter brain imaging initiative by the NIH, with a major aim of unraveling brain properties of chronic pelvic pain, is in fact concentrating on examining brain properties by resting state fMRI. As the technique is relatively simple one can compare the brain dynamics within and across different chronic pain conditions, both before and after various manipulations. The main complication is the limited number of tools available for comparing resting state brain activity outcomes. Yet, given the large community of scientists interested in the topic, the latter should improve rather quickly.

Brain anatomical changes with chronic pain

Over the last few years it has been discovered that the anatomy of the human brain in chronic pain is abnormal. Both gray and white matter properties show abnormalities, and even the inter-relationship between gray and white matter seems abnormal. Decreased regional gray matter density was first described in chronic back pain patients [36]. Since this description, more than 50 studies document brain regional decreases in gray matter density or volume or thickness in a now long list of clinical chronic pain conditions, including women with menstrual pain [37], and people suffering from pain in the general population [38]. It has been argued by others that the regional decrease in gray matter density is limited to the acute pain-related ‘neuromatrix’ [39], although our results suggest that these changes are not specific to any fixed set of brain areas and involve widespread regions of the brain. Moreover, these changes can distinguish between distinct chronic pain conditions, and the whole brain gray-matter network properties are reorganized in specific patterns in different chronic pain conditions (manuscript submitted). Multiple labs now also show that the decrease in gray matter density is at least partially reversible when underlying pain is properly treated [40-42]. These studies are important as they indicate that at least some of the morphological changes must be a direct consequence of the presence of the pain, and related sequelae, and most likely the underlying mechanism is based on synaptic plasticity that tracks the impact of the pain on the brain. A recent elegant study further expands on these notions by showing that when chronic pain is effectively treated, specific regional gray matter decreases are reversed, and this reversal is related to the extent of pain relief and also to renormalization of cognitive abilities [43]. An earlier study also shows that decrease in complex regional pain syndrome (CRPS) pain symptoms are associated with reversal of abnormal brain activity, yet also demonstrates sustained abnormal activations as well [44]. Exact mechanisms responsible for brain gray matter morphological changes remain unclear [39], and multiple processes may be involved because morphological changes can be observed at multiple time points from initial injury [45,46]. In addition, different chronic pain conditions are undoubtedly associated with unique emotional and cognitive loads and involve specific coping mechanisms, all of which carve the brain into a specific new synaptic profile.

There is less evidence regarding white matter changes in chronic pain. The first evidence was in patients with CRPS where relationships between gray matter and white matter abnormalities were determined and inter-related [47]. Perhaps the most surprising finding in that study was the observation that global white matter property in relation to whole-brain gray matter volume is disrupted. We recently replicated this result in chronic pelvic pain patients [48]. The observation again implies that distinct chronic pain conditions impact the brain globally, as well as locally, and that chronic pain is not just a simple sum of pain and a normal brain. Again specific mechanisms underlying the observation remain unclear. Yet, the implication is that the fine balance between brain size, or number of neurons in the brain, in relation to the number of axons or amount of myelination that exists in healthy subjects and that is determined by genetic and developmental forces, is globally disrupted in chronic pain patients. The implication is that the efficacy of communication across brain regions is reduced by the presence of chronic pain, most likely as a consequence of interactions between multiple sequelae of chronic pain and their impact on brain plasticity.

Physiological evidence that chronic paininduced cortical reorganization was first shown by Flor and colleagues in patients with phantom pain, based on localization of electrical evoked activity in the cortex [49]. Since then similar observations have been made mainly regarding expansion and contraction of various portions of the somatosensory and motor cortices in especially CRPS, which again at least partially reverses when the pain is diminished [17]. This result has been replicated by multiple groups and for a variety of chronic pain conditions [44,50-53]. A shift in insular evoked potential was recently shown in pancreatitis [54]. Relationships between these physiological activity shifts and anatomical changes have not been addressed, yet they are surely interrelated and need to be explored.

Metabolic measures

MRI technology enables measuring concentration of various metabolites noninvasively in the human brain. Such measures in chronic back pain provided the first evidence for structural abnormalities [18]. Most magnetic resonance spectroscopy studies have observed local decreases in concentration of N-acetyl aspartate in multiple chronic pain conditions, and this chemical is the major identifiable peak in magnetic resonance spectroscopy and is a marker for neuronal density [55-58]. More recent studies also examine glutamine and glutamate [58-60], as the latter may indicate actual neurotransmitter levels in the brain [61]. Even though the technology has the potential of providing important information regarding brain metabolic processes, it continues to suffer from many shortfalls complicating interpretation of obtained results. The main limitation of the approach remains the fact that few brain areas can be examined, with questionable reproducibility and the studies are done in small subject groups, complicating integration of the results into a coherent view of metabolic properties of chronic pain.

Pharmacological brain imaging: what has it delivered?

Large claims have been made as to the potential of using brain imaging for advancing the understanding of treatment efficacy, site of action, mechanisms, and tools for developing novel drug therapies, especially for chronic pain [62-65]. Borsook *et al.*, for example, states that neuroimaging is revolutionizing therapeutic approaches to chronic pain [66]. What have we really achieved along this idea? There is good evidence that therapies that modulate pain perception result in identifiable brain activity changes both in healthy subjects and in chronic pain conditions [26,27,29,67-72]. Such studies certainly point to brain circuitry involved in the drug manipulations studied, thus suggesting specific circuitry. They do not, on the other hand, distinguish between direct action from responses to actions at remote sites, such as the periphery or the spinal cord. Importantly, to date we have no studies that

point to a new putative drug therapy based solely on human brain imaging technology, although such an approach can certainly be envisioned. Borsook *et al.* has proposed using animal models for chronic pain in combination with brain imaging to differentiate between classes of analgesics [73]. It remains, however, to be shown that the approach will lead to novel drug discoveries. On the other hand brain imaging in animal models is already being used as a tool with which specific brain site and mechanisms of action can be explored for novel drug therapies for chronic pain [74,75].

Targeting pain where it resides: in the brain

The title for this section is from a recent commentary regarding a pair of studies that identify a cortical target for treatment of neuropathic pain [76]. The studies identify anterior cingulate cortical potentiation as a mechanism for maintenance of chronic pain and show that one can develop novel drugs for this target [77,78]. Previously we have similarly reasoned that medial prefrontal cortex activity may be critical for chronic pain and tested two potential chemicals for their putative ability in controlling tactile allodynia in neuro pathic animals [79,80]. It should be clear from the current review that these cortical targets have only come about based on initial human brain imaging studies. Although it remains to be seen whether these specific compounds will have actual clinical efficacy, they are the starkest demonstration that human brain imaging is providing novel brain and molecular targets for treating chronic pain. These results are also consistent with the recent evidence showing that osteoarthritis pain can be adequately managed by drugs that most likely are acting at the cortical level [81].

There is little doubt that most pain medications cross the blood-brain barrier and as such their effects on the neocortex may be an essential part of their efficacy, even though the common clinical position is that these targets are mainly responsible for side effects rather than efficacy. The novelty of the above studies is that they are designed to specifically target circuits and receptors in the neocortex to relieve chronic pain, and in at least one instance the drug was shown to have no efficacy in the spinal cord [79]. The long-term success of this approach remains unclear, yet it certainly opens new opportunities for better therapies for chronic pain.

Emotions, learning & chronic pain

The present article makes the point that the brain in chronic pain is far more complicated than the classical view; that is, chronic pain is not simply the strengthening of nociceptive signal transmission from the spinal cord through the spinothalamic pathway. The results reviewed here indicate that chronic pain affects large circuits within the brain and induces massive reorganization of the cortical anatomy and physiology. In a series of reviews it has been argued that the driving force for such massive reorganization must be due to the saliency of pain and its ability to induced emotionally driven learning and related synaptic reorganization [8,9,11]. Although direct evidence for the theory remains to be generated, overall the concept is that continued unrelenting pain impacts limbic structures in the brain that in turn entrain the cortex to reflect both the suffering and coping strategies that develop in chronic pain patients. This reorganization in turn would be reflected on spinal cord processes through descending modulatory pathways and would also affect cognitive abilities.

Conclusion & future perspective

This article emphasizes the novel ideas emanating from human brain imaging regarding chronic pain. It highlights the general idea of moving away from the classic localizationist attitude that pain is in this or that part of the brain, and to consider chronic pain as a driving

force that carves cortical anatomy and physiology, creating the chronic pain brain/mind state (note that there is a vast amount of literature regarding the interaction between personality and chronic pain, summarized mainly by the biopsychosocial models [82]; although this literature makes large claims the actual supporting evidence remains weak). The power of the approach in both advancing new therapies and appreciating the cost of living with unrelenting pain should be evident. Still, these ideas are novel and the evidence remains preliminary in most domains. Thus, much more work remains to be done; yet there is clear potential for making significant advances in the science and the practice of treating chronic pain.

It should be clear that the type of information garnered by brain imaging is far more specific than we have ever had in the past. In the immediate future combining various brain imaging modalities, as well as cognitive studies, should be able to show the specific brain circuitry involved in each and every chronic pain condition, with clear clues as to the types of drugs or other therapies that would best fit each condition. There is also much work that needs to be done in the reverse translational studies, wherein the ideas coming from human brain studies are then tested in animal models with more invasive methods. This approach would first validate the appropriateness of the animal models used, and then identify the specific cellular and molecular pathways involved in such conditions.

The other gaping hole in our knowledge of brain circuitry in chronic pain is the extent to which the observed brain reorganization is a causal response to the condition or a predisposing factor that dooms the subject with the particular injury, where the majority of subjects with the same injury properly heal, into becoming a chronic pain condition. The only road to addressing these issues would be to perform longitudinal brain imaging studies, perhaps simultaneously in humans and animals. One hopes that such studies are already in the immediate horizon.

Overall, the pain – especially when it is chronic – is in the brain and only by directly probing the human brain are we going to better treat such patients. The good news is that the technology of brain imaging and its application to the field of chronic pain is moving at an unprecedented pace and novel unexpected observations are continuously being published.

At least in this author’s opinion, in the next 5-10 years we will dramatically change our knowledge in the field and as a result we will provide far better science-based, mechanism-specific treatments for different chronic pain conditions. Within this time span we should be able to pinpoint specific brain circuitry for various chronic pain conditions and identify related therapeutic targets, identify brain circuitry that pinpoint subjects more vulnerable to developing chronic pain and identify therapies that would decrease this vulnerability, and identify brain circuitry that would decrease or dramatically ameliorate the suffering associated with distinct types of chronic pain.

An important and unexpected novel basic scientific outcome of the current brain imaging work has been the demonstration that chronic pain provides a unique viewpoint regarding human brain plasticity, and in this direction it may be a unique model with which whole-brain plasticity can be studied in humans.

The integration of human brain imaging with small animal brain imaging, together with the already existing animal models of chronic pain, should make the translational applicability of animal research far more efficient, expediting development of novel therapies with direct application to the human.

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Practice Points

- Chronic pain is in the brain and its underlying mechanisms can be identified by human brain imaging techniques.
- Brain regions involved in human chronic pain seem distinct from those commonly identified for acute pain in healthy subjects.
- Chronic pain preferentially activates prefrontal and limbic and paralimbic brain areas.
- Distinct clinical chronic pain conditions activate primarily distinct brain areas.
- Chronic pain is accompanied with gray matter decreased density, which seems to have common as well as distinct components for different chronic pain conditions.
- The inter-relationship between brain gray and white matter is also disrupted in chronic pain.
- The myriad functional and anatomical reorganization of the human brain in chronic pain is also beginning to be studied in animal models where similar effects are being observed.
- Brain imaging can provide the direct path for integrating human pain mechanisms to rodent models of chronic pain.