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Abstract

The great advances in brain imaging techniques over the last few decades have determined a shift in our understanding of chronic pain conditions and opened the door for new opportunities to develop better diagnoses and perhaps better drug treatments. Neuroimaging has helped shape the concept of chronic pain from a disease affecting mainly the somatosensory system, to a condition in which emotional, cognitive, and modulatory areas of the brain are affected, in addition to degenerative processes. All these contribute to the development and maintenance of pain symptoms and comorbid features, including alterations in anxiety, depression, and cognitive processes. In this article the authors review the current understanding of the brain changes in chronic pain and the developments made possible by the use of various brain imaging techniques. They also discuss the possible applications of brain imaging to developing a “pain phenotype” that could aid in diagnostic and treatment choices of chronic pain conditions.

Keywords

pain, neuroimaging, emotion, cognition, sensory

The Problem with Pain

Pain, Pain over here, Pain over there, Pain in my heart,
pain in my soul, Pain in my mind. . . .

(Ellen Kang)

The poem epitomizes the problem of chronic pain, a condition that causes millions of individuals to suffer, and captures the notion of the “pain affects the brain.” Chronic pain represents an enormous problem to society—at an individual and societal level. The figures from recent epidemiological surveys have identified the level of this crisis. For example, in a recent survey of chronic pain that was conducted in 15 countries in Europe and included Israel (Breivik and others 2006), 34% of respondents had severe pain (numeric rating scale > 8/10, where 0 = no pain and 10 = worst pain). One-third of chronic pain sufferers were not receiving any treatment, whereas a majority used nonmedication treatments (i.e., acupuncture, massage, physical therapy) and over-the-counter drugs (e.g., NSAIDs). Only a small percentage of patients used strong opioids, and 40% of the patients reported inadequate control of their pain. These numbers are reflected in other surveys in the United States, Canada, and Australia (Blyth and others 2001; Elliott and others 1999; Tripp and others 2006). Clearly, we need an improved understanding of chronic pain that could pave the way for the

development of improved diagnoses and better treatments. We are a long way from the specificity and efficacy provided by therapies such as antibiotics for bacterial infections.

Remarkable advances in understanding pain and providing improved treatments have come through scientific discoveries, improved training and access to specialized clinics, organizations (e.g., International Association for the Study of Pain [IASP, www.iasp-pain.org], patient advocacy groups (e.g., National Fibromyalgia Association, www.fmaware.org), and pain clinics that provide specialized treatment (Lynch and others 2007). However, our clinical armamentarium is relatively limited in providing relief in chronic pain conditions. In the past, the basic therapy has included, for the most part, 1) drugs mostly belonging to three classes—opioids (e.g., morphine), nonsteroidals (e.g., Tylenol, aspirin), and local anesthetics (e.g., lidocaine); 2) interventional treatments (e.g., nerve blocks, surgical procedures); and 3) psychological support (e.g.,

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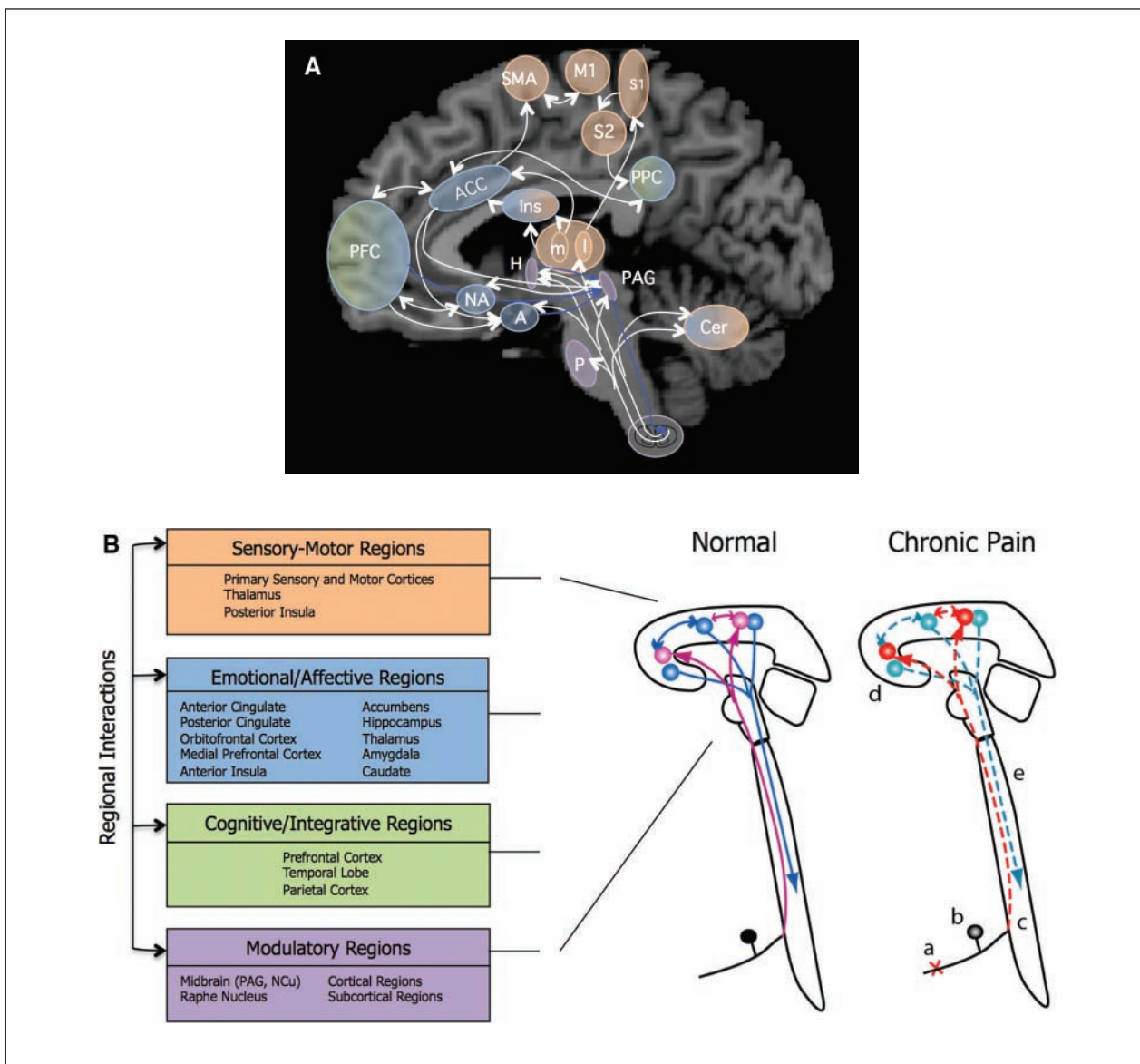


Figure 1. A, Overview of pain pathways and altered neural systems in chronic pain. White arrows = ascending and intracerebral pain pathways; blue arrows = modulatory descending pathways; A = amygdala; ACC = anterior cingulate cortex; Cer = cerebellum; H = hypothalamus; Ins = insula; l, m = lateral and medial thalamus; M1 = primary motor cortex; NA = nucleus accumbens; PAG = periaqueductal gray; PFC = prefrontal cortex; PPC = posterior parietal cortex; S1, S2 = primary and secondary somatosensory cortex; SMA = supplementary motor area. B, Schematic of anatomical sites and pathways that show changes in chronic pain. *Left*, Sensory-motor, emotional/affective, cognitive/integrative, and modulatory regions are involved in the complex processing of pain, with some areas being involved in more than one pain domain. One example is insula, which contains a somatotopic representation of pain, and also processes emotional aspects of pain experience. *Right*, Loss of afferent fibers (a), loss and changes in function in the dorsal root ganglion (b), plasticity in the dorsal horn neurons (c), as well as changes in the brain areas that are processing sensory, emotional, cognitive, and modulatory aspects of pain (*right*; d), and in descending modulatory pathways (e) have been described.

cognitive behavioral therapy). For all of these efforts, the number of outcome studies of nonpharmacological trials is limited, and most pharmacological studies show poor efficacy of treatment in chronic pain (Deyo and others 2009). Pain researchers, pharmaceutical companies, and clinicians have struggled to break the barriers of finding

treatments for pain that are both specific and efficient and have limited side effects. One reason that makes this task difficult is that there is no clear, widely accepted determination of what represents “success in chronic pain treatment outcomes” (Turk and others 1993). Therapeutic efficacy in well-controlled studies of pharmacological agents show

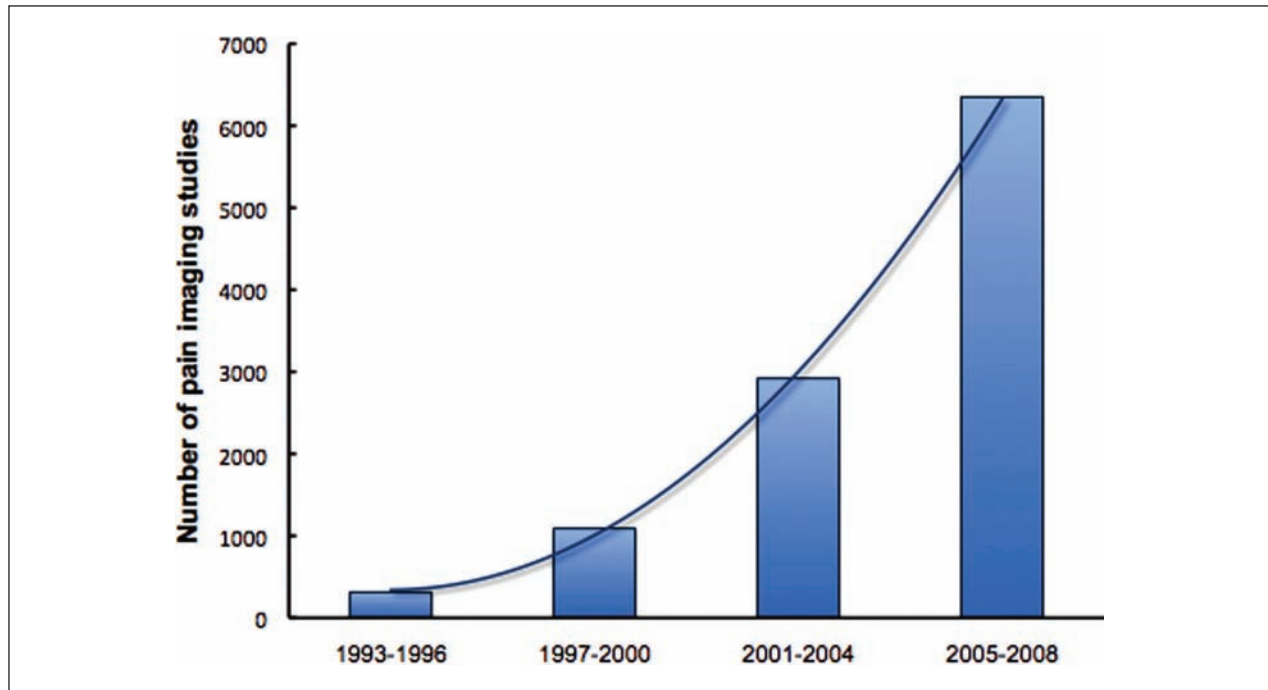


Figure 2. Imaging publications on pain. We used Google Scholar (scholar.google.com) to search for articles containing the keywords “pain” and “functional magnetic resonance imaging” during 4-year intervals. Although the total number of articles may be overestimated by this method, similar exponential increasing trends were seen with more stringent search terms.

a 30% benefit compared to placebo, and generally the improvement is small, of about two points’ decrease in pain on a 10-point numeric rating scale (NRS) (Schwerla and others 2008), perhaps because of the complexity of chronic pain (Fig. 1). These issues point to the desperate need for an objective measure of pain that would redefine how we evaluate and treat patients. This would allow us to better understand what treatments will work most effectively in different patients.

Part of the problem we have faced is a new realization that chronic pain is a disease of the brain. Until recently there has been a lack of ability to measure changes in the brain that are a consequence of chronic pain. Anatomical, functional, and chemical neuroimaging have opened the door to new vistas and new opportunities for a better understanding of chronic pain, for better diagnostic possibilities, and perhaps better drug treatments to be developed. Although genetic and other molecular approaches in the pain field have shown tremendous advances, only in recent years has brain imaging contributed to the revolution in understanding pain and greatly changed the field of pain research. The major insight that emerged from neuroimaging studies is that chronic pain is a disease of the brain and thus all therapeutic modalities will need to take this into consideration.

The ability to explore the human brain in human volunteers or patients has dramatically changed our understanding of pain. Imaging has the ability to define

theoretical constructs of numerous thinkers in the field of brain processing in chronic pain in the human condition. Imaging has allowed unprecedented interrogation of brain systems in terms of brain circuitry, the effects of analgesics on neural networks, transition of acute into chronic pain, definition of brain regions that heretofore may not have been considered important (e.g., nucleus accumbens, striatal regions), brain plasticity including functional and morphological changes, networks that are involved in the placebo response and alterations in neurochemistry in chronic pain (Fig. 1). The magnitude of the “imaging revolution” in the pain field is exemplified by the volume of literature published every year. In a Google Scholar search (scholar.google.com), the number of citations of pain and functional imaging (keywords “pain” and “functional imaging”) showed an exponential rise (314 articles during 1993 to 1996, to 1090 articles between 1997 and 2000, 2920 between 2001 and 2004, and 6350 between 2005 and 2008; Fig. 2). Although there is always an intellectual excitement of new technologies that may advance the pursuit of academic questions the real question is: How has or could functional imaging of pain make a difference in the lives of chronic pain patients now or in the future? We explore the rapid development of functional imaging in the pain field and try to put this question in context. It is now increasingly understood that pain represents a multifaceted process shaped by a multitude of factors (somatosensory, emotional, cognitive, genetic) and,

in turn, affecting behavioral responses as well as producing an altered brain state. In addition, imaging may allow us to provide an objective measure of pain—one that may be complex and require taking into account sensory, emotional, and modulatory processes in the context of expectations and life experiences. Imaging pain has already produced far-reaching changes in the way we think about chronic pain (Apkarian and others 2009; Borsook and Becerra 2007; Tracey 2008; Tracey and Mantyh 2007) and defining a signature of changes in the brain that contribute or are part of the chronic pain syndrome, which will eventually result in better pain treatments. Indeed, the number of studies investigating the effects of therapy using imaging methods has also shown an increasing trend since 1993, reaching more than 6000 studies published between 2005 and 2008 (source: Google Scholar).

Pain Imaging: Methods 101 (Fig. 3)

The development of a number of noninvasive magnetic resonance imaging (MRI) methods, including morphological/anatomical imaging of gray matter (voxel-based morphometry, VBM), white matter tract connectivity (diffusion tensor imaging, DTI), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS), has paved the way to an unprecedented boom in brain research. MRI methods, as well as other techniques like magnetic encephalography (MEG) and near-infrared spectroscopy (NIRS), are rapidly evolving as novel analytical methods and more sophisticated equipment become available. Because their noninvasive nature allows in vivo longitudinal studies of the dynamic structural and functional changes in the brain as a result of pain, these approaches (described in Fig. 3) have produced a shift in our understanding of chronic pain. From the original definition as an “unpleasant sensory and emotional condition,” chronic pain is now understood to be a multidimensional “disease affecting the central nervous system,” influenced by a variety of biological and psychosocial factors, such as genetics, hormones, emotions, memories, or social expectations (Borsook and Becerra 2007; Borsook and Becerra 2006; Borsook and others 2007b). Application of combined novel research approaches (i.e., brain imaging and genetic and molecular studies) will likely have a great impact on the pain field by improving clinical evaluation methods (disease phenotype) and treatment of pain conditions.

Anatomical Imaging

Voxel-based morphometry (VBM). VBM measures the local concentration of gray matter in different brain voxels. In the pain field, VBM has been used to measure changes in the volume of subcortical structures including

the hippocampus, basal ganglia, thalamus, and amygdala (Jovicich and others 2009). Most recently, techniques that allow measurement of small changes in cortical thickness have been developed (<http://surfer.nmr.mgh.harvard.edu>). These techniques will allow documentation of alterations of gray matter that occur in chronic pain conditions.

Diffusion tensor imaging (DTI). DTI investigates white matter tract integrity by measuring microstructural changes in directional water diffusion in the brain (Alexander and others 2007; Mukherjee and others 2008). In the pain field, the technique has been used in fibromyalgia to document alterations in the brain’s microcircuitry in the thalamus, insula, amygdala, hippocampus, and frontal and anterior cingulate cortex (Lutz and others 2008). By overlaying DTI and fMRI brain maps, future studies may help advance our understanding of functional anatomical mapping in chronic pain conditions.

Functional Imaging

Blood oxygen level-dependent (BOLD) fMRI measures changes in the local concentration of deoxyhemoglobin and provides an indirect index of neuronal activity. Several BOLD methods have been applied to pain research and have revealed the neural correlates of pain perception and modulation by characterizing the brain response to evoked stimuli (e.g., pain, allodynia), task-driven responses, or drugs (phMRI).

Evoked-stimuli fMRI. Evoked-stimuli fMRI has been commonly used in the pain field because of the relative ease of presenting well-characterized objective stimuli during the imaging session (i.e., cold and hot temperatures, somatosensory stimulation). Functional imaging has helped uncover the neural circuitry involved in pain processing and modulation, and described the brain areas that reflect sensory, cognitive, and affective dimensions of pain (May 2007).

Resting state networks (RSN) and functional connectivity. This approach uses low frequency BOLD signal fluctuations to evaluate the functional brain connectivity during resting states as opposed to task performance. These default mode networks are consistent across healthy subjects (Damoiseaux and others 2006) and can be used to define disease phenotypes by differentiating disease states (i.e., chronic back pain; Baliki and others 2008) from healthy states. Simultaneous imaging of structural and functional connectivity may provide a better understanding of pathological processes by uncovering changes in specific brain networks as a result of disease.

Pharmacological MRI (phMRI). phMRI investigates the functional effects of drugs on the brain and links levels of drug exposure to the changes in evoked responses or RSN activity. More recently, arterial spin labeling (ASL)

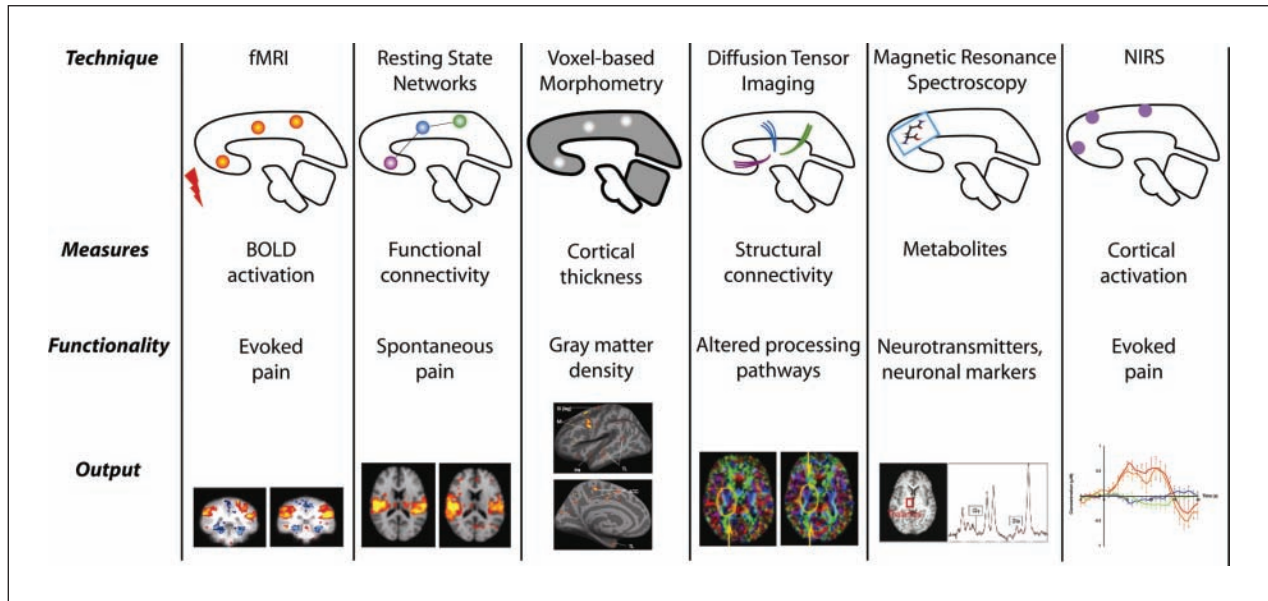


Figure 3. Imaging methods (Sava and others 2009).

methodology, which measures blood flow changes with improved contrast and signal-to-noise ratio through magnetization of the blood, has been used to measure the regional dose-related effects of drugs on brain function (Detre and others 2009). These measures can be used to monitor the functional effects of drug receptor binding and the dose relationship of central responses and provide objective indices of therapeutic efficacy in pain conditions.

Chemical CNS Measures

MRS. MRS is used to noninvasively assess different metabolites and neurotransmitters in the brain (Soares and Law 2009), to characterize the composition of neuronal and synaptic markers (e.g., glutamate, glutamine, and γ -aminobutyric acid [GABA]) in different brain regions and to identify relationships between disease states and changes in the brain metabolic or chemical composition. MRS techniques have been widely applied in the study of psychiatric diseases as well as pain syndromes (Prescot and others 2009). Recently, analytic technologies such as ^{13}C -based flux analysis have been developed. This fluxometric method allows real-time analysis of metabolic changes in brain networks. Although this technology has so far been applied to mammalian cells grown in tissue culture but not to the human brain *in vivo*, it represents a potentially promising technique that, in the future, could aid the understanding of the disease-associated metabolic changes in the brain.

Brain receptor mapping. A novel approach that could aid the localization of functionally activated brain regions in

the brain is mapping of multiple neurotransmitter receptors sites (Zilles and Amunts 2009). Although not yet applied to pain conditions, this approach may provide a better understanding of the underlying basis of neurotransmission in healthy and disease states by correlating brain data obtained through different techniques (anatomical, functional) with cytoarchitectonical and molecular brain maps.

NIRS. NIRS or diffuse optical tomography (DOT) is a noninvasive technique that can detect changes in blood hemoglobin concentrations associated with neural activity and therefore assess the brain function through an intact skull in human subjects (Boas and others 2004). NIRS has a great potential in measuring pain effects on the brain. Recently, it had been shown that it is possible to record a pain-specific signal using NIRS, and this signal was similar to that observed in previous fMRI studies (Becerra and others 2008).

MEG. MEG is a noninvasive imaging technique that measures the magnetic field produced by synchronized synaptic currents in the brain. Similar to electroencephalography (EEG), MEG measures parameters of neuronal activity directly. A rich literature exists that describes the correlation between neuronal oscillations as recorded by MEG and different brain functions, including attention, visual processing, or motor planning (Bandettini 2009). Recently, a growing number of studies have employed both MEG and fMRI, taking advantage of the strengths of each method (i.e., excellent spatial resolution of fMRI and the millisecond temporal resolution of MEG) to help uncover the mechanisms of cortical processing (Auranen and others 2009).

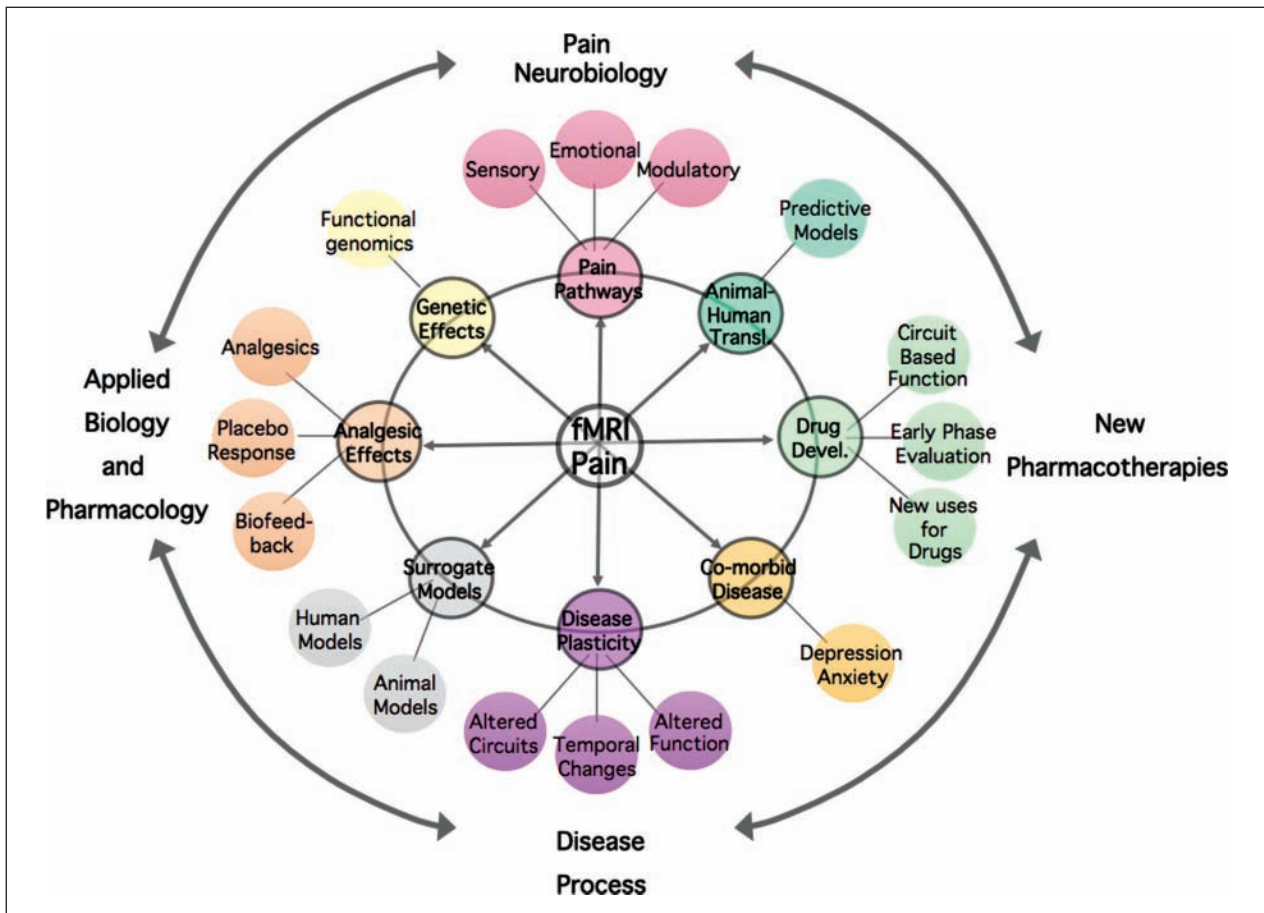


Figure 4. Broad applications of functional magnetic resonance imaging in pain (reprinted with permission, Borsook and Becerra 2007, Current Pain and Headache).

Pain Imaging: Driving the New Revolution in Pain Research (Fig. 4)

Imaging Pain in Healthy Brains—The New Neurobiology

The early pain imaging studies used positron emission tomography (PET) and reported on pain responses to noxious heat (see below). Since then, functional imaging studies in healthy volunteers have either confirmed brain regions involved in pain processing (thalamus, somatosensory cortex, anterior cingulate cortex) or added important new components of pain processing (e.g., nucleus accumbens, insula, dorsolateral prefrontal cortex, basal ganglia, and cerebellum). Thus, there is a new complexity in understanding brain function in pain that allows for sensory, emotional/affective, modulatory, and cognitive responses to pain. Functional imaging research in healthy subjects has provided new insights into these regions and their possible role in pain. As such, these studies have been invaluable

in providing a basis to explore changes in the clinical condition and evaluation of analgesic drugs on brain function.

Brain Regions and Pain Function

In the first imaging study of pain, “Multiple representations of pain in the human cerebral cortex,” Talbot and colleagues reported on activation in several brain regions in response to noxious heat, including the contralateral anterior cingulate cortex and primary and sensory somatosensory cortices (Talbot and others 1991). This study opened up the path for brain imaging of pain, which initially focused on “expected areas” such as the thalamus. What these studies did is raise issues of pain processing in regions beyond the primary somatosensory cortex (Bushnell and others 1999; Treede and others 2000). Subsequently, numerous cortical regions have been shown across pain imaging studies to be activated by painful stimuli (reviewed in Apkarian and others 2005; Peyron and others 2000; Treede and others 1999). Overall, these

meta-analyses reported that pain produced activation in the primary and secondary somatosensory, insular, anterior cingulate and prefrontal cortices, and thalamus. Some regions such as the cerebellum (Borsook and others 2008), the anterior cingulate, and insular cortices, are consistently activated across most functional imaging pain studies, but have remained an enigma as to a specific role in pain processing. More recent studies have begun to dissect the pain-induced brain activation as it relates to specific functions, such as sensory processing, emotional/affective and cognitive processing, and pain modulatory processing. The more focused studies have allowed for a better understanding of these regions in pain function.

Imaging somatosensory pain processing. Somatosensory processing of pain stimuli classically includes the thalamus and somatosensory cortices. Other studies have used imaging to trace a pain pathway (trigeminal) from the periphery (ganglion) to the dorsal horn (trigeminal nucleus in the brainstem), and traditional sensory pathways through the thalamus and to the cortex (Borsook and others 2003; DaSilva and others 2002). Insula is a recent addition to brain regions involved in the evaluation of pain intensity, and imaging studies have uncovered the somatosensory representation of pain in the insular cortex (Brooks and others 2005). Still, investigations of the insular functions warrant a broader look at the potential involvement in sensory and emotional evaluative components, as well as interoception (i.e., sensing the physiological condition of the body). As it turns out, this region is intricately involved in complex pain and analgesic processing (see below).

Imaging emotional pain processing. The notion that pain is not only a sensory but also an emotional experience required neuroimaging to help define an underlying brain circuitry that contributes to the emotional processing of pain. Generally, greater acute and chronic pain intensity is associated with higher negative emotional state. The experience of pain is able to trigger emotional responses, and the emotional state can also affect the perception of pain. Studies indicated that the classic reward circuitry, which includes regions such as the amygdala, nucleus accumbens, and orbitofrontal lobe, were all activated by noxious heat (Becerra and others 2001, 2004). Specific connectivity between entorhinal cortex and cingulate regions involved in anxiety and anticipation of pain was also described (Ploghaus and others 2001). Such studies contributed to the characterization of a brain network that could underlie, in addition to emotional responses to pain, the placebo and nocebo responses (Craggs and others 2007; Scott and others 2008), as well as empathy of pain in others (Danziger and others 2009). This network has also been involved in the development of comorbid symptoms (e.g., depression, anxiety) frequently associated with pain (Borsook and others 2007a). A recent review suggested

that the reciprocal effects of pain on emotional state could be explained by the common anatomical brain network shared by these two processes (Duquette and others 2007). Many brain regions have been discussed in previous reviews (Bruehl and others 2009). Perhaps the dorsolateral prefrontal (DLPFC) and medioprefrontal (mPFC) cortices, the cingulate cortex (CC), and basal ganglia are worthy of further mention because of their relative importance in understanding chronic pain. Besides their role in the emotional pain processing, the DLPFC, mPFC, and the CC are also part of the modulatory networks that can alter pain perception, as well as networks involved in cognitive processing (see below). The anatomical overlap of these neuronal networks and the known roles of the frontal cortical regions in emotion and cognition may explain the wide effects that pain has on multiple brain functions.

Pain and analgesia are at opposite ends of the reward-aversion spectrum. However, the neural circuits that support these functions are similar (Leknes and Tracey 2008). Endogenous systems including opioidergic and dopaminergic may provide useful models for evaluating these opponent processes in chronic pain and nocebo and placebo responses (Scott and others 2008).

Cognitive Processing and Pain

Pain can affect cognitive processing, but the neural substrates of this interaction are not well elucidated. Given that acute pain has an adaptive role of signaling injury to the body, it represents a stimulus that can induce rapid emotional learning involving the prefrontal-limbic circuitry (amygdala, insula, the anterior cingulate and orbitofrontal cortex; Sehlmeier and others 2009). Patients with chronic pain, however, often complain of attention and memory deficits. It has been postulated that pain modulates an attention-specific network that includes the DLPFC, anterior and posterior cingulate cortices (ACC and PCC), posterior parietal cortex, and medial frontal cortex (Seminowicz and Davis 2007).

Imaging modulatory circuits. Understanding modulatory pain processing (both pro- and antinociceptive effects) has enormous implications for evaluating alterations in disease state and analgesic drug effects (Porreca and others 2002). The basic neurobiology of modulatory circuits had been defined previously (Basbaum and Fields 1984). A network of subcortical and cortical regions (predominantly frontal areas) has been involved in endogenous pain modulation. Functional imaging studies have been able to evaluate descending modulatory processes in experimental pain and have shown a direct participation of well-described regions such as the periaqueductal gray (PAG; Becerra and others 2001) and less well understood regions such as the nucleus cuneiformis (NCF) in pain processing.

Among cortical areas, the mPFC exerts an inhibitory effect on the perception of pain (Seifert and others 2009a). The DLPFC, orbitofrontal cortex (OFC), and cingulate cortex were also found to have key roles in cortical mechanisms of pain modulation. The pain-modulating roles of the frontal cortices might be mediated by cognitive interference during nociceptive stimulation (Wager and others 2004), inasmuch as patients with chronic pain show increased “vigilance” toward pain and pain-related information. Recent studies have proposed that an altered interaction of pain-inhibitory and pain-facilitatory mechanisms may contribute to the development or maintenance of chronic pain states (Bingel and others 2007).

Applied Neurobiology—From Theory to Function

Imaging analgesic effect in healthy volunteers with phMRI. Although many drugs used as analgesics influence CNS function, little is known about the direct effects of these agents on the brain or the mechanisms through which they provide analgesia in humans. phMRI studies use two approaches: evaluating the brain regions that show activation by the drug and the drug effect on the modulation of pain processing in the brain. In healthy volunteers, studies have evaluated opioids, including morphine (Becerra and others 2006a) and remifentanyl (Wagner and others 2007; Wise and others 2002), naloxone (Borras and others 2004), ketamine (Rogers and others 2004; Sprenger and others 2006), local anesthetics (Seifert and others 2009a), cox inhibitors (Maihofner and others 2007b) and drugs used in neuropathic pain, including gabapentin, and imipramine (Borsook and Becerra 2006; Gottrup and others 2004; Iannetti and others, 2005). Overall, these types of studies have provided a basis to investigate pharmacological effects on brain systems (Borsook and others 2006) as provided by the following three examples. 1) Morphine, a well-characterized drug behaviorally, affects neural circuits that are expected to define these behavioral features of the drug (e.g., sedation, reward, analgesia; Becerra and others 2006a). 2) Gabapentin, although having a measurable antinociceptive effect on activation patterns, has a more profound antihyperalgesic effect, suggesting that the drug may be more effective in modulating pain when central sensitization is present (Iannetti and others 2005). 3) Activation patterns in specific brain regions such as mPFC were shown to inversely correlate with individual extent of central hyperalgesia and predict individual pharmacological antihyperalgesic treatment response (Seifert and others 2009a). Although remarkable progress has been made, the real advances are still to come in using fMRI on drug development to evaluate new drugs (Borsook and others 2006; Wise and Tracey 2006).

Imaging gender differences. Given that many chronic pain conditions predominantly affect women (e.g., complex

regional pain syndrome, CRPS; Birklein and others 2000; fibromyalgia: Hooten and others 2007; temporomandibular disease: Dao and LeResche 2000; irritable bowel syndrome: Chial and Camilleri 2002; headache: Silberstein 1992), it is possible that gender differences exist in pain processing. Although some of the gender variability in pain thresholds and pain may result from genetic differences at loci on the sex chromosomes, current data on pain sensitivity in women (Fillingim and others 2009; Wiesenfeld-Hallin 2005) and brain activation studies suggest a hormonal contribution as well, supported by the finding that differences in the response to pain are found during the follicular and luteal phase (Choi and others 2006). Still, many pain imaging studies do not account for the menstrual phase in women who are selected as part of a cohort. In addition, menstrual phase alters reward-related functions (Dreher and others 2007) as well as chemistry in cortical regions (Epperson and others 2002) that may have an impact in chronic pain conditions where there is a hedonic deficit syndrome. Importantly, the data suggest that differences in pain responses in women as a result of the modulatory effects of sex hormones may have important implications for therapy.

Imaging and surrogate pain models. One of the big questions in pain research is the translation of surrogate models to the clinical condition. Because brain circuits can be measured in both the surrogate model (e.g., capsaicin-induced central sensitization) as well as in human models, imaging may help define the utility of such models for testing analgesic efficacy or understanding brain processes that contribute to the chronic pain condition.

Imaging the placebo response. Imaging has allowed for a better understanding of the biological mechanisms systems that determine the placebo response (Benedetti and others 2005; Zubieta and Stohler 2009). The placebo response in pain is based on beliefs, expectations, and anticipation of pain. The neural mechanisms of this effect relate to brain regions involved in expectancies (cognitive processing) and also reward related functions that include dopaminergic (Wise 2004) and opioidergic systems (Henriksen and Willoch 2008). Both improvement (placebo/therapeutic response) or worsening (nocebo/adverse response) of pain may result from altered brain processing. Functional imaging has focused on a few approaches that investigate the placebo response as provided by the three examples that follow. 1) Altered expectations in the response to painful stimuli: Functional MRI experiments using manipulation of expectations in healthy volunteers showed that placebo analgesia resulted in a decrease in activation in thalamus, insula, and ACC with a corresponding increase in activity in the prefrontal cortex in anticipation of pain (Wager and others 2004). Studies such as this one provided evidence for the involvement of pain-related structures in the placebo response. 2)

Alterations related to opioidergic and dopaminergic function: Prior studies had evaluated the role of endogenous opioid systems in the placebo response using PET (Petrovic and others 2002). The data indicated that both opioid and placebo analgesia are associated with increased activity in the rostral ACC and in the brainstem, suggesting that placebo-induced analgesia affects the pain circuitry. More recently, this approach has been extended to include evaluation of underlying endogenous chemical processes. Two neurotransmitter systems, one involved in analgesia (opioidergic) and another in reward (dopaminergic), were examined for their potential role in placebo and nocebo responses (Scott and others 2008). The results of this study are highly significant in furthering our understanding of these responses. Consistent with the Petrovic study, opioid neurotransmission was increased in the ACC, insular cortex, nucleus accumbens (NAc), amygdala, and PAG, whereas dopaminergic neurotransmission was increased in the basal ganglia with the placebo response. Placebo effects correlated with increased opioidergic and dopaminergic responses in the NAc, whereas nocebo effects were associated with decreased response of both neurotransmitters. 3) Placebo responses in diseases where expectations may be altered: In patient populations, the study of the placebo responses and how they may be affected by disease has enormous implications for treatments and clinical trials, as the loss of expectation makes analgesic therapies less effective (Benedetti and others 2006).

Acupuncture. Imaging has advanced acupuncture from “a difficult to understand” process to a more plausible process that has scientific underpinnings. Although the basis for neural systems involved in acupuncture has not clearly been differentiated from placebo response, some new data add important information on the underlying CNS processes involved in acupuncture-induced pain control. One such study, using PET, differentiates traditional acupuncture from sham acupuncture based on differences in effects on opioid receptors (Harris and others 2009) suggesting a basis for mediation of analgesic effects in real acupuncture. In a similar vein, differentiation of acupuncture analgesia and expectancy-evoked placebo analgesia seems to involve different brain networks (Kong and others 2009).

Imaging, genetics, and pain. Given the tendency of chronic pain syndromes to aggregate within families, these differences might be genotypically mediated, despite that no definitive pain-susceptibility genes have been identified thus far. Despite that the influence of shared environmental factors cannot be excluded, recent twin studies highlight the genetic contribution to pain sensitivity (Nielsen and others 2005). The most notable imaging and genetic studies to date have evaluated the contribution of the catecholaminergic and opioidergic systems to pain (Oertel and others 2008; Zubieta and others 2003).

Imaging Chronic Pain—Disease Process and New Discoveries

Imaging patients with chronic pain has been a greater challenge than imaging healthy volunteers, owing to a number of confounding factors like current treatments and duration of disease. Nevertheless, advances have been made in imaging of several chronic pain conditions, including chronic back pain (Apkarian and others 2001), complex regional pain syndrome (Lebel and others 2008; Maihofner and others 2004), neuropathic pain (Becerra and others 2006b; Geha and Apkarian 2005), fibromyalgia, and gastrointestinal disease (Kwan and others 2005). Such studies are attempting to define specific brain phenotypes for different chronic pain conditions, and they could greatly advance diagnostic methods and therapy, with the final goal of developing disease-modifying treatments. Several important and novel insights related to pain processing and treatment effects have been described in these patient populations.

Functional reorganization. Functional reorganization and chronic pain was most clearly defined in a report on patients with upper extremity amputation and pain (Flor and others 1995). Since then, several articles have described how plasticity occurs in neural circuits in several chronic pain conditions, including complex regional pain syndrome (Maihofner and others 2007a; Maihofner and others 2006). Most important, it seems as if appropriate treatments “reconstitute” or normalize brain activation patterns concomitant with remission of pain (Flor 2003).

Altered pain modulation. Chronic pain patients may have decreased opioid receptor availability (Harris and others 2007) as well as enhanced pain responses or impairment of antinociceptive modulatory processes (Jensen and others 2009; Seifert and others 2009b). An alteration in the tone of inhibitory vs. facilitatory systems may underlie the unmasking or exacerbation of chronic pain syndromes. In this type of data, imaging has helped define specific regions that show abnormal activation patterns and provided a method to determine if effective therapies alter these abnormal patterns.

Altered morphometry. In recent years several laboratories have reported on decreased cortical and subcortical gray matter (using voxel-based morphometry) in chronic pain in a variety of conditions, including chronic back pain (Apkarian and others 2004), neuropathic pain (DaSilva and others 2008), and fibromyalgia (Kuchinad and others 2007). These changes in brain structure seem to be related to the chronicity of the pain and have redefined chronic pain as a degenerative disorder. Although the precise mechanism of altered brain volume is not fully described, some studies have pointed to the potential loss of neurons and dendritic spines as potential contributors (Metz and others 2009). As such, our treatment approaches to chronic

pain should be radically redefined to include methods of preventing neuronal degeneration and promoting neuronal survival.

Altered chemistry. Chemical measures using MRS have shown altered neurotransmitters in chronic back pain (Grachev and others 2000), migraine (Prescott and others 1993), complex regional pain syndrome (Grachev and others 2002), and fibromyalgia (Harris and others 2008).

Brain measures of spontaneous pain. The spontaneous component of chronic pain is a critical component of pain symptomatology, and neuroimaging is exploring CNS circuits that are involved in spontaneous or ongoing pain. A few reports have evaluated spontaneous pain in diabetic neuropathy (Cauda and others 2009) and treatment effects of ketamine (Becerra and others 2009). Default mode resting states are disrupted in chronic pain (Baliki and others 2008). Although still early, this approach holds the promise of defining new evaluative processes for disease state and therapeutic effect.

Pain Imaging: Clinical Relevance and Future Clinical Applications

Our understanding of the brain changes in chronic pain and the brain responses to pharmacological or other therapeutic interventions has been significantly changed as a result of developments in neuroimaging of the CNS (Borsook and Becerra 2006; Borsook and others 2007b; Casey and others 2003; Moisset and Bouhassira 2007). These domains have already changed the way in which we think of pain—it should now be considered an altered brain state in which there may be altered functional connections or systems concurrent with degenerative aspects of the CNS. In addition, future developments will inevitably lead to major progress in several areas (see below) that will enhance our understanding of pain and eventually have significant impact in the clinic.

Going beyond subjective ratings. Experimental studies have shown that identical stimuli applied to research volunteers elicit widely variable pain responses (i.e., thresholds, tolerance) and psychophysical ratings (Nielsen and others 2005). Interestingly, the individual differences in pain ratings correlate with cortical activation differences observed on fMRI studies, but not with thalamic activation, suggesting that despite that the afferent input is similar at thalamic level, it is being modified at the cortical level resulting in the subject-specific experience of pain (Nielsen and others 2005). Imaging methods should allow us to go beyond visual or verbal analog scale evaluations of pain for several reasons. First, subjective measures are highly variable and we usually evaluate these along a single scale (e.g., pain intensity or sensory experience), whereas imaging is clearly more objective and also provides an assay of potential function in multiple brain regions involved

in the pain experience. Second, imaging provides evidence for changes that may have affected the brain over time. Third, imaging provides the ability to define changes across different brain measures, from functional to anatomical integrity and chemical changes. Pain is obviously a chronic disease and the ability to take a snapshot that provides so much additional information should be useful in the clinical domain.

Brain “pain” phenotype: an objective biomarker for pain and analgesia. In clinical practice, as noted above, the use of drugs for treatments pain diseases is frequently empirical. The defining of an objective brain phenotype for “drug effect” or “disease state” would obviously be a major step forward in understanding and discovering new treatments. Defining a brain pain phenotype or biomarker will allow for a correlation of brain activity with pain measures (i.e., duration, intensity, frequency) and the changes in brain activity in response to therapeutic interventions that lead to pain alleviation. This will surely transform the way we understand pain and allow researchers to use the measures of brain function as an intermediate phenotype for studying pain processing and for developing new therapies. For drug development, defining a pain phenotype through imaging might translate into potential regulatory acceptance of using fewer subjects in FDA-approved trials.

Analgesic drug development. Currently, few effective treatments for pain are available. Translation from preclinical to the clinical domain has proven to be highly inefficient, with most analgesic drug candidates failing because of bothersome side effects or low efficacy. phMRI and functional imaging may provide early readouts for “go” or “no go” decisions in drug development (Borsook and others 2006).

Application in the clinic. Given that a brain “engram” provided by imaging could provide information on 1) diagnosis; 2) measure of changes in sensory, emotional, and modulatory circuits; 3) measures of morphological change; 4) measures of chemical changes; 5) drug effects—both in terms of symptomatic treatment and disease modification; and 6) underlying brain changes that may precede subjective changes, the opportunity for the “pain clinic of the future” could parallel the fMRI application in neurosurgery (Chakraborty and McEvoy 2008). In addition, segregation of addiction vs. analgesic effects may also be possible, affording better therapy in those patients who may need addictive medications to control their pain.

Transition from acute to chronic pain. It is still unknown why some individuals develop chronic pain after an injury or disease process. This represents a great clinical challenge. Some examples include surgery (even relatively minor surgery such as third molar tooth extraction) leading to chronic neuropathic pain (Katz and Seltzer 2009) or acute to chronic migraine (Lipton 2009). Some studies have suggested that genetic (Tegeger and Lotsch 2009)

and other premorbid factors (Young Casey and others 2008) may contribute to the development of chronic pain. Imaging studies have only recently begun to address the process of pain “chronicization,” with the expectation that having an early readout of this process would allow interventional therapeutic trials to be conducted.

Imaging and patient evaluation for disability. Although there is great interest in objective measures of pain-related disability from insurance companies and the law, we have some ground to cover before brain imaging could be used as a diagnostic tool, because it first must meet several criteria to be validated and accepted (Borsook and Becerra 2005). These issues are being addressed from different perspectives, including neuroethics. If objective valid processes can be established for detecting/defining pain, this would have enormous implications for the insurance industry and legal field, as a significant number of cases relate to pain, suffering, and disability (Kolber AJ. 2007. American Journal of Law & Medicine (Brain Imaging & The Law Symposium). 33:433, San Diego Legal Studies Paper No. 07-9). Also, it will provide patients with objective evidence of their condition and its change over time.

Going Forward—The Challenges

Evidence from imaging studies in humans points to the pain experience as being complex and involving not only somatosensory pathways but also brain systems that regulate the processing of emotion, motivation, and memory. Individual expectations and even perception of social roles can shape the way subjects perceive pain. Consequently, the way we approach pain management should shift from treating a symptom to treating a disease that greatly affects the brain. Because a multitude of factors contribute to the pain experience, it is expected that successful therapies will produce normalization across multiple pain domains and limit the development of long-term consequences.

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