Pain perception in relation to emotional learning  
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Noninvasive brain imaging has established the participation of the cortex in pain perception and identified a long list of brain structures involved. More recent studies show the interaction between clinical chronic pain conditions and the reorganization of the brain functionally, anatomically, and chemically. Mechanisms underlying this reorganization hint to essential links between pain, especially its affective component with emotional learning and memory. This review is a discussion of the rationale and evidence for the interaction between these modalities, emphasizing underlying mechanisms.

Introduction
The role of the cortex in human pain perception remained controversial until the advent of noninvasive brain imaging technologies. Over the past 15 years solid evidence was generated indicating that multiple cortical and subcortical structures are involved in human pain perception [1,2]. The general assumption from the studies performed in healthy subjects and studying primarily pain after acute, experimental stimuli is the notion that the activation of a fixed set of brain structures evokes this percept, and that clinical pains must be due to small variations in the details of activations across these elements. More recent studies have emphasized the active role of the cortex in clinical, primarily chronic, pain conditions, and suggest that distinct chronic pains may have unique associated brain activity, reorganize the brain in unique ways, and also impact modulation of information processing in specific ways. The brain circuitry interfacing acute pain representation and diverse chronic pain conditions involves areas commonly thought to be essential in emotional learning and memory, and in reward and addictive behavior. This evidence is reviewed from the viewpoint of new insights regarding the role of reward circuitry and related behavior in pain perception, especially in clinical conditions.

Perceptual dimensions and types of pain
The definition of pain segregates it in two dimensions: an unpleasant sensory and emotional experience associated with actual or potential damage, or described in terms of such damage. As the threat for damage has negative survival connotations, perception of pain is always accompanied by negative emotions. Moreover, pain has a strong attentional tone; motor responses (pain leads to escape related reflexes); and autonomic/homeostatic responses. Classically, pain representation in the brain is subdivided along the dimensions of sensation and emotion, and these subdivisions have been generally mapped into the medial and lateral spinothalamic pathways as initially proposed more than 40 years ago [3]. Yet, the plurality of ascending pathways signaling nociceptive information cephalad [4], coupled with the multiple distinct brain regions activated during pain [1,2], renders this dichotomous parcellation suspect and simplistic.

Pains are also subdivided along the temporal scale. Acute pains lasting a short duration (seconds to minutes) are directly coupled with a physical stimulus, and subside with the cessation of the stimulus or soon thereafter. Associated sensations are interpreted as a consequence of transient activation of nociceptive circuitry. When pain is more persistent it becomes clinically more relevant. While the pain persisting past the inciting injury and related healing processes are defined as chronic, these are the conditions that patients repeatedly seek medical help for and for the vast majority of which there are no adequate treatments. From a basic research point of view, chronic pain conditions can be subdivided into inflammatory and neuropathic categories. However, in the clinical setting these subdivisions are rarely observed independently. The type of injury most likely also has unique underlying physiology and thus specific pain perception and underlying circuitry. For example, bone cancer pain seems to have unique properties that make it distinct from both inflammatory and neuropathic conditions, due to because of the interaction between bone and its innervation by small fibers [5]. Similarly, one expects unique physiology to be associated with persistent or chronic pain conditions involving muscles and viscera. Studies in animal models for persistent neuropathic and inflammatory pain conditions indicate an elaborate reorganization of the peripheral and spinal cord properties, where depending on the type of injury the details of the reorganization seem to impact distinct cell
types and receptor types in the periphery as well as the spinal cord, giving rise to enhanced nociceptive transmission cephalad probably through distinct pathways [6,7].

**Cortical and subcortical circuitry for acute pain**

The two brain structures most consistently activated in acute pain studies are the insula (INS) and anterior cingulate (ACC), while subcortically the most consistent activations are seen in the thalamus (TH) and basal ganglion (BG) [11]. This activity pattern already suggests that pathways outside of the spinthalamic inputs are involved in acute pain since at least the activations in BG must be mediated through a separate nociceptive pathway [8]. Additional activity is observed in multiple other brain structures. Most importantly, primary and secondary somatosensory, lateral prefrontal, and posterior parietal cortices, as well as the cerebellum. More recent studies have elaborated on activations observed in the brainstem [9], where periaqueductal gray, ventral tegmental area, rostral ventromedial medulla and the parabrachial nuclei are observed activated for anticipation and perception of pain, regions corresponding to the descending modulatory circuitry implicated in controlling the gain of nociceptive information transmission from the spinal cord. Our own unpublished analyses of temporal properties and correlations to stimulus and perception parameters indicate that TH and BG reflect the nociceptive stimulus quite faithfully, and this is in fact consistent with many earlier reports [1*]. Earlier studies indicate that ACC activity comprises multiple regions with distinct properties. Our own analyses show that a major part of ACC seems to be an early anticipatory response together with a more anterior region activated later and better reflecting nociceptive stimulus parameters. Our results also show that the insula INS can be subdivided into two functional portions, one reflective of nociception and a second we now think is involved in the general task of reflecting perceived magnitudes independent of the sensory modality, that is it assesses ‘how muchness’ in general (M Baliki, PY Geha, AV Apkarian, The neural basis for magnitude perception, Proc Natl Acad Sci USA, unpublished data). The ACC, and occasionally also the INS, has been most consistently attributed as being involved in the affective dimension of pain [10], while somatosensory regions are thought to better reflect sensory dimensions, such as intensity and location. However, recent data challenge this construct because the evaluation of spatial locations of noxious stimuli engages many brain regions outside of the somatosensory cortex [11]. Moreover, given the recent observations that ACC and INS are engaged in autonomic control and representation [12*], there is a dire need to disentangle the interaction between cortical representation for pain and the autonomic responses that accompany pain.

**Cortical and subcortical circuitry for chronic pain**

It can be asserted that there is increased activation of prefrontal cortical regions (PFCs) in clinical chronic pain conditions [1*], which in and of itself implies that chronic pain distorts cognitive and emotional perception/processing of everyday experiences, and is consistent with the vast clinical data indicating that such patients usually suffer from elevated anxiety and depression, and decreased quality of life. Chronic pain, defined as pain persisting past the healing process is characterized by spontaneous pain (perception of pain in the absence of physical stimuli), as well as exaggerated responses to physical stimuli (hyperalgesia and allodynia). Recent studies have examined brain activity for these various components of chronic pain, contrasting resultant brain activity with acute painful stimuli on normal/healthy skin. We have studied brain activity for spontaneous pain in chronic back pain (CBP) and in postherpetic neuralgia (PHN) patients [13,14*]. These studies are based on the basis of the observation that spontaneous pain unpredictably fluctuates in its intensity in the scale of seconds to minutes and that the properties of these fluctuations have a specific signature for diverse chronic pain conditions [15]. Using the same methodology we observe distinct brain regions involved in spontaneous pain in the two patient populations. In CBP the medial prefrontal cortex (mPFC) best reflected the properties of spontaneous pain, while in PHN (where activity modulation to therapy was also investigated) amygdala and ventral striatum portion of BG showed best relationship to spontaneous pain, to its modulation with therapy, and in relation to questionnaires regarding the properties of spontaneous pain and its changes with therapy. Although the results point to distinct brain structures, these areas are tightly interconnected and implicated in hedonics, addiction, and emotional learning and memory [16–18]. A more recent study of brain activity for joint pain in rheumatoid arthritis patients where the interaction between pain, depression, and brain activity was investigated indicated that mPFC activity best reflected this interaction, and this activity was also related to amygdala and BG activity [19]; while a study of brain activity for spontaneous pain in osteoarthritis also shows that mPFC is active together with many of pain sensory related regions [20]. Thus, there is accumulating evidence that in chronic pain the emotional and hedonic circuitry is better related to spontaneous pain than brain regions more commonly seen for acute nociception.

Brain activity patterns for allodynia and hyperalgesia remain more varied and controversial. Part of the complication regards the influence/interaction between spontaneous pain and stimulus-evoked pain. We have discussed this issue at length in the past, in relation to acute painful stimuli applied to patients with chronic pain [1*]. Two recent observations provide new insights on the
were related to the duration and severity of CBP [23]. In another recent study we also demonstrated that in a trivial visual bar length rating task brain activity in CBP patients is distorted in comparison to normal subjects, only in brain regions that decrease in activity during the task, and the connectivity of the brain regions that decrease with the task is abnormal as compared to the normal subjects, despite both groups performing the task equally well, suggesting that the brain resting state network is distorted by presence of pain [13]. In contrast, the presence of an acute painful stimulus does not affect resting state network properties and only enhances the task-related network [21]. These observations demonstrate that the brain in chronic pain is distinct from that of healthy subjects, and the distortion generalizes to performing trivial tasks. The mechanisms inducing these changes remain to be understood, yet this must partly be due to the anatomical reorganization of the brain seen in chronic pain patients.

**Chronic pain and brain atrophy**

Contrasting brain metabolites between CBP and healthy subjects shows that N-acetyl-aspartate is diminished in multiple prefrontal regions in these patients [22], implying brain atrophy by decreased neural density in those regions. When this idea was directly tested using automated morphometry we were able to show that dorsolateral prefrontal cortex (DLPFC) and TH exhibit decreased gray matter density, and that these decreases were related to the duration and severity of CBP [23*]. Following this report, other studies have shown brain atrophy in distinct cortical regions for various clinical pain conditions [24–26]. We also have new results in chronic complex regional pain syndrome (CRPS) patients indicating that gray matter as well as white matter atrophy can be seen in these patients, that regional gray matter atrophy is accompanied with decreased long distance white matter connectivity coupled with increased connectivity to specific targets, and the specific brain regions involved include mPFC, ventral striatum portion of basal ganglia, insula, and ACC [27**]. Functional reorganization of the somatosensory cortex has also been shown in CRPS patients; this seems to renormalize with therapy [28]. Thus, there is increasing evidence that the brain in chronic pain has distinct anatomical properties, the specifics of which seem to depend on the severity, duration, and clinical characteristics.

**Supraspinal reorganization in chronic pain: evidence from animal studies**

Recent animal studies show that cortical manipulations can modulate pain behavior [29–33]. Results emphasize the role of the INS, ACC, mPFC, and amygdala in pain, limbic structures with strong interconnectivity. Particularly relevant is the study by Johansen and Fields [30] demonstrating that ACC/mPFC activity is necessary and sufficient for noxious stimuli to produce an aversive memory, via a glutamate-mediated neuronal activation.

**Pain and emotional learning and memory are intimately related, and chronic pain can be defined in this context**

Chronic pain is defined as a state of continued suffering, sustained long after the initial inciting injury has healed. In terms of learning and memory one could recast this definition as: Chronic pain is a persistence of the memory of pain and/or the inability to extinguish the memory of pain evoked by an initial inciting injury. From this viewpoint the peripheral afferent barrage can be considered as part of the inciting event and the central representation/reorganization/sensitization as the memory trace; relative contributions of each would then delineate types of pain conditions (acute, inflammatory, and neuropathic) within the framework of mechanisms of memory of pain.

Part of the survival value of pain is its intimate association with learning. Pain induces single event learning, the memory of which can last the rest of life. This property is taken advantage of in Pavlovian paradigms studying learning and memory, especially in fear conditioning where the more painful the unconditioned stimulus the fewer trials it takes to establish an aversive emotional association to a conditioning stimulus that was originally affectively neutral [34]. The ability to extinguish aversive associations of fearful or painful events with repeated exposure to the unconditioned stimulus is also important for normal behavior; impaired ability to extinguish is clinically relevant, and its mechanisms seem to involve the interaction between mPFC, BG, and amygdala [35,36]. The novel hypothesis that we advance is that chronic pain is a state of continuous learning, in which aversive emotional associations are continuously made with incidental events simply due it is a source of pain. Simultaneously, continued presence of pain does not provide an opportunity for extinction because whenever the subject is re-exposed to the conditioned event he/she is still in pain. Failing to extinguish, therefore, makes the event become a reinforcement of aversive association. A concrete example might further clarify this idea: a person with chronic pain enters a familiar space. Depending on the intensity of the pain at that moment, the person establishes a negative association with that space (place conditioned avoidance), and the stronger the pain the longer lasting will be the memory of this negative association. Given that the person has pain all the time, whenever he/she re-enters the same space, the negative association is reinforced, and thus there is no chance for extinction by exposure to the space in the absence of pain. The person is of course is rationally aware that this place is not the source of the pain, yet his/her emotional system continues to provide contradictory cues. We propose that living with this
conundrum and the effort of disentangling its associations underlie at least some of the suffering of chronic pain.

If one regards chronic pain as continuous presence of an unconditioned stimulus and as an inability to extinguish its associations with random events, then the brain circuitry underlying reward/punishment induced learning must be in a heightened state, and this is exactly what the recent brain imaging studies seem to emphasize in chronic clinical pain conditions. Moreover, this state should interfere with or decrease the ability of associative learning for other events, especially for associations mediated through emotional cues. The distorted resting state in CBP may be a direct product of the latter. We have tested this general notion in an animal model for neuropathic pain where manipulation of NMDA-mediated neurotransmission at the level of mPFC and amygdala was shown to result in antineuropathic behavior [37**]. Direct interaction between pain, learning, and emotions specifically in chronic pain is consistent with the recent evidence showing the active role of the amygdala in animal models for persistent pain states, where there is now evidence for an interaction between spinal cord excitability of nociceptors and amygdala neurons which become sensitized in persistent pain conditions [38**]. Moreover, the evidence that the manipulation if the INS can produce both nociceptive and anti-nociceptive [29] also highlights the essential role of cortical circuitry in pain behavior.

The hypothesis advanced here regarding the interaction between emotional learning and chronic pain is new and based on the basis of observations of brain activity in humans in chronic pain and pharmacological interventions in animal models of chronic pain. It can be viewed as an extension of older psychological theories of chronic pain that incorporate operant and behavioral learning as part of the chronic pain behavior [39-41]. These ideas emphasize that the chronic pain behaviors (limping and grimacing) are a result of conditioned learning, and if followed by reinforcing events they persist long after the initial inciting pain events. The biospsychosocial models [40] emphasize the role of fear behavior and catastrophizing in chronic pain. These theories have been used in predicting chronic pain on the basis of personality traits and in designing therapies to decrease pain suffering (usually resulting in minimal therapeutic efficacy; a topic outside of the current review). Within these general theories classical conditioned learning has been examined in chronic pain patients and diminished extinction (decreased ability in forgetting the association) is shown for verbal responses as well for cortically evoked potencies [42], with more recent results implicating the primary somatosensory cortex in such conditioned learning [43]. The fact that chronic pain patients display reduced ability in extinguishing conditioned aversive learning can be construed as evidence for the more general hypothesis that we advance here regarding the actual definition of chronic pain.

Conclusions

The above discussion suggests that the definition of chronic pain should be modified to incorporate the active role of the cortex and its reorganization, rendering such conditions at least partly a neurodegenerative disease. The cortical reorganization seems to impinge mainly on circuitry involved in emotional learning and memory; as such this circuitry must be considered part of the definition of chronic pain.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


The series of studies in the topic indicate that many of brain regions that usually are implicated in nociception are also involved in autonomic representation and control.


The above two studies are the only ones identifying spontaneous pain in the brain. The results strongly implicate emotional and hedonic circuitry in chronic pain.


This is the first study showing evidence for brain atrophy in chronic pain.


The first study showing the inter-relationship between gray matter atrophy and white connectivity changes in chronic pain.


32. Han JS, Neugebauer V: mGluR1 and mGluR5 antagonists in the amygdala inhibit different components of audible ultrasonic vocalizations in a model of arthritic pain. Pain 2005, 113:211-222.


This is a reverse translational study where based on the basis of results from human brain imaging of chronic pain demonstrates the potential of developing new pharmacotherapy for neuropathic pain in rodents using a drug that potentiates extinction of aversive conditioning.


The review illustrates the multiple pathways involved in the bidirectional control between the amygdala and the spinal cord regarding persistent pain. More recent results in the topic nicely complement the ideas presented in this review.


The study demonstrates that chronic back pain patients have reduced extinction ability for aversive conditioning perceptually as well as on the basis of brain activity.