Imaging CNS Modulation of Pain in Humans

Pain is a highly complex and subjective experience that is not linearly related to the nociceptive input. What is clear from anecdotal reports over the centuries and more recently from animal and human experimentation is that nociceptive information processing and consequent pain perception is subject to significant pro- and anti-nociceptive modulations. These modulations can be initiated reflexively or by contextual manipulations of the pain experience including cognitive and emotional factors. This provides a necessary survival function since it allows the pain experience to be altered according to the situation rather than having pain always dominate. The so-called descending pain modulatory network involving predominantly medial and frontal cortical areas, in combination with specific subcortical and brain stem nuclei appears to be one key system for the endogenous modulation of pain. Furthermore, recent findings from functional and anatomical neuroimaging support the notion that an altered interaction of pro- and anti-nociceptive mechanisms may contribute to the development or maintenance of chronic pain states. Research on the involved circuitry and implemented mechanisms is a major focus of contemporary neuroscientific research in the field of pain and should provide new insights to prevent and treat chronic pain states.

According to the classical Cartesian view, pain was considered to be a hard-wired system in which noxious input was passively transmitted along sensory channels to the brain (FIGURE 1, LEFT). However, today it is generally accepted that this is far from the truth and that the experience of pain is not at all simply driven by noxious stimulus characteristics. Analogous to well known visual perceptions, such as ambiguous figures, the resultant pain experienced to the same sensory input can vary considerably. Along these lines, clinical and everyday life teaches us how cognitive and emotional variables such as attention, expectation, prior experiences, and mood shape our perception of pain (FIGURE 1, RIGHT).

Until recently, research on pain mechanisms concentrated on the assessment of changes that occur at the peripheral nociceptor and those within the spinal cord. The mechanisms of central nociceptive processing and its modulation were largely unknown, although it was clear that the brain is the structure where the subjective perception of pain emerges and is critically linked with other cognitive processes. The advent of modern, noninvasive neuroimaging techniques in combination with elegant paradigms has greatly expanded our knowledge concerning the CNS processes underlying pain perception and its modulation in humans. More recently, the contribution of these processes to the development of chronic pain and even drug action in the context of pain control is being further understood.

Here, we review the current state of neuroimaging research in this field. These include studies on functional connectivity of pain processing regions, functional imaging of the brain stem and spinal cord, pharmacological imaging (phMRI), and structural measures. With respect to the authors’ expertise and word count limitations, this review will focus on these processes to the development of chronic pain and even drug action in the context of pain control is being further understood.

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The Cerebral Signature for Pain

Because pain is a complex, subjective experience comprising sensory, cognitive, and emotional components, a large distributed network is accessed during nociceptive processing (FIGURE 2). The brain areas most commonly observed in the context of pain include the primary and secondary somatosensory, insular, anterior cingulate, and prefrontal cortices as well as the thalamus (3). However, subcortical areas like the brain stem, amygdala, and cerebellum also play a role in the multi-factorial experience of pain. This assembly
of brain areas, often referred to as the “pain matrix,” should not be seen as a stand-alone and static entity but rather as a substrate that is significantly and actively modulated by a variety of brain regions depending on the precise interplay of factors that contribute to the individual perception of pain (e.g., cognition, mood, injury, etc.). Looking at it from that perspective may resolve some of the ongoing ambiguity in the literature regarding the precise definition of which areas should be included in the term “pain matrix.”

Only recently have researchers using neuroimaging begun to put more emphasis on the distinct neural underpinnings of pathological pain conditions, including evoked pain in neuropathic pain patients (for review, see Refs. 50, 70) or the ongoing and spontaneous pain in chronic pain patients (6, 26). Even though the results obtained have been variable (probably reflecting the heterogeneity of patients in terms of etiology, symptoms as well as different testing conditions), first evidence from these studies implicates that clinical pain conditions are associated with a distinct neural representation in the brain that, although overlapping, may differ substantially from our conventional pain matrix concept. To date, these differences seem to mainly involve representations in frontal cortical regions, insular cortex, and brain stem nuclei (5, 70). Future studies will need to further disentangle distinct neural representations of specific clinical conditions and also account for the contribution of pain-related psychiatric comorbidity (depression, anxiety, sleeping disorders) to the observed brain patterns (71). To further elaborate the issue of spontaneous or ongoing pain, a shift in applied methodology may be needed as blood oxygen level dependent (BOLD) MRI, representing the currently commonest tool for the study of pain, provides only low sensitivity for low task frequency (as spontaneous fluctuations of chronic pain) and is incapable of providing a signal for tonic pain. Newer methods utilizing quantitative measures of blood flow, such as arterial spin labeling perfusion imaging (43), might therefore be more appropriate tools for assessing the neural underpinnings of key clinical pain symptoms.

The Modulation of Pain

The descending pain modulatory system

Proof that spinal cord transmission is modulated via descending influences from the brain, which are principally inhibitory in function, dates back to the pioneering work of Sherrington, showing that nociceptive reflexes were enhanced after transection of the spinal cord (73). Based on the original observation in the 1960s, that electrical stimulation of the PAG can produce analgesia, a series of electrophysiological and pharmacological studies elaborated that descending influences on spinal nociceptive processing involves the PAG and essentially the rostral ventromedial medulla (RVM), which seems to be the final common output for descending influences from rostral brain sites (22, 48) (FIGURE 3). Intriguingly, the RVM was later shown to be able to also display facilitatory influences on spinal nociceptive transmission (23, 25). These findings paved the way for the concept of a bidirectional central control of nociception that could either alleviate pain in situations where antinociceptive reflexes were enhanced after transection of the spinal cord and also account for the contribution of pain-related psychiatric comorbidity to the observed brain patterns (71). To further elaborate the issue of spontaneous or ongoing pain, a shift in applied methodology may be needed as blood oxygen level dependent (BOLD) MRI, representing the currently commonest tool for the study of pain, provides only low sensitivity for low task frequency (as spontaneous fluctuations of chronic pain) and is incapable of providing a signal for tonic pain. Newer methods utilizing quantitative measures of blood flow, such as arterial spin labeling perfusion imaging (43), might therefore be more appropriate tools for assessing the neural underpinnings of key clinical pain symptoms.
number of higher level brain areas including cingulo-frontal regions, the amygdalae and the hypothalamus (28), that may represent the basis by which cognitive and emotional variables interact with nociceptive processing to influence the resultant pain experienced.

“Top down” modulation of pain

Placebo analgesia is the prime example of the cognitive modulation of pain. It represents a complex phenomenon that can be attributed to different psychological mechanisms including expectation, Pavlovian conditioning, and reduction of anxiety (for a comprehensive review on this topic see Ref. 11). To date several studies have complemented the pioneering PET study on placebo analgesia that revealed a shared neural network of rACC and PAG underlying both opioid and systemic placebo analgesia (55). These studies, applying different procedures to induce a placebo analgesic response (including fake analgesic creams, sham acupuncture, and others), support a common underlying mechanism of expectation induced placebo analgesia that is mediated by an enhanced coupling of the rACC with subcortical brain structures such as the PAG and the amygdalae (13, 35, 66). This supports the notion that placebo analgesia involves a top down activation of endogenous analgesic activity via the descending modulatory system. The additional contribution of emotional regulation processes, of which the amygdala is a fundamental part, needs to be further addressed. But it is most likely a combination of both of these effects that contributes to the placebo-induced reduction in pain perception.

The neurophysiological bases of other mechanisms of cognitive pain modulation, such as attention, hypnosis, anticipation, control over pain, and the influence of religious beliefs, have similarly been addressed using neuroimaging methods. These studies support the importance of the anterior cingulate cortex and the frontal lobes for pain perceptual modulation (7, 49, 55, 58, 60, 64, 86, 87). Intriguingly, a coupling of cingulo-frontal regions with subcortical areas of the descending modulatory system has been confirmed for several strategies of pain modulation, including attentional modulation and placebo analgesia (13, 41, 55, 83).

Taken together, these studies strengthen the notion that the interplay of cingulo-frontal regions with the descending modulatory system represents one major pathway of pain modulation in humans. However, it is not yet established whether the descending pain modulatory system represents the final common pathway of all mechanisms that cognitively or unconsciously/reflexively modulate pain and whether all those mechanisms that seem to recruit the descending modulatory pathway do so by using an identical cortical control network. Beyond interactions with the descending control system, cortico-cortical interactions between regions involved the processing of sensory and emotional information of pain need to be considered (88).

FIGURE 2. The cerebral signature of pain
Increased BOLD activity in response to thermal painful stimuli overlaid on a structural T1-weighted MRI.
The role of the prefrontal cortices. Even though brain areas such as the rACC and PAG seem to have an important role in mediating analgesic effects during the cognitive modulation of pain, we believe it is unlikely that they actually initiate this response. According to current concepts, here the prefrontal cortex comes into play. In placebo studies, activity in the dorsolateral prefrontal cortex was found in the period preceding noxious stimulation, which correlated with activity in the PAG and the subsequent placebo analgesic response (84). In a study of experimentally induced allodynia, increased activity in the lateral PFC was related to decreased pain effect, supposedly by inhibiting the functional connectivity between the medial thalamus and the midbrain (41). Several authors investigated the analgesic effects of perceived control over pain and also found them to correlate with activity in the anterolateral/ventrolateral PFC (65, 87). Taken together, the prefrontal cortex is most likely responsible for the generation, maintenance, and integration of expected pain relief inherent to concepts such as control or placebo. Apart from these studies illustrating a substantial role in the cognitive regulation of pain, the prefrontal cortex is also involved in the emotional regulation of pain. Kalisch and colleagues found the anterolateral prefrontal cortex regulates anticipatory anxiety related to pain and its influence on subsequent pain processing (33). In a recent study investigating the emotional augmentation of clinical pain, the medial prefrontal cortex is suggested to mediate the relationship between depressive symptoms and clinical pain severity in patients with rheumatoid arthritis (71).

We would like to posit that the PFC most likely represents the pivotal source of modulation that, at least within one conceivable pathway, initiates downstream analgesic activity and/or emotional modulation. The clinical relevance of these characteristics is illustrated in a study by Benedetti and colleagues, who assessed the interaction of lidocaine patch and placebo mechanisms in patients with Alzheimer’s disease (10). By combining neuropsychological and electrophysiological measures, they showed that loss of fronto-lobal-mediated expectancy mechanisms disrupts placebo analgesia and thus makes analgesic therapies (which in the clinical environment always have this additional expectancy component) less effective.

Future studies are needed to further elucidate the exact functional connectivity of different prefrontal cortex areas, the rACC, and downstream or intracortical pathways during various cognitive interventions. How psychological variables (hypervigilance, catastrophising, anxiety, and depression) that are known to contribute to the development of chronic pain states interact with this descending pain modulatory system via these prefrontal cortical regions is a current focus of research.

The role of the brain stem. Even though animal studies strongly suggest a key role for the brain stem in the control of ascending nociceptive input, detailed investigations of the brain stem in humans used to be difficult due to several technical limitations. These include poor spatial resolution, local field inhomogeneity-induced signal losses, image distortion, arterial pulsation, and lack of adequate template images. Recent technical and methodological advances in imaging techniques allow a more complete investigation of the role of the brain stem and spinal cord in pain processing (15, 19, 80).

Beyond the common observation of the brain stem’s involvement in opioid and placebo analgesia (13, 55, 84), recent studies nicely illustrate the relevance of its modulatory influence by investigating how anticipation-related activity modulates subsequent pain processing (21, 34). Fairhurst and
colleagues (21) found activity in a number of brain stem nuclei during anticipation and during actual painful stimulation. Importantly, applying connectivity analyses to determine the functional significance of these preparatory activations, they found that activity in the posterior insula during receipt of painful stimulation was predicted by activity in the PAG, ventral tegmental area, and entorhinal cortex during anticipation of pain. Similarly, Keltner and colleagues (34), using a different design, found that the modulatory effect of pain expectancy acts via a network that converges with afferent nociceptive input in the nucleus cuneiformis of the brain stem. The brain stem’s involvement in pro-nociceptive and sensitization processes has been beautifully illustrated in a study by Mainero and colleagues (44), who succeeded at dissociating distinct sets of brain stem nuclei in response to primary and secondary dynamic mechanical allodynia in a heat/capsaicin model. This complements previous data by Zambreanu and colleagues (93), who first documented the involvement of the brain stem (PAG and NCF) for secondary hyperalgesia in humans.

**Are “classical” pain-processing regions modulated when the pain experience is altered?**

Another central question occupying current thoughts relates to the following: Is the perceptual modulation of the pain experience (e.g., reduced pain ratings during placebo analgesia) actually associated with altered (reduced) activity in brain regions involved in the intensity coding of pain? Or does the altered pain experience “simply” result from a higher cognitive re-evaluation of otherwise unchanged nociceptive input to the brain?

The studies on placebo analgesia suggest that the reduced pain ratings during placebo analgesia are indeed paralleled by decreased activity in the classical pain-related areas, such as the thalamus, insular, and somatosensory cortices (13, 55, 84). Notably, this is also found when studying placebo effects in a clinical pain situation (61). Attenuated activity in pain-related areas has been reported when pain perceptions are shaped in response to manipulation by expectancy or when pain perception is attenuated by attentional modulation such as distraction or simultaneous performance of demanding tasks (7, 31, 56). Taken together, these studies provide evidence that active afferent inhibition of nociceptive input is one way by which cognition modulates the perception of pain. This, in turn, evokes the question at which level of the afferent nociceptive system this modulation occurs. If the modulation of pain by cognitive factors involves the same brain-to-spinal-cord-inhibitory mechanisms as demonstrated in the animal literature, then cognitively triggered modulation most likely affects spinal cord processing.

**Modulation at the spinal cord level.** This issue was addressed in a very elegant behavioral study by Matre and colleagues (46), who investigated the effect of a placebo manipulation on secondary hyperalgesia, which is thought to result from sensitization at the level of the spinal dorsal horn. They found that expectation of pain relief (placebo) significantly reduced the size of the developed secondary hyperalgesic skin area and thus provided intriguing evidence that placebo analgesia can actually influence processes at spinal cord level.

Recent advances in MR physics have made fMRI of the spinal cord technically feasible in both humans and animals (45, 77). Spinal cord fMRI in the rat has been shown to anatomically distinguish signal changes related to motor, pain, and tactile activity (40, 91). The study by Lilja et al. (40) also showed a pharmacological modulation of the spinal cord signal in response to morphine, which could be reversed by naloxone. Again in the rat, functional plastic changes at the spinal cord level following experimental spinal cord injury have been revealed by a recent fMRI study (20). After these piloting studies on the motor system, the somato-sensory system is also now successfully investigated in humans (44, 91). These studies convincingly demonstrate that fMRI can be used to explore the function of the spinal cord in pain processing. This technique provides an ideal opportunity to explore the missing link in most previous studies on pain, namely the crucial interaction between cerebral structures and the spinal cord in the processing of nociceptive inputs to alter the pain experience.

**Additional mechanisms for modulating the pain experience.** As mentioned previously, it is unknown whether all forms of pain modulation occur via this integrated “frontal to brain stem to spinal cord” system. Indeed, recent work suggests that the experience of pain can be behaviorally modulated without going via this descending system. Wiech and colleagues (86, 87) show that some mechanisms of cognitive pain modulation, including reappraisal, control, and coping mechanisms related to religious beliefs, produce measurable changes in the pain experience without any activity changes within the “classical” pain-processing regions but rather alters activity within specific prefrontal cortical regions that appear to be sufficient to drive a change in pain perception (86, 87).

**The Neurochemical Underpinnings of Pain Modulation.**

The endogenous opioid system is one of the principal systems involved in the modulation of pain (1), and there is converging evidence that this system is activated in a variety of reflective but also cognitively triggered states producing analgesia (90). In accord with this view, [$^{11}$C]carfentanil-PET illustrates changes in
The clinical relevance of this phenomenon is illustrated by a study on transgenic mice with spontaneously developing pancreatic cancer. These mice, like humans with pancreatic cancer pain, usually only display spontaneous visceral pain-related behaviors when the cancer is severely advanced. However, following the administration of a CNS penetrant opioid antagonist in mice with early pancreatic cancer who displayed no pain-related behavior before injection now demonstrated robust visceral pain behavior (72). This finding strongly suggests that activation of the central endogenous opioid system masks early stage pancreatic cancer pain. Even though the opioid-ligand studies on human chronic pain patients, for methodological reasons, are slightly less conclusive, these studies support the notion that the opioid-dependent antinociceptive system tries (more or less successfully) to counteract nociception in chronic pain states (30, 42, 75).

Since the 1970s, pharmacological studies implicate that placebo analgesia is, at least in part, mediated by the endogenous opioid system (9, 27, 39). In support of this, opioid-ligand PET demonstrates activation of μ-opioid receptor-mediated neurotransmission during placebo analgesia in those cortical and subcortical brain regions previously associated with placebo analgesia (Refs. 85, 94; FIGURE 4, RIGHT). These latter studies provided the first direct evidence that cognitive factors (e.g., expectation of pain relief) are capable of modulating physical and emotional states through site-specific activation of μ-opioid receptor signaling in the human brain. However, activation of the endogenous opioid system is clearly not the sole pathway of pain modulation in humans. In accordance with this view, neuropharmacological studies have convincingly dissected opioid- and non-opioid-dependent mechanisms of placebo analgesia (2). Future studies will continue to put more emphasis on studying the other neurotransmitter systems likely to be involved in pain control, such as the dopaminergic, serotonergic, and cannabinoid systems (for an extensive review, see Refs. 48, 53).

The pharmacological modulation of pain

Although the clinical efficacy and peripheral mechanisms of action are usually well characterized, in general little is known about their action on the human brain. The use of neuroimaging in combination with neuropharmacological challenges provides an ideal opportunity to determine dose, task, and disease-specific effects of different substances on distinct brain systems and on different components of pain processing (8, 32, 51, 69, 76). This is nicely illustrated by a recent phMRI study revealing differential dose-dependent changes of alfentanil on the sensory and affective processing of painful stimuli depending on the \( \mu \)-opiod receptor state (52). In primarily sensory-related brain regions (SI, SII, prefrontal cortex) increasing alfentanil doses linearly dampened pain-related responses. This was significantly modulated by the \( \mu \)-opiod receptor gene state. In contrast, in brain regions known to process the affective dimensions of pain-related activations disappeared at the lowest alfentanil dose without genotype difference. This finding explains the common clinical observation that low doses of opioid analgesics reduce the affective but not the sensory dimension of pain. In

**FIGURE 4.** Effects of pain and placebo on the activation of \( \mu \)-opioid receptor-mediated neurotransmission

Activation of the \( \mu \)-opioid system detected by radioligand \([11C]carfentanil PET during a tonic pain (A) and placebo analgesia (B). Amy, amygdala; DACing, dorsal anterior cingulate; DLPFC, dorsolateral prefrontal cortex; Ins, insula; MPFC, medial prefrontal cortex; NAcc, nucleus accumbens; RACing, rostral anterior cingulate cortex; Tha, thalamus. Figure was adapted from Ref. 94.
a similar manner, the differential effects of ketamine on the sensory and affective dimension of pain were revealed (76). A phFMRI study on amitryptiline in patients with irritable bowel syndrome (IBS) nicely illustrates the context-dependent contribution of a drug. In this study, IBS patients were subjected to painful rectal stimulation, which was combined by stressful acoustic noise in some of the trials (51). Amitryptiline led to reduced activation to visceral pain in cingulate and posterior parietal cortex but only in the stressful condition. In another study, the effect of gabapentin in a model of capsaicin induced secondary hyperalgesia, which may parallel some aspects of neuropathic pain, was assessed (32). Remarkably, even a single dose of gabapentin reduced activation in the brain stem during central sensitization. These studies are excellent examples of how fMRI helps to shed light on drug effects, which are specific to distinct components of nociceptive processing or the experience of pain. Combining whole brain and spinal cord pharmacological imaging with sophisticated paradigms will greatly expand our current understanding of drug action in humans. Once the “acute” analgesic action of different gold-standard drugs is established, it will be of enormous interest to perform longitudinal studies in patients to understand how the action of these drugs unfolds over time and how this interacts with the subjective pain experience.

The Descending Pain Modulatory System and Chronic Pain

Descending modulation with its pro- and anti-nociceptive components should not be thought of as a simple “on-off” phenomenon, whereby a change in facilitation produces an equivalent yet opposite change in inhibition. Rather, we posit the two systems are independently controlled yet interact so that an appropriate “balance” of net effects can be achieved for any particular situation. This provides maximum flexibility for the behaving organism. Disruption of these normal regulatory processes and this interactive balance may represent a point of vulnerability for the development and maintenance of chronic pain (25, 59). Such failure of inhibition or increased facilitation of interoceptive inputs has especially been implicated to contribute to disorders like fibromyalgia, irritable bowel syndrome, chronic pelvic pain, or related conditions that are associated with discomfort of pain but where tissue pathology is often lacking (79, 81). However, even though this hypothesis of an altered descending modulatory function in chronic pain is tempting, a solid experimental deactivation in the insula and the dorsal brain stem during central sensitization. These studies are excellent examples of how fMRI helps to shed light on drug effects, which are specific to distinct components of nociceptive processing or the experience of pain. Combining whole brain and spinal cord pharmacological imaging with sophisticated paradigms will greatly expand our current understanding of drug action in humans. Once the “acute” analgesic action of different gold-standard drugs is established, it will be of enormous interest to perform longitudinal studies in patients to understand how the action of these drugs unfolds over time and how this interacts with the subjective pain experience.

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Evidence from functional and behavioral studies. Several lines of evidence, however, do support this concept of an altered pain modulatory system (either a dysfunctional descending inhibition or enhanced descending facilitation) in chronic pain states.

Animal studies convincingly show that brain stem-related pro-nociception via the RVM plays a key role in the generation and maintenance of central sensitization states and hyperalgesia (25, 59, 78), and recent fMRI studies in humans further support the brain stem’s contribution to sensitization processes in humans (44, 93).

Habituation to repetitive painful stimulation represents an important protective element against the chronification of pain and has recently been shown to be mediated, at least in part, by increased antinociceptive activity in the rACC (14). Intriguingly, a lack of habituation to painful (but also for other) stimuli has been observed in different populations of chronic pain patients (17, 24, 54, 62, 82). However, the question whether this lack of habituation in these patients is the source or the consequence of chronic pain is still unresolved.

A recent study by Berman and colleagues (12) investigated preparatory and pain-related responses to aversive pelvic visceral stimulation in patients with irritable bowel syndrome. In contrast to healthy controls, the IBS patients showed markedly less anticipatory deactivation in the insula and the dorsal brain stem. These alterations in preparatory responses were correlated with subsequent brain responses to the delivered painful stimuli and were significantly modulated by measures of negative affect (12). These findings support the notion that the hypersensitivity to visceral/gut stimuli, characteristic of IBS patients, is related to deficits in the inhibition of interoceptive stimuli and importantly, that this failure in anticipatory downregulation is mediated by negative emotions. This leads to the fundamental issue of whether chronic pain patients have a failure of their descending modulatory system “per se” or whether psychological factors like hypervigilance, catastrophizing, and anxiety (all factors known to play an important role in pain psychology) functionally incapacitate and hinder these patients from an adequate engagement of this system.

This issue is of considerable importance when interpreting the results of studies that aim at investigating human models of “diffuse noxious inhibitory control” (DNIC). DNIC is a phenomenon primarily characterized in the rat and refers to the phenomenon where the application of a nociceptive stimulus (DNIC-conditioning stimulus) leads to an inhibition of convergent neurons in the dorsal horn in any other body part, which is then associated with a depression of pain-related sensory and motor responses (RII-reflex) (37, 38). DNIC effects in the animal are sustained by a complex spino-bulbo-spinal loop, with a substantial contribution of the nucleus reticularis dorsalis in the lower brain stem. The contribution of other brain stem structures involved in the “classical” descending modulation network, such as the BVM and the PAG, to the DNIC, is not quite clear. What is unequivocally clear from animal studies is that DNIC in the rat works without the contribution of cortical brain areas.
The integration of basal reflexes into the control of cortical areas subserving more complex behaviors or cognitive functions is a key feature of the evolutionary development of the human being. So, while the contribution of cortical areas and cognitive aspects to the DNIC response can easily be ruled out in rats by cutting off their brain at the brain stem level, the possibility of cognitive factors influencing or even mimicking the DNIC response needs to be considered when studying humans.

A classical model to study “DNIC” responses in humans is the cold pressor task: Here one limb is immersed in cold water while pain stimuli are concomitantly applied to another part of the body to assess the effect of diffuse descending inhibition. Apart from hopefully provoking such reflexive DNIC behavior observed in the rat, this procedure implicates substantial attentional effects, e.g., toward your foot in ice water and distraction from heterotopic stimuli, which alone has been convincingly shown to modulate pain processing and perception (7, 63). Many studies have now used this or similar models to test for a potential failure of the DNIC in patients and reported impaired DNIC responses for a variety of chronic pain conditions (36, 47, 57) or recently even pre-operative pain free patients who develop post-surgical pain (92). Furthermore, neuroimaging studies using DNIC models are now being performed and reveal clear differences, for instance, in brain activation patterns between controls and IBS patients to rectal balloon distension both with and without heterotopic stimulation (74, 89). The important issue for all these studies in humans comes down to one of interpretation.

First, it could mean that patients do indeed suffer from a failure of their “reflexive” DNIC response, and the Yarnitsky study identifying preoperative patients at risk by impaired DNIC responses, would support that this is actually a predisposition to the condition. However, this phenomenon could also be related to the fact that patients, or those who tend to develop chronic pain, rather than controls have difficulty in disengaging their attention from pain, especially a clinically meaningful one, toward the distracting stimulus. Finally, it may be that the patients’ DNIC output is actually functional but that cognitive phenomena such as anxiety, hypervigilance, or the above-mentioned attentional effects interfere with the cortical initiation of this downstream response. Taken together, a variety of factors, and most likely a context-dependent combination of all these factors probably contribute to the results found in such study design.

Neuroimaging in combination with sophisticated experimental manipulations that avoid or control for such cognitive confounds will be needed to unravel the interaction of reflexive and cognitively controlled components of the DNIC response or, in more general terms, descending modulation in humans and to identify how distinct brain stem nuclei contributing to this mechanism are linked to higher cortical areas that may influence their way of action.

Evidence from structural imaging. Illustrative of the current philosophy that pain when chronic might be considered a “disease in its own right,” recent evidence provides support for a possible reclassification as a disease. A number of recent morphological studies implicate that chronic pain states are associated with structural changes in the brain. Patterns of gray matter changes vary slightly across the different chronic pain conditions, but an intriguing overlap of changes is observed in brain areas related to antinoception, such as the cingulate cortex, prefrontal cortex, and brain stem but also somato-sensory areas (4, 18, 67, 68), which in two studies correlate with the duration of chronic pain. Although the issues related to cause and effect are difficult to unravel from these studies, they support the notion that time-dependent reorganization on a structural level in brain circuits of pain control might contribute to the process of pain chronification. The detailed underlying cellular substrate as well as the reversibility of these structural changes with successful treatment for patients’ pain remains to be determined.

Outlook

The true clinical challenge is the inter-individual variance of the pain experience and its contributing factors. Such inter-individual and gender differences in pain perception were recently recognized to have a functional correlate in the brain (16, 29) and are most likely to result from both environmentally and genetically driven factors. Recent studies support that our genes considerably influence nociceptive information processes and how our nociceptive system copes with peripheral injury. Neuroimaging studies are beginning to link such genetic influences on human nociceptive processing with physiological processes in the human brain (95). Future studies will need to explore how the long-term exposition to psychosocial and environmental factors (e.g., upbringing, cultural influences, etc.) shape nociceptive information processing and resultant pain experiences. The link-age of nature- and nurture-driven influences on behavior and brain function will become a major research topic in pain research for the next decade.

Combining the recent advances in neuroimaging of pain, including imaging of brain stem and the spinal cord with sophisticated designs, molecular imaging of neurotransmitter systems, pharmacological modulation, and/or genetic investigations in healthy subjects and patients with distinct pathological states, will hopefully expand our understanding of the development of chronic pain and finally lead to better treatment strategies.

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