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The Brain in Pain

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Abstract

Pain, while salient, is highly subjective. A sensation perceived as painful by one person may be perceived as uncomfortable, not painful or even pleasant to others. Within the same person, pain may also be modulated according to its threat value and the context in which it is presented. Imaging techniques, such as functional magnetic resonance imaging and positron emission tomography, have identified a distributed network in the brain, the pain-relevant brain regions, that encode the sensory-discriminative aspect of pain, as well as its cognitive and affective/emotional factors. Current knowledge also implicates the prefrontal cortex as the modulatory area for pain, with its subdivisions forming the cortico-cortical pathway, an alternative pain modulatory pathway distinct from the descending modulatory pathway of pain. These findings from neuroimaging in human subjects have paved the way for the molecular mechanisms of pain modulation to be explored in animal studies.

Keywords: *pain, modulation, cognitive, affective, prefrontal cortex*

"...as often as their skins are roasted through, we shall exchange them for fresh skins that they may feel the torment..."

(Holy Quran An-Nisaa v 56)

Unlike other sensations associated with specific areas in the brain, such as vision, touch, and hearing, there is no one specific cortical area dedicated to pain. Imaging studies of pain reveal a distributed network of brain regions that are activated during pain (1), reviewed in Peyron et al., (2). Following observations of phantom limb patients, Melzack (3) coined the terms neuromatrix and neurosignature to denote several brain areas that receive nociceptive and non-nociceptive sensory input and function in an integrated manner. The phantom limb phenomenon, in which the absent or amputated limb continues to be felt, cannot be explained by nerve endings in the stump or at the spinal cord level because transection of the spinal cord does not abolish the phantom feeling. Neither can it be explained by the somatosensory cortex, as the phantom feeling returns after excision of the post-central gyrus. The existence of a neural network in the brain that serves this function is therefore the most plausible explanation (3).

The term neurosignature implies that the pattern of activation in the brain is peculiar to each person and congenitally programmed. The term pain matrix was introduced as a means to group areas that are consistently activated during pain. However, this term has been the subject of much debate because the areas also serve other non-nociceptive function and are therefore only partially specific to pain (4). Nevertheless, these 'pain-relevant' areas have been shown to correlate with the intensity of pain, are modulated by factors modulating pain, and evoke painful sensation on direct electrical stimulation or during epileptic seizures (5).

The experience of pain is multidimensional. The sensory-discriminative aspect of pain involves the intensity, quality and location of pain, while the cognitive and affective/emotional factors constitute more subjective psychological variables, such as attention, anxiety, fear, expectation, and anticipation (6). Both types of modulation are coloured by a person's past experience. The cognitive and affective/emotional variables can be differentially modulated, giving rise to distinct behavioural and neural correlates that subserve each variable. The cognitive and affective/emotional factors are often considered separately: cognitive referring to mental processes, such as attention, expectation and reappraisal; and affective/emotional referring to short-lasting, contextually dependent mood or more chronic clinical mental states, such as depression and anxiety (7). However, the coexistence and interdependence of the two factors make them difficult to tease apart. Cognitive modulation may alter both pain intensities and unpleasantness, whereas the emotional modulation of pain is more likely to change the unpleasantness of the pain rather than its intensity (8).

Threat Value of Pain

Pain is influenced by its threat value (7). The threat value of pain determines how much attention will be assigned to the pain, resulting in the modulation of pain perception. Conflict in pain arises when there is a need to disengage from pain in favour of the more salient need for survival, the 'fight or flight' response (9). Attentional bias towards pain has been demonstrated by studies that show increased engagement to and difficulty disengaging from pain signals (10), cognitive interference associated with pain-related words (11), and visual-processing bias to the pain location (12). This prioritisation of pain over other stimuli is an innate response to threat (13).

Psychological/cognitive tasks are used in pain studies to distract or pull attention away from pain. In these studies, both the task and the pain stimuli are applied at the same time; hence, the effects are mainly due to pulling attention away from pain and towards the task. Cognitive tasks, such as the Stroop task (14), have been widely used in studies to manipulate attention and modulate pain (15), resulting in altered pain ratings and variations in pain responses. Although pain is salient, attention towards pain is not absolute and is more accurately termed "divided attention" (16). Bandura et al., (15) used the perceived inability to cope during a mathematical task to induce analgesia, while Levine et al., (17) manipulated a cognitive task to induce a perceived failure situation that led to significantly higher pain ratings compared to control. These differences can be attributed to the heightened processing of pain during conflict with other stimuli.

The attentional bias towards pain over other stimuli is modulated by various factors (18). First, the pain stimulus itself as characterised by its threat value, which is modulated by its nature, novelty, uncertainty, anticipation and controllability, as well as information about the pain. Second, the response is affected by the characteristics of the person experiencing the pain according to the presence of various traits, such as pain catastrophising (19), affect, depression, anxiety predisposition (20), hypervigilance (21) and pain-related fear (22). Third, the response is affected by the environment in which pain occurs, which includes expectancies of the potential benefit from pain, or the emotional valence of concurrent attentional demands (18).

The threat value of pain may be modulated cognitively by providing information about the pain in advance. Boston and Sharpe (23) modulated a pain-related threat by providing fear-inducing information on the pain stimuli (a cold pressor task). Subjects in the threat condition were given information about the painful stimuli, which was described using the biomedical term 'vasodilatation task', and the extreme effects of cold exposure, such as frostbite, were explained, whereas the control subjects were only given information that referred to the painful stimuli as 'the cold pressor task'. A study by Van Damme et al., (24) also used information to manipulate the threat value of an electrocutaneous stimulus, telling the subjects in the pain group that the stimulus 'stimulates the pain fibres and that most people find this kind of stimulation unpleasant', while the control subjects were told that the vibrotactile stimulus 'stimulates the touch fibres and that most people find this kind of stimulation not unpleasant'. A similar set of instructions was also used by Vancleef & Peters (19), to increase the threat value of electrical stimulation among their subjects. In addition, the subjects were told that the reaction to the stimulus varied across people, inducing a state of uncertainty about the expected sensation.

The significance of the threat value of this type of information is that it is capable of manipulating the perceived potential of tissue injury associated with the pain stimulus. This manipulation will induce a heightened sense of awareness of the effect that the pain stimulus has on the body, i.e., increased interoception towards the threatening stimulus (25) that results in more attentional bias towards it.

The nature of pain also determines its threat value. Higher intensity pain has a higher threat value than lower intensity pain (26). Certain types of pain are more threatening than others, depending on the potential for harm and tissue injury. Dannecker et al. (27), showed that heat and ischaemic pain are deemed more threatening than delayed-onset muscle pain. Another factor that increases the threat value of pain is the timing of pain administration (28). Intermittent pain (29) engages more attention than does continuous pain (30).

The presence of pain-predictive cues has been found to induce an increased engagement of attention towards pain (31) and increased pain perception (32,33). Pain-predictive cues represent the threat associated with an aversive outcome. Using pain cues creates an expectancy of the pain stimulation that is related to the degree of certainty regarding the outcome (34). If the certainty is high that the outcome will be painful, fear of pain results and will eventually lead to a reduction in

the pain sensation. However, a cue followed by a high degree of uncertainty will induce anxiety that results in increased pain perception (33). A study by Brown et al. (35), however, showed that this outcome is only true for low-intensity pain conditions. For high-intensity pain, certain expectations caused increased pain ratings.

The meaning of pain may itself also be threatening. For example, heat pain is deemed more threatening than cold pain (36), or delayed-onset muscle pain (27), and pain due to cancer is perceived as more intense than pain that is not cancer-related (37). The potential for harm or tissue injury also increases the threat value of pain (36). Another factor that increases the threat value of pain is novelty. In a study of cancer patients, experiencing pain in a new location has been shown to positively correlate with worrying about the pain and focusing on emotions while in pain (38). Experimentally, however, novelty as a threat value of pain is not a factor that has been widely studied.

The motivation-decision model by Fields (9), stated that analgesia may be the result of averting a bigger threat than pain or the anticipation of obtaining a reward. In the face of a menace, such as the threat of a predator, attending to the dangerous situation takes precedence over attending to the pain, resulting in analgesia. Likewise, in situations in which reward is to be gained, the motivation for reward obviates the sensation of pain, resulting in analgesia. These concepts summarise the behavioural reactions to stress that produce analgesia, i.e., in stressful situations in which survival depends on confronting (or fleeing) the stressor, attending to the pain ceases to be the priority.

Pain Imaging Studies

Pain imaging has provided inroads into identifying and mapping the pathways of pain in the brain. Pain imaging studies in healthy volunteers or patients, especially chronic pain patients, utilise either acute or tonic pain stimuli to mimic the actual pain experienced by humans. The responses, in the form of blood-oxygen-level dependent (BOLD) activation in functional magnetic resonance imaging (fMRI) or receptor availability in positron emission tomography (PET), to pain and its modulation are mapped.

Functional neuroimaging reveals that certain brain regions are primed to decide whether a stimulus is painful. Bilateral anterior insula activation pre-stimulation predicts whether a subsequent stimulation is painful or not (39). Giving prior information to create a bias towards pain has been shown to activate the anterior insula during pre-stimulation and the midcingulate cortex (MCC) during stimulation (40). Functional connectivity between the anterior insula and MCC is increased by the anticipation of pain, suggesting their role as the 'salience network' (41).

While studying the attentional modulation of pain, Petrovic et al. (42), used cold pressor pain during an attention-demanding maze task to demonstrate decreased activity in the somatosensory association areas and the periaqueductal grey accompanied by lower ratings of pain and increased activation in the orbitofrontal cortex. Using the counting Stroop test as the distractor and applying noxious thermal heat, Bantick et al. (43), showed reduced activation in several pain-relevant areas (thalamus, insula, cognitive division of the anterior cingulate cortex; ACC) and increased activation in the affective division of the ACC and the orbitofrontal cortex. Valet et al., (44) used a colour-word Stroop task and heat pain to exhibit a reduction in pain-relevant areas and increased activation in the cingulofrontal cortex, the periaqueductal grey, and the posterior thalamus.

Although the studies mentioned above use phasic pain as the pain stimulus, Wiech et al. (40,45), studied the effects of a concurrent attention-demanding task on capsaicin-induced hyperalgesia as a model of tonic pain. Tonic pain has been deemed a better model of clinical pain. Using a 2 × 2 factorial design with the factors PAIN INTENSITY (low vs high intensity) and DEMAND OF TASK (easy vs hard task), the results showed that pain intensity ratings were significantly lower during the hard task compared to the easy task. The results from fMRI reveal an interaction between cognitive load and pain in the medial prefrontal cortex (PFC) and cerebellum, indicating that the pain-related activation in both brain regions was higher during performance of the easy task compared to the hard task.

Differences in the experimental approaches (28) of studies examining the relationship between attentional bias to pain or concurrent stimuli frequently modulate the threat value of pain, explaining the many discrepancies found in the outcomes of these studies. Most studies reported a reduction in pain perception both for models of acute pain (44) and tonic pain (45) during concurrent engagement in a task. Imaging studies show that distraction causes either inhibition (42,44) or increased pain-evoked activity of the anterior cingulate cortex (46). Similarly, the threat value of pain determines the attentional

bias towards pain or concurrent stimuli, resulting in changes in task performance that lead to either deterioration (29) or no significant worsening (30).

The controllability of pain is another factor that contributes towards pain modulation. An fMRI study by Wiech et al. (47), evaluated the effects of perceived control on pain perception. Self-controlled stimulation is accompanied by less pain and anxiety, with higher activation in the dorsal ACC, right dorsolateral prefrontal cortex (DLPFC), and bilateral ventrolateral prefrontal cortices (VLPFC). The perceived control over pain activates the DLPFC during the anticipation of pain and the VLPFC during painful stimulation. VLPFC activation correlates negatively with pain intensity (47), illustrating the beneficial effect of pain modulation by the PFC. These results suggest that the analgesic effect of perceived control relies on activation of the VLPFC.

Another study of the cognitive modulation of pain (48) identified 2 types of pain responders, fast and slow, based on the participants' reaction time during the Stroop task while being subjected to painful median nerve stimulation. The attenuation of pain-related activation is observed in several brain regions (primary and secondary somatosensory cortices and the insula) but not in others (caudal and rostral ACC and the ventroposterior thalamus) due to cognitive modulation. However, this effect is observed in the faster reaction time group only. Brain activity associated with attention during the cognitive task is not modulated by pain.

In a separate study, the same investigators (49) used the multisource interference task (MSIT; 50) to create a design that included 3 levels of task difficulty combined with 2 levels of pain in response to transcutaneous electrical stimulation (TENS) to study brain activity responses to various combinations of cognitive load and pain intensity. The greatest interaction was found between the higher pain intensity and the easy task, suggesting that an intense pain-evoked response is more sensitive to attenuation by a cognitive task. Pain, however, does not affect activity in cognitive-related areas except when the cognitive load was minimal. These findings suggest that pain and cognitive-related activity interact in the brain, possibly due to shared neural resources.

It has been shown that anxiety causes an exacerbation of pain associated with increased activity in the hippocampus (33), thus suggesting strategies to reduce pain by disengaging the hippocampus during potentially painful clinical procedures. A study using PET showed that psychological stress in humans causes mesolimbic dopamine release (51). Using pain as a stressor, another PET study showed that basal ganglia dopaminergic activity is involved in pain processing and in variations in the emotional aspects of pain stimuli (52). Nigrostriatal dopamine D2 receptor activation can be attributed to the sensory aspect of pain, while mesolimbic dopamine D2/D3 receptor activity is related to the negative affect and fear in the subjects. This finding outlines the regions involved in physical and emotional responses to pain stress in humans.

The neural substrate for the detection of threat has been shown to be the amygdala, with the PFC acting as the controller of attentional engagement (53). In the face of threat, individuals who are prone to anxiety show reduced activation of the PFC and increased amygdala activation (54) under a low but not a high perceptual load. Anxiety is also associated with an increased detection of altered interoceptive sensations following altered aversive interoceptive processing by the anterior insula (25). An fMRI study showed that, depending on the person's expectations of pain or analgesia, pain perception and the underlying neural substrates are modulated accordingly despite receiving similar dose of analgesic (55).

In a study by Stoeter et al. (56), a cognitive task alternating with an emotional stressor before a pin prick pain stimulus are used to assess healthy participants and patients with somatoform pain disorder. In healthy participants, pain ratings increase after both cognitive and emotional stressors, indicating hyperalgesia. However, brain activation during pain stimuli after cognitive stress is reduced, while activation after emotional stress is increased. Another example of the emotional modulation of pain is demonstrated by a recent study that delivered laser pain stimulation to healthy volunteers in the presence or absence of a loved one. The results indicated that the presence of a person emotionally close to the person subjected to pain may actually induce changes in brain activation in the pain-relevant brain regions compared to the absence of a loved one (57).

Pathways of Pain Modulation

The classic pain pathway, as previously understood, consists of a three-neuron chain that transmits information from the periphery to the spinal cord and relays the signal to the thalamus before terminating in the cerebral cortex (58–60). Advances in pain studies have rendered obsolete the concept of a hard-wired classic pain pathway

that transmits pain signals (61). Beyond this classic pain pathway is the presence of multiple potential target nuclei, as well as several efferent pathways, that exert modulatory control on pain transmission (62). The most fully described pain modulatory circuit, the descending pain modulatory pathway, includes the amygdala, periaqueductal grey (PAG), dorsolateral pontine tegmentum (DLPT) and rostroventral medulla (RVM) in the brain stem. This circuit controls pain transmission via the effects of neurotransmitters released by two distinct types of neurons: OFF neurons that are activated by mu opioid receptor agonists, thereby inhibiting responses to noxious stimuli, and ON neurons that are activated by noxious stimuli and facilitate responses to noxious stimuli (13).

The descending pathway has long been considered the pathway underlying pain modulation. Through this pathway, analgesia is signalled from the brain to the spinal cord and the periphery, with opioids as the intermediary compounds (13). Descending modulation of pain is utilised during placebo analgesia, stress, fear and intense exercise and is subserved by structures such as the rostral ACC, hypothalamus, periaqueductal grey, rostroventral medulla and spinal cord (63). Because pain is a complex process that transcends somatosensory perception and involves both cognitive and emotional processes, this opioid-sensitive descending modulatory pathway may therefore not be the only pain-modulating network, and other neurotransmitters besides opioids also play a role in producing and/or modulating analgesia.

Existing knowledge has implicated higher areas of the brain in the cognitive and emotional modulation of pain. Another pain modulatory pathway, the cortico-cortical modulatory pathway, has been suggested to mediate this process (7). Studies manipulating the cognitive aspects of pain, such as reappraisal, control and coping, produce changes in the higher regions of the brain that are not accompanied by alterations in the pain-relevant areas (47), suggesting that modulation occurs in the higher prefrontal regions. Modulation of these higher brain regions while driving changes in pain perception does not induce a change in the lower or subcortical 'pain-relevant' brain regions. This modulation is achieved through the cortico-cortical connectivity of prefrontal regions, such as the DLPFC and VLPFC, while bypassing areas already established to be activated during pain, namely the ACC, SI, SII, insula and thalamus. A meta-analysis of pain imaging studies reported activation of subdivisions of the PFC alongside that of the pain-relevant brain regions, supporting the supervisory role played by the PFC in pain modulation (64).

Lesion studies have also shown that functional disruption of one pain-relevant brain region is accompanied by augmentation in the pain-induced activation of one or more of the other pain-relevant brain regions, as well as the PFC, suggesting interconnection of the pain-relevant brain regions with each other and with the PFC (65). This functional connectivity is supported by diffusion imaging and white matter tractography, suggesting structural connectivity between subdivisions of the PFC with pain-relevant brain regions (66–68). Furthermore, depending on the functions they serve, the pain-relevant brain regions are also shown to be differentially connected (in terms of connection probability) to subdivisions of the PFC (69).

It has been shown that the PFC plays a role in "keeping pain out of mind" (70). It is postulated that this function is achieved through modulation of the cortico-subcortical and cortico-cortical pathways, employing both somatosensory (non-emotional) areas and areas that process emotionally salient stimuli. The extent of functional connectivity to these areas may in turn depend on the threat value of pain and differences in the personality state and traits of the individual. The result of these differences is the modulation of pain through facilitatory or inhibitory pathways and changes in pain perception.

Reverse Translation: Animal Studies

Despite the obvious ethical limitations involved in subjecting humans to various types of pain, functional neuroimaging provides a means of studying brain activity associated with pain in vivo. While animal models are capable of distinguishing specific pain modalities (71), human pain includes overlapping aspects of specific pain types. What separates the responses observed in animals from those in humans is the higher level cognitive processing in the human brain, and these in turn are determined by various factors: past experiences, learning, and memory moulded by the plasticity of the central nervous system (72). Nevertheless, neuroimaging is not without limitations.

Although animal models of pain are not always a good predictive model for pain in humans, they are by no means obsolete. Despite their limitations, animal models of pain provide a means by which underlying molecular responses to pain may be deduced (73–76). Animal studies

on SIA, for example, are considered a model of anecdotal reports of reduced pain sensation under extreme conditions in humans, allowing the molecular responses to be intensively investigated (77,78). Based on findings from neuroimaging, a new concept has been identified, namely 'reverse translation', whereby information from human brain imaging is used in animal studies (79) to improve understanding of the underlying molecular responses.

Conclusion

The experience of pain is more than the movement of nociceptive impulses through hard-wired pain pathways from the periphery to the brain. The crucial journey actually occurs inside the brain itself, through pain-relevant brain areas and top-down cortico-subcortical routes, as well as through the cortico-cortical highway, which gives meaning to pain in terms of intensity, quality and salience. Given its vast and varied role in pain modulation, it may be somewhat ironic (or perhaps imperative) that unlike the skin with its abundant pain receptors, the brain is totally devoid of them.

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