

Pain Perception Within Consciousness

Cengiz Mordeniz

ABSTRACT

As a psychological state, pain is perceived by the affected individual and it corresponds to a form of conscious awareness as a subjective conscious experience mediated in part by beliefs or emotions. Regardless of its 'physical' origins, pain, like all other perceptions, is a mental experience at different degrees of consciousness. The experience of pain requiring a stimulus, a feeling or emotion, and an effect or result, consists of an intermingling of chemical, biological, psychological, physiologic, socioeconomic, cultural, ethnic backgrounds, and emotional and cognitive factors. Not only the activation but also the connections are involved in conscious pain perception. Moreover, interconnectivity between the periaqueductal matter and orbitofrontal cortex is the key to cognitive-emotional responses associated with pain. Thus, the central pain control processes arising from interactions among the cognitive-evaluative, motivational-affective, and sensory-discriminative systems characterize the pain response, being also influenced by both noxious input and cognitive self-regulation. Neuroimaging studies (Davis *et al.*, 2015) in healthy volunteers showed that pain cannot be localized in an isolated "pain center" in the brain, but it rather encompasses a neural circuitry.

Key Words: pain perception, consciousness, pain experience, pain matrix

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Introduction

In 1979, the subcommittee on taxonomy of the International Association for the Study of Pain adapted the following official definition of pain. "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." (Loeser *et al.*, 2008)

Pain is actually more than a just qualitative experience or set of experiences, it is rather a conscious experience, an interpretation

of the nociceptive input influenced by memories, emotional, pathological, genetic, and cognitive factors. Pain processing begins with nociception and ends with motor output or a conscious experience. Relating neural activity changes to the varied pain experiences lead to increased awareness and factors such as cognition, emotion, and context in which injury can separately influence pain perception. But, resultant pain is not related linearly to the nociceptive drive or input and it is not solely for vital protective functions. This is especially true in chronic pain states. The behavioral response to a painful event is modified according to what is appropriate or possible in any particular situation. Pain is a complex, multifactorial subjective experience, resulting from a large distributed brain network, so-called pain "neuromatrix," or just "pain matrix;" having lateral (sensory-discriminatory) and medial (affective-cognitive-evaluative) neuroanatomical components. Pain perception emerges from the

Corresponding author: Cengiz Mordeniz, Ph.D.

Address: Namik Kemal University Medical Faculty, Dept. of Anesthesiology, Intensive Care and Pain Medicine, Suleymanpasa, Tekirdag, Turkey.

Phone: + 90 505 510 7675

e-mail ✉ cengizmorster@gmail.com

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flow and integration of information among specific brain areas with the involvement of brainstem structures in attentional modulation (Coghill *et al.*, 2003; Baars, 2005).

The subjective and behaviorally relevant experience of pain is particularly susceptible to attentional modulation. Psychophysical studies (Roy *et al.*, 2011) indicate that attention can modulate sensory and affective aspects of pain. Functional imaging (Bilevicius *et al.*, 2016) studies have showed that distraction from pain reduces pain-related activations in most brain areas related to sensory, cognitive and affective aspects of pain, including the primary and secondary somatosensory cortices (SI and SII), thalamus, insula and anterior cingulate cortex (ACC). Furthermore, attention yields an increase in functional coupling between brain regions involved in pain processing, and attentional modulation and it does not only result in altered local activation but also affects the functional integration of activation. Attention might modulate pain perception via a pain-specific opiate-sensitive descending modulatory pathway that regulates nociceptive processing at the level of the spinal cord dorsal-horn. This pain modulatory system might complement, interact and overlap with a more general system of attentional control. The subjective experience of pain unpleasantness comprises several dimensions that reflect the felt internal state of the body associated with autonomic activity, the desire to produce behavioral responses upon the motivational state, and the anticipated outcome. Attention processes refer to the information processing analysis of brain function, but pain refers to subjective experience. Attention is effective in modulating the sensory and affective aspects of the pain experience which may lead to the attentional control of pain (Ogino *et al.*, 2007; Marquand *et al.*, 2010).

Research has (Cano *et al.*, 2009) shown that beliefs about the extent to which pain can be controlled is one of the most powerful determinants of adjustment to pain and the development of incapacity. Pain patients who perceive themselves as lacking the capacity to acquire self-management skills might be less persistent, more prone to frustration, and more apt to be non-compliant with treatment recommendations. How people cope with pain and how they react to pain are important determinants of the future pain treatment course. Patients use a wide range of behavioral and

coping strategies in order to limit the effects of pain. Choice of strategies will depend on patients' beliefs about pain, on their confidence in being able to influence events, and to cope with behaviors, ranging from the simple to the complex ones such as posture, facial expression, verbalizing, lying down, taking medication, seeking medical assistance, and receiving compensation (Dworkin *et al.*, 2003).

The perception of pain is sensitive to various mental processes such as feelings and beliefs about pain. It is not exclusively driven by the noxious input. Pain is a highly subjective sensation with a complex and non-linear relationship between nociceptive input and pain perception (Hartley *et al.*, 2015). A variety of cognitive processes have been shown (Tracey, 2008) to influence pain perception and nociceptive processing in the human brain. For example, pain is perceived less intense when somebody is distracted from pain, and more intense when attention is focused on pain (Sprenger *et al.*, 2012). Attentional processes interact with mechanisms supporting the formation of expectations about pain and reappraisal of the experience or meaning of pain, influenced by prior experience. For instance, patients whose pain is resistant to medication might feel helpless and, as a consequence, allocate more attention to pain than other patients (Wu *et al.*, 2002; Shibasaki, 2004; Apkarian *et al.*, 2005; Lautenbacher *et al.*, 2007) The term 'cognitive' has a wider application and refers to a range of factors influencing the perception of pain, such as the thought processes involved in judgment or appraisal, and coping styles or strategies. Patients who believe they can control their pain and avoid catastrophizing about their condition function better than those who do not (Treede *et al.*, 2008).

According to Tracey *et al.* (2007), for both chronic and acute pain sufferers, mood and emotional state have a significant impact on the resultant pain perception and ability to cope. Hypervigilance, catastrophizing, anxiety, or depression influence pain perception in chronic pain sufferers via the descending pain modulatory system. As a negative cognitive mood, catastrophizing is significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to



amygdala), and motor control (Gracely *et al.*, 2004). Catastrophizing magnifies pain-related symptoms, such as rumination about pain, feelings of helplessness, and pessimism about pain-related outcomes. Pain catastrophizing, independent of the influence of depression, is significantly associated with increased activity in brain areas related to anticipation of pain (medial frontal cortex, cerebellum), attention to pain (dorsal ACC, dorsolateral prefrontal cortex), emotional aspects of pain (claustrum, closely connected to amygdala), and motor control. Catastrophizing influences pain perception through altering attention and anticipation, as well as heightening emotional responses to pain. Anticipating and being anxious about pain can exacerbate the pain experience. When a stimulus like pain is identified as emotive, it produces an affective state, which is dependent upon activity in many regions of the brain such as the amygdala, insular, ventral striatum, ACC, hippocampus, and prefrontal cortex (PFC). Central nervous system (CNS) inhibitory or facilitatory mechanisms are able to amplify or decrease the pain experience. The emotional, cognitive, and interoceptive components of pain conditions change pain intensity perception. Anterior insular activity is not only found during subjective feelings of pain, but also associated with anxiety, depression, irritable bowel syndrome, chronic fatigue, fibromyalgia, somatization, and fear (Mcbeth *et al.*, 2001). A specific link exists between pain, homeostasis, and interoception. All the forms of cognitive modulation are not equal, but different forms of psychological modulation can influence pain and emotion via distinct systems (Tracey *et al.*, 2009).

Pain might be perceived as more threatening if one believes that it signals a life-threatening pathological process that will have a long-lasting impact on one's life. Although pain is commonly perceived as threatening because of its warning character, the degree of threat depends upon the belief of the individuals in their own coping resources. A heightened perceived threat value of pain, for instance, by catastrophic thinking with increased anxiety levels, produces higher pain-intensity ratings linked to maladaptive coping. Conversely, a less threatening reappraisal of pain leads to a decrease in pain ratings. If expectations about upcoming events enable an organism to adjust sensory, cognitive, and motor systems for adequate neural and behavioral responses, it is

vital to detect discrepancies between expected and perceived features. If coping resources are sufficient, pain can be perceived as controllable. People who perceive a low degree of control, show more passive coping in response to stressors such as pain. Thus, perceived control triggers reappraisal processes to change the pain experience. Self control as opposed to external control over pain has been shown to reduce pain intensity. The placebo effect decreases pain intensity and cerebral responses to pain in brain areas such as the ACC, insula, and thalamus (Wiech *et al.*, 2008). It's not the placebo substance itself that causes analgesia but the actual meaning we attribute to it (Van Damme *et al.*, 2004; Jackson *et al.*, 2005). In the affective aspect of pain, beyond its immediate unpleasantness, emotions are experienced in the anticipation of pain and in response to the meanings and to the perceived future consequences of pain. Functional brain imaging studies confirm the activation of a similar network of brain structures during pain and the anticipation (Tracey *et al.*, 2007) of pain, although the specific sites of activation have been shown to shift slightly rostrally in the ACC and the insula in the anticipatory state. Furthermore, nonpainful stimuli presented in the context of painful stimuli as expectation of pain, can produce feelings of unpleasantness. During the anticipatory phase, the reduced activity in the ACC and VMPFC increases the predictability of pain and affects the emotional response. This role in anticipation is not restricted just to pain but is also involved in the expectation of abstract rewards and punishments. The ACC, along with other structures such as the amygdala and ventral striatum, contributes to the self-regulation of endogenous pain modulatory systems. The overlap observed between the patterns of cerebral activity associated with feelings of pain, emotions and motivational states in the ACC, and other body-related structures, such as the insular cortex, is consistent with their contribution to basic aspects of self-representation, self-regulation and consciousness (Wiech *et al.*, 2008). As a psychological state, pain perception corresponds to a form of subjective conscious awareness mediated by beliefs or emotions. This definition describes a reaction to pain, rather than pain itself. The inability to communicate verbally does not exclude the possibility that an individual is experiencing pain because evoked potentials and other measurable



brain electrical activity correlating with conscious perceptions occur following *the response of the* subject to those perceptions. Patients who have persistent pain can become quite anxious about their pain and engage in fear avoidance behaviors. Both clinical and experimental studies suggest that pain-related anxiety and fear are important predictors of how patients adapt to persistent pain (Vlaeyen *et al.*, 2000; Laureys, 2005; , Boly *et al.*, 2008; Demertizi *et al.*, 2015). Self-efficacy refers to a person's confidence in one's ability to engage in a course of action sufficient to accomplish a desired outcome, such as control of his or her pain. Self-efficacy not only relates to self-reported measures of pain but also to more objective measures, such as observed pain behavior and the perception of controlled pain stimuli (Bandura, 2011).

Anxiety, fear, depression, and anger are the four emotions which best characterize the distress of chronic pain sufferers. Specific anxieties and fears are common features of pain patients, particularly when they have not been given a clear explanation for their pain. Such specific concerns should be distinguished from global or generalized anxiety in which there is no clear focus to the patient's concerns. Unfocused anxiety is based on specific fears of hurting/harming, distorted ideas about the nature of pain. The initial reaction to a painful injury is usually recognized in terms of anxiety, shock and fear rather than depression. With the passage of time, and the failure of treatment, a patient's coping skills can become exhausted and depression or anger can become evident. Patients may be angry about the severity or persistence of their pain, the effect of their pain on daily activities: sleep, sexual functioning, or their ability to work. They may also be disaffected by their previous treatment or the socioeconomic consequences of their pain associated incapacity. Pain-associated depression, a form of 'learned helplessness' can develop after many different types of chronic unresolved stress as an example of psychological consequences of persistent pain (Gracely *et al.*, 2004; Bowen *et al.*, 2012).

Within the classical conditioning paradigm, pain behavior can be viewed as an unconditioned response to a pain stimulus. Pain can become conditioned as well as secondary pain behavior. Memory of the circumstances can reproduce pain without new occurring injury. If the pain behavior is successful in reducing pain,

or leads to pleasant consequences such as increased attention from a spouse or absence from a stressful job or financial compensation, it will increase in frequency. Initial pain behavior produced as an escape from the painful stimulus can turn into a pattern of complete avoidance. 'Fear of pain' can become more disabling than pain itself (Jensen *et al.*, 2001; Ostelo *et al.*, 2008).

Non-specific reactions to pain such as skin sweating, heart rate and general physiological arousal are not normally painful but may increase the perception of pain. Specific reactions are themselves algogenic (causing pain) and can be a source of nociception in susceptible individuals. For example, site specific muscle hyper-reactivity has been identified in patients with chronic low back pain and tension headaches, and alterations in vascular flow have been found in some migraine sufferers (Guignard, 2006).

Pain has both physical and emotional properties. From a physiological and psychological perspective, pain is a combination of stimulus, perception, and feeling or emotion as a result of a complex integration of physical, psychological, and environmental factors. Pain can also be present in the absence of noxious stimulation. Pain is distinct from the classical senses because it is multifaceted as a discriminative sensation, an affective motivation, a potent autonomic drive and a reflexive motor stimulus. Pain is both an aspect of interoception and a specific behavioral motivation. The basic homeostatic 'feelings,' or modalities, including temperature, itch, visceral distension, muscle ache, hunger, thirst, 'air hunger' and sensual touch, generate an emotion that drives homeostatic behavior not different from pain. Pain can be either unpleasant or pleasant when it relieves an intense itch. Pain is one of many homeostatic emotions that directly reflect an adverse condition in the body that requires a behavioral response. It generates reflexive autonomic and motor responses under cortical control (Craig, 2003).

Regardless of its 'physical' origins, pain, like all other perceptions, is a mental experience at different degrees of consciousness. The experience of pain requiring a stimulus, a feeling or emotion, and an effect or result consists of an intermingling of chemical, biological, psychological, physiologic, socioeconomic, cultural, ethnic backgrounds, emotional, and cognitive factors. While parents, education,



ethnicity, financial status, vocational status, and society as a whole create the social dimension of pain, its biological mechanisms include neurons, nerve fibers, spinal cord, brain stem, and the cerebrum or cerebral cortex. The brain combines incoming information with stored information to build “mental representations,” or internal models, of the external world. The mental representation of a past event is a memory, the mental representation of a present event is a perception, and the mental representation of a future event is a simulation (Gilbert *et al.*, 2007).

The experience of a sensory event is highly subjective and can vary substantially from one individual to the next. This individual variation may result from the manner in which past experience and future predictions about a stimulus are used to interpret afferent information. Expectations inconsistent with sensory information can alter the sensory experience. In the case of pain, positive expectations can reduce the subjective experience of pain whereas negative expectations may result in the amplification of pain. Furthermore, expectations in which there is a high degree of certainty, may activate descending control systems to diminish pain, whereas expectations associated with uncertain outcomes may amplify pain. Expectations of decreased pain reduce the subjective experience of pain-related brain activation (Koyama *et al.*, 2005).

The modulation of pain-related activation by expectations is positively related with the subjective expectation of pain magnitude of brain activation supporting a mental representation of pain. A mental representation of an event relies on information from past experience and must incorporate information from brain regions associated with memory recall. Modulation of pain by expectation is linked with subjective expectation-induced brain activation. All of the cerebral cortical areas receiving afferent nociceptive information can be modulated by expectation-induced information. Since expectations are future predictions derived from past experience and present context, this flow of expectation-related information may be crucial for the development of a perceptual set, a highly distributed process. The multiple sites at which expectation-related and afferent-related information interacts comprise a widely distributed mechanism supporting a perceptual set. The integration of expectation-related information with afferent information is critical

for a complete cognitive experience of pain. Patients with insular cortical lesions have been reported to identify a noxious stimulus as painful but are unable to properly appreciate the meaning of their pain. Similarly, terminal cancer patients who have had prefrontal lobotomies (Schott, 2007), can fully appreciate novel pain but less the implications of their cancer related pain. Active mental representations of past or impending sensory events play critical roles in discriminative processes where afferent information is compared with information from memory (Koyama *et al.*, 2005).

Not only the neurocortical activation but also neuronal connectivity is involved in the conscious perception of pain. Specifically, interconnectivity between the periaqueductal matter and orbitofrontal cortex is the key to cognitive-emotional responses associated with pain (Lorenz *et al.*, 2003). Thus, the central pain control processes arising from interactions among the cognitive-evaluative, motivational-affective, and sensory-discriminative systems characterize the pain response, influenced by both noxious input and cognitive self-regulation. It is the pain perception that impacts cognitive performance. The chronic pain patients display a specific cognitive deficit compared to controls (Jongsma *et al.*, 2011). Pain is a completely subjective phenomenon with all of the characteristics of mind: self-experience, representational, and cognitive states. Attention given to the noxious event plays the decisive role in pain experiences and is an essential key to understanding the neuroplastic mechanisms that make pain chronic (Laureys, 2005; Vogt, 2005; De Ridder *et al.*, 2011).

Without consciousness there is no pain. This fact is best known by the anesthesiologists. General anesthesia makes the patient unconscious, eliciting withdrawal reflexes, and changes in blood pressure, circulation, and heart action. The patient doesn't feel pain, though the nociceptive impact evoked by the operation may still reach pain-relevant structures in the brain. Moreover, the vegetative responses are commonly used to estimate the depth of narcosis, although they do not reflect pain. Under general anesthesia, the relevant brain structures are not able to translate cerebral activity into conscious pain experience. In the first months of life the central nervous system is still developing; relevant unmyelinated thalamocortical



projections are too slow for a conscious handling of external or internal events (Bromm, 2001).

Perception is the act of interpreting and organizing a sensory stimulus to produce a meaningful experience of the world and of oneself. How this is represented information transformed into the individual awareness of a conscious percept? The sensory encoding, perception, and consciousness are challenged with a further degree of complexity in the case of phantom perception, the conscious awareness of a percept in the absence of an external stimulus. Nociceptive stimuli induce gamma oscillations in the primary somatosensory cortex (S1), which vary with objective stimulus and subjective pain intensities and this γ -band activity in the sensory cortex correlates with phantom pain. Almost every amputee experiences a phantom percept, but not everybody perceives the phantom as aversive or painful (Dahaene *et al.*, 2006; Sterzer *et al.*, 2009).

Pain perception has been described as a "hard-wired" system in which pain impulses are passively transmitted along sensory nerves, spinothalamic and thalamocortical pathways, until "perception" occurs. Instead, the participation, function, and neurochemical profiles of multi-layered networks of nociceptors, nerve fibers, neurons, and glia, distributed in multiple spinal and supraspinal areas, form diverse feed-back and feedforward loops at varying times. The conscious perception of pain requires peripheral pain receptors, connections to the spinal cord through an afferent system, fibers that connect the spine and the thalami, and connections between the thalamus and the subplate zone or cerebral cortex. Pain impulses are also processed in other subcortical structures, including the hypothalamic pituitary system, amygdala, basal ganglia, and brain stem. All of these interactions are dynamic and consistently changing. Thus, the pain that is perceived to be of a certain intensity or at one time may, at another time, be perceived as being either less or more intense, even though all other factors appear to be the same. It is the relationship between the stimulus to the nervous system and the registration of that stimulus in the brain that causes the experience of pain. Pain

includes not only the perception of an uncomfortable stimulus but also the response to that perception (Lowery *et al.*, 2007).

Neuroimaging studies (Owen *et al.*, 2008; Hartwigsen *et al.*, 2010) in healthy volunteers showed that pain cannot be localized in an isolated "pain centre" in the brain, but it rather encompasses a neural circuitry. Two distinct brain networks have been implicated in pain perception: a lateral pain system or sensory network processing nociception (lateral thalamic nuclei, primary and secondary somatosensory and posterior parietal cortices) and a medial pain system or affective network (medial thalamus, anterior cingulate, prefrontal and insular cortices) process the emotional aspects of pain (Tracey *et al.*, 2009; Diekhof *et al.*, 2011).

One can only experience pain if he or she can interpret the stimuli and perceive it as pain. For example, if a conscious patient with a fully functioning nervous system undergoes an operation without a general anesthetic, the stimulation sent to the brain at the commencement of the operation would result in pain because of the existence of a stimulus (the incision) causing a sensation (a biochemical impulse generated at the nerve endings or *pain receptors* on the skin) that travels from the incision to the cerebrum (Hartwigsen *et al.*, 2010; Panagiotaropoulos *et al.*, 2014) where it is interpreted and perceived, resulting in a conscious emotional reaction. If this same patient undergoes the same surgery under general anesthesia, painful sensation of the operation would still travel to the cerebrum but the brain's ability to perceive the stimulus and subsequently to experience pain would be eliminated because the patient is in unconscious state regardless of the cause of unconsciousness, either an anesthetic, or hypoxia or ischemia to the brain. Even this simple example shows the evidence that pain perception is strongly correlated to consciousness which brings the studies on pain perception and consciousness to the same platform where the clinical implementation of different states of consciousness could be tested in chronic pain patients or critical care patients of different alterations of consciousness.

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