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Review Article

Brain and Pain: Brain for Perception Not for Feeling - An Insight

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ABSTRACT
In exploring the rare connection of the brain and pain, we come across many complex concepts. The absence of pain receptors in the brain and brain being the seat of perception is just formidable to understand. This information has been used since the last several decades to perform awake brain surgeries. Pain as sensory stimuli is just like a tip of the iceberg because it has a multitude of dimensions. Tracing the journey of pain impulse is indispensable to understand the concept of pain perception. It was a strenuous job to locate the pain matrix and discover the functions of distinct areas of the brain in pain perception. The endogenous analgesic system forms the substratum in the arch of Descending pain modulatory pathway which decides whether the pain is terrible or tolerable. It is very important to understand the difference between a headache and brain ache. Emotions and pain are like the two faces of the same coin. This review is a general topic of interest and discusses the concept of pain perception and modulation.

Key words: Nociceptors, Pain matrix, Awake craniotomy, Pain modulation, Headache.

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INTRODUCTION

Brain is the vital organ of our body which processes the pain by interpreting the incoming signals and information through nerve terminals. The brain features a vast role in defining pain dimensions and acts as a seat of perception of pain. However, interestingly the brain itself doesn't feel pain. Oh my god! I just typed it, and my mother began to cry that, "my head is paining a lot!!" How is it possible? I discussed above that brain is insensitive to pain then how my mother got a headache? You'll get answers to all your questions within the subsequent part of the article.

"Our cells stimulate our pain receptors in order to get our brain to focus and pay attention.
Once my brain acknowledges the existence of the pain, then it has served its purpose and either lighten up in intensity or goes away."

– Jill Bolte Taylor

PAIN: ALARM OF AN INJURY OR DAMAGE

Pain may be defined as a physiopsychosocial and complex phenomenon arising from many cognitive and affective processes with the interaction of multiple neurochemical and neuroanatomical systems. This suggests pain is not just a sensory experience but is influenced by emotions, memories, expectations, age, sex, social relationships, etc.[1] Pregnancy labor pain is an intolerable pain but still, mothers feel this pain happily and with the eagerness of parturition to her child. This pain is typically reduced when she is together with her loved once. Thus, the experience of pain varies from person to person and is different under different circumstances. Based on the origin of impulses, pain is assessed as nociceptive, neuropathic and psychogenic pain. Reckoning on the duration of pain it might be either acute or chronic pain.[2]

The sensory receptors which respond only when a stimulus is robust enough to cause a threat to the body are called nociceptors. These are usually free nerve endings located in various parts of our body except within the brain. There are different types of nociceptors. Few detect harmful chemicals; some detect harmful temperature and other bodily damage. Pain impulses from nociceptors are transmitted through the peripheral nervous system to central and also to the autonomic nervous system.[3]

This information processing is understood as nociception. Experience of pain is far more than just a movement of impulse from pain receptors to the brain. Instead, it's a complex phenomenon where the brain has a vital role in pain modulation, but the irony is that it's completely devoid of pain receptors.

Difference between Pain and Nociception

Yes, we can make a distinction between nociception which is the nervous signal as an alarm of injury to our body and pain which is the result of activation of nociceptors leading to an unpleasant emotional and cognitive experience. Even though these two are closely related, sometimes nociception may be dissociable from the experience of pain. Nociception can occur without pain for instance, during a motor vehicle accident victim exhibit a

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stoic painless state despite the severe injury.[4] Conversely, sometimes the experience of pain is without nociception observed in functional pain syndrome who displays anger even in the absence of any damage to the body.

BRAIN AND PAIN: FEEL Vs PERCEIVE

First of all, can the brain feel pain? The answer is 'no' because there are no receptors in the brain tissue. The reason for its absence is still not clear. Nevertheless, few scientists believe that probable reason would be that because of exclusive protection to the brain, hardly any pain stimulus can elicit the pain receptors of the brain. Even if the stimulus is dangerous enough to activate the pain receptors of the brain then it would be too late to initiate any recovery or protective mechanism. Thus, there was no much evolutionary advantage of having such receptors in the brain. Also, during embryology development of the fetus, the cells responsible for making nociceptors are not present in the cells which make up brain tissue.Now, can the brain perceive the pain? Yes, it's the seat of perception of pain. There are pain receptors in various parts of the body including the tissues surrounding the brain, in meninges, blood vessels of the brain, etc. These pain receptors usually are free nerve endings, which have a lot of branches especially in the region surrounding the brain.[5] Hence, two-point discrimination of stimuli is difficult around the brain.

Feeling or sensation is the result of activation of receptors by adequate stimuli. Whereas perception includes recognition, comparison, discrimination and integration of these stimuli with the help of the brain. Perception is our conscious interpretation of the external world as created by the brain form a pattern of nerve impulses delivered to it from sensory receptors. We don't have all kinds of receptors and also received impulses are modified, thus there is always a difference between reality (feeling) and perception. For instance look at Figure 1, where we can see the white square which is never there it is just the combination of three-fourth of four red squares. Thus, the sensation is at the level of receptor and perception is at the level of brain.

PAIN IMPULSE: ORIGIN AND COURSE

Activation of receptors first leads to pain withdrawal reflex, then an acute sensation of pain followed by duller one. Hence, there is a dual sensation of pain, first sharp pain because of fast pain pathway through A-delta fibres and next dull pain because of slow pain pathway through C fibres. (Table 1) Along with eliciting pain, these nerve fibres transmit the information about the chemical, mechanical, lesion or any kind of the damage for that matter in few milliseconds to the entire nervous system.[6] These afferent fibres from pain receptors first relay in the spinal cord. The spinal cord is the potential site for regulating the transmission of these impulses to the brain. Melzack and Wall, in their Seminal Gate Control Theory of Pain, proposed that substantia gelatinosa (lamina II) of dorsal horn cells acts as a gate for the perception of painful stimuli by integrating afferent impulses from receptors and descending modulating impulse from the brain.[7]

Figure 1: Do you "see" White square that is not really there?

Table 1: Dual Pain Pathway.

Characteristics	Fast/ Neospinothalamic Pathway	Slow/ Paleospinothalamic Pathway
Stimulus	Damage to skin or superficial layer by mechanical and thermal stimuli	Destruction of tissues both superficial and deep, which is unbearable includes mechanical, thermal and chemical stimuli
Receptors	Free nerve endings	Free nerve endings
Afferents	A-delta fibres	C fibres
Velocity	6-30 m/s	0.5-2 m/s
Synapse In Spinal Cord	Lamina I and V of dorsal horn cell	Lamina II and V of dorsal horn cell
Second Order Neurons	Anterolateral column	Anterolateral column
Termination	Spinal cord to reticular formation to thalamus (ventrobasal complex and posterior group of thalamus) to somatosensory cortex	Spinal cord to reticular nuclei, tectal area of mesencephalon, periaqueductal grey region to thalamus (intralaminar nuclei)
Capacity Of Localization	High	Poor
Neurotransmitter	Glutamate	P-substance

PAIN MATRIX: AMALGAM OF PAIN CENTRE AND SEAT OF PERCEPTION

The scientific research for a single pain centre has proven fruitless. If there was a single pain centre then we could have got rid of this pain perception easily, by removing that part of the brain. But alas! There is no such thing. Existence of so many ascending pathways gives us a massive hint that there is a multitude of pain centres, collectively called a pain matrix (Figure 2). But most notable pain centres are primary and secondary somatosensory cortexes, as well as the anterior cingulate cortex and the insular cortex.[8]

Now let us trace the journey of pain signals from the Spinal cord. The first structure of the brain which receives the impulses is the reticular formation area of the brainstem. This area if activated results in awakening, alertness, change in heart rate, blood pressure and vital functions that can be affected by pain. If we are busy performing other tasks then this area allows these impulses to remain unnoticed.[9]

From reticular formation, area impulses travel to medial thalamus, VPL (Ventral posterior lateral) nucleus of the thalamus, intralaminar nuclei of thalamus and hypothalamus. The impulses going to hypothalamus increase the secretion of stress hormone along with activation of the sympathetic nervous system. VPL nucleus of thalamus plays a major role in the localization of pain and projects its fibres to the somatosensory cortex (SA-1). Medial thalamus has less discriminative function and projects into the motor cortex which generate motor reactions to ensure that we try to remain far away from the noxious stimuli and those reaching intralaminar nucleus of thalamus extends till the frontal lobe as well as to the limbic system. This is responsible for the emotional

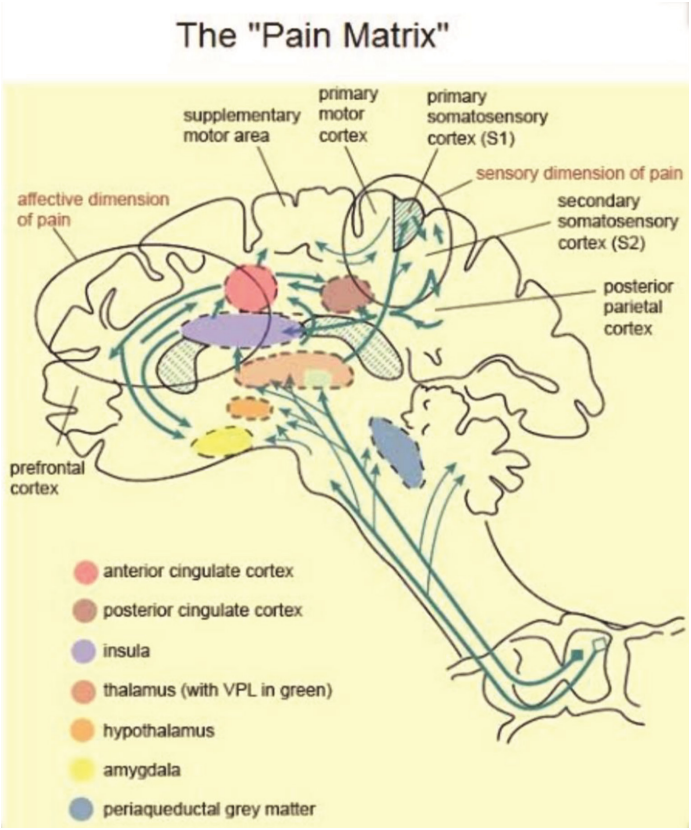

Figure 2: Pain matrix: includes mainly primary and secondary somatosensory cortexes, as well as the anterior cingulate cortex and the insular cortex.

component associated with the pain. Once this information reaches the cortex it's very hard to trace their footprints but let us try our best.[10] As described above, SA-1 receives an impulse from VPL nucleus of thalamus whereas SA-2 (sensory association area) receives from both SA-1 and from thalamic nuclei. SA-1 discriminates various properties of pain whereas SA-2 recognizes the pain and compares it with past experienced pain. The intensity of pain can be assessed by SA-1 in association with the anterior cingulate cortex whose activity proportionally rises with pain intensity. The anterior cingulate cortex which is connected to amygdale cognitively processes the incoming pain signals and produces an effective motor reaction to pain that is associated with immediate avoidance behaviour. But before reaching the anterior cingulate cortex, these impulses are received by the posterior cingulate cortex. Both anterior cingulate cortices and posterior cingulate cortices extend the connection to the prefrontal cortex which is involved in anticipating and controlling the pain.[11] Using its connectivity with parietal cortex, posterior cingulate cortex merges the negative emotions related to pain and produces unified perception. The parietal cortex also contributes to forming the attentional network associated with pain. Thus, these integrated thalamocortical and corticolimbic structures of pain matrix are the major reason for our perception of pain.[12]

PAIN MODULATION: TOLERABLE OR TERRIBLE

Descending pain modulatory system exerts influence on the transmission of nociceptive input from the spinal cord. This network includes the amygdala, periaqueductal grey, dorsolateral pontine tegmentum and rostroventral medulla. By virtue of this organization, the brain selectively controls signal transmission from specific parts of the body. This pathway may have an anti-nociceptive or pro-nociceptive effect. This circuit controls pain transmission through neurotransmitters using two types of neurons: OFF neurons which are activated by mu-opioid agonist receptors thus inhibiting noxious stimuli and ON neurons are activated by pain stimuli which positively facilitate the transmission of these signals easily to various parts of CNS.[13]

Pain has been shown to activate the anterior insula during pre-stimulation. fMRI reveals that certain areas of the brain are activated during painful stimulation, especially mid cingulated cortex(MCC) which are primed to decide whether a given stimulus is noxious or not. Functional connectivity between the anterior insula and MCC is increased by the anticipation of pain, suggesting their role as the 'salience network'.[14]

Attentional bias towards pain over other stimuli is modulated by various factors. First of all, the stimulus has its threat value, which is determined by its nature, anticipation, etc. if we add external fear in people who are receiving the painful stimuli then this fear will increase threat value of pain and more the threat value more it will be prioritized for perception over other stimuli. For example, touch pathway and pain pathway almost go hand in hand. If we have a fall or anywhere in our body there is sudden pain, then we feel relief from pain if we get a gentle massage.[15] Here touch stimulus of massage masks the effect of pain stimuli whereas in the same situation if someone starts to scares us then our perception of pain increases even more. The response is also affected by emotions and the environment in which it occurs. Ventrolateral prefrontal cortex activation is positively associated with the extent to which pain is viewed as controllable whereas interpretation of pain as unpleasant is due to the activation of the anterior cingulate cortex.[16]

PAIN SUPPRESSION: ENDOGENOUS ANALGESIA SYSTEM

This system comprises of three components. The first component produces analgesic signals which incorporate, Periaqueductal grey and periventricular area of the mesencephalon, upper pons which is surrounding aqueduct of sulviyus and 3rd and 4th ventricle. Signals from the first component move to the second component which has a raphe nucleus. From raphe nucleus 2nd order neurons project to the dorsal horn cells of the spinal cord. The 3rd component of our analgesic system that is 'pain inhibitory complex' located in the dorsal horn cells of the spinal cord. In this analgesic complex, a signal can block the transmission of pain signals to the brain. Important neurotransmitters involved in this system are Enkephalin and Serotonin.[17]

DISCREPANCY: HEAD ACHE AND BRAIN ACHE

If there are no pain receptors in the brain, then how my mom got a headace? Though brain tissue is devoid of them, these receptors are present in layers of connective tissue, meninges, blood vessels and muscles around the brain. Headache is a problem caused by damage or injury of these structures. Hence, it is called as headache and not brain ache (which is never possible). As I had mentioned it's really difficult to localize pain especially in regions of head and neck. Thus, we feel as if the pain is coming from brain which is completely false. Thus never blame the brain for a headache because it just perceives pain from other structures.[18] There are different types of headache: a migraine, tension-type, sinusitis, brain freeze, etc. These may sometimes cause serious problems. Hence, we must consult physicians to understand the precise cause of a headache and follow the precautions to avoid it.[19]

EMOTIONS AND PAIN

Pain induction in case of negative emotions elevates the sympathetic nervous activity. There will be increase in heart rate, increased contraction of muscles especially of neck and back. It will lead to worsened situation if there is hyper tonicity leading to painful spasms. This sympathoexcitatory reaction coupled with emotions like stress and fear may reflect an evolutionary coping response that may temporarily dampen pain via norepinephrine release but when this response is prolonged then the situation may worsen. It may intensify pain, interpret the pain as unpleasant and control over pain is not possible. Pain often results in feeling of sadness, anger and fear depending on how pain is cognitively appraised. If person feels "why always I must get pain" leads to anger and when person feels "I am helpless, I am feeling so much of pain" then the person feels sad instead and sometimes may attempt to end his/her life.

Insula's particular anatomical location and its close connection with limbic system, links pain and emotions. However, these emotions related to pain are controllable. We must never think negative when we are in pain. Along with this we must also be engaged in those works which makes us feel better and must stay with our beloved once. Experiments have proven that, mentally and physically active people who are doing their favourite work when given painful stimuli perceive much less pain than those who are in not doing their lovable work. Thus, few people feel pain whereas others won't for the same stimuli. Difference in pain sensitivity from person to person is not due to difference in receptors but difference in the way individuals processes and perceives the signals sent from receptors.

NO PAIN IN BRAIN: BOON FOR SURGEONS

Absence of pain receptors in the brain helps in the procedure of Awake Craniotomy in which our brain tissue proper is not medicated by anaesthesia. Awake craniotomy (Figure 3) is an intracranial surgical procedure where the patient is deliberately awake for a portion of the surgery. During the last several decades, this procedure has gained lots of demand, because there is much evidence that patients receiving awake craniotomy have better outcomes in many aspects and improvement in anaesthetic agents and techniques, especially shorter and more dependable durations of actions has played its vital role in increasing the popularity of awake brain surgeries.[20] Minimally invasive procedures done through a burr hole, for example, placement of deep brain electrodes for Parkinson's Disease, are also technically awake brain surgeries.[21]

Though the brain doesn't have pain receptors its adjoining skin, soft tissue, periosteum, scalp, etc., possess them. Scalp blocks are given to the patients, in whom nerves supplying scalp are numbed by injecting local anaesthetic medications around the nerves. This will prevent pain perception while having an incision on the connective tissues of the brain and closing the wound while stitching (Figure 4). This type of surgeries will only happen if surgeons want to check the specific brain and neuron function while the patient is physically active. Patient's response helps the surgeon to ensure that he or she treats the correct area of the brain. This procedure also lowers the risk of damage to functional areas of the brain that could affect your vision, movement or speech.[22]

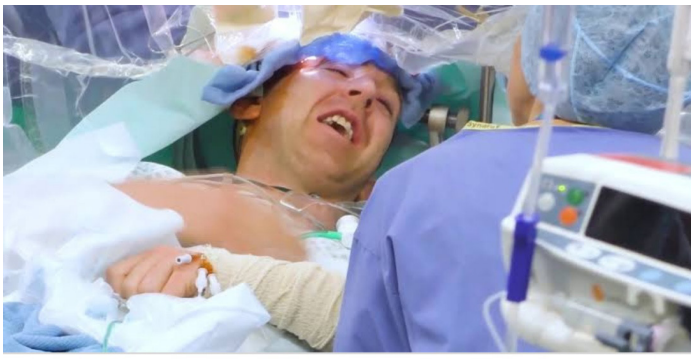

Figure 3: Awake Brain Surgery.

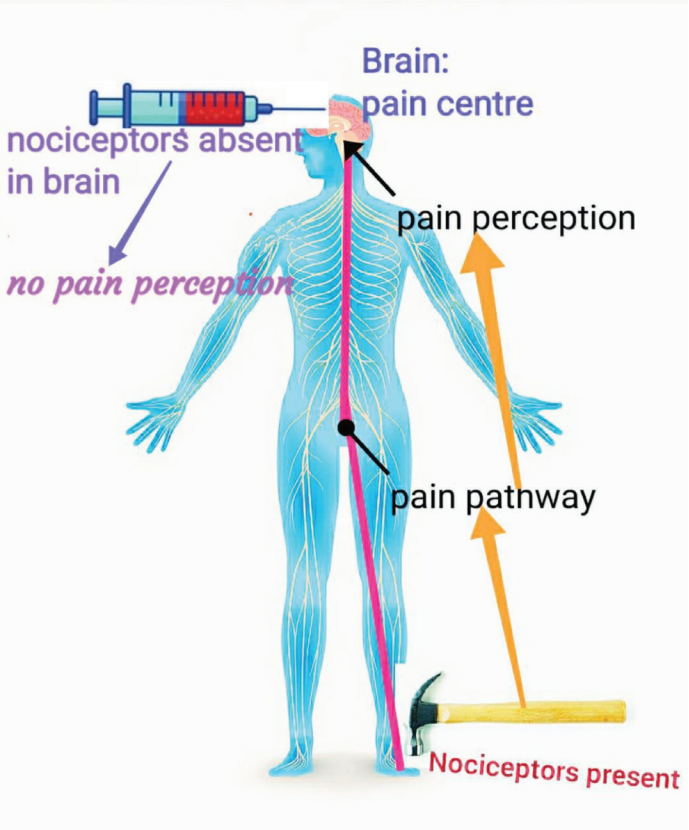

Figure 4: Concept Map: Brain for pain perception, not for feeling.

CONCLUSION

The need of an hour is to utilize the available information to the best of the abilities to discover various treatments to develop the medical infrastructure especially in the field of neurophysiology. We must be positive and brave when we are in pain. Along with this, we must also be engaged in those works which make us feel better and must stay with our beloved once. Experiments have proven that mentally and physically active people who are doing their favourite work when given painful stimuli perceive much less pain than those who are not doing their lovable work. Thus, few people feel pain whereas others won't for the same stimuli. The difference in pain sensitivity from person to person is not due to the difference in receptors, But the difference in the way individuals processes and perceives the signals sent from receptors.

Always keep in mind, self-induced pain leads to less pain perception than externally generated pain. Thus whenever you commit any mistake, accept it and punish yourself. It has two advantages. Because you are punishing yourself you will not repeat that mistake again and because punishment is self-induced, pain is perceived less.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest

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