Pain perception and its genesis in the human brain

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Abstract: In the past two decades, pain perception in the human brain has been studied with EEG/MEG brain topography and PET/fMRI neuroimaging techniques. A host of cortical and subcortical loci can be activated by various nociceptive conditions. The activation in pain perception can be induced by physical (electrical, thermal, mechanical), chemical (capsaicin, ascoric acid), psychological (anxiety, stress, nocebo) means, and pathological (e.g. migraine, neuropathic) diseases. This article deals mainly on the activation, but not modulation, of human pain in the brain. The brain areas identified are named pain representation, matrix, neuraxis, or signature. The sites are not uniformly isolated across various studies, but largely include a set of cores sites: thalamus and primary somatic area (SI), second somatic area (SII), insular cortex (IC), prefrontal cortex (PFC), cingulate, and parietal cortices. Other areas less reported and considered important in pain perception include brainstem, hippocampus, amygdala and supplementary motor area (SMA). The issues of pain perception basically encompass both the site and the mode of brain function. Although the site issue is delineated to a large degree, the mode issue has been much less explored. From the temporal dynamics, IC can be considered as the initial stage in genesis of pain perception as conscious suffering, the unique aversion in the human brain.

Key words: human pain perception; brain measures; nociceptive pain; pathological pain; anatomy-physiology; genesis

1 Histological perspectives

Since the dawn of evolution, pain has been inflicted in animals and humans. Originally, pain serves a crucial surviving function for warning of bodily injuries in acute pain and/or persistent pain. Nevertheless, it becomes maladapted that pathological dynamics may modify neural organization and pain becomes a disease condition in chronic pain. Therefore, perception of pain in the human brain has to be examined in this dynamic context. So far, A large majority of research has touched mainly on the experimental activation of the nociception system in acute condition, largely on the healthy subjects and some on the patients inflicted with pain suffering. Our knowledge of pain perception can be summarized as: (1) Large amount comes from nociceptive pain in healthy subjects; (2) Some amount comes from nociceptive pain modulated by the pathological conditions; (3) Few amount comes from the pathological pain in pain patients per se. It seems we are advanced with research on “sensitivity” of experimental pain over “validity” of pathological pain. Certainly, ease of study dictates our priority of scientific knowledge.

To begin with, it is worthwhile to list the milestones of review papers published in the past 15 years regarding pain perception in the human brain, on a chronological clarity. This chronological order is often related to technical prowess in defining the scientific knowledge. Non-invasive EEG/MEG topography (measuring electric/magnetic and source of brain activity) and PET/fMRI tomography (measuring receptors in PET, metabolite-blood flow in both) are the main techniques in studying pain perception in the human brain. Three periods can be divided to characterize the scientific progress. Only those pertinent to the activation, but not modulation, of human pain perception in the brain are cited here.

I. Early period (1990-1999):
Chen (1993): EEG/MEG mapping of human pain[1].
Kramer (1997): EEG and headache[5].
Bromm (1998): Neurophysiological evaluation of pain[7].
Casey (1999): Forebrain mechanisms of nociception and...

II. Middle period (2000-2004):
Kakigi (2000): Pain-related SEP.
Casey (2000): Concept of pain mechanisms.
Lorenz (2003): Attentional and cognitive factors in LEP.
Chiapparini (2004): Neuroradiological findings of headache.

III. Recent period (2005-2008):

May (2005): Imaging in the pathophysiology and diagnosis of headache.
Favier (2005): Chronic cluster headache.

2 Sites of pain activation in the HUMAN brain

2.1 Research in healthy subjects: nociceptive pain
Casey [3] has early stated that the principle “Multiple peripheral, segmental, and supraspinal neuronal activities control nociceptive processing at all levels of the neuraxis”,
and later emphasized the complexity mechanisms in perception also involved pain-inhibitory and pain-facilitating pathways linked to cognitive, emotional, and stress-response systems. Among the complexities, the forebrain mechanisms act in all levels of neuraxis. The major determinant factors can be empirically examined: gender, the type of noxious stimuli, and origin of nociceptive input. The brain structures invoked by noxious stimulation across the various factors emerged are: the bilateral thalamus, the contralateral insula and anterior cingulate cortex (ACC), premotor cortex, and the cerebellar vermis. The cortical representation of pain was early summarized by Treede et al. and pursued by Peyron et al. have made the following points: (1) Cerebral blood flow (CBF) increases to noxious stimuli are almost constantly observed in SII and insular regions, and in ACC. (2) The responses are slightly less consistent in the contralateral thalamus and SI. (3) Activation of the lateral thalamus. SI, SII and insula are thought to be related to the sensory-discriminative aspects of pain processing. (4) The thalamic response is bilateral, probably reflecting generalized arousal in reaction to pain. (5) ACC appears to participate in both the affective and attentional concomitants of pain sensation, as well as in response selection. (6) Increased blood flow in the posterior parietal and prefrontal cortices is thought to reflect attentional and memory networks activated by noxious stimulation. (7) Less noted but frequent activation concerns motor-related areas such as the striatum, cerebellum and supplementary motor area (SMA), as well as regions involved in pain control such as the periaqueductal grey at brainstem.

The affective dimension of pain perception was articulated by Price and delineated the central network consisting of (1) a direct spinal pathways to limbic structures and medial thalamic nuclei provide direct inputs to brain areas involved in affect, (2) an indirect spinal pathways to somatosensory thalamic and cortical areas and then through a cortico-limbic pathway integrates nociceptive input with contextual information and memory to provide cognitive mediation of pain affect, and (3) both direct and cortico-limbic pathways converge on the same anterior cingulate cortical and subcortical structures whose function may be to establish emotional valence and response priorities.

Based on the knowledge up to 2000, Chen introduced a general model of pain perception in the human brain (see Fig. 1 in the section on mode of pain perception). The pain impulse transmission at brain stem, thalamus, SI and SII for ascending activation in sensory-discriminative function and descending regulation. The transaction of aversion and affect memory in perception take place at insular, hippocampus, and amygdale nuclei. The translation of cognitive attention and execution in pain perception resides at ACC for attention/autonomic regulation and posterior cingulate cortex (PCC) for pain memory, at the parietal cortex for spatial vigilance and PFC for executive function of cognitive-evaluative function. This model is fairly consistent with that articulated by Apkarian et al. from a meta-analysis taking into account of variation in noxious stimuli (electrical, thermal, mechanical), measurement techniques (EEG, PET, fMRI), and sample categories (healthy volunteers, patients). Acute pain network is shown to include thalamus, SI, SII, ACC, IC and PFC.

In addition to the above brain responses by physical activation of pain perception, chemical activation in the healthy subjects by ascorbic acid is worthy notice. The tonic noxious chemical stimulation by ascorbic acid activates the cingulate cortex and the putative foot representation area of SI. Pain-related activation in the majority of subjects is shown in SI, cingulate, motor, and premotor cortex, while negative correlations can be found in medial parietal, perigenual cingulate, and medial prefrontal regions. Furthermore, anticipation to pain per se activates distributed cortical parietal, cingulate and frontal regions, probably reflecting the dynamic anxiety in pain activation.

Finally, pain perception in the human brain can be invoked by psychological activation. Anticipation of chemical nociception enhanced the putative representation area of the contralateral SI but decreased during anticipation in other portions of the contralateral and ipsilateral SI, and in the anteroventral cingulate cortex. A top-down process by anticipation seems to modulate cortical systems involved in sensory and affective components of pain even in the absence of actual noxious input. It suggests that cognitive factors can directly influence the activity of cortical nociceptive networks.

Another controlled type of psychological activation is
2.2 Experimental activation in patients with pain: pathological sensitization

Most experimental stimuli conducted on the pain patients involve physical activation, some chemical activation, and few psychological activation. The study goals are simulated to probe pathological condition in alteration of experimental pain in the patient brain. Thus, it allows isolation and identification of brain of pathological changes in patients.

To begin with, the brain of pain patients may be sometimes maladaptive to the persist or even chronic pain conditions in response to peripheral and central nervous system injury, as in alldynia behavior. Abnormal pain evoked by innocuous stimuli in alldynia has been associated with increase of the thalamic, insular and SII responses, but a paradoxical CBF decrease in ACC[39]. Allodynia is usual physiological effect, and can induce hyperalgesia in response to non-noxiously tactile or thermal stimulation in healthy subjects. Brain responses in allodynia by tactile mechanical stimulation differ slightly from those by thermal stimulation. Both of them excite SI, SII, IC and frontal cortices, but add cingulate and somatosensory cortices in thermal hyperalgesia.

In studying neuropathic pain of patients due to peripheral or central neurological lesions with exhibition of alldynia, Moisset and Bouhassira[66] from meta-analysis indicate: (1) spontaneous pain is associated with changes of thalamic activity in the medial pain system in relation to pain affect, (2) allodynia activation can be varied due to both intrinsic and extrinsic factors, and (3) there is no unique pain matrix or allodynia matrix. The brain areas activated in alldynia of neuropathic pain are seemed well to cicomscribe the general pain matrix: thalamus, and SI, SII, IC, ACC and PFC.

2.3 Research in pain patients: fibromyalgesia, headache

Recently, the default mode network of brain function[81], i.e. resting brain function devoid of any activation, has been well identified in various conditions of brain diseases. Likewise, it becomes necessary to identify the default mode network of clinical pain conditions. In this context, the chronic low back pain patients[82] exhibit reduced deactivation in several key default mode network regions, which is suggested to underlie the cognitive and behavioral impairments accompanying chronic pain. However, pain perception studied in fibromyalgesia patients has been investigated to explore probable maladapted brain regions. But, little gross abnormality in brain activities is yet defined[57].

Likewise, studies of patients respectively with severe cluster headache, migraine, and headache of persistent nature have come to a general profile[62, 65]. Cluster headache is related with the activation of the posterior hypothalamic grey matter, migraine with the brainstem area, at time of cortical hyperexcitability and interacts with trigeminal nociceptive system[66].

3 Modes of pain activation in the human brain

It is almost granted that knowledge of the sites of brain activation is fully necessary, but has to be regarded as not sufficient, in the understanding of pain processing in the human brain. After nearly 15 years of intensive pain investigation in neuroimaging, we now have to turn to our spare knowledge in understanding the mechanisms, i.e. mode of action, in human pain perception. Perception is singular psychological construct, with a complex physiological phenomenon in the brain, as that of consciousness. The mode of action can involve in several stages: sensory transduction and transmission, affective translation, and cognitive transaction. The Chen model (Fig. 1) provides a good spatial and temporal illustration in conception, but is not good enough to understand how the hierarchy organization of information processing in parallel function. We have little knowledge of the input/output linkage of electrical signals and chemical mediators in this regard at the site of brain areas identified for pain processing in the human brain.

The mode of pain perception can be defined in three distinct conceptual stages and functional neuraxis sets shown in Fig. 1. (1) Sensory transmission at the brainstem area, also acting in descending regulation, and the thalamic relay nuclei, while sensory discrimination of spatial/temporal features in SI cortex. (2) Affect transaction at the SII, IC, amygdala and hippocampus cortices for aversive learning, visceral nociception, and autonomic effect. (3)
Fig. 1. A general model of pain perception in the human brain. Transmission of sensory nociception is largely considered as serial processing from brainstem (BS), thalamus (T), SI and SII. This sensory-perceptual system participates in the cerebral functions of detection, localization, timing, learning, relay, integration, ascending transmission and descending regulation of pain. The transaction of painful emotion is probably considered as parallel processing at sites of insular cortex (IC), amygdala (A), hippocampus (Hip), hypothalamus (H) and cingular cortex (Cg). This affective-motivational system participates in the functions of affective reaction, visceral activation, multi-sensory integration, homeostasis regulation, fear and memory. Translation of painful cognition is assumed to be carried out by the integration of several cortical areas in prefrontal cortex (PFC), primary motor cortex (MI), supplementary motor cortex (SMA) and posterior parietal cortex (PPC). This cognitive-evaluation system participates in the functions of executive control, co-ordination of action/intention and spatial/bodily attention. Nevertheless, the biophysical and physiological mechanisms of these pain processings in the brain still remain unknown[7].

Cognitive attention at the ACC, PFC, as well in response selection or action planning. This extensive network, widely distributed in the human brain, in pain perception may operate in hierarchy or in parallel under both spatial-temporal dynamics. The mode of action in pain perception is conjectured after empirical verification at present.

In terms of time scale at the initial stage of pain activation in the brain, the bilateral areas are near sylvian feature command special attention and considered as the first cortical relay station in the central processing of noxious stimuli[13]. Using somatosensory evoked potentials (SEPs) in response to intracutaneous galvanic stimulations, the measured cortical topographic maps display clear different activation maps between non-painful and painful stimuli. At the middle latency phase (70-140 ms), the anatomical substrates are isolated and identified. In fact, this recent study (Chen and Theuvenet, paper in submission) has identified both temporal differentiation and spatial segregation of SII and IC. The contralateral SII source at 93 ms and the N114 IC are separated by 21 ms in time, and segregated by a Euclidian space of 23.2 mm in distance. The model of the IC as the generator of pain perception in the discrete noxious activation in the brain is illustrated in Fig. 2, and the dipole identifications in Fig. 3.

4 Conclusions

In 15 years of pain research of pain perception in the human brain by non-invasive EEG/MEG tomography and PET/MRI tomography, a network of wide distributed brain areas is identified as sites in processing noxious activation. These core areas include thalamus relay in sensory transmission, the somatotopic organization of SI serves in sensory discrimination of spatial and temporal nociceptive event, with SII in recognition, memory, and learning of pain information. The IC involves in affective-motivation function to aversion and autonomic effect. The ACC participates mainly in attention and response selection. The PCC consolidates affective memory and emotional displays. The PPC acts in sensory registration and selected awareness. The PFC commands in executive control over cognitive-evaluative aspect of pain perception. The sites
of pain perception are well replicated in studies of healthy subjects. In patients of fibromyalgia and neuropathic pain, discrete brain mal-adaption in noxious processing has yet to be specifically identified. Nevertheless, cluster migraine of enhanced activation in the brainstem area and cluster headache at the posterior hypothalamus grey matter are considered to be pain-related disease specific. Given the mode of function, subscribed than empirically verified in each brain area for pain perception, much less is really known in the virtual mechanisms of pain processing within the nociceptive neural network. By controlled discrete intracutaneous galvanic stimulation, we contend that IC at

Fig. 2. Scalp field potentials at three stages (73 ms, 93 ms, 114 ms) in middle latency. At the peak 73 ms in the middle latency period, a main contralateral centro-medial negativity was focalized. At the peak 93 ms and 114 ms stages, three main focal negativities (contralateral centro-medial site, contralateral left temporal site, ipsilateral right temporal site) were isolated along with the associated medial-frontal positivity at the forehead. At 114 ms, the somatosensory evoked potentials (SEPs) recorded at the focal electrodes showed the largest activity (note the 2-fold increase in scale bars) and was located at the centro-medial site. While the SEPs at the contralateral site was larger than the ipsilateral site (redlines denote the study time at 114 ms), the ipsilateral peak latency lagged 13 ms compared to the contralateral peak (Chen and Theuvenet, paper in submission).
Fig. 3. Correlation of scalp potentials, dipole sites and insular structure. Three main dipoles are depicted as the generators for the respective topographic maxima in Fig. 2, and the anatomical substrates identified are respectively the ipsilateral lentiform cortex, vertex SMA and contralateral main insular generator in response to painful galvanic stimulation. The inlet image displays a real post-mortem brain, with the lateral cortex dissected to reveal the shape, size, and position of the insular cortex (courtesy of Digital Anatomist Project, University of Washington, Seattle, USA). The virtual relation of the left insular dipole is indicated by red arrow. This supports the role of the insular cortex in the genesis of pain perception in human (Chen and Theuvenet, paper in submission).

the middle latency stage (70-140 ms) may be a valid candidate for the generator of pain perception in the human brain.

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