Democratic organization of the thalamocortical neural ensembles in nociceptive signal processing

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Abstract: Acute pain is a warning protective sensation for any impending harm. However, chronic pain syndromes are often resistant diseases that may consume large amount of health care costs. It has been suggested by recent studies that pain perception may be formed in central neural networks via large-scale coding processes, which involves sensory, affective, and cognitive dimensions. Many central areas are involved in these processes, including structures from the spinal cord, the brain stem, the limbic system, to the cortices. Thus, chronic painful diseases may be the result of some abnormal coding within this network. A thorough investigation of coding mechanism of pain within the central neuromatrix will bring us great insight into the mechanisms responsible for the development of chronic pain, hence leading to novel therapeutic interventions for pain management.

Key words: pain; perception; emotion; central coding; neuromatrix

1 Introduction

Pain is a very common experience among somatosensory perceptions. Except for congenital painless condition[1], almost everybody will experience various types of pain during his life. The observation that people born with insensitivity to pain often die in childhood because they fail to notice injuries and illnesses has been viewed as compelling evidence that the ability to perceive pain has great survival value, as speculated earlier by Leonardo da Vinci[2]. Nonetheless, for most patients with chronic pain, the persistent agonies they suffered are highly unnecessary. The existence of chronic pain syndrome has very often gone beyond an indicator for noxious stimuli; rather, they have become pathological conditions maintained by activities of the central nervous system. In recent years, chronic pain has gradually been viewed as a group of diseases that requires special attention and treatment. Thus, it will be very interesting to describe how pain perception is formed within the brain network.

By the end of last century, cumulating evidences gradually revealed that pain signals activate the free nerve endings of a group of unmyelinated or thinly myelinated sensory fibers (C- and Aδ-fibers). Central terminals of these fibers project to the superficial and deep layers of spinal dorsal horn neurons, respectively. The latter then send ascending signals to various cortical areas via thalamic nuclei. However, all efforts looking for the highest pain center in the pain hierarchy failed. On the other hand, it has been noticed that chronic pain can survive the transection of spino-thalamic projection, indicating possible generators in super-spinal areas (for a comprehensive review of supraspinal contributions to hyperalgesia see the reference[3]). Studies on the neural mechanisms of analgesia induced by transcutaneous electric nerve stimulation (TENS) or acupuncture revealed modulation of pain signals within spinal-, brain stem-, and limbic-circuits[4]. In addition, pain behaviors are highly flexible and can be fully modified by psychological conditions[5], as indicated by the behavior of the behavioral artists in Fig. 1. These evidences suggest that the perception of pain might not be direct products of peripheral nociceptive stimuli, but results of complex signal processing within the central nervous system.

In 1900, Sherrington acknowledged that pain was composed of sensory and affective dimensions. He also suggested that mind rarely, probably never, perceives any
object without an affective attribute. Therefore, pain was a primary sensation that had cognitive and emotional reactions\[6\]. In 1968, Melzack and Casey provided a novel and concrete description of this argument. They suggested that the neospinothalamic projecting system (lateral pathway) processed sensory discriminative information about the location, intensity, and duration of the stimulus, while impulses from the paleospinothalamic tract and paramedial ascending system (medial pathway) activated reticular and limbic structures that provoke the aversive drive and unpleasant affect that triggers action in the organism. Neocortical central nervous system processes, such as evaluation of input based on past experience, exert control over discriminative and motivational systems\[7\]. From then on, it has been gradually accepted that pain is composed of several interactive dimensions including sensory, affective, and cognitive. Possible central substrates for each of the components had also been suggested\[8,9\]. However, it is only with the development of functional brain imaging and neural ensemble recording techniques in the last decades of the 20th century, that it was becoming possible to investigate pain-related activities in many central areas simultaneously, and to correlate these activities with sensory, affective, or cognitive aspects of pain. The current review will focus on recent progresses in this area.

2 Extensive central responses to noxious stimulation

2.1 Evidences from functional brain imaging studies

Rainville and colleagues conducted two positron emission tomography (PET) experiments to evaluate the effect of hypnotic suggestions to alter pain affect\[10\] or pain sensation\[11\]. The suggestions for pain affect modulation produced significant and specific changes in pain unpleasantness ratings and in anterior cingulate cortex (ACC) activity. Regional cerebral blood flow (RCBF) in ACC was significantly correlated to pain unpleasantness ratings\[10\]. Conversely, suggestions directed at the sensory intensity of pain produced parallel modulation of pain intensity and unpleasantness ratings, accompanied by significant changes in brain activity mainly in primary somatosensory cortex (SI)\[11\]. Taken together, these results indicate a partial segregation of cerebral regions involved primarily in pain sensory or affective processes.

However, painful stimulation by no means activates only a couple of cortical areas. Our functional magnetic resonance imaging (fMRI) studies revealed that pain-specific response based on the contrast between 2 °C vs 18 °C was related with the activation in contralateral primary somatosensory and motor area (SI/MI), bilateral SII, MPFC, BA32, midbrain, pons, cerebellum, ipsilateral BA7 and middle temporal gyrus (BA37)\[12\]. Similar with other reports cited in recent reviews\[13-16\], our result indicated that painful stimulation activated cortical and subcortical areas related to sensorimotor, emotional, and cognitive functions.

2.2 Evidences from ensemble neuronal activity studies

2.2.1 Hypothesis of cell assembly pain coding

In 1949, based on his famous cell assembly coding theory, Hebb proposed a central integration mechanism in which synchronized firing in the thalamocortical neural circuits provided the signal for pain. The loss of sensory control of the synchronized activities would lead to excessive synchronous firing in brain cells that would distort the normal cognitive and perceptual patterns, which lead to pain\[17\]. However, due to technical limitation, this hypothesis could not be evaluated and was largely ignored until recently.

2.2.2 Noxious radiant heat induced pathway-related response pattern in many neurons
With the help of multiple channel single-unit recording technique in awake freely-moving subjects, we focused our studies on neurons within the aforementioned medial and lateral pathway\(^8\), i.e., ACC, SI, and medial dorsal (MD) and ventral posterior (VP) nucleus of thalamus. Unlike previous results obtained from anesthetized animals, a majority of cortical and thalamic neurons in awake rats responded to nociceptive radiant heat stimulation. In the lateral system, the responses appeared in 73%-91% neurons and were exclusively excitatory. Similarly, more than half of neurons in the medial system (56%-69%) changed their firing rates, with a small part (7%-15%) being inhibitory\(^9\). Neurons in the lateral system displayed a brief and intense responding pattern, in accordance with the coding of sensory-discriminative features (intensity, location, timing features, etc.) of the stimuli. Medial system neurons, however, exhibited slow and moderate nociceptive response. Some even showed anticipatory responses as soon as the heat light was turned on. These were complied with the presentation of the affective attribute of the stimulation\(^{18}\) (Fig. 2).

These findings are parallel with previous human studies. Ploner et al. described differential magnetoencephalographic (MEG) response patterns of SI and ACC, with a first-pain correlated sharp peak appeared in SI and a second-pain related persistent activity in ACC\(^{19}\). Correspondingly, single-unit recording with human deep-brain electrode\(^{20}\) as well as event-related fMRI study\(^{21}\) all supported that ACC neurons responded anticipatorily to pain.

### 2.2.3 Neural responses to other brief nociceptive stimuli

Electrical and laser pulse stimuli generated similar global changes of neural activities in thalamocortical pain pathways. Brief electrical pulse stimulation generated both brief and persistent responses in about 70% of cortical and thalamic neurons (Fig. 3)\(^{22}\). Similar responding ratio was observed after laser beam pain test, with a bi-model responding pattern (Fig. 4). These responses had been considered as A\(\delta\) and C responses, respectively\(^{23}\).

### 2.2.4 Neural responses to persistent noxious stimulation

Our findings indicated that a brief noxious stimulation can activate many neurons in the thalamocortical pathways. The question then arises as what will be the neuronal response to persistent pain. In a formalin test model, we...
demonstrated that in the first hour after formalin injection, 44% of neurons within the thalamocortical pathways showed excitatory responses. Around 8% neurons, almost exclusively from cortices (mostly from ACC), displayed inhibitory responses. However, at the end of the first hour when the second phase of nociceptive behavior discontinued, almost all excitatory neuronal responses disappeared. They were replaced by wide-spread inhibition of spike activities across recording thalamic and cortical areas\[24\].

Although the experimental animals exhibited clear-cut bi-phasic nociceptive behaviors, only 10% of neurons (almost exclusively from VP) demonstrated bi-phasic increase of spike frequency. The remaining neurons showed only mono-phasic excitation that lasted for 20-60 min. Half of them showed a delayed response started at the onset of the second phase. These findings indicated that emergence and submergence of the second-phase pain behavior in the formalin test may be the result of dynamic processing within central neural networks. Again, more than 70% of neurons showed response to this persistent nociceptive stimulation (Fig. 5)[24].

### 3 Coding of nociceptive signals requires activation of central neural networks

From the previous discussion, pain stimuli evoked activities of large amount of neurons in many central areas. What would be the meaning of this widespread activation? Is it a simple addition of parallel responses to peripheral stimulation? Are neurons organized as a network for further integration?

According to Hebb’s theory of cell assemblies, neurons will be grouped together to form relatively stable circuits because of repetitive co-activity. Each of these circuit activities represents a specific neuronal event[17]. Thus, noxious stimulation should also induce similar synchronized firing of cell circuits, which serves to code sensory, emotional, and cognitive characteristics of the stimulation. We can infer from this hypothesis that the functional connection between thalamic and cortical neurons will be strengthened during the stimulation processing, which is similar to what can be drawn from classical theory of specific projection. However, the classical theory predicted specifically an increase of ascending signal; while the cell assembly theory suggested increases of both ascending and descending information, and even the connection between different pain pathways. Which inference then could
3.1 Nociceptive stimulation enhanced the connectivity of thalamo-cortical neuronal activities

Our result of cross-correlation analysis revealed that the correlation between activities of thalamic and cortical neurons was significantly enhanced during noxious thermal stimulation\cite{25}. An increase of correlated activities was also observed between neurons in the medial and lateral pathways\cite{25}. More interestingly, a subtle change of the major project direction occurred between thalamic and cortical neurons in these correlated spike activities, i.e., more cortical neurons tended to lead thalamic neurons during pain processing, while the opposite was true under control condition (Table 1). This indicated that the signal projection from cortex to thalamus increased to a larger extent during nociceptive stimulation. This evidence provided a preliminary proof for Hebb’s cell assembly theory of pain coding.

3.2 Nociceptive stimulation altered central information flow pattern

The combination of signal processing techniques with ensemble neuronal activities recording renders it possible to understand how information flows between neural ensembles of different central areas. Among these techniques, partial directed coherence (PDC) analysis proposed by Sameshima and Baccalá\cite{26} should be doubtlessly considered a most important contribution. PDC analysis reveals the Granger causality among many signal sources in the frequency domain. In other words, it discloses the direct

![Table 1. Time delay between correlated thalamic and cortical neural activities](image)

*Where P values are derived from Students’ t-test. Reproduced from reference\cite{25}.*

![Fig. 6. Change of information flow induced by noxious heat stimulation. A: Ratios of PDC relative to the baseline were shown in the bar chart. B: Example of information in the time and frequency domain between brain areas. ACC: anterior cingulate cortex; SI: primary somatosensory cortex; MD: medial dorsal nucleus of the thalamus; VP: ventral posterior nucleus of the thalamus; control: sham stimulation; contra: contralateral nociceptive heat stimulation; ipsi: ipsilateral nociceptive heat stimulation. Reproduced from Wang et al, 2007\cite{27}.*
influence of one signal to the future of the other signal. Thus, it can reflect changes of the amount and direction of information flow between two brain areas. Our experimental data indicated that, compared with sham stimuli, nociceptive stimuli induced a large increase of information flow from cortex to thalamus, while the total amount of information flow of the opposite direction remained unchanged (Fig. 6). These results, together with aforementioned change of cross-correlation, gave us further proofs that descending projection was enhanced during the formation of pain perception[27].

Consistently, long-lasting changes of information flow were also observed under a condition of persistent pain. Our result revealed that in the second phase of the formalin pain model, directed coherence from cortex to thalamus increased significantly, which is in parallel with the presentation of pain behaviors. Simultaneously, increases of PDC from the medial to the lateral pain pathway also presented across the first and second phase of formalin model. However, these tendencies were dramatically reversed by the end of the second behavioral phase (for an example see Fig. 7). These results again indicated that the emerging and submerging of the second-phase pain behavior may be the consequence of active alteration of central signal coding[24].

This extensive descending flow of information during pain perception is similar as what have been found recently in the study of tactile sensation[28]. This revealed that the formation of pain perception may not be a passive procedure of sensory projection, but the result of some active cortical “seeking” or “coding” of nociceptive information out of the abundant peripheral projection signals[29]. This view of pain mechanisms can better explain why fierce sensation and affect of pain can be generated by a slight nociceptive or even innocuous stimulation under the condition of chronic pain. It also explains how factors from a simple peripheral sensory stimulation to hypnotic suggestion at the cognitive level can alter the perception to noxious stimulation.

4 Central modulation of nociceptive coding procedures

For many years, pain perception has been known to be susceptible to many modulating factors, both subjective (e.g., cognitive, affective) and objective (e.g., nociceptive or non-nociceptive sensory stimulation). As a traditional therapy in Chinese medicine, acupuncture has been accepted as an effective analgesic method. After several decades of research, we have now known that acupuncture could release many neural transmitters and neuropeptides in the spinal level, and activate many brain stem areas. fMRI study revealed that acupuncture could activate many cortical areas. However, it was not known for many years how acupuncture modulates the pain coding procedures in the brain.

4.1 Acupuncture modulates central pain responses

In the past decade, a lot of functional imaging papers have been published about acupuncture activating many central areas. However, most authors take it for granted that all brains areas activated by acupuncture are related to its an-

Fig. 7. An examples of altered information flow pattern after formalin injection. A: Normalized PDC increased significantly in the first and second behavioral phase from SI to VP. But in phase 3, the opposite direction increased significantly. B: Temporal dynamics of summed information through all frequency bands. SI: primary somatosensory cortex; VP: ventral posterior nucleus of the thalamus. Reproduced from Huang et al., 2006[24].
algesic effect. In fact, acupuncture could change many human functions. Thus, it would be improper to equalize acupuncture-induced activation and mechanism of analgesia.

A more reasonable way is to consider the influence of acupuncture on central pain responses. In an fMRI study, we investigated the effect of transcutaneous electric acupoint stimulation (EAS) on neural response of cold pain in normal substrates. Our result showed that the effect of acupoint stimulation was not exclusively inhibitory. On the contrary, activations in the following brain areas increased after real EAS treatment: (1) bilateral motor and premotor cortex (BA4, 6), SII, rostral ACC (BA32/24), orbital frontal cortex, MPFC, paracentral lobules, thalamus, midbrain, pons and cerebellum; (2) ipsilateral SI, LPFC, posterior temporal lobe (BA21, 22, 37), and putamen[12]. Usually we poner the pons and cerebellum; (2) ipsilateral SI, LPFC, posterior temporal lobe (BA21, 22, 37), and putamen[12]. Usually we will simplify the situation by considering acupuncture-enhanced activities as central analgesic modulation, while acupuncture-inhibited activities as mechanisms of pain itself. However, this over-simplification may soon be broken, given the web-like nature of central pain matrix.

Results of electrophysiological study are obviously more helpful for revealing the modulation of acupuncture to the dynamic coding procedure of pain at neural circuit level. We have successfully demonstrated that electroacupuncture inhibited the nociceptive response of lateral pain pathway neurons (SI and VP). For the medial pain pathway, electroacupuncture only partially inhibited ACC neural activity, while enhanced MD activity instead. Acupuncture also selectively inhibited the cross-correlation between thalamic and cortical neuronal activities[25]. These results indicated that acupuncture may selectively inhibit the central processing of pain signals by suppressing nociceptive projection in the lateral system. For medial pathway which is in charge of affective aspect, acupuncture exhibited a bi-directional modulation (inhibiting part of the activities and enhancing the other part), similar as seen in our fMRI study[30].

4.2 Central effect of acupuncture correlates with behavioral changes

To evaluate whether the acupuncture-induced central activities are related with its analgesic mechanism, a better way is to consider the correlation between central activities and behavioral changes. This was adapted in our fMRI study on acupuncture activation and its analgesic effect[30]. Our result indicated that among all the activated brain areas, this type of neural-behavioral correlation only exist in part of them. In both high (100 Hz) and low (2 Hz) frequency groups, the averaged fMRI activation levels of bilateral secondary somatosensory area and insula, contralateral anterior cingulate cortex and thalamus were positively correlated with the stimulation-induced analgesic effect across the subjects. In 2 Hz group, positive correlations were observed in contralateral primary motor area, supplementary motor area, and ipsilateral superior temporal gyrus. In 100 Hz group, positive correlations were observed in contralateral inferior parietal lobule, ipsilateral anterior cingulate cortex, nucleus accumbens, and pons. Interestingly, negative correlations were found in bilateral hippocampus (2 Hz group) and contralateral amygdala (100 Hz group). Namely, deactivation of these brain areas was correlated with better analgesic effect.

The aforementioned studies might better describe the central mechanism of acupuncture analgesia, because they reflected the relationship between central activities and behavioral responses. In a study of thalamocortical neural ensemble activities, we found similar correlation between spontaneous spike-train activities and followed behavioral responding threshold to noicceptive stimulation in about 6%-10% thalamocortical neurons. Interestingly, after electroacupuncture stimulation, the number of MD neurons displaying this type of correlation was increased by 3-5 folds. This result strongly suggested that MD area may be closely related with the central mechanism of acupuncture analgesia[25]. Compared with lateral pathway areas such as SI and VP, ACC neurons also show a slight increase of similar correlation. Thus, neural circuits of the medial pathway may more likely be involved in modulation of pain perception, and thus mediate the effect of acupuncture-induced analgesia.

5 Conclusions

Recent developments of technologies such as functional brain imaging, awake-animal electrophysiology, and bioinformatics analysis, have provided new possibilities for the study of pain perception, especially the mechanism of dynamic coding in central neuromatrix. Studies about tactile sensation have gained great progress along this direction. However, similar studies about pain are just at the beginning. All evidences we have undoubtedly support the genius prediction from Sherrington, Hebb to Melzack, that dynamic neural-circuit activities may be employed in the central nervous system to find out possible noicceptive stimulation from millions of sensory inputs that occur every second within sensory pathways, and to present them as painful
sensory and emotional events at the conscious level. Further studies will provide clearer details for this prospect.

REFERENCES