·Minireview·

Neuronal nociceptive responses in thalamocortical pathways

Fei LUO, Jin-Yan WANG

Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing 100101, China

Abstract: The sensation of pain is critical for the survival of animals and humans. However, the brain mechanisms underlying pain perception remain largely unknown. How does the brain decode the pain-evoked activity into a particular sensory experience? Over the past decade, attempts have been made to answer these questions by employing electrophysiological, functional brain imaging, and behavioral approaches, and some basic properties of pain formation have been revealed. Researchers have gradually recognized that there exists a distributed neural network that participates in the transmission and processing of pain information. These studies will further guide the development of more effective treatment for many disorders such as chronic pain.

Keywords: sensory coding; pain; thalamocortical circuit; neural network

1 Introduction

How is pain sensation formed? It is generally thought that any nociceptive stimulation can be perceived whenever it exists. Thus, it will be surprising that the perception could be modified, deformed, or even illusioned. There have always been two contradictory ideas about how senses are coded. The "specificity" theory maintains that different sensory functions are mediated by activations of distinctly different neurons with highly specific stimulus sensitivities[1]. The "pattern" theory claims that different functions are represented by unique patterns of activity in populations of neurons with relatively broad stimulus sensitivities[1,2].

However, since the activity of one neuron is not equivalent to the sense *per se*, how is it perceived after being transmitted into the brain by either specific "labeled line" or neuronal population? Is it necessary to have a decoder, in the form of either "grandma cell" or "homunculus", which resides in the cortex and observes all that goes on below[3]? If a sensory signal is considered to be conveyed in the esthetic pathway, it seems natural that it should finally reach some kinds of the end. However, evidence suggests that the concept of a read-out decoder may be not necessary, and that sensory signals may be transformed between populations of neurons until behavioral output is generated[3,4]. Meanwhile, a form of vivid perception does exist in our psychological experience. Therefore, what is the neural mechanism underlying this cognitive perception of the environment?

With the help of some novel technologies, such as population neural recording, functional brain imaging, and electroencephalographic brain mapping, more knowledge has been gained concerning how pain information is processed. Here we explore some recent ideas on these questions, mainly to clarify how pain processing works in the thalamocortical circuits composing somatosensory pathway.

2 Population coding

2.1 Dynamic receptive fields The "specific" theory holds that each stimulus submodality or quality within a sense modality is encoded by excitations of different specific nerve

Corresponding author: Fei LUO
Tel & Fax: +86-10-64844991
E-mail: luof@psych.ac.cn

fibers or neurons[1]. Electrophysiological studies have provided evidence for this theory with descriptions of place- and modality-specific neurons, namely, the concept of receptive fields. If different classes of cells signal the nature and the position of stimulation, and if each cell responds to a specific range of stimuli, it seems natural to adopt the "specific" theory.

However, it has gradually become a consensus that the idea of static receptive fields is derived from the simple stimuli employed by the researchers[2,5]. Once complex stimulation is applied, changes or modulations of receptive fields become very common. For example, receptive fields of both peripheral nociceptors and central nociceptive neurons will be significantly enlarged under peripheral hyperalgesia, a phenomenon observed under tissue inflammation or nerve injury condition[6-8]. Central motor areas will also send commands to modulate the sensory receptive fields while delivering motor commands[9,10]. Hurley *et al.* have even suggested that neuromodulators like NE and 5-HT in sensory networks can modulate specific receptive field properties of individual sensory neuron and alter population representations of sensory stimuli[11].

The idea of submodality specificity, on the other hand, is due to the average of the experimental results. Many neurons are sensitive to various stimulations, with different sensitivities. However, researchers have classified the receptors according to the stimuli that they "best" respond to[12,13]. If only limited number of simple stimuli were tested, it will be quite easy to conclude that a neuron is "submodality specific'. Therefore, the receptive fields of sensory neurons are not strictly static, instead, they are under dynamic modulations.

2.2 Primary afferent fibers Primary afferent fibers are the only pathway that conveys all the peripheral sensory information into the central nervous system. However, how is the information conveyed? In the chemical sensation study, Pfaffmann has demonstrated that taste quality is encoded in some distinctly different amounts of responses produced by a stimulus across one, several, or all of the 4 classes of broadly tuned neurons. This gives birth to his "cross-groups" idea of taste quality coding, which was later called "across-fiber

patterns" (AFP)[14]. These AFPs, or across-neuron response patterns (ANRPs), may be the main route for primary afferent fibers to convey the environmental information, for example, the sizes and the organizations of receptive fields, "on" and "off" responses, and even the rate of adaptation of mechanosensitive nerve fibers of the raccoon vary considerably with stimulus location and intensity[15].

2.3 Thalamocortical neuronal responses Neuronal population within thalamocortical pathways obviously adopt, if not expand, the ensemble coding strategy in primary afferent fibers. For example, Ghazanfar and Nicolelis have demonstrated that in the rodent somatosensory pathway, stimulation of individual whiskers results in responses that extend beyond a single barrel cortical column or ventroposteromedial thalamic (VPM) nucleus barreloid[16]. Via the pain studies, Wang and her colleagues have found that a large population of neurons distributed across many brain areas are dynamically activated by a variety of noxious stimulations including radiant heat[17], mechanical[18], electrical[19] or chemical stimulations[20] on rat hindpaw (Fig. 1). Functional imaging study has also revealed a distributed activation in human brain with the application of noxious stimuli[21,22]. Based on the evidence that the brain possesses a neural network that integrates multiple input to produce the output pattern which evokes pain, Melzack has proposed the "neuromatrix" hypothesis to challenge the classical "pain center" theory. The "neuromatrix" theory holds that the development of pain perception involves a widely distributed neural network that is responsible for generating a characteristic coding pattern for the representation of pain[23-26].

3 Information flowing

3.1 Correlated neuronal response The central nervous system presents the sensory information as a pattern of spike emitted by populations of neurons. The populations that are active during the presentation of even the simplest stimuli can be rather large, and the firing of these neurons is often highly correlated[27]. This correlation of neural spikes seems to have behavioral significances. For example, Wang *et al.* have reported that nociceptive stimulation could significantly increase the cross-correlation between neurons in thalamo-
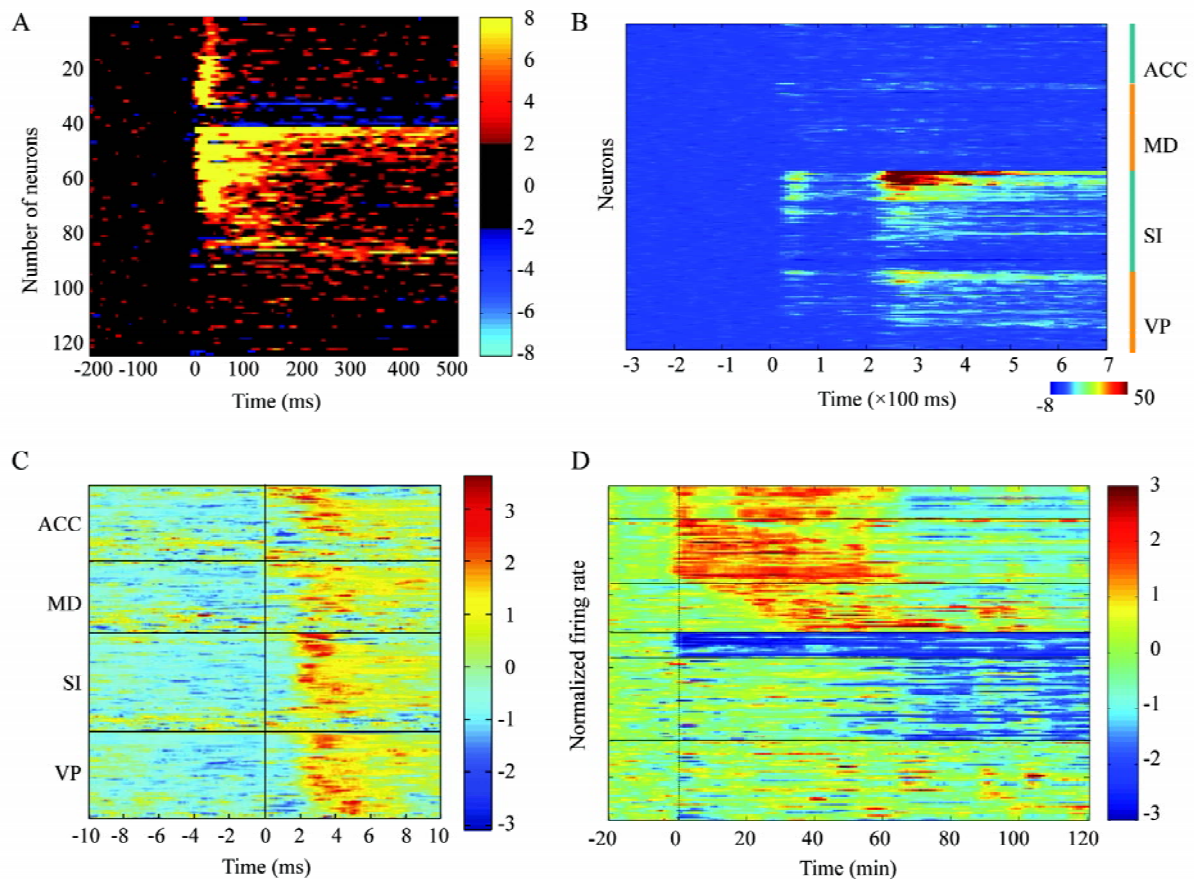
Fig. 1 Temporal and spatial coding patterns produced by noxious stimulations of (A) electric pulse, (B) laser pulse, (C) radient heat (adopted from Wang JY *et al.*)[17-19], (D) subcutaneous injection of formalin (adopted from Huang J *et al.*, 2006)[20].

cortical pathways, and more cortical neurons are found to precede their thalamic partners[28,29]. After receiving peripheral electric stimulation that can induce analgesia, this cross-correlation is greatly reduced. Erchova and Diamond have revealed that the strength of co-activity between columns in the barrel cortex can be modified by sensory input patterns during discrete and intermittent intervals time-locked to bursts, indicating that cross-correlation may help convey sensory information[30]. Swadlow has demonstrated that the thalamocortical feed-forward inhibitory network, revealed by cross-correlation and related analysis, is well suited to provide a fast, potent, sensitive, and broadly tuned inhibition that will suppress spike generation following all but the most optimal feed-forward excitatory inputs[27]. Thus, neuronal correlation, or connectivity, seems to be functionally very important for sensory coding.

3.2 Descending modulation of sensory transmission   If the sensory information is encoded by neural network activity rather than individual cells or nuclei, the functional connections within the network will be strengthened during the delivery of somatic stimulation, and a large amount of information flow should be found along sensory transmission pathways. Undoubtedly, the sensory transmission is enhanced in the ascending pathway in response to environmental stimulation. Thus, the intensified communication between neurons would be better evidenced by an increase in the descending information flow in the sensory pathway.

Recently, Wang *et al.* have reported that somatosensory (SI) cortex has descending influence on thalamic neurons during pain processing[29]. In their study, the amount of information flow was significantly increased from SI cortex to ventral posterior (VP) thalamus following noxious heat

stimulation, while it remained unchanged or even decreased from VP to SI (Fig. 2). This result is consistent with that of Huang *et al.,* who observed that the information flow was changed between cortical and thalamic areas in formalin-induced pain model[20]. Taken together, these results provide strong evidence that the sensory processing depends on mutual connectivity between network neurons but not on simple signal transmission in the ascending pathway.

Cross-correlation analysis has revealed similar findings on the increase in correlated neuronal activity during nociceptive transmission within thalamocortical neural network, with cortical neuron firing ahead of thalamic units[29]. This further supports the hypothesis that the somatosensory cortex ex-

erts more influence on thalamic neurons than thalamus on cortex during the central processing of nociceptive input.

3.3 Cross talk between parallel sensory pathways Generally, sensory inputs reach the central nervous system through parallel pathways. For example, the nociceptive signals are transmitted by dual systems. One is the lateral (sensory) pathway in which the SI cortex receives projections from lateral thalamus, and both of them are engaged in the sensory discriminative dimension of pain. The other is the medial (affective) pathway in which anterior cingulate cortex (ACC) and medial thalamus are involved in mediating the emotional component of pain[31-36]. Then, is the sensory information processed within independent ascending pathway or trans-
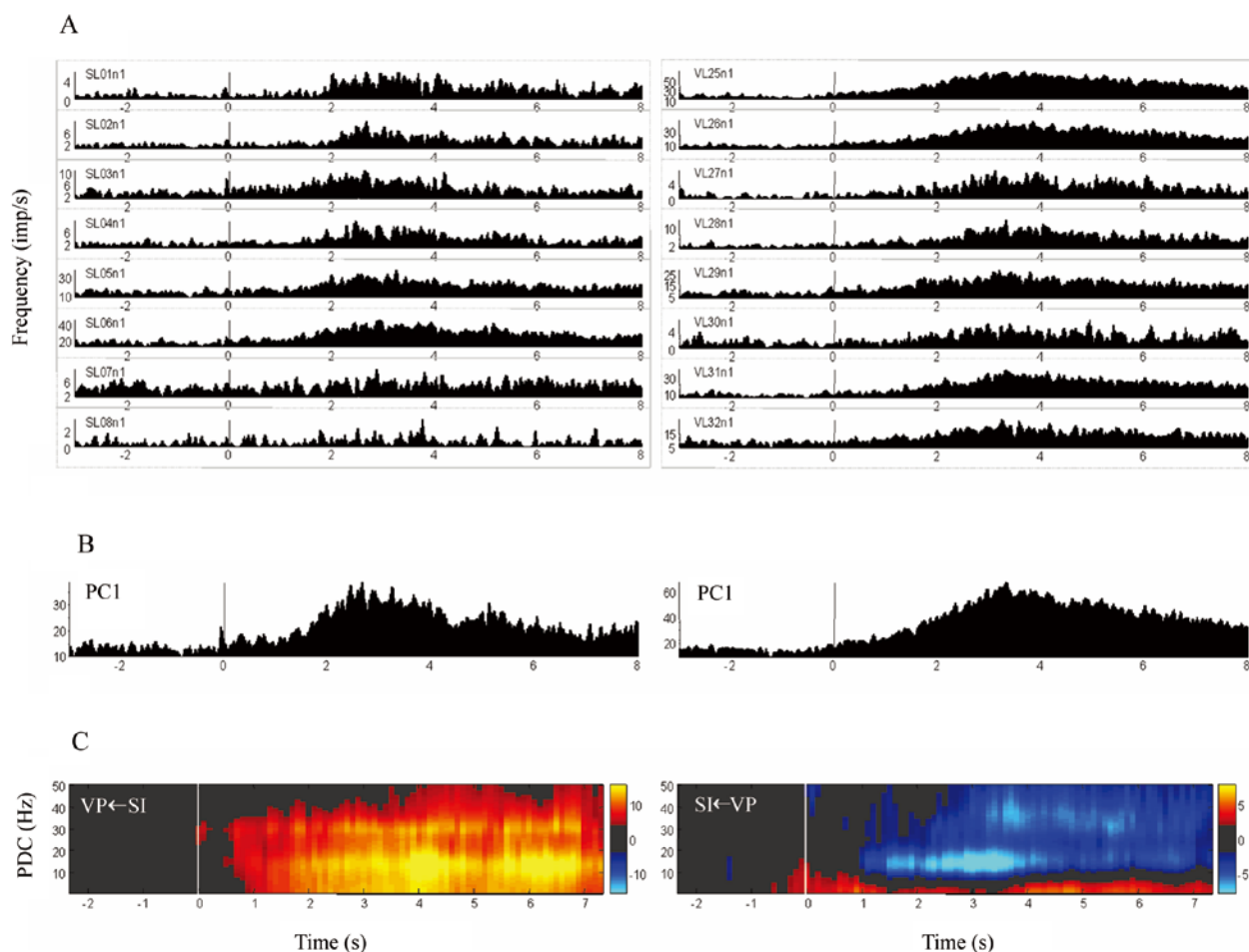
Fig. 2 Information flow between SI and VP following noxious stimulation. A: SI and VP neurons exhibited significant responses to noxious stimulation; B: principal component analysis revealed the similarity in nociceptive response between SI and VP neurons; C: the amount of information flow was significantly increased from SI to VP, while it was decreased from VP to SI (adopted from Wang *et al.*, 2007)[29].

mitted across pathways in a network pattern? Our recent finding supports the latter by demonstrating that the information flow is not limited to a single pathway when rat has received subcutaneous injection of formalin[20]. In the first 60 min (phases 1 and 2) of formalin test, the amount of information flow significantly increased from medial to lateral pathway, whereas it decreased from lateral to medial pathway. Interestingly, this direction predominance was dramatically reversed in the following 60 min (phase 3). The change in the direction of information flow may help explain the reduction of nociceptive behavior in the third phase while the formalin-induced inflammation remained unchanged. This finding suggests that the cross-talk between different pathways is necessary for the nociceptive signal processing, and the sensory coding involves distributed, instead of single, brain structures that constitute an organized coding network.

Subsequent findings by independent component analysis (ICA) of multichannel field potentials in rats[37] and functional connectivity analysis of human fMRI data[38] confirm the hypothesis that a network of brain regions participates in the nociceptive or tactile processing in a functional connective mode.

4   Conclusion

It is generally thought that peripheral inputs are transmitted along specific pathways and converge on neurons at a higher level of the brain. As a result, the sensory processing should be more integrated at a higher level in the neuraxis and finally accomplished at the highest center—the cerebral cortex. In other words, there are a few "head neurons" that essentially "perceive" the sensory signals and thereby form sensation. Up to date, however, the assumed "head neurons" have not yet been identified. Thus, researchers begin to realize that sensations are actually processed in a neural network, and it is the particular activation pattern that presents a particular sensation. This conforms to the well-known "cell assemblies" theory that was first proposed by Hebb[39] and later elucidated by Palm[40].

From this perspective, the concept of sensory "coding" exists in the absence of a decoder. Halpern has even suggested that the problematic construct of sensory coding and its concomitant decoding, should be replaced with more neutral and physical concept of transformation. He also proposed the elimination of the notion of representation or reconstruction of the world in some special nervous system locus. Since distributed, parallel processing is a natural corollary of transformations, no "command and control center" or fully-informed executive is needed in a parallel, distributed system[4].

From the perspective of psychology, one can perceive sensory image at any time. The environmental change is indeed presented in a particular manner in our consciousness, although it may be greatly modified and therefore not "true"[41]. Given the fact that we can not find a decoder in the brain that is responsible for sensory perception, how does our consciousness recognize the specific activation pattern representing some sensation and correctly realize what we are experiencing?

The human brain works in a way that is similar to a computer. The operation mode of the computer is analogous to the physical process of consciousness. The computers are controlled by programs that consist of a series of procedures for data processing. However, there does not exist a physical program and we can not "locate" the program inside a computer. The fact is that the procedures are carried out by many electrical and mechanical substrates. Information processing in a computer depends on both intact electric circuit and power supply. Similarly, human consciousness may not have physical presence as well. The substrates underlying consciousness are the neural circuitry. As part of human consciousness, the sensory perception is virtually the dynamic activity of the neural network. Just like the computer program process information without specific electronic line, the brain does not have specific structures for consciousness or perception generation. This suggests that the sensory perception is never objective. The consciousness "knows" environmental information indirectly from the activity of neural network that is influenced by internal or external factors, which means that we do not perceive things as they are in themselves but only the modified or distorted versions of them.

Taken together, the sensory processing is an opening

closed-loop system. Bottom-up information originates from the environment, starts as low-level sensory signals, and arrives at higher levels of the neural hierarchy in a parallel tempo-spatial pattern. The sensory perception gives rise to motor process and in turn generate top-down influence on the environment. The central sensory coding may involve many anatomically independent but functionally interacted structures within a neural network. The content of sensory perception is determined by the firing pattern and reciprocal communication of the network neurons.

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丘脑皮层通路神经元的伤害性反应

罗非，王锦琰

中国科学院心理研究所，中国科学院心理健康重点实验室，北京 100101

摘要：痛觉对于人类和动物的生存具有重要意义，但其脑机制长期不明。大脑如何解码痛觉诱发活动，并最终形成对于疼痛的知觉经验？在过去10年间，人们综合运用电生理、脑功能成像以及行为学手段开展了大量研究，试图回答这一问题。这些研究已经开始揭示疼痛形成的一些基本特征。人们逐渐认识到，参与痛觉信息传递和处理的是一个庞大的分布式神经网络。这些研究对于促进慢性疼痛新疗法的出现具有重要意义。

关键词：感觉编码；痛觉；丘脑皮层通路；神经网络