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REVIEW ARTICLE

Modulation of Central Nociceptive Coding by Acupoint Stimulation

Fei Luo · Jin-Yan Wang

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Abstract It is universally accepted that acupuncture or acupoint stimulation can produce analgesic effect on patients with painful disorders. The past decades has seen remarkable progress in exploring the central mechanisms of acupuncture-induced pain relief, including the neurotransmitter release and expression of particular receptors and genes in the spinal cord and the brain stem regions. Development of new techniques makes it possible to record and image the brain network patterns underlying pain perception and modulation, and to investigate the role of higher-level brain areas in mediating acupuncture analgesia. This review will present the current understanding of the neural network that is implicated in the modulation of pain by acupuncture.

Keywords Acupuncture · Analgesia · Neural network · Neural ensemble activity · fMRI

Introduction

Over the past 40 years, clinical observations and laboratory researches have established the overwhelming recognition that acupoint stimulation can produce analgesic effect. As one of the leading neuroscientists in this field, Professor Ji-Sheng Han worked over decades with his colleagues on the subject of pain mechanisms and analgesia. Their studies provided strong evidence that acupuncture stimulation can induce the release of neuropeptides such as opioid peptides in a variety of regions in the central nervous system (CNS) [1]. Using animal models of chronic inflammatory pain, Liu et al. showed that electric acupoint stimulation (EAS) can be effective for both pain relief (central mechanism) and tissue recovery (peripheral mechanism) [2]. In studies of chronic neuropathic pain, EAS of certain frequency was shown to change the discharge threshold of neurons in spinal cord dorsal horn [3]. It is known that the full recognition of pain perception involves three important dimensions: sensory-discriminative, motivational-affective and cognitive-evaluative. These dimensions are known to be mediated by physiologically specialized systems in the brain. By employing new techniques of functional brain imaging, event-related potentials and multichannel single-unit recording, the anatomical and functional organization of the neural circuitry underlying acupuncture analgesia have been extensively investigated. Studies with these advanced techniques have brought to light the fact that the central coding of pain signals involves a network of neurons, rather than a local "pain center". The neurons in this network are widespread distributed across the levels of neuraxis. Then, what are the network mechanisms underlying acupuncture analgesia? This review will address the question based on recent findings in this field.

Brain Regions Responding to Acupuncture

Early work by Yu et al. suggested that there might exist a specific circuit in the CNS mediating acupuncture analgesia, including the habenula, the nucleus accumbens, and the periaqueductal grey [4]. The subsequent studies by Ma et al. demonstrated that acupuncture stimulation activated

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F. Luo (✉) · J.-Y. Wang
Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, 10A Datun Road, Chaoyang District, Beijing 100101, People's Republic of China
e-mail: luof@psych.ac.cn

a network of brain structures rather than a local circuitry [5–11]. Evidence from nuclei lesion and stimulation studies revealed distinct neural pathways mediating low- and high-frequency electroacupuncture (EA)-induced analgesia [12–17]. This has been confirmed by morphological data using Fos gene expression as a marker of brain activation in rats [18]. These early findings suggest that acupuncture stimulation is capable of modulating distributed brain regions that comprise a functional neural network, with at least part of which related to the analgesic effect. Then two questions are followed. Do humans share the common mechanisms of acupuncture effects with those in rodents? Which brain structures activated by acupuncture are responsible for the pain-relief rather than other modulatory effects?

With the development of brain functional imaging techniques came the opportunity to non-invasively examine the neurobiological correlates of acupuncture analgesia in humans. Using these new techniques, a variety of investigations have focused on the brain mechanisms of acupuncture. However, the results are not consistent due to some influential factors such as stimulation modes, acupoint selection, and electrical current strength [19]. All the studies have emphasized the contribution of distributed regions, including sensory pathway and limbic system, to the pain-relief effect of acupuncture [20, 21]. Our functional magnetic resonance imaging (fMRI) study in human volunteers demonstrated that EAS of low frequency (2 Hz) activated contralateral primary somatosensory area (SI), the supplementary motor area (SMA), the caudal anterior cingulate cortex (cACC), the putamen, and bilateral secondary somatosensory area (SII), the insula, the ventroposterior thalamus (VP), the temporal lobe, and deactivated bilateral hippocampus. In contrast, that of high frequency (100 Hz) activated bilateral SI, SII, the insular, the nucleus accumbens (NAc), the thalamus, and contralateral Brodmann Area (BA) 40, the pons, and ipsilateral cACC, and deactivated bilateral amygdala and hippocampus [22]. As a result, the authors often proposed that these brain structures mediate the mechanisms of acupoint-stimulation induced analgesia.

Aside from the analgesic effect, acupuncture may have other therapeutic effects. Accordingly, the brain areas activated by acupoint stimulation may be as well involved in many other physiological modulatory functions in addition to its analgesic actions. In a recent study, we explored the correlation between acupuncture activated brain regions and behavioral antinociceptive responses. The brain regions that had positive correlation to both 2- and 100-Hz acupuncture analgesia included bilateral SII and insula, and contralateral cACC and thalamus. Areas showing correlations with 2 Hz EA analgesia were contralateral primary motor cortex (MI) and SMA, ipsilateral superior temporal lobe (positive correlations), and bilateral hippocampus (negative correlations). Areas showing correlations with 100 Hz EA analgesia involved contralateral parietal BA40, ipsilateral cACC, NAc, and the pons (positive correlations), and contralateral amygdala (negative correlations). Although bilateral SI and ipsilateral middle temporal lobe were activated by acupoint stimulation of both 2 and 100 Hz, no obvious linear correlations were observed between the activations and behavioral analgesic effect [22].

Therefore, we reached the conclusion that acupuncture can regulate the functional activity in a variety of brain regions, only part of which was responsible for the pain-relief effect. On the other hand, the increased blood flow or hemodynamics measured by imaging signal may reflect the changes in firing rates of a large number of neurons. It is possible that the activation of small population of neurons that is typically measured with single-unit electrophysiological methods cannot be detected by the imaging technique. Consequently, various different kinds of measurements are needed to correlate with each other.

Modulation of Central Nociceptive Coding by Acupuncture

It remains a controversy how CNS codes information. In 1949, Hebb first proposed the "cell assembly" theory. Neurons in a network tend to fire in given reverberatory sequences which are called cell assemblies. Each cell assembly represents a concept or sensory target [23]. For pain coding, Melzack proposed a related neuromatrix theory in which the nociceptive inputs from the periphery undergo cyclical processing and synthesis in the distributed neural network which can persist even after the injury has been cured [24]. These hypotheses were tested in our later studies.

A great deal of progress has been made in the past decade in identifying pain-related neural circuitry with functional imaging technique. However, the resulting data are not consistent and even quite different, due to such factors as paradigm design, property and organization of stimulus, and task performance of subjects. Acute painful stimulation applied on body surface often evoked activations of the SII, the insula, the ACC, the SI, the prefrontal cortex (PFC), the posterior parietal cortex, the thalamus, the brainstem, and the limbic system [25]. In contrast, visceral pain mainly activated lateral PFC, the SI, the SII, the parietal cortex, the thalamus and the cerebellum [25, 26]. However, researchers have recognized that the subareas activated by visceral pain or somatic pain are distinct in a certain brain region [27]. Moreover, the brain activations induced by painful stimulation are not identical between healthy subjects and patients with chronic pain [27, 28].

Based on the previous findings, we investigated the modulation of pain responses by EAS in the human brain. Nociceptive activations in the following brain areas increased after EAS treatment: (i) bilateral motor and premotor cortex (BA4, 6), the SII, the rostral ACC (BA32/24), the orbital frontal cortex, the medial PFC, the paracentral lobules, the thalamus, the midbrain, the pons and the cerebellum; (ii) ipsilateral SI, the lateral PFC, the posterior temporal lobe (BA21, 22, 37), and the putamen. Moreover, the range of increased activation in ipsilateral SII is larger than that of contralateral. On the other hand, the following areas showed attenuated pain activation after EAS: (i) contralateral SI, the lateral PFC, and the inferior temporal area (BA20, 37); (ii) bilateral cACC (BA24), the parietal BA7, the medial cuneus, the midbrain, the pons, and the cerebellum; (iii) ipsilateral parietal BA 39, and occipital BA19. It should be pointed out that although the temporal lobe, the ACC, the cerebellum, the midbrain, and the pons were involved in both positive and negative modulation of EAS, different sub-areas were related with different effects; no obvious overlap was found between them [29].

Thus, it is clear that EAS could modulate the pain-specific activation in the brain that involves the sensory, emotional, and cognitive neural circuitry. It is known that pain is a subjective experience that comprises sensory-discriminative, motivational-affective and cognitive-evaluative dimensions. One of the important characteristics of pain experience is behavioral avoidance. To further understand the neural basis underlying EA-induced analgesia, we examined the nociceptive activity modulated by acupuncture within thalamocortical neural network using multichannel single-unit recordings in awake rats. In the preliminary study, we found that noxious radiant heat induced discharges of a large percent of neurons (50–90%) within the sensory (lateral thalamus and SI cortex) and affective (medial thalamus and ACC) pain pathways. The most common response was excitatory; a small amount of inhibitory responses were encountered in the medial pain pathway [30]. Moreover, the results revealed a fundamental difference in temporal and spatial coding patterns of pain signal between the two pathways. Neurons for sensory coding displayed a strong and sharp excitatory response with short duration and significant contralateral bias. In contrast, those for emotional coding presented moderate and longer-lasting increase of neural activity, bilateral receptive fields without contralateral preference, part of which exhibited anticipatory response at the onset of noxious stimulus [30]. These findings were consistent with the previous studies using MEG [31], human electrophysiology [32], or functional brain imaging techniques [33].

To determine the neural substrates mediating EA analgesia, experiments were done to examine the pain-related neural activity modified by peripheral acupoint stimulation in rats using the multiple channel single-unit recording method. The results showed that peripheral electrical stimulation significantly attenuated the nociceptive responses in VP thalamus and somatosensory cortex, indicating an inhibition of nociceptive processing. In contrast, the analgesic stimulation produced a significant increase in mediodorsal (MD) thalamus while a less significant decrease was observed in cingulate cortex, reflecting a complicated effect associated with combined antinociceptive activation and nociceptive suppression [34]. These results support the idea that EAS can ultimately alter the pain perception by specifically inhibiting the nociceptive transmission in the sensory pathway while mobilizing the antinociceptive action in the affective pathway, thus to produce pain relief.

Cumulatively, these results support the view that acupoint stimulation is able to modulate the nociceptive signals at higher brain centers that process sensory and affective components of pain perception, as well as activating specific brain regions by itself. Further study on the nature of acupuncture modulation of neural network should be of great significance.

Modulation of Central Dynamic Activity by Acupuncture

The CNS is an extremely complicated network system. Information flow occurs at every level of the neuraxis. Considering the complex nature of pain experience, painful stimulation should necessarily induce a change in the information flow and functional connectivity in the nociceptive neural network. For example, recent functional neuroimaging study indicated the existence of a highly distributed functional connectivity network related to affective touch in the resting brain. Compared to the pleasant touch, the unpleasant aversive touch led to a significantly different functional connecting pattern between brain regions [35].

Similarly, in a laser-evoked field potential study in rats, we observed that nociceptive evoked potentials could be separated into several independent components, which represented the activities of anterior and posterior parietal area, medial frontal area, and anterior cingulate cortex, respectively [36]. Partial directed coherence (PDC) and cross-correlation analysis showed that the direction and amount of information flow between cortical areas presented stable and periodical changes after brief noxious laser stimulation. This suggested that transient noxious stimulation may lead to repeated reciprocal flowing of nociceptive related information within the central neural network [36].

With multichannel sing-unit recording technique in awake rats, we also found that noxious stimulation produced an increase in the cross-correlations between individual neurons within the thalamocortical circuitry [34]. The somatosensory cortex had enhanced descending influence on thalamic neurons during pain processing [37]. Directed coherence analysis revealed that the amount of information flow between cortex and thalamus was strongly influenced by peripheral noxious stimulation. The top-down modulation was shown to exist from somatosensory cortex to sensory thalamus [37], which was consistent with that demonstrated by cross-correlation analysis. More importantly, this phenomenon was observed not only in the condition of brief noxious stimulation, but also in that of formalin-induced persistent pain [38].

The above results suggested that central coding of pain signals concerned the dynamic processing related to information flowing among neural populations in the CNS. Therefore, the mechanisms underlying acupuncture analgesia may be associated with interfering in the process of information flowing between brain nuclei. In a recent study, EAS of various frequencies was used to investigate the modulatory effect on the information flow within thalamocortical neural network. Just as we expected, cortical and thalamic neurons exhibited frequency-specific responses at both single-neuron and ensemble levels. The information flowing between cortex and thalamus was altered (enhanced or inhibited) in a frequency-specific pattern during stimulation [39]. This finding provides evidence for the hypothesis that the mechanisms underlying acupuncture analgesia are relevant to the disturbing of dynamic information flowing between brain regions.

Further confirmation came from the studies of the functional relationship between thalamic and cortical neurons following noxious heat stimulation in rats, using the cross-correlation analysis. Interestingly, it was found that EAS was able to weaken the correlation enhanced by painful stimulus [34].

Specificity of Stimulation Sites and Parameters to Acupuncture

In Chinese acupuncture, the therapeutic effect of acupuncture is closely related to the stimulation mode. There has been a great of difference in the experimental data according to the stimulation paradigm [19]. Then, can we corroborate the specificity of stimulation sites and parameters to acupuncture using the advanced modern techniques?

Using animal models of chronic pain, we compared the therapeutic effect of acupuncture applied in different brain site with different frequency. The results suggested that the acupuncture therapy resulted in frequency-dependent effects on chronic inflammatory [2] or neuropathic pain [40] in rats. In addition, acupuncture stimulation applied on different body sites produced significantly different effects, which varied with stimulation frequency [41]. For example, high-frequency (100 Hz) stimulation effectively treated ankle joint arthritis with needles in Zusanli (ST36) or Yongquan (Kid1) acupoint but not in Laogong (PC8) acupoint; in contrast, low-frequency (2 Hz) stimulation produced analgesic effect only in Kid1 but not ST36 or PC8 acupoint. These data indicated that high-frequency acupuncture stimulation exerted analgesic effect in a broader range of body areas than the low-frequency stimulation; and the latter had better effect only on adjacent inflammatory pain [41].

With fMRI method, we compared the brain activations induced by acupuncture stimulation of different frequency. We found that high- and low-frequency stimulations did activate distinct but overlapped brain networks [22]. We also investigated the effect of 1- to 100-Hz peripheral electrical stimulations on the spike activity of thalamic and cortical neuronal populations in awake rats. The results showed that cortical and thalamic neurons exhibited frequency-specific responses at both single-neuron and ensemble levels [39]. A few individual neurons showed frequency-locked responses, while others did not track the frequency of peripheral stimulation. This suggested that distinct neuronal networks were activated by different frequency of stimulation. Each brain areas in the thalamocortical pathways also displayed distinct response pattern to stimulation frequencies. Further analysis revealed great difference in the information flow corresponding to different frequency ranges within thalamocortical areas, a "fingerprint" like property [39]. Given the evidence of dynamic changes in nociceptive neural network induced by pain, modulation of the brain network responding by specific stimulation frequency should be the important mechanism underlying frequency specific acupuncture analgesia.

On the other hand, the acupoint-specific effects of acupuncture in human subjects are rarely reported. In a study designed to test whether acupoint stimulation in the same spinal segments could induce different central responses, we found evidence to support the site-specific effects of acupuncture [42]. Stimulation of acupoints ST36/SP6 (Zusanli/Sanyinjiao) or GB34/BL57 (Yanglingquan/Chengshan) shared some brain activation and de-activation in common. However, ST36/SP6 stimulation specifically activated orbital frontal cortex and ventral thalamus, de-activated hippocampus and parietal BA7. Most of these areas were regarded to be involved in visceral modulation. In addition, stimulation of GB34/BL57 activated dorsal thalamus and inhibited those of primary motor area and premotor cortex.

GB34 and BL57 were important acupoints for functional modulation of muscles and tendons. Thus, stimulation of acupoints in the same spinal segments induced distinct though overlapped cerebral response patterns, i.e., different coding, which indicated the existence of acupoint specificity [42]. Moreover, the activation/de-activation pattern observed in this study may reflect the role of acupuncture in modulating special physiological functions.

Conclusions

Development of advanced techniques in neuroscience research field leads to a better understanding of the mechanisms underlying acupuncture analgesia. Pain is a subjective experience that has multiple dimensions including sensory, emotional, and cognitive components that involves higher level of central processing. Thus, successful modulation of pain by acupuncture stimulation or other analgesic approaches should implicate these dimensions. The study on mechanisms regarding high-center coding of acupuncture will bring new perspective to the knowledge of pain and analgesia, and promote the clinical management for the patients with chronic pain.

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