

Study on the mechanism of acupuncture analgesia from the perspective of psychosomatic medicine

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Author contributions

Xue Pu and Xin-Yao Kong drafted the manuscript. Tian-Cheng Xu contributed to the conception of the study. The authors critically reviewed the manuscript.

Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Abbreviations

CAM, Complementary and alternative medicine; SP, Substance P; KOA, Knee osteoarthritis; EA, Electro-acupuncture; MA, Manual acupuncture; ADHD, Attention deficit hyperactivity disorder; IBS, Irritable bowel syndrome; PSD, Poststroke depression; TNF- α , Tumor necrosis factor- α ; IL, Interleukin; GABA+, γ -aminobutyric acid; 5-HT, 5-hydroxytryptamine; DA, Dopamine; ICCs, Interstitial cells of Cajal; POI, Postoperative ileus; DRG, Dorsal root ganglion; Glu, Glutamate; TNF-R1, Tumor necrosis factor receptor 1; CRF, Cancer-related fatigue; TRPV1, Transient receptor potential V1 receptor; MDD, Major depressive disorder; PTSD, Post-traumatic stress disorder; PI, Psychological intervention; IA, Internet addiction; NCDs, Chronic non-communicable diseases; TRPV1, Transient receptor potential V1; TLR4, Toll-Like Receptor 4.

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Background

Acupuncture has been practiced in more than 183 countries and regions, some of which included acupuncture in their medical insurance [1]. Acupuncture is recognised in Namibia, which has passed legislation on acupuncture, including it in the national health insurance system in 2020 [2]. In the United States, thirty-three states consider acupuncture to be within the scope of practice of physicians. As a therapy for chronic low back pain, acupuncture has been covered by Medicare since 2020 [3,4]. In Japan, it is a complementary and alternative medicine (CAM) therapy which has been covered by the national health insurance partially [5]. In Germany, there was statutory insurance coverage for medical cost of acupuncture for chronic lower back or knee pain. German women who suffer back and knee pain have a high-using rate of this type of therapy, receiving great benefits after repeated treatment [6]. Acupuncture and traditional Chinese medicine account for the largest proportion, up to

Abstract

Acupuncture is a kind of traditional Chinese therapy which has gained increased attention in recent years. It has been shown that acupuncture is effective in treating many types of pain pathologically as well as psychologically. For instance, as a promising therapy for psychiatric disorders, acupuncture is helpful to alleviate depression, reduce the adverse effects of drug treatment at the same time. It is most widely utilized for management of chronic, noncancer pain in adults. As a non-pharmaceutical measure, acupuncture has the potential to make contribution to reduction in opioid overuse. Acupuncture analgesia can be analyzed from the perspective of psychosomatic medicine, contributing to a better understanding of its mechanism and function. The mechanisms are closely related to regulation of neurotransmitters and inflammatory factors, including down-regulation of Glutamate, 5-hydroxytryptamine, dopamine, Substance P, Tumor necrosis factor- α , Interleukin (IL)-1, IL-6 and up-regulation of β -endorphin, endogenous opioid peptide, γ -aminobutyric acid, etc. Electro-acupuncture (EA) has pain-relief effects under some specific parameter values. Low frequency EA is more commonly used in clinical practice than high frequency EA. Our study conducts a comprehensive analysis of acupuncture analgesia and discusses associated characteristics of its mechanisms.

Keywords: Acupuncture, Analgesia, Psychosomatic medicine, Pathological pain, Psychological pain

21% in a study which intended to examine the usage of CAM practices among German elders who have health insurance. Similar to an alternative whole medical system originating in Western Europe, acupuncture has established its system in Germany [7].

Numerous clinical trials of acupuncture have demonstrated its effectiveness in treatment of pain. Nowadays, acupuncture is clinically proven to be a powerful, safe and economical therapy, managing numbers of medical conditions effectively [3].

The 2021 Nobel Prize in Physiology or Medicine is in helping interpret how acupuncture and moxibustion works, too [8]. Acupuncture analgesia can not only abate the substantial pain on the body, but also have a great therapeutic effect on the mental pain feeling. In the United States, opioids, introduced in the late 1990s, are currently the most widely used and highly effective analgesic drugs. However, opioids have many toxic side effects, including addiction, constipation and respiratory depression. The death from respiratory depression caused by opioid addiction directly contributed to the widespread opioid crisis. Opioid abuse has caused so much

unnecessary expenditure that it has brought a heavy economic burden to the US government. Moreover, the crisis has also been a threat to human health, affecting the quality of life. In a study, nearly 4% of mature Americans abused prescription opioids and overdose of legal or illegal drugs caused death of over 33,000 people in 2015 [9]. Despite widespread recognition of the role prescription opioids play in the opioid epidemic, heroin and synthetic opioids account for the majority of overdose deaths related to opioids. It is imperative that people pay more attention to factors surrounding the illicit use of heroin and fentanyl. It will also be critical to reshape existing prevention strategies for the opioid crisis [10]. In light of the heightened focus on the opioid crisis in America, acupuncture may be helpful for treatment of military beneficiaries who suffer insomnia and chronic pain as a way of effective nonpharmacological pain management [11]. From a biomedical and physiological perspective, acupuncture's mechanism of action is the enhancement of the release of analgesic endogenous substances, decreasing the release of substances which can induce pain and damage to neural systems [12,13]. Acupuncture analgesia can be analyzed from the perspective of psychosomatic medicine, contributing to a better understanding of its mechanism and function.

Classification of pain from the physical and mental medical perspective

Pain may occur due to external physical damage to the body, lesions of tissue cells or internal dysfunction associated with social, environmental and other emotional factors. According to the definition of pain, it is an unpleasant sensory and emotional experience that begins with a peripheral stimulus that is processed by a physiological process to produce the sensation of pain, including pathological pain and psychological pain [14]. In order to accurately classify chronic pain conditions, reliable and valid pain assessments are required. Moreover, pain assessment serves several additional functions, including documenting the severity of the pain condition, tracking the longitudinal course of pain, and providing mechanistic information. Pain assessment must address multiple domains of pain, including sensory and affective qualities, temporal dimensions, and location and bodily distribution of pain. Where possible, pain assessment should also incorporate methods to identify pathophysiological mechanisms underlying the pain [15]. The pain mechanisms that have been discovered so far include dysfunction in nerve fibers [16], neurogenic inflammation caused by the substance P (SP)-induced mast cell degranulation the production of catabolic factors [17], long noncoding RNA (lncRNA) XIST's activating the NF-κB pathway via the miR-340-5p/RAB1A axis [18] and so on. In general, pain can be divided into the following categories (Figure 1).

Pathological pain

Pathological pain refers to pain caused by various injuries or diseases [19]. Pain that is spontaneous, hyperalgesic, abnormal in nature, and has abnormal sensory characteristics can be symptoms of it. Neuropathic pain, as the most well-studied example, is a direct consequence of lesions or diseases of the somatosensory system and is relatively common among all the types of pain [20]. The International Pain Research Society defines neuro-pathic pain as pain on account of damage or lesions to the nervous system [21]. Depending on the site of the neurological damage, neuropathic pain can be grouped into central neuropathic pain and peripheral neuropathic pain [22]. The treatment of neuropathic pain is mainly conducted according to different causes: Firstly, trigeminal neuralgia can be treated for carbamazepine, gabapentin, and pregabalin. It should be noted that carbamazepine can cause dizziness or drowsiness and the risk of severe exfoliative dermatitis. Secondly, vascular inflammatory peripheral neuropathy or amyloid peripheral neuropathy caused by neuropathy, can be given hormone or C ball shock treatment, while giving symptomatic analgesic treatment, but also to give nutritional nerve drugs, mainly vitamin B1, B12, methocobalamin. Thirdly, diabetic peripheral neuropathy can also cause obvious pain in patients. On the basis of blood sugar control, give nutritional nerves and drugs to improve the microcirculation, such as prostadil, pancreatic kinin-releasing enzyme, and can be treated with antioxidants, mainly with alpha-lipoic acid. Fourthly, central neuralgia, mainly with neuropathic pain drugs, such as pregabalin, duloxetine, etc.

Psychological pain

In addition to pathological pain, pain is also a special type of psychological activity, which has complex definition and connotations. It is a persistent unpleasant and unsustainable feeling characterized by an inability or deficiency of the self with social disconnection and frustrated psychological demands [23]. The affective dimension of pain is made up of two aspects. One is unpleasant feeling, termed primary unpleasantness which is always accompanied by pain stimulation, such as fear. In addition, secondary pain affect, a lasting emotional response, is emotions in relation to future implications. It is closely associated with learning, remembering, imagining, cognitive appraisal and etc [24]. Depression is a good example. With the accelerated pace of life, the incidence rate of depression has increased year by year, which has brought tons of trouble to people's life and work. In order to prevent and treat more effectively, we should realize that depression not only affects emotions, but also leads to physical pain. From the perspective of their occurrence mechanism, there is also a close relationship between them. We all know that pain is a subjective psychological experience, and the brain, spinal cord and peripheral nerves play their respective roles in the transmission of pain, which is finally felt by the brain.

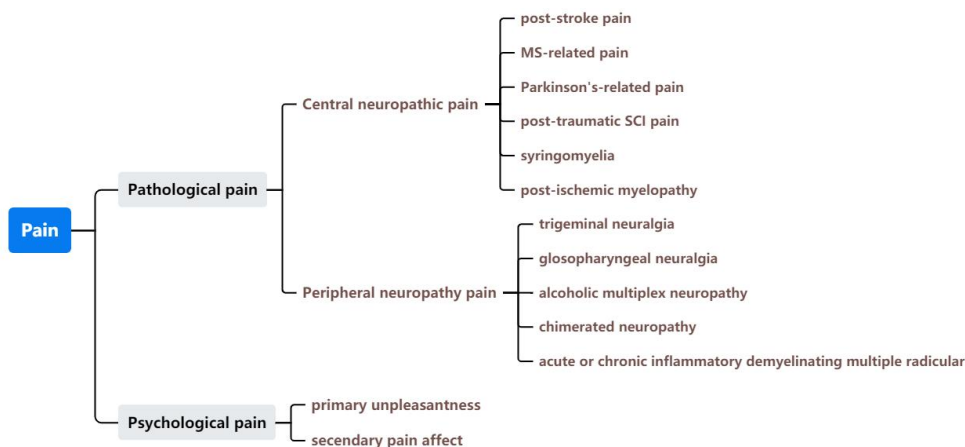


Figure 1 Classification of pain from the physical and mental perspective

The central nervous system (spinal cord and brain) plays a key role in pain perception. In the central nervous system, there are two substances called serotonin and norepinephrine, which play an important role in pain signal processing and pain regulation. The functional state of these two substances may determine a person's perception of pain. At present, there is a large amount of medical evidence indicating that there is a causal relationship between the dysfunction of the above two substances and the occurrence of depression. In this way, a possible link is established between pain and depression. The dysfunction of 5-hydroxytryptamine (5-HT) and norepinephrine leads to depression, but at the same time, it also causes the brain to be too sensitive to pain signals, and even amplifies the pain signals, which eventually leads to patients' pain. A considerable number of patients have been repeatedly seeing doctors in general hospitals for a long time due to various kinds of pain, but no reason can be found. It seems effective to take various painkillers, but it will lead to drug dependence and increase the pain of patients. The headache caused by depression is usually persistent and systemic. People with depression often say that their headaches are worse in the morning and at night. These are most likely tension headaches, which occur when the neck and scalp muscles are tense or contracting. In addition to headaches, back pain is also common in patients with depression. This discomfort may also include pain or stiffness in the spine, as well as severe pain in the neck, upper back, or lower back. This is the place where people bear most of the pressure. During the day, all the pressure is on their neck and shoulders. The thinking and movement of patients with depression are in a slow state. If they do not like to exercise regularly, their muscles will not get a good rest and pain follows. Moreover, their brains are too sensitive to pain signals, and even amplify pain signals, leading to unbearable pain. In addition to these two kinds of pain, muscle and joint pain, inexplicable chest pain, stomach pain or abdominal pain and other kinds of pain are bothering patients with depression. Psychological strategies for treating chronic pain are an essential component of the multidimensional treatment. The following techniques have been shown to be effective: relaxation training, biofeedback, hypnosis and cognitive-behavioral therapy. There is a direct impact of these techniques on pain sensory processing, psychologic distress, and the maladaptive coping mechanisms that people develop in response to pain [25].

Clinical application and mechanism of acupuncture analgesia

Main types of acupuncture analgesia

There are several main types of acupuncture analgesia in nearly five years, including pathological pain and psychological pain (Table 1). Recent researches have made progress in some certain areas when it comes to acupuncture treatment for pathological pain. People have attached most attention to knee osteoarthritis in recent years. Knee osteoarthritis (KOA) is a common chronic degenerative bone and joint disease [26]. Latest therapies for KOA include abdominal acupuncture combined with warm needling [27], Electro-acupuncture (EA) and manual acupuncture (MA) [28, 29] and warm acupuncture combined with meloxicam and comprehensive nursing [30]. Fibromyalgia pain, herpes zoster and postoperative pain are also concerned types. What's more, acupuncture may have effects on the treatment of chronic low back pain, headache and myofascial pain [31].

Psychological pain is always relevant to pathological pain in some certain cases. It is proven that negative emotions such as emotional distress, anxiety and hopelessness interact with pain closely [32]. An increasing body of evidence suggests that there is a bidirectional association between chronic pain and psychological disorders [33]. On the one hand, pathological pain can intensify psychological pain. For example, postpartum depression, the most common complication of childbirth, is a serious psychiatric disease. It always gives rise to suicide, making up about 20% of postpartum deaths [34]. One of the latest studies has shown that postpartum pain was linked to 6-month postpartum depression symptoms [35]. That is to say labor and

postpartum pain may give rise to formation and aggravation of postpartum depression to some degree. On the other hand, psychological pain occupies an important position in the motivating factors of pathological diseases progression. For instance, there is an emerging view that psychological pain plays a vital role in the mechanism of pelvic pain. Combined with psychotherapy, somatosensory stimulation has shown significant effects in reducing psychological symptoms such as pain and anxiety [36]. Besides acute pain, chronic pain and the psychological pain it rises have an effect on each other [37]. Numerous trials in clinic have confirmed that patients with chronic pain invariably experience psychiatric disorders such as anxiety and depression. Patients who suffer chronic pain are more likely to have anxiety and depression, and the more pain people feel, the more anxious and depressed they are [38].

The advantages of acupuncture in the treatment of mental illness are gradually emerging at present. Some studies have confirmed that acupuncture combined with psychological intervention can not only relieve simple negative emotions, but also play an effective role in treating some combined syndromes with psychological disorders, including attention deficit hyperactivity disorder (ADHD) and internet addiction [39-40]. Emotional dysregulation, a related trait, is likely to be a core component of ADHD in children [41]. Some children with ADHD often suffer from anxiety and depression due to criticism from teachers and parents and rejection from peers. Similarly, people with internet addiction have psychological trait: social anxiety [42]. In addition, acupuncture is a good choice for treatment of emotional disorders with somatic symptoms such as irritable bowel syndrome (IBS) and hypertension. IBS is a chronic gastrointestinal disease, featured by abdominal pain or discomfort [43]. In a latest clinical trial, acupuncture may enjoy great advantages over some laxative and spasmolytic such as PEG 4000 and pinaverium bromide in the treatment of IBS [44]. Hypertension is one of the most important cardiovascular disease which has a negative effect on health [45]. It is common to see psychological symptoms such as anxiety and depression in patients with pulmonary arterial hypertension [46]. It has also been evidenced that the symptoms of anxiety are associated independently with hypertension [47]. Acupuncture might have antihypertensive effects on patients with stage I hypertension [48]. Last but not least, as an appropriate alternative nondrug therapy, acupuncture is helpful to reduce the adverse effects and drug dependence for people with psychological disorder. It is common to see poststroke depression (PSD) among all the complications of stroke [49]. Some antidepressants seem to increase the risk of drug-drug interactions such as fluoxetine hydrochloride in spite of the effectiveness in treating PSD [50]. For example, when it comes to treating patients who are receiving clopidogrel, fluoxetine and fluvoxamine are always forbidden [51]. As a promising alternative therapy for PSD people, acupuncture is prospective to have larger application area in terms of psychological diseases treatment [52].

According to the quality, causes of pain can be classified into several aspects (Table 2). Pain is not only a kind of experience, but also a negative influence on mentality. In clinic, psychosomatic comorbidities are common in pain associated with neuropathy, inflammation, malignancy. For example, patients who suffer migraine chronification may report negative feelings like fatigue, depression and anxiety [53]. Psychological stress is associated with increased inflammation, increasing the risk of coronary heart disease [54]. Psychosocial factors may be considered risk factors for specific types of cancer and are of great importance in the cellular aging process [55]. In a word, acupuncture analgesia is increasingly playing a vital role in the treatment of neuropathic pain, inflammatory pain and cancer pain pathologically and psychologically.

Mechanism of acupuncture analgesia

Among all the mechanisms of acupuncture analgesia in terms of pathological pain, the level of inflammatory factors in serum has a significant function (Figure 2). Studies have evidenced that acupuncture shows the possibility of alleviating inflammation by reducing the levels of proinflammatory cytokines [56]. Tumor

necrosis factor alpha (TNF- α) has been the inflammation biomarker which people studied a lot in the aspect of acupuncture, and interleukin-1 (IL-1) is the same [57,58]. As a pathological component of autoimmune diseases, TNF- α has recently been proven to exert additional important functions [59]. TNF- α plays a key role in the complex immune network by adjusting other inflammatory cytokines [60]. IL-1 has long been associated with inflammation and innate immunity [61]. IL-1 β is the most studied of the IL-1 family of cytokines, including 11 members [62]. In the studies of knee osteoarthritis therapy, it has been proven to have analgesic effects. Improvement in pain relief partly benefits from changes of major inflammatory factors, including reduction of IL-1 β and TNF- α . Compared with MA, EA reduced TNF- α more significantly [29]. There also exist several other important and irreplaceable inflammatory factors which have close relationship with pathological pain such as rheumatoid factor. The adjuvant function of abdominal acupuncture in treating rheumatoid arthritis has been proven to be effective in relieving the symptoms of patients in clinic. The mechanism is related to the decrease of rheumatoid factor in terms of inflammatory factors. What's more, the changes of erythrocyte sedimentation rate and C-reactive protein also play a role in this process [63].

What's more, there exist some other special mechanisms in some certain cases. Firstly, acupuncture therapy can regulate neurotransmitters to exert analgesic effect, including increasing the release of endogenous opioid peptide and γ -aminobutyric acid (GABA+) and reducing the secretion of neurotransmitters such as 5-HT, dopamine (DA) and SP [64, 65]. Reducing the secretion of 5-HT, DA and SP and releasing endogenous opioid peptides are obviously effectual to treat headache which is always caused by stroke [66]. Reduction of pain severity in treating fibromyalgia pain is bound up with increase of GABA+ in the anterior insula [65]. In another clinical study, acupuncture is proven to provide benefits for patients with chronic migraine, reducing frequency of migraine attack, pain intensity and cerebral blood flow velocity. Its mechanism may be related to regulation of calcitonin gene-related peptide, 5-HT and vascular endothelial growth factor [67]. Secondly, acupuncture therapy leads to early mechanistic changes in somatosensory processing. Symptoms of chronic low back pain can be alleviated by acupuncture in course of reducing S1-back gray matter volume and increasing S1-back adjacent white matter fractional anisotropy [68].

Table 1 Main types of acupuncture analgesia

Classification of pain	Diseases that cause pain	Mechanisms of acupuncture analgesia
Pathological pain	Chronic low back pain	Reduced S1-back GMV and increased S1-back adjacent white matter FA
	Knee osteoarthritis	Decreased VEGF and Ang-1 Increasing TGF- β 1 content Changes of major inflammatory factors TNF- α , IL-1 β and IL-13 Decreased PGE2, SP, DA, 5-HT, and MDA
	Irritable bowel syndrome	The modulation of the expressions of 5-HT3R and 5-HT4R mRNA in colon tissue
	Postmenopausal osteoporosis	Regulate the neuroendocrine function
	Headache in the recovery phase of ischemic stroke	Down-regulate the pain-related factors and up-regulate endogenous opioid peptides in plasma
	Fibromyalgia pain	Changes in serum serotonin and SP levels Increased S1 leg-anterior insula connectivity and increased levels of γ -aminobutyric acid in the anterior insula
	Chronic migraine	Regulate serum levels of 5-HT, CGRP and VEGF
	Rheumatoid arthritis	Reduction of ESR, RF and CRP
	Herpes zoster	Changes in serum serotonin and SP levels Reduction of serum IL-6, IL-8 and SP levels
	Postoperative pain	Reduction of the expression of inflammatory cytokines Modulation of inflammation
	Acute herpetic neuralgia	Exert neuroprotective effects
	Labor pain	Down-regulating plasma glutamate level
	Primary dysmenorrhea	Regulate the serum levels of PGF2 α and PGE2
	Trigeminal neuralgia of wind and heat	Regulation of serum IL-6, TNF- α , VIP and β -EP
	Diabetic gastroparesis	Alleviate the damage of interstitial cells of Cajal
	Perioperative pain	Increase of plasma concentration of β -endorphin
	Endometriosis-associated pain	Neurobiological mechanism
	Cancer-related fatigue	Down-regulate serum levels of the relative inflammatory factors
	Paclitaxel-induced peripheral neuropathic pain	Suppressing TLR4 signaling and TRPV1 upregulation in dorsal root ganglion neurons
	Psychological pain	Depression
Anxiety		Neurobiological mechanism
Attention deficit hyperactivity disorder		Regulation of cerebral blood flow
Cancer-related fatigue		Down-regulate serum levels of the relative inflammatory factors
Chronic fatigue syndrome		Decrease of the levels of IL-6 and INF- γ in serum
Internet addiction		Increased NAA and Cho levels in prefrontal and anterior cingulate cortices
Irritable bowel syndrome		The modulation of the expressions of 5-HT3R and 5-HT4R mRNA in colon tissue
Hypertension		Downregulating p47 phagocyte oxidase mRNA and protein expression in the rostral ventrolateral medulla

Table 2 Classification of pain according to its quality

Quality of pain	Representative diseases	Mechanisms of pain	Therapies
Postoperation pain	Hernia surgery in children	Physical damage to part of the nerve	Auricular point pressing combined with EA
	Gastric cancer surgery		Transcutaneous electrical acupoint stimulation
	Upper extremity trauma surgery		Opioid
	Arthroscopic knee surgery		Non-steroidal anti-inflammatory drug
Neuropathic pain	Chronic low back pain	Somatosensory processing disorders	Acupuncture therapy Physical therapy
	Chronic migraine	Maladaptation of the top-down pain modulation and subsequent sensitization of trigeminal system may be important in the pathogenesis of chronic migraine	Acupuncture therapy Topiramate Monoclonal antibodies targeting the CGRP pathway
	Trigeminal neuralgia	Central etiology, peripheral etiology and role of immune and biochemical factors	Acupuncture therapy Traditional Chinese medicine therapy Carbamazepine, dilantin
Inflammatory pain	Fibromyalgia pain	Oxidative stress, central pain sensitization, genetic polymorphism of transporter protein, abnormal content and function of biogenic amines, excessive release of inflammatory factors, intestinal flora disorder or vitamin d deficiency	Acupuncture therapy Extracorporeal shock wave Amitriptyline, tramadol
	Knee osteoarthritis	Release of inflammation-related bioactive substances, peripheral and central sensitization	Acupuncture therapy Mesenchymal stem cells Range-of-motion-based rehabilitation program Extracorporeal shockwave therapy
	Acute low back pain	Tissue damage	Nonsteroidal anti-inflammatories Physical therapy Educating patients on prognosis
	Coronary heart disease	Abnormal lipid metabolism in the body	Acupuncture therapy Drug therapy Psychological interventions Coronary stenting
Cancer pain	Cervical cancer	Persistent high-risk human papillomavirus (hr-hpv) infection	Acupuncture therapy Immunization therapy Surgery
	Osteoradionecrosis	Radiation, trauma and infection	Hyperbaric oxygen therapy Surgery
	Bone metastasis	Acidification of the bone microenvironment	Non-steroidal anti-inflammatory drugs Opioid
Psychological pain	Depression	Monoamine neurotransmitter hypothesis	Acupuncture therapy Drug therapy Psychotherapy
	Anxiety	Neurotransmitter disorders, changes in neuronal excitability, imbalance of cytokine levels	Acupuncture therapy Drug therapy Psychotherapy
	Attention deficit hyperactivity disorder	Neurotransmitter abnormalities, inherited genetic abnormality	Acupuncture therapy Drug therapy Psychotherapy

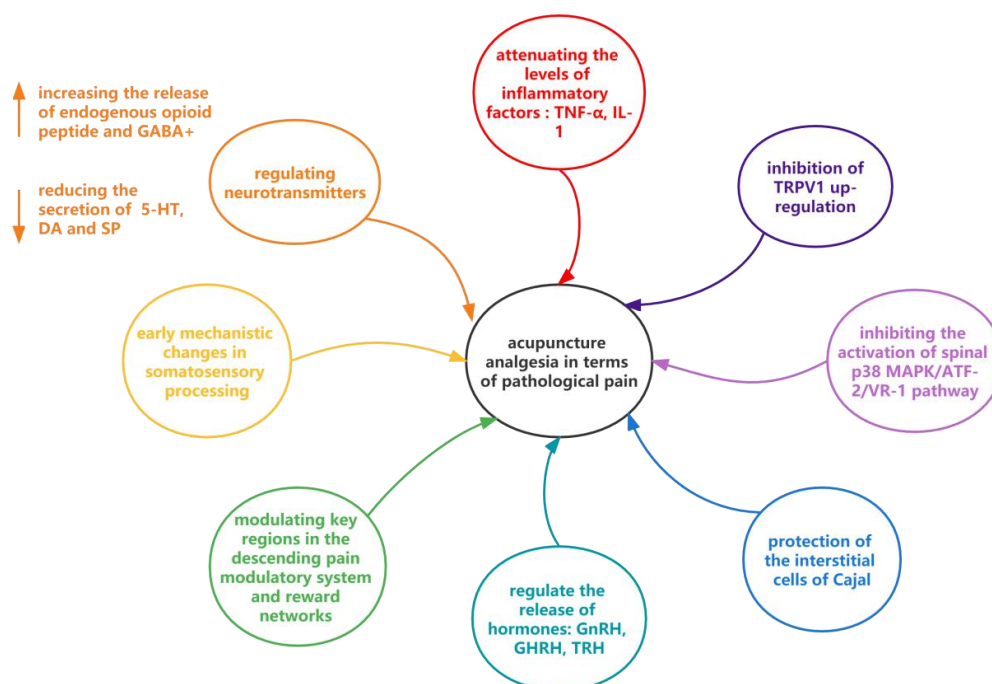


Figure 2 Mechanisms of acupuncture analgesia in terms of pathological pain

Thirdly, acupuncture have great effects on regulating core regions in the descending pain modulatory system and reward networks [69]. Fourthly, acupuncture may regulate the release of hormones, relieving pain indirectly in this way. When it comes to treating postmenopausal osteoporosis, acupoint embedding is widely applied. It may improve the neuroendocrine function by regulating the secretion of diverse hormones such as gonadotropin-releasing hormone, growth hormone-releasing hormone, and thyroid-stimulating hormone-releasing hormone through monoamine neurotransmitters, adjusting the bone mass [70]. Fifthly, the mechanism may be related to protection of the interstitial cells of Cajal (ICCs). The state of ICCs during postoperative ileus (POI) plays a vital role in the restoration of gastrointestinal motility [71]. Animal experiments have proved that acupuncture provides protection for ICC's partly by regulating miR-222 in model of POI [72]. In another study, acupuncture improves POI by protecting ICC via the IL-6-miR-19a-KIT axis [73]. EA may be dependent on the HO-1 positive macrophages to protect the networks of ICC, mediating anti-inflammatory and antioxidative stress effects [74]. Sixthly, inhibition of the activation of spinal p38 MAPK/ATF-2/VR-1 pathway. It may be one of the main mechanisms via central signal transduction pathway in the process of anti-inflammatory pain by EA in CFA rats [75]. Seventhly, acupuncture has a significant ability to regulate nerve signaling pathways. EA can play an analgesic role by regulating transient receptor potential V1 (TRPV1) neurons in dorsal root ganglion (DRG). Previous studies have confirmed that inhibition of TRPV1 up-regulation in ipsilateral adjacent undamaged DRGs contributed to low frequency EA analgesia for mechanical allodynia induced by spinal nerve ligation [76]. Another research's results demonstrated that EA alleviates paclitaxel-induced peripheral neuropathic pain by inhibiting Toll-Like Receptor 4 signaling and TRPV1 upregulation in dorsal root ganglion neurons [77]. EA also has pain-relief effects under some specific parameter values. In a study, the level of the hypoalgesic efficacy of EA was closely associated with frequency and EA had better effects at 100 Hz than at 2 Hz, which has something to do with mediation of the protein level of TRPV1 and P2X3 expression in DRG [78].

Comparing cases in pathological pain with ones in psychological pain, acupuncture can treat both pathologically and psychologically in one type of disease. The mechanisms are closely related to the changes of neurotransmitters and inflammatory factors. There are two vital and representative neurotransmitters, including glutamate (Glu) and β -endorphin. Glu is the most important excitatory neurotransmitter of the mammalian central nervous system [79]. Accumulating evidence has supported the role of Glu which is the excitatory amino acid neurotransmitter in the treatment of depression recently [80]. For example, transcutaneous electrical acupoint stimulation can alleviate labor pain and reduce the incidence of postpartum depression by down-regulating the plasma glutamate level [81]. Besides Glu, β -endorphin is vital for pain relief too. It is universally acknowledged that opioids are the most commonly applied and effective medicine for severe pain, acting on the endogenous opioid system [82]. In a clinical trial, auricular point sticking therapy, one kind of acupuncture, can not only relieve perioperative pain, but also regulate anxious and depressive feelings in patients with partial lung resection. It seems to be the consequence of increasing plasma concentration of β -endorphin [83]. Researchers have shown that some related inflammatory factors also play an irreplaceable role in the analgesic process. A study observed that patients with depression may have imbalance of the immune system [84]. This may explain the dual function of acupuncture analgesia. Immune modulating effect of IL-6 family cytokines and interferon has been extensively studied among cytokines [85,86]. IL-6 holds a vital position in maintaining homeostasis. It is produced immediately when homeostasis is disrupted and protects the host by activating an immune response [87]. In addition, tumor necrosis factor receptor 1 (TNF-R1) may be a state marker of disease activity in psychological disorders such as bipolar disorder [88]. TNF- α can give rise to improvement of immune cells' activity and promotion of the secretion of pro-inflammatory cytokines, playing an important role in the formation and development of bipolar disorder [89]. Some studies have suggested that acupuncture can improve psychiatric disorders, headache and other related symptoms in patients with cancer-related fatigue (CRF), by reducing the levels of associated inflammatory factors effectively such as IL-6, TNF- α and sTNF-R1. It may be its possible mechanism on

treating CRF [90]. As a kind of Ca permeable ion channel, TRPV1 matters in the development of chronic pain and depression in response to inflammation of brain. Some novel results has shown that some inflammatory mediators in plasma are great modulators of TRPV1 signaling pathway, providing new potential targets for treatment of chronic pain and depression [91]. Furthermore, after acupuncture, reduction in brain connectivity related to anterior hippocampus induce improvement in patients' anxiety [92]. When it comes to comorbid cases and emotional disorders with somatic symptoms, the mechanisms are also related to modulation of mRNA and protein. Major depressive disorder (MDD) and chronic pain often coexist and chronic pain is of high prevalence in patients who suffer MDD [93]. In a study, after development of a comorbidity model with characteristics of both MDD and chronic pain, the levels of mRNA and protein for NF- κ B-p65 and I κ B α were increased [94]. For example, in studies of acupuncture for irritable bowel, the therapeutic mechanism may be associated with regulating the levels of T lymphocyte subsets and modulating the expressions of 5-HT3R and 5-HT4R mRNA in colon tissue [95]. Some researchers have found that EA can not only reduce arterial BP and inhibit sympathetic nerve activity, but also increase the baroreflex sensitivity in hypertensive rats. Its mechanism may be associated with its function of downregulating p47 phagocyte oxidase mRNA and protein expression in the rostral ventrolateral medulla [96].

There are some differences between the mechanisms of acupuncture analgesia in terms of psychological pain and pathological pain, especially in the aspects of combined diseases with psychological syndromes. In the treatment of mental illness, the mechanism of acupuncture analgesia is mainly related to regulate inflammatory factors. Based on the theory of traditional Chinese medicine on the relationship between brain and kidney, acupuncture therapy can regulate fatigue and potential symptoms, improving the sleep quality in the patients of chronic fatigue syndrome by decreasing of the levels of IL-6 and INF- γ in serum [97]. Besides, some proteins matter in the mechanism of acupuncture treatment on psychological pain. Post-traumatic stress disorder (PTSD) is a persistent mental disorder in which an individual experiences actual death, or threat, or serious injury involving themselves or others. EA might improve PTSD by the way of promoting the binding of cAMP-response element binding protein to the synaptic key protein PSD95, regulating the interaction of the synaptic plasticity and BDNF-TrkB signaling pathway [98]. What's more, it has been evidenced that EA has a definite effect on regulating the pitch of pain emotion, and the optimal frequency of its treatment for pain emotion can be high frequency (100 Hz). In one study, EA treatment with 100 Hz increased motor function more significantly than 2 Hz, 15 Hz, or 2/100Hz in animal trials, alleviating depression effectively [99]. However, in contrast to psychological pain, EA with 4/20 Hz has a good analgesic effect on inflammatory pain and is the most widely applied clinically. In a clinical study, EA improved pelvic venous congestion and indirectly alleviated depression [100]. When it comes to combined diseases with psychological syndromes, there are several newest mechanisms. Acupuncture therapy for ADHD children is possibly connected with the regulation of cerebral blood flow [41]. EA and psychological intervention (PI) play a significant role in improving adolescent internet addiction (IA), especially in the aspects of psychological activities and behavior. EA might be more effective than PI in terms of controlling impulsivity and protecting brain neuron. The therapeutic mechanism for IA might be associated with increasing level of N-acetyl aspartate and Choline in prefrontal and anterior cingulate cortices [42]. When treating diarrhea predominant IBS with psychiatric disorders, EA with 2 Hz/100 Hz has been confirmed to be superior to medication by animal trails in reduction of psychological symptoms and improvement of intestinal status. Its mechanism may be associated with down-regulation of ROCK and RhoA which are vital proteins in our body [101].

Summary

Key findings

Chronic non-communicable diseases (NCDs) are a group of diseases involving multiple systems, which seriously pose a threat to the health of Chinese residents [102]. In addition, chronic diseases are the primary causes of mortality and morbidity, indicating that effective therapies should be taken into consideration [103]. Pain belong to NCDs and could be divided into pathological pain and psychological pain. The two types of pain always have an effect on each other in some cases and chronic pain is closely related to psychological illness. With the continuous understanding of traditional Chinese medicine, acupuncture plays an increasingly important role in clinical analgesia. It is most frequently applied for treating chronic and noncancer pain in adults [104]. Accumulating evidences have shown that acupuncture therapy is effective to both pathological and psychological disorders. Though there exist some differences between pathological pain relief and psychological pain relief, their mechanisms are both chiefly related to regulation of neurotransmitters and inflammatory factors, including down-regulation of Glu, 5-HT, DA, SP, TNF- α , IL-1, IL-6 and up-regulation of β -endorphin, endogenous opioid peptide, GABA+ and etc. What's more, in face of a national opioid epidemic in America, non-pharmacologic treatment options have been attached more importance to by federal regulatory agencies. Among all the non-pharmacologic therapies, acupuncture stands out as the immediately available one based on strong evidence to fulfil these needs, having the potential to alleviate the opioid crisis [105, 106].

The relationship between acupuncture analgesia and stimulation parameters

Acupuncture therapy can be divided into manual acupuncture and EA. Recent studies have shown that EA has advantages over MA in the treatment of some certain chronic diseases such as knee osteoarthritis, whose mechanism is related to changes of inflammatory factors [29]. EA therapies with different frequencies have their own mechanisms, which will be selected according to diverse conditions in clinic. The effect of EA depends on the frequency of stimulation. There are different results with the change of frequency in animal trials (Table 3). Besides animal trials, we also choose several clinical trials of EA analgesia (Table 4).

We find that EA has a parameter-specific effect on pathological pain relief and treatment of pain emotion and low frequency acupuncture is applied a lot. It is interesting that EA at 2Hz does not always have great advantages in both pathologic and psychological pain treatment than at 100Hz. In one case, EA at 100Hz has a better effect on chronic inflammatory pain relief [78]. However, 2Hz is superior to 100Hz in the treatment of neuropathic pain [107]. What's more, evidences have shown that waveforms can also affect the efficacy of EA and further clinical research is needed due to the lack of detail of EA waveforms. In short, diverse frequency apply to their corresponding diseases and it is predictable that acupuncture analgesia can serve humankind better with the more profound research of its mechanism and application.

Limitation and future trends

The connotation of needling analgesia needs to be elaborated, and the extension of needling analgesia also needs to be expanded. The specificity and non-specificity of acupoints still need to be determined research. Although acupuncture has a very suitable disease, it has its own limitations, such as the inability to completely treat some critically ill patients with organic lesions. For example, hungry, overfed and overworked people, abdomen and lumbosacral region in pregnant women and areas of broken skin are not suitable for acupuncture therapy. At present, some research conclusions on acupuncture and moxibustion analgesia are relatively fragmentable, and almost no systematic theory has been formed. Several clinical trials or laboratory studies often focus on only a few individual substances or channels. The specific analgesic mechanism has not been clearly concluded. With the gradual deepening of the research on acupuncture, more detailed mechanisms of acupuncture analgesia is expected to be revealed. If acupuncture technology can be further promoted, not only the opioid crisis can be alleviated, but also many

physical and mental diseases can be better treated. In a word, paying attention to the prevention and control of chronic diseases, improving residents' health awareness, early detection and early treatment, and

striving to reduce the incidence, disability and mortality of chronic diseases with acupuncture are beneficial to human health. We hope that our work can provide some ideas for future research.

Table 3 EA analgesia at different frequencies in animal trials

Stimulus frequency	Appropriate type of analgesia	Other results of relevant studies	Mechanisms and explanation
2Hz	Neuropathic pain: spared nerve injury (SNI)	Better than 100 Hz	EA ameliorate increase of the cytosol protein expression of P2X3 in the L4-L6 dorsal root ganglia and decrease of the expression of TRPV1 in the SNI model
2/60Hz	Psychological pain: spatial memory deficits		EA promoted hippocampal neurogenesis and synaptic plasticity via activation of BDNF/TrkB/Erk signaling
2/100Hz	Chronic inflammatory pain: ulcerative colitis Neuropathic pain, psychological pain	Better than 100 Hz Maximally increased the blood-brain barrier permeability compared with other frequencies	Bilateral <i>Tianshu</i> (ST 25) and bilateral <i>Shangjuxu</i> (ST 37) were selected EA enhanced the permeability of the BBB and promoted the entry of beneficial substances into brain tissue
10 or 30 Hz	Acute inflammatory pain: postoperative ileus		EA at ST36, ST37, ST39, or CV4 significantly inhibited local MPO activity, immune cells infiltration, and increased α -SMA
100Hz	Chronic inflammatory pain	Better than 2Hz	May be related to mediation of the protein level of TRPV1 and P2X3 expression in DRG

EA, Electro-acupuncture.

Table 4 EA analgesia at different frequencies in clinical trials

Stimulus frequency	Appropriate type of analgesia	Other results of relevant studies	Mechanisms and explanation
2Hz	Neuropathic pain		Stimulation with 2-Hz EA near the cervical sympathetic trunk increased parasympathetic nerve activity and reduced heart rate
	Psychological pain: polycystic ovary syndrome (PCOS)	Had superior/similar effects to metformin	The abnormal regulation function of hypothalamic-pituitary-ovarian (HPO) axis in human body leads to the corresponding abnormal hormones in the body, and then the vicious cycle of hyperandrogenemia and persistent anovulation
2/15 Hz	Chronic inflammatory pain: chronic pelvic pain	EA combined with drug therapy was more effective than drug therapy alone	<i>Guanyuan</i> (CV 4), <i>Shuidao</i> (ST 28), <i>Guilai</i> (ST 29), <i>Shenshu</i> (BL 23) and <i>Ciliao</i> (BL 32) were selected
2/100Hz	Postoperation pain	The EA analgesic effect of 2 /100 Hz dilatational wave is better than 2 Hz and 100 Hz continuous waves	<i>Xialiao</i> (BL 34) and <i>Chengshan</i> (BL 57) were selected
6Hz	Psychological pain: loss of high-load working memory (WM)	Better than 40 Hz	<i>Baihui</i> (DU 20) and <i>Shenting</i> (DU 24) were selected
25Hz	Chronic inflammatory pain: functional dyspepsia	Superior to medication	Zusanli (ST 36) and Neiguan (PC 6) were selected, mechanism may be related to the regulation of 5-HT release from intestinal chromaffin cells and the direct activation of PIEZO2 by cyclic nucleotides

EA, Electro-acupuncture

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