17 Acupuncture Analgesia: A Review of Peripheral and Central Mechanisms

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Abstract

Acupuncture is an ancient needling modality within Traditional Chinese Medicine used for chronic pain management. Western biophysical and Chinese meridian theory views of pain differ, and so do their respective management practices. The reversible effect of naloxone on the acupuncture induced analgesia is well known. Research has also shown correlations between acupuncture and its effect on the peripheral nerve endings, connective tissue, neurotransmitters, and inflammatory mediators. Centrally, studies with functional imaging and dynamic quantitative sensory testing substantiate the modulatory role of acupuncture in the “wind-up” phenomenon of spinal wide dynamic range neurons and different brain areas related to pain perception and modulation. Despite this increased understanding in the mechanisms and the analgesic efficacy of acupuncture, controversy continues to evolve around the issues of placebo effect and its potential therapeutic role in the main stream medicine.

Keywords

Acupuncture · Pain · Acupuncture mechanism · Traditional Chinese medicine · Acupuncture analgesia · Supraspinal pain modulation · Peripheral pain modulation

1 Introduction

Chronic pain can cast a profound negative impact on quality of life in the general patient population. In the United States alone, pain affects approximately 100 million adults, costing $560–$635 billion per year, which is greater than the combined annual healthcare cost for heart disease, cancer, and diabetes [1]. Current pain medications can cause various negative side effects, including gastrointestinal upset, liver toxicity, cardiac toxicity, and respiratory depression. It has been estimated that in the United States alone, 44 people per day die from misusing prescription pain killers [2], and 7,000 people per day are seen for other complications related to misuse of analgesics [3]. Although various regulatory

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policies have been implemented nationwide to track aberrant behavior of patients (for example, doctor shopping), data from a recent study reveals that the United States continues to have a pain medication overdose epidemic [3]. This ongoing conundrum calls for alternate effective pain treatment modalities with fewer side effects. More and more chronic pain patients are now turning to Integrative Medicine, which combines Complementary Alternative Medicine (CAM) modalities such as acupuncture with other conventional (allopathic) modalities for pain management [4]. Among these modalities, acupuncture emerges as one of the most studied and applied methods in pain management.

Acupuncture is a treatment modality within Traditional Chinese Medicine (TCM). It is often used in combination with herbal remedies, physical manipulation, exercise, and lifestyle modification. It has been used for pain analgesia for thousands of years, with the first document dating back to about 100 BC in "The Emperor's Classic of Internal Medicine" [5]. A recent report called "Acupuncture: Review and Analysis of Reports on Controlled Clinical Trials", released by the World Health Organization (WHO) and the National Institutes of Health (NIH), states that acupuncture can be used for 43 different clinical areas including analgesia for the head and face, the locomotor system, gout, biliary and renal colic, traumatic or postoperative pain, dentistry, childbirth, surgery, and post-chemotherapy nausea and vomiting [6]. Although auricular (ear) acupuncture (Fig. 1) is less well known than conventional meridian based body acupuncture, it has gained recognition and utilization in clinical practice over the past few decades. In 1990, the WHO standardized 39 ear points, and created a standard translated nomenclature to facilitate teaching of this modality of acupuncture [7].

There have been multiple systematic reviews supporting the clinical efficacy for both ear [8, 9] and body acupuncture in analgesia [10] while the reported side effects are generally minor and transient [11]. Aside from efficacy assessments, there has been ongoing effort in investigating the acupuncture-related analgesia mechanisms based on the current understanding in neuroanatomy, molecular biology, and physiology. These investigations are often conducted in correlation with the traditional acupuncture practice principles.

Fig. 1 Ear acupuncture

This chapter reviews several key issues relevant to acupuncture analgesia as follows:

1. The historic background of acupuncture in the Western societies;
2. Pain from the viewpoints of both the Western Medicine and TCM;
3. The current understanding in both peripheral and central mechanisms of acupuncture analgesia;
4. The pros and cons of the methodology behind acupuncture research.

2 Background of Acupuncture

Although acupuncture has been applied for treating different illnesses or symptoms, its application in treating pain is likely more accepted by patients than any other indications. A 2010 survey of hospitals in the United States showed that the top four uses of Complementary Alternative Medicine (CAM) were pain-related [4], and that analgesia was one of the main reasons for patients to seek acupuncturists to either complement or substitute conventional care. Despite ongoing research efforts, studying acupuncture using the randomized controlled trials (RCTs) has been challenging due to a lack of consensus on placebo, and difficulty of study blinding.

2.1 Clinical Efficacy

There is an abundance of acupuncture analgesia literature that are not RCTs (see Table 1). Despite concern over placebo effect, potential conflict of interests, study biases, and conflicting data, these early investigations opened the doors for some of the better designed RCTs conducted more recently.

Table 1 List of non-RCT related to acupuncture analgesia

Positive	Negative or equivocal to comparator
Occipital neuralgia [12]	Local anesthesia for inguinal hernia repair
Cancer pain [13–15]	Labor pain [29]
Cervical radiculopathy [16]	Postpartum surgical repair (compared to lo anesthetic) [30]
Increase pain threshold during athletic training [17]	Supraspinatus tendinitis [31]
Headaches after non-penetrating blast exposure [18]	Tooth pain [32]
Acute dental pain [19]	Trigeminal neuralgia (similar to comparator carbamazepine) [33]
Rheumatoid arthritis [20, 21]	
Posterior pelvic pain and low back pain in pregnancy [22]	
Post total hip arthroplasty [23]	
Endometriosis [24]	

In a 2012 systematic review and meta-analysis of acupuncture analgesia related RCTs, Vickers et al. analyzed data from 29 clinical trials including 17,922 patients and found that acupuncture was more superior than sham acupuncture and placebo for relieving chronic back (Fig. 2) and neck pain, osteoarthritic pain, chronic headache, and shoulder pain [10]. Usichenko et al. reviewed RCTs of ear acupuncture for postoperative pain. 9 out of 23 trials fulfilled inclusion criteria, which included surgical patients with a thoracotomy, burn, hip replacement, knee replacement, oocyte aspiration, molar extraction, knee arthroscopy, or laparoscopic nephrectomy. Results were interpreted as "promising but not compelling" [9]. Another group, Asher et al., analyzed 17 trials which met inclusion criteria, and concluded that ear acupuncture may be effective to treat various types of acute and chronic pain conditions, but further well-designed studies are warranted [8].

2.2 Side Effects

The side effect profile of acupuncture is relatively low, minor, and transient compared to the possible side effects known to occur in other invasive allopathic pain treatments. A 2013 systematic literature review reported that known side effects associated with auricular acupuncture may include short-term local pain, skin irritation, minor bleeding, and dizziness [11]. In a 2015 review of adverse events for acupuncture and moxibustion, tissue, nerve and internal organ injuries (especially pneumothoraxes), though low in frequency, were reported as the main major complications. Other minor side effects may include syncope, infections, hemorrhage, allergy, burn, aphonia, hysteria, cough, thirst, fever, somnolence, and broken needles [12]. Despite theoretical concern with abortion as a possible side effect, the authors of this chapter have not found any published cases of accidental acupuncture-induced abortions in the English-language literature. To the contrary, acupuncture has been safely used for pregnant women with chemical dependence [13], fertility

Fig. 2 Acupuncture for low back pain

treatments [14] and reversal of breeched babies [15, 16].

3 Western and Traditional Chinese Medicine View of Pain

3.1 Western Medicine View of Pain

The Western medical understanding of pain is based on a biopsychosocial model containing interactions among various neuropsychological and neurosensory mechanisms [17]. The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [18].

3.1.1 Peripheral and Central Pain Processing

In a broad sense, peripheral afferent neurons carry pain signals to the spinal cord where they synapse to excitatory or inhibitory secondary ascending neurons in the dorsal horn. The spinal cord then transmits pain signals up to the brain. The actual experience of pain is multifactorial and subjective. Supraspinal pain processing involves the anterior cingulate gyrus, thalamus, primary and secondary somatosensory cortices. In addition, prefrontal cortices and the amygdala are known to modulate both efferent and afferent signals. Functional magnetic resonance imaging (fMRI) studies have shown that many factors can affect pain perception. These factors include, but are not limited to: the frequency of stimuli [19], placebo analgesia [20], words [21], music [22] mood [23, 24], and even genetics [25, 26].

While peripheral signaling of pain originates distal to the spinal cord and central pain processing occurs in both spinal and supraspinal levels, these nervous systems appear to be highly interactive in pain signal processing and modulation. Central pain mechanistic alterations can often contribute to a peripheral neuropathic pain condition. For example, in painful diabetic neuropathy [27], spinal fMRI reveals that decreased central descending inhibition can contribute to the mechanical hyperalgesia and allodynia observed in the periphery [28], while the maintenance of pain requires continued peripheral noxious input [29].

3.1.2 Nociceptive Versus Neuropathic Pain

Aside from dividing pain mechanisms into central and peripheral, pain can also be broadly classified as nociceptive or neuropathic [30].

Nociceptive pain is usually caused by damage to body tissue and involves specific peripheral nociceptors that detect and transform noxious stimuli as electrical signals via nerve axons. Synaptic excitatory and inhibitory neurotransmitters including amino acids (e.g., glutamate, GABA), gasotransmittors (e.g., NO, CO), monoamines (e.g., dopamine, norepinephrine,

epinephrine, histamine, serotonin), peptides (e.g., substance P, opioid peptides), purines (e.g., ATP, adenosine), and acetylcholine can modulate the transmission of pain signals from the peripheral to the central nervous system, or vice versa.

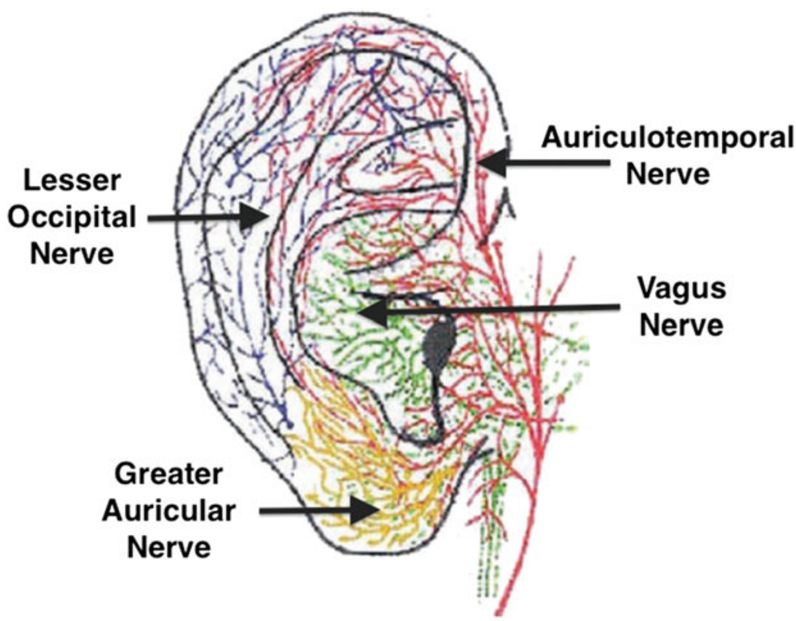
Neuropathic pain usually occurs when there is nerve damage or recurrent pain sensitization to the peripheral and/or central nervous systems. Primary peripheral pain sensitization can occur when inflammatory mediators such as bradykinin, serotonin, cytokines, and prostaglandins are released after peripheral tissue injury. These mediators stimulate the nociceptors directly, leading to the activation threshold reduction in the afferent signal transmission. Several types of afferent sensory fibers including A-beta, A-delta, and C-fibers can be found on the skin, viscera, meninges, muscles, and joints. A-beta afferent fibers are moderately myelinated and transmit touch and pressure. A-delta-fibers are mildly myelinated and transmit pain and temperature. C-fibers are unmyelinated, and transmit mechanical, thermal, and chemical information. While acute somatic pain is mostly transmitted via A-delta and C-afferent fibers, visceral pain is largely innervated by slow conducting C-fibers. Thus, visceral pain is often poorly localized and perceived as diffuse and dull. These visceral fibers can also be closely associated with post-ganglionic autonomic changes [31], leading to symptoms such as nausea, vomiting, and changes in heart rate variability. Referred pain can occur when both somatic and visceral afferent fibers converge onto the same spinal dorsal horn resulting in the sensation of visceral pain being felt at a site distant from the visceral source [32].

3.1.3 Autonomic Nervous System Contribution to Pain

It is well known that neuropathic pain states can be mediated or augmented with increased sympathetic outflow [33]. The sympathetic system has been one of the targets for interventional pain treatments [34], and enhancing parasympathetic efferent output has been perceived as one of the ways to mitigate sympathetically mediated pain. One potential way that acupuncture may enhance the effect of the parasympathetic nervous system is by needling the outer ear due to the neuroanatomical makeup of the ear.

Various sensory nerves (Fig. 3) that innervate the ear include the lesser occipital nerve (cervical nerve roots), the greater auricular nerve (cervical nerve roots), the auricular-temporal anterior branch of the trigeminal nerve (CN-V3), the posterior auricular branch of the facial nerve

Fig. 3 Ear innervation



(CN-VII), and the auricular branch of the vagus nerve (CN-X). It is interesting to note that the ear is the only peripheral anatomical structure that directly receives vagal innervation. Therefore, directly stimulating the ear provides an effective way to enhance the vagal tone. One particular study has found that auricular acupuncture can affect cardiovascular, respiratory, and gastrointestinal systems [35]. Another study showed that stimulating areas of the external ear innervated by the auricular branch of the vagus nerve can potentially enhance the vagal effect on various organ systems [35]. As discussed earlier, there have been multiple studies showing how ear acupuncture is effective for pain analgesia [8, 36]. In addition, there have been comparative studies showing that electroacupuncture to the ear is more effective for pain control than conventional auricular acupuncture, in patients with chronic neck pain, chronic low back pain or undergoing oocyte aspiration [37].

3.1.4 "Psychogenic" Pain

Psychogenic pain is a term used to describe pain behavior or perception, predominantly caused by various psychological factors [38]. This term is being mentioned to acknowledge that pain threshold can be changed by various psychological components. Later in this chapter, acupuncture's effect on mood and simultaneous effect on pain analgesia will be revealed.

3.2 Traditional Chinese Medicine View of Pain

A TCM practitioner treats a disease state based on the entirety of the person instead of just the presenting symptoms. To illustrate this model of medical practice, 3 patients present with similar low back pain symptoms. At baseline, they have different individual characteristics. The first patient is pale, depressed, and shy. The second patient is ashen, anxious, and often sweaty. The third patient is a large football player with a deep voice and is fierce in personality. In the Western medical setting, they may all be given the same diagnosis, prescribed similar analgesic medications, and sent for physical therapy. On the contrary, a TCM provider will consider the acute complaints of the individual, along with their baseline physical attributes, and treat the imbalance of *Qi*. Understanding the key principles of Yin-yang and *Qi* is crucial in assessing the patient's baseline characteristics, and formulating diagnoses and a treatment plan in TCM.

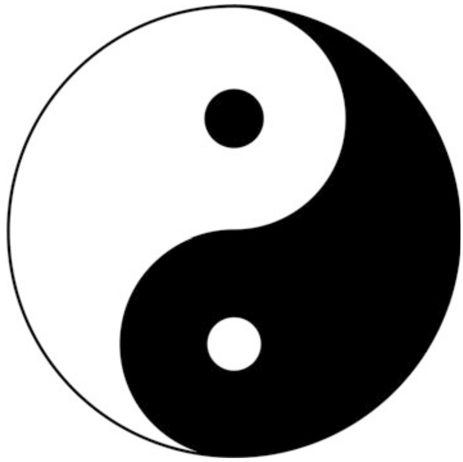


Fig. 4 Yin-Yang

3.2.1 *Yin-Yang* Theory

Yin-yang theory encompasses the assumption that a part can only be understood in relation to its whole [39]. It describes an opposing and yet complementary duality that is not all or nothing, but rather a balance of two polar entities (Fig. 4). *Yin* and *yang* create and can transform each other [39]. Metaphysical examples of *yin-yang* include: moon–sun, inside–outside, female–male, and moist–dry. In the human body, the lower body is designated as *Yin*, and upper as *Yang* [40].

Yin-yang theory can also be used to characterize disease symptoms. For example, TCM providers will describe yin or yang imbalance as excess or deficient, as illustrated in the following examples:

- *Yin* deficit: heat sensations, possible night sweats, insomnia, dry pharynx, dry mouth, dark urine, a red tongue with scant fur, and a "fine" and rapid pulse.

- *Yang* deficit: aversion to cold, cold limbs, bright white complexion, long voidings of clear urine, diarrhea, pale and enlarged tongue, and a slightly weak, slow, and fine pulse.

In essence, TCM treatments aim to reestablish the balance of *yin-yang*. Acupuncture needling is only one of the modalities of TCM, which also includes other modalities such as herbal remedies, Tai Chi, Tui-Na, and diet and lifestyle changes.

3.2.2 Five Element Theory

Embedded in TCM is also the Five Element theory (Fig. 5). This theory presumes that the universe can be broken down into 5 elemental qualities: metal, water, fire, wood, and earth. Individuals' environmental factors or physical appearances are often used to assign their associated elemental qualities, which in turn consist of predefined interactional relationship.

3.2.3 Chinese Anatomy

Qi

Although there may not be a perfect direct English translation for *Qi*, by and large, it consists of several main connotations including energy, life force, blood, defense mechanism, and breath. In TCM, *Qi* is perceived to circulate through the meridians (to be explained below), and has branches connected to bodily organs and functions. Various attempts have been made to quantify *Qi*. Some say that it has a known frequency [41], while others say it encompasses 4 fundamental physical or energy sources: gravitational, electromagnetic, strong nuclear, and weak nuclear [42]. Although many instruments available directly to consumers claim to be able to measure energetic fields, none have been validated by research. TCM practitioners rely on their perception of *Qi* as part of the *yin-yang* system to treat patients, despite *Qi* having not been validated by quantifiable research. The term *De-Qi* refers *to* a sensation that signifies the arrival of *Qi* at a needled acupoint. The mechanistic assessments of *De-Qi* are discussed in the *De-Qi* section of this book chapter.

Blood (*Xue*) and Body Fluids (*Jinye*)

Equally as important as *Qi* in TCM are the 2 other metaphysical terms known as *Xue* and *Jinye*. *Xue* in TCM correlates with the western

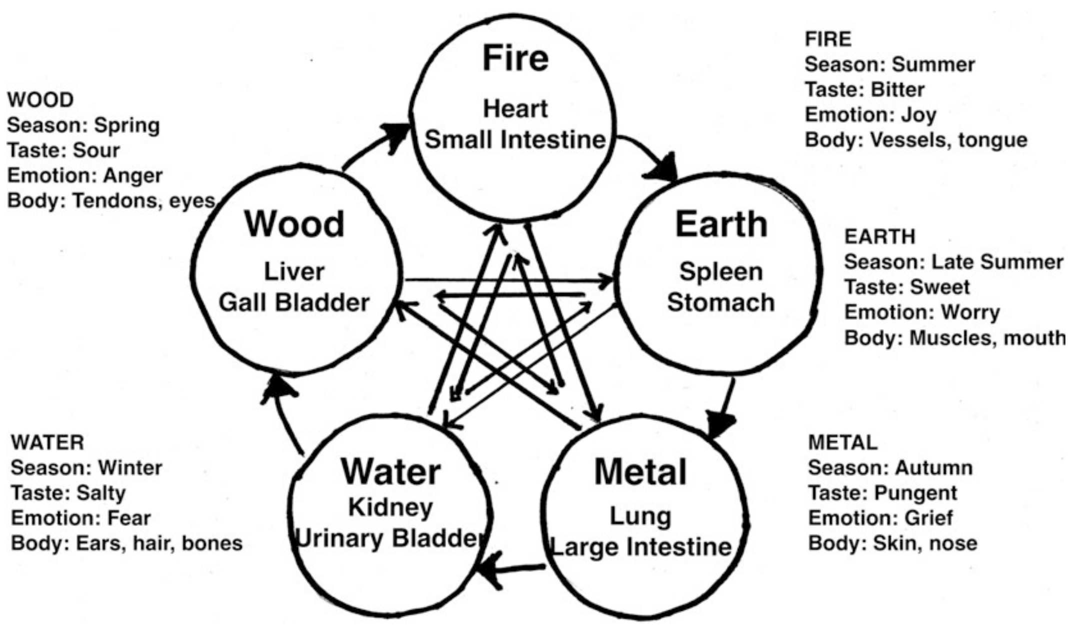


Fig. 5 Five element theory

physical form of blood, whereas, body fluid, known as *Jinye*, nurtures and moisturizes different structures of the body and also helps with secretion (e.g., tears, urine, sweat, joint fluids, gastric acid). *Jinye* is extracted from ingested food items which aids in the creation of *Xue*. Conversely, *Xue*, can also be transformed into *Jinye* [43].

Meridians

In TCM, the meridians are considered channels in which *Qi* travels (Fig. 6). The meridian network is typically divided into 2 categories, the *Jingmai* and the *Luomai* ("collaterals"). The *Jingmai* contains: 12 tendinomuscular meridians, 12 divergent meridians, 12 principal meridians, 8 extraordinary vessels as well as the *Huato* channel, and a set of bilateral low back points. The *Luomai* ("collaterals") contains 15 major arteries that connect the 12 principal meridians in various ways, in addition to interacting with their associated internal organs and other related internal structures. This collateral system also encompasses branching,and capillary-like vessels. There are 361 acupuncture points (not counting bilateral points twice) [44], most of which are situated along the major meridians each of these points is known to have specific functions in various TCM treatment algorithms, which are beyond the scope of this chapter.

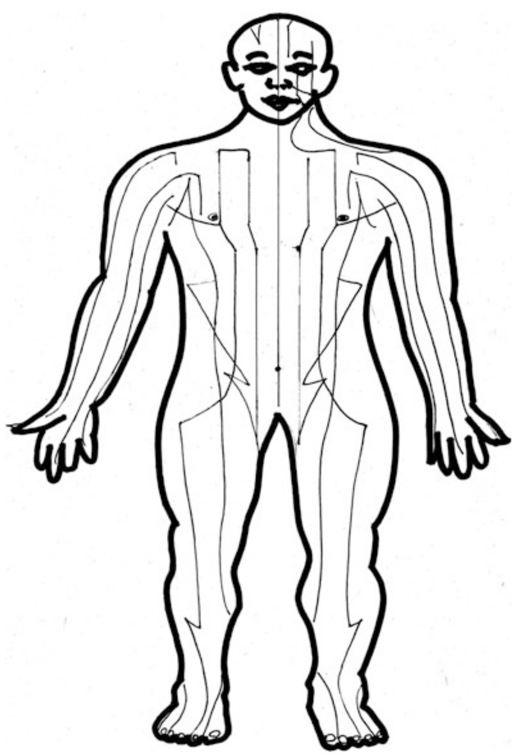


Fig. 6 Merdian lines

3.2.4 Treating Pain in TCM

Pain in TCM is generally viewed as part of the clinical presentation associated with *Qi* imbalance. In order to treat pain, a TCM practitioner may ask their patients detailed questions regarding their pain, sleep pattern, bowel movement types, emotions, and exercise tolerance. The practitioner may holistically evaluate a patient by palpating pulses at various body locations and examining the patient's tongue and other physical characteristics and in order to formulate the diagnoses of *Qi* deficiency or stagnation, even if a patient only presents with a single complaint of pain [45].

TCM-related pain diagnoses can present as follows:

- Large Intestine Meridian Excess heat: skin lesions and potential cancers
- Kidney *Qi* deficiency: osteoporosis, kidney stones, and arthritic joints
- Spleen *Qi* Deficiency: muscle atrophy and digestive disorders
- Gallbladder *Qi* Deficiency: connective tissue and tendon conditions [46].

Although the naming of organs in the meridian system may have little to do with the actual organs themselves, *Qi*-meridian-based diagnostic approaches serve as the foundation for the acupuncture intervention to follow. Consequently, the mechanistic validation of meridian-based acupuncture treatment paradigms has been the focus of many recent investigations.

4 Mechanisms of Acupuncture Analgesia

4.1 Peripheral Mechanisms of Acupuncture Analgesia

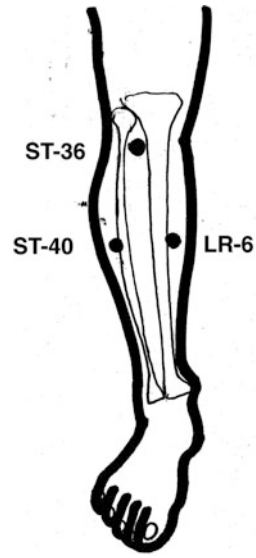
While meridian-based acupuncture treatment has been used for thousands of years with appreciable efficacy, especially in the area of pain management, the correlated physiological and neuronal mechanisms associated with analgesia have only been recently assessed. Several important aspects of these recent discoveries are discussed in the following sections.

4.1.1 De-Qi

In acupuncture, *De-Qi* generally refers to as the "arrival of *Qi*" or the process of "obtaining *Qi*". Some acupuncturists use *De-Qi* to assess treatment efficacy as recipients report a spreading, dull, aching sensation associated with the needle manipulation. In a survey study, it was found that 7 sensations were closely associated with *De-Qi*: aching, dull, heavy, numb, radiating, spreading, and tingling. The sensations of *De-Qi* are distinguished from the 9 sensations known to be correlated with acute pain at the site of needling: burning, hot, hurting, pinching, pricking, sharp, shocking, stinging, and tenderness [47]. In another study, objective measures were used to quantify *De-Qi*. Thirty healthy volunteers (without controls) were given acupuncture treatments with *De-Qi*, and the treatments were noted to increase blood flow, displace tissue, and increase amplitude of electricity created by muscle fibers [48]. In this study, acupuncture treatment also induced fMRI signal changes in different brain regions [48].

In order to differentiate acupuncture points versus control points, a 2015 research endeavor used EEG, event-related fMRI, and resting-state functional connectivity fMRI to assess neural responses to needle stimulation of the acupuncture point ST-36 in the lower leg (Fig. 7) and 2 control point locations located in the same and different dermatomes of the acupoints. Results suggested that stimulation at acupuncture points may modulate somatosensory and saliency-processing regions (to segregate relevant information) more than non-acupuncture points. In addition, the study also suggested potential modulation of pain perception due to specific locations of acupuncture stimulation [49].

Fig. 7 ST-36



Acupuncture points have also been suspected to exhibit particular direct current, low-frequency electrical and optical properties compared to surrounding skin. A pilot study reveals that dielectric properties of acupoints differ from non-acupuncture sites [50]. Based on a review of the literature, one group concluded that the available evidence did not conclusively support the claim that acupuncture points had distinct electrical properties [51]. A counter article showed that in regards to electrophysiology, *De-Qi* can differ between manual and electroacupuncture, with an observed difference in transcutaneous conduction between true and non-acupuncture points [52].

4.1.2 Acupoints and Peripheral Nerve Endings

Given that acupuncture is perceived as a form of peripheral neuromodulation, the relationship between acupoints and peripheral nerve endings has been explored. A cadaveric dissection study in the 1970s showed that out of 324 acupoints located on meridians, 323 exhibited rich innervation mainly in the deep tissues, indicating that the relationship of the meridian systems to the peripheral nerve endings [44]. Overall, the role of C-fiber involvement in acupuncture analgesia has been controversial. Despite C-fiber activity depletion by capsaicin, it was shown in a rat model that electroacupuncture could still result in reduced analgesia compared to controls [53]. On the other hand, in a separate study done on syringomyelia patients, who suffered damage to the anterior commissure of the spinal cord and have reduced C-fiber and A-delta mediated nociception, it was shown that these patients responded to electroacupuncture poorly. This observation provides the assertion that C-fibers may be essential for acupuncture analgesia [54]. In a more recent investigation done on afferent nerve endings found within acupoints, rat hind feet were used in vivo for recordings of A-alpha, A-beta and A-delta fibers actiivities. It was found that the distribution of receptive fields was closely associated with cutaneous acupoints for both A-fibers and C-fibers. In addition, most of the muscular sensory receptors were also located in the muscular acupoints. These observations strongly suggest that acupoints are closely associated with excitable muscle/skin–nerve complexes with high density of nerve endings [55].

4.1.3 Tendinomuscular Meridians

Tendinomuscular meridians (TMM) are used for acute pain relief [56]. The treatment protocols call for stimulations of the *Ting* Points (at digits of the affected extremities) and Gathering Points (at the location of the injury in the extremity). These meridians are considered to be superficial, and not to be considered as a “root treatment”, or deep organ problems. Nonetheless, the protocol is highly effective for acute pain relief [57]. In a study that aimed to characterize the role of *Ting* points in acute pain management, 13 healthy subjects were examined. It was established that a short (30 s) duration of electroacupuncture (5 Hz) treatments at SP-1 and LR-1 (Fig. 8) can result in significant warm threshold increases in the extremities suggesting that *Ting* points have an inhibitory effect on C-fiber afferents and that the analgesic results are likely A-delta mediated [58].

Fig. 8 Electroacupuncture at Ting Points (SP-1 and LR-1) [58]

4.1.4 Connective Tissue: Fascia

A very high degree of anatomical correlation can also be found between myofascial planes and acupuncture meridians in the truncal region. Although it has been theorized that the physical makeup of meridians may comprise of a combination of neurovascular bundles, neuromuscular attachments, sensory nerve endings, perivascular space and perineurial vessels, none of these theories have been substantially proven [59, 60]. In manual acupuncture, the main stimulation comes from a combination of the mechanical pressure of the needle being moved up and down, in conjunction with the mechanical rotation that is done by the practitioner. This motion, which leads to tissue tugging and distortion, stimulates mechanoreceptors, sends off neural signals, and results in the sensation of *De-Qi* [59, 60].

A review article in 2011 suggests that the fascial network is consistent with some of the meridian patterns, and that the efficacy of acupuncture needling relies on interactions with this network [61], which is thought to mediate active mechanical transference between the muscles and bones. The analogy has been made that a disruption in *Qi* flow constitutes disease, and a disruption in fascia physiology is associated with neurogenic inflammation and pathology [61]. In a different paper, it was noted that when acupuncture was compared to no needling physical manipulation, the positive effects on pain analgesia were apparent, whereas when acupuncture was compared to "sham acupuncture" (consisting of needling a non-acupoint), less significant differences between the 2 were noted [62]. Although this observation does not discredit analgesic effects of acupuncture needling, it does discount the specificity of acupuncture needling effects on fascia.

4.2 Neurotransmitters and Neuromodulation

Neurotransmitters and neuromodulators related to analgesia can be found within the peripheral and central nervous systems. Some of the better known acupuncture mechanistic research in this area includes inhibition of NADPH oxidase-mediated oxidative stress [63], activation of opioid receptors (reversible with naloxone) [64], activation of cholinergic muscarinic receptors, and anti-inflammatory signaling (reversible with atropine) [65]. Main investigations assessing the acupuncture needling effects on amino acids, monoamines (serotonin, dopamine, norepinephrine), peptides (opioid peptides, substance P), purines, and inflammatory markers are discussed below.

4.2.1 Amino Acids

Excitatory amino acids, such as glutamate, are abundant in the presynaptic neurons. Aberrant glutamatergic signaling disrupts normal tissue homeostasis and induces pain. Glutamate's role as a neurotransmitter at the synaptic level has been known for many decades. It has even been shown to regulate neurogenesis, neurite outgrowth, synaptogenesis, and neuron survival, playing an integral role in neuronal plasticity [66]. It has been demonstrated that electroacupuncture at the gallbladder meridian, correlated with the distribution of the median nerve (P-5 and P-6, Fig. 9), could attenuate the visceral

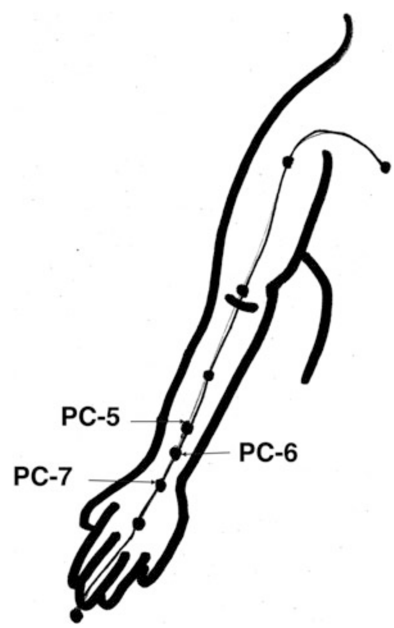


Fig. 9 PC-5 and PC-6

sympathoexcitatory reflexes with diminished bradykinin and glutamate expression/binding at the ventrolateral medulla [67]. Electroacupuncture has also been shown to upregulate Glutamate Transporter-1, and inhibit the excessive release of glutamate in the striatum after ischemic reperfusion brain injury [68]. In the rat model, it has been shown that through the action of central arginine vasopressin, glutamate induces hypothalamic paraventricular nucleus brain signaling with acupuncture analgesia [69].

Inhibitory amino acid transmitters, such as gamma-aminobutyric acid (GABA), also play an important role in the perception of pain. GABAergic neurons known to play an important role in pain perception and modulation are widely distributed throughout in the central nervous system. This neurotransmitter system has been shown to regulate control of sensory information processing in the spinal cord. In animal pain models, it has been discovered that GABA receptor agonists displayed anti-nociceptive properties [70]. In a specific rat study using a middle cerebral artery occlusion model, it was shown that acupuncture could modulate the expressions of GABA receptors in rats that have endured this occlusion [71].

There have been various research endeavors showing the effects of GABA on pain reduction. Systemic administration of a GABA-A receptor antagonist was shown to reduce acupuncture analgesia [72], whereas intrathecal diazepam (a GABA agonist) injection was shown to potentiate acupuncture analgesia [73]. Furthermore, in a research study comparing intracerebroventricular administration of GABA-B versus GABA-A, it was shown that GABA-B (but not GABA-A) receptor antagonist administration decreased acupuncture analgesia. However, the study result from a different group suggests that only GABA-B receptors in supraspinal structures contribute to acupuncture analgesia, whereas both GABA-A and GABA-B receptors in the spinal cord are associated to pain reduction via acupoints needling [74]. Although the contribution of the different GABA receptors may differ, the fact that these receptors play a role in acupuncture analgesia is well supported in the literature.

4.2.2 Monoamines

Various monoamines such as serotonin, dopamine, and norepinephrine also play a role in pain modulation, and have been researched in the context of acupuncture. Some of the investigations are discussed as follows.

Serotonin

Serotonin (5-HT) is present in central and peripheral serotonergic nerve terminals and is also released from platelets and mast cells after tissue injury. Depending on the sites of action and receptor subtypes, 5-HT can elicit pain or have analgesic effects. In regards to eliciting pain, 5-HT, acting in combination with other inflammatory mediators, may also ectopically excite and sensitize afferent nerve fibers, thus contributing to peripheral sensitization and hyperalgesia [75].

In a study that 5-HT antagonists were used to test the pain inhibitory mechanisms of electroacupuncture against the nociceptive responses in the trigeminal nucleus caudalis in rabbits, 5-HT1 (except 5-HT1A), 5-HT2 (except 5-HT2A), and 5-HT3 receptors were shown to be positively involved in electroacupuncture-induced analgesia. On the contrary, activation of 5-HT1A and 5-HT2A receptors was shown to suppress electroacupuncture-induced analgesia [76]. In rats with neuropathic pain, it was found that low-frequency (2 Hz) electroacupuncture was found to be more efficacious for treating cold allodynia than high-frequency electroacupuncture (100 Hz). Both 5-HT1A and 5-HT3, but not 5-HT2A seratonergic receptors also played important roles in mediating the pain analgesic effects of low-frequency electroacupuncture [77].

Many studies have shown that acupuncture treatments can modulate the content and the activity of central 5-HT [78]. An investigation in a rat model assessing the role of peripheral and spinal 5-HT[3] receptors in formalin-induced secondary allodynia and hyperalgesia in rats demonstrated that the stimulation of peripheral 5-HT 3 receptors induced long-term secondary allodynia and hyperalgesia [79]. In addition, electroacupuncture was also noted to activate the seratoninergic raphe-spinal neurons in the nucleus raphe magnus, one of the serotonin-releasing nuclei connecting the lower pons with the medulla in the descending pain inhibitory pathway [80].

Dopamine

The role of dopaminergic neurotransmission via serotonin or norepinephrine in pain perception and modulation is well known [81–86]. These neurotransmitters are found to interact with various pain-related supraspinal regions including the basal ganglia, insula, anterior cingulate cortex, thalamus, and periaqueductal gray in the descending pain inhibitory pathway. Abnormalities in dopaminergic neurotransmission were found in painful clinical conditions such as Parkinson's disease, burning mouth syndrome, fibromyalgia, and restless leg syndrome [85].

The effects of acupuncture on dopamine activities have been varied. In the rabbit model, D2 receptor antagonists (e.g., haloperidol, clozapine) as well as D1 receptor antagonists enhanced acupuncture analgesia [87]. In addition, chlorpromazine (dopamine antagonist) was shown to attenuate electroacupuncture analgesia [87, 88]. A separate animal study done on rats suggests that D2 receptors are involved in pain modulation, and activation of D2 receptors enhances acupuncture analgesia in the spinal cord. However, such effect is absent in D1 receptors and inactivation of the D1 receptors attenuates acupuncture analgesia [89, 90]. Additional receptor-binding studies provide further support that dopamine receptor antagonists can also potentiate electroacupuncture analgesia [91].

Norepinephrine

Norepinephrine (NE) is an important neurotransmitter known to be involved in the process of opioid dependence and pain modulation in the central nervous system. Noradrenergic neurons originate from various brain areas including the raphe nuclei, locus coeruleus, periaqueductal gray, and various nuclei of the brainstem, which then projects to the forebrain and descends along the dorsolateral tracts of the spinal cord [83, 92]. In 2015, a rat study was done to examine the role of NE on the evoked discharges of pain-excitation neurons (PENs) and pain-inhibition neurons (PINs) in the nucleus accumbens using a morphine-dependent model. Results showed that NE inhibited the evoked discharges of PENs and attenuated the inhibition of PINs. In addition, Phentolamine enhanced the evoked discharges of PENs and facilitated the inhibition of PINs. It was concluded that the inhibitory action of NE on pain modulation acted through alpha adrenoceptors in the nucleus accumbens of morphine-dependent rats [93].

The norepinephrine transporter (NET) inhibition has an additional effect on μ-opioid receptor (MOR)-mediated anti-nociception in inflammatory and neuropathic pain [94]. In a rat model, it was shown that electroacupuncture at GV-26, GV-16, PC-6, and BL-15 (Fig. 10) could upregulate the expression of both middle cervical-stellate ganglion complex NET mRNA and myocardial beta1-AR mRNA in cerebral-cardiac syndrome [95]. However, the specificity of each acupuncture point in inducing the observed effect was not assessed in the study. A different study, however, showed the opposite result with a decrease in release of NE with acupuncture. The content of NE in the nucleus reticularis paragigantocellularis lateralis (RPGL) during acupuncture treatments was studied and it was found that pain thresholds increased after 20 min of electroacupuncture, while the content of NE from the RPGL decreased, suggesting NE served as a crucial role in acupuncture induced analgesia [96].

In the spinal cord, NE may have different effects, depending on the receptor subtypes. Studies have showed that spinal alpha2-adrenergic but not alpha1-adrenergic receptors play important roles in mediating the pain relieving effects of 2 Hz electroacupuncture on cold allodynia in neuropathic rats [77].

4.2.3 Peptides

Endogenous opioid peptides have long been considered as one of the main mediators of acupuncture analgesia, with research dating back several decades. In more recent years, there has been a rise in interest regarding the role of acupuncture in regulating the pain signal mediator, substance P.

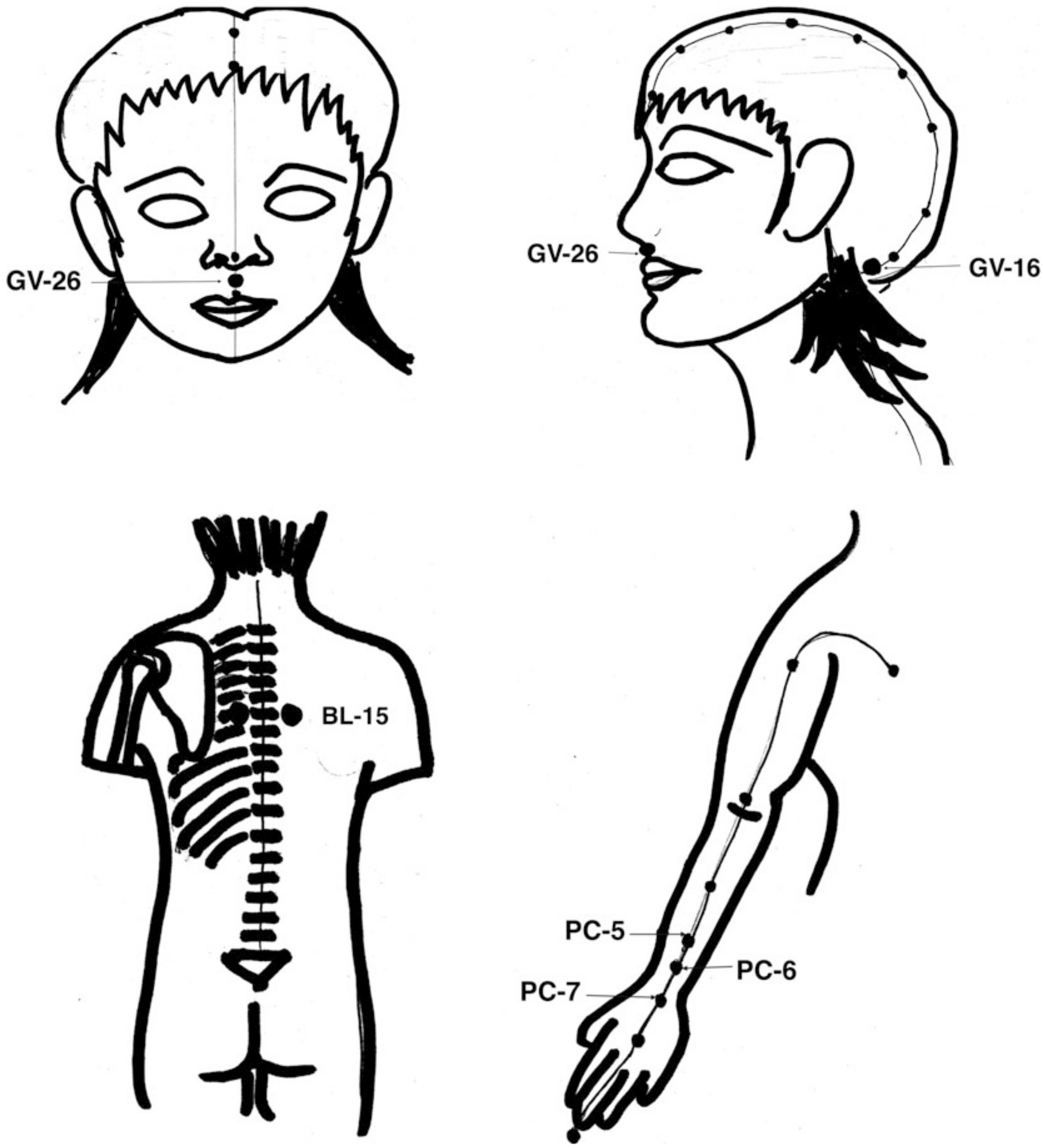


Fig. 10 GV-26, GV-16, PC-6-BL-15

Opioid Peptides

It is well known that acupuncture stimulates the release of endogenous opioids. The effect of acupuncture on both the peripheral and central opioid peptides has been investigated. In the early stages of inflammation, opioid-containing neutrophils are directed into inflamed tissue, stimulating opioid peptide release [97] and aiding in pain reduction.

In 1977, researchers were excited to find that naloxone, an opioid receptor antagonist, could partially reverse the analgesic effect of acupuncture on electrically induced pain on tooth pulp [98]. The acupuncture analgesic reversal effect of naloxone was further demonstrated in chronic pain patients in 1978 [44]. With recent advancement in molecular cloning technology, subtypes of opioid receptors including mu, delta, and kappa [99] have been identified for respective opioid peptide subtypes including beta-endorphin, enkephalins, and dynorphins.

Electroacupuncture has been found to induce long-term anti-nociception, which is blocked by anti-opioid peptide antibodies. In an animal model study, acupuncture was found to increase chemokine CXCL10 release and opioid peptide-containing macrophages expression in an inflammatory state. In control rats that did not get acupuncture, repeated injection of CXCL10 triggered opioid-mediated anti-nociception as well as increased opioid-containing macrophages. On the other hand, neutralizing CXCL10 decreased electroacupuncture-induced anti-nociception and the expression of opioid-containing macrophages [100].

Acupuncture's opioid-effect on the central nervous systems has also been investigated in rabbits. Naloxone was seen to reduce the intensity and duration of the antipyretic action of acupuncture [101]. There is even compelling evidence to support frequency-dependent acupuncture analgesia. Radioimmunoassays of the spinal perfusates from a rat were tested after electroacupuncture was applied at low (2 Hz) and high (100 Hz) frequency. It was found that low-frequency electroacupuncture facilitates the release of encephalin (mu receptor), but not dynorphin (kappa receptor). On the contrary, high-frequency electroacupuncture facilitates release of dynorphin, but not encephalin [44]. Further studies using intrathecal administration of antagonists of mu, delta, and kappa receptors have showed that low-frequency electroacupuncture analgesia is reduced by blocking mu and delta receptors, whereas high-frequency electroacupuncture analgesia is reduced by blocking kappa receptors [44, 102].

Substance P

Substance P is known to facilitate pain transmission in both the peripheral and central nervous systems. It coexists with glutamate in primary afferent fibers, and increased levels of Substance P are found in patients with various pain conditions [103], inflammation [104, 105], stress, and anxiety [106]. Various noxious stimuli can elicit Substance P release in the spinal cord. Electroacupuncture at ST-36 was found to decrease substance P and increase beta-endorphin [107]. In addition, it was noted in a rat model of irritable bowel syndrome, daily electroacupuncture at ST-25 and ST-37 decreased the number of Substance P and its receptor expression in the colon [108].

4.2.4 Inflammatory Markers

Acupuncture also modulates inflammatory processes associated with pain [109]. Peripheral tissue injury causes the release of inflammatory mediators, which in turn leads to initial peripheral pain sensitization. A subsequent chain of reactions ultimately leads to central sensitization in the spinal dorsal horn and other CNS neurons [110]. One of the widely studied inflammatory conditions is arthritis. Electroacupuncture has been shown to reduce the activities of T and B cells in the lymph nodes and enhances natural killer cells in arthritic mice [111]. Pilot data suggests that acupuncture may be a feasible and effective treatment modality for decreasing subjective pain and inflammation as measured by the expression of white blood cells, and for treating patients with acute appendicitis pain [112]. A 2012 review assessing the effect of acupuncture on knee osteoarthritic pain concluded that acupuncture provided significantly better pain relief and improvement in knee function when compared to sham acupuncture, standard care, or waiting treatment [113]. Although clinically, acupuncture continues to be used for various arthritic conditions, not all studies favor acupuncture for inflammatory pain. A 2008 review on acupuncture for rheumatoid arthritis concluded, "despite some favorable results in active-controlled trials, conflicting evidence exists in placebo-controlled trials concerning the efficacy of acupuncture for rheumatoid arthritis. Rigorous and well-controlled randomized trials are warranted" [114].

4.3 Central Mechanisms

Aside from neurotransmitters working on a central level, there are other supraspinal mechanisms that can affect the outcome of acupuncture analgesia. These include psychological and behavioral factors.

4.3.1 Placebo Effect and the Debate on Controls

Methods of control used in acupuncture studies continue to be controversial. Active acupuncture treatment is often compared to sham treatment consisting of needling non-meridian points, stimulating classic acupoints with beads, changing needling depth, using a retractable needle, or using acupressure. However, some of these sham methods such as acupressure or beads along the meridians may still have actual physical and physiological effects on the peripheral nervous/meridian systems, and therefore cannot be considered as an optimal sham. More importantly, manipulation of any kind can induce a placebo analgesic effect. Given that many analgesic investigations, not just acupuncture, are often concluded to not be better than placebo, it is important for the reader to understand the possible effects of placebo analgesia. In 1979, a study was done where intravenous placebo pain medication was given to patients after wisdom tooth extraction. The placebo response was greater if the initial pain was greater than 2.6 on the VAS. This group also reported significantly greater mean analgesia than those reported with initial lower pain values [115]. Over the past several decades, numerous studies have shown that the expectation of being treated for pain [116], physician characteristics, the color of a pill, and the medication package [117] can all affect the perception of pain.

A meta-analysis of 25 neuroimaging studies on placebo analgesia and expectancy-based pain modulation revealed that placebo effects and expectations stimulated regions of the brain which control pain pathways, and even affected the mood related supraspinal regions [116]. In a different meta-analysis involving data from multi-center RTCs for chronic hip OA pain, chronic knee OA pain and low back pain, it was found that high number of planned face-to-face visits predicted the magnitude of the placebo response [118]. Given the effectiveness of placebo analgesia, as well as the positive physiological effects of needling non-meridian points for pain reduction [116, 119], it is conceivable that if acupuncture is shown to be as effective or significantly more effective than placebo analgesia (or sham acupuncture), then the treatment modality can be considered to be clinically effective.

4.3.2 Psychological Contributions and Correlations

Since pain is a subjective sensory experience, the effect of acupuncture on emotional state can potentially affect pain perception. Although it has been shown that *De-Qi* has more of a physiological effect on acupuncture analgesia than psychological factors [120], the psychological contributors of pain perception and their effect on acupuncture analgesia cannot be ignored. It has been shown, for example, that depression independently reduces pain thresholds [121]. Clinical and experimental studies show that the onset of acupuncture effect on depression is more rapid than the effect of selective serotonin reuptake inhibitors, a class of antidepressants [122]. Studies have also shown that antidepressants suppress neuropathic pain by a peripheral beta2-adrenoceptor mediated anti-TNF-alpha mechanism [123]; these neurotransmitters are affected by acupuncture needling as discussed in the Neurotransmitter section.

Aside from depression, it is known that stress can also affect pain perception [124]. In an animal study with cold as a stressor, active ST-36 stimulation prior to cold stress significantly decreased ACTH and cortisol levels, when compared with sham acupuncture or no treatment groups. The active ST-36 treatment group was also effective at preventing stress-induced elevation of adrenal Neuropeptide Y mRNA. The authors concluded that electroacupuncture at ST-36 could block the chronic stress-induced elevations in the hypothalamic–pituitary–axis and sympathetic pathways [125]. Knowing the correlation of stress on pain perception, one can infer that acupuncture can reduce stress hormones contributing to the perception of pain analgesia.

4.3.3 Dynamic Quantitative Sensory Testing

Aside from the visual analogue scale (VAS), peripheral non-noxious and noxious sensory thresholds can be assessed via Quantitative Sensory Testing (QST) (Fig. 11) under specific established protocols [126]. QST refers to tests of sensory perception thresholds during the administration of stimuli. It has proven to be an important instrument to characterize mechanisms underlying somatic and neuropathic pain disorders, but its reliability has not been fully established in patients with visceral pain [127]. QST is also known as psychological testing and can be subdivided into Static QST and Dynamic QST. In Static QST, the states of the peripheral nervous system are measured whereas, the dynamic QST takes measurements after agitation of the pain modulation system [126].

Temporal Summation (TS) and Conditioned Pain Modulation (CPM) are dynamic QST paradigms that have been utilized in acupuncture analgesia related studies. TS and CPM represent the ascending facilitating and descending inhibitory aspects of pain perception respectively [128]. This next section will discuss these 2 outcome measures for acupuncture analgesia, which were included in a 2012 review article [126].

Temporal Summation

Temporal summation refers to increased pain perception in response to repetitive noxious stimuli over time. It correlates with the "windup" phenomenon occurring in the spinal wide dynamic range (WDR) neurons observed in the dorsal horn with repetitive C-fiber stimulation.

In a 2010 RCT that assessed the effect of acupuncture on pain temporal summation, 36 healthy volunteers were randomized into three groups: electroacupuncture (2 and 100 Hz), manual acupuncture, and sham acupuncture. These three different acupuncture treatments were delivered to ST-36 and ST-40 (Fig. 11) on the dominant leg by a blinded practitioner and pain thresholds to single and repeated electrical stimulation pulses were recorded. It was concluded that electroacupuncture induced bilateral, segmentally distributed, and prolonged analgesia for both single pain thresholds and temporal summation thresholds. On the other hand, manual acupuncture increased single pain thresholds and temporal summation thresholds, but these changes were not significantly different from the sham treatments [129]. In a separate randomized crossover pilot study, the effect of acupuncture on endogenous analgesia in chronic whiplash-associated disorders (viewed as

Fig. 11 QST in acupuncture analgesia research

temporal summation/chronic pain model) was investigated. Thirty-nine patients received 2 treatment sessions with an identical induration: acupuncture or relaxation therapy, and then randomly crossed over. One session of acupuncture resulted in acute improvements in pain sensitivity in the necks of patients with chronic whiplash disorder, but had no effect on conditioned pain modulation or temporal summation due to repeated pressure stimuli, suggesting the effect of acupuncture on pain temporal summation is limited [130].

Conditioned Pain Modulation

CPM is a paradigm that uses a conditioning stimulus to influence a testing stimulus. It assesses the perception of a noxious stimulus after a conditioned noxious stimulus. This "treating pain with pain" approach is often referred to as diffuse noxious inhibitory control (DNIC) [131]. The terms are used interchangably although some distinguish DNIC as a neurophysiologic process, and CPM as a behavioral correlate of this process [126].

The underlying CNS physiology of CPM is thought to be a global reduction of wide dynamic range sensitivity due to a single, heterotopic, and noxious stimulation [126]. Various conditioning stimuli have been used to research CPM. One report indicated that the approximate median magnitude of CPM represents about a 29% decrease in pain rating, regardless of the test stimulus [132]. Acupuncture analgesia studies in CPM, where needling certain points is considered the conditioning stimuli, are very limited with only 2 direct studies found comparing acupuncture analgesia to CPM or DNIC.

The first acupuncture and DNIC study was done by recording the convergent neurons in the trigeminal nucleus caudalis of rats. Innocuous and noxious mechanical stimuli were applied to one side of the muzzle. The *Zusanli* (ST-36) acupoints on the right hindlimb was compared to a sham acupuncture point. Acupuncture was also compared to noxious thermal stimulation of the left hind limb (DNIC). Acupuncture (either applied at the *Zusanli* or at the sham point) and noxious thermal stimulation induced similar strong inhibitory and long-lasting effects on the C-fiber-evoked responses of trigeminal convergent neurons. These analgesic effects were significantly reduced by systemic naloxone [64]. A separate study was done on healthy humans to investigate DNIC as a possible mechanism of acupuncture analgesia by comparing acupuncture to non-penetrating sham acupuncture (involving tapping) and cold water bath-induced DNIC. Forty-five subjects were randomized to 1 of 3 interventions and the analgesic effect was measured using pressure algometry at the second toe before and after each of the interventions. Pain pressure detection threshold was significantly increased in the DNIC test compared to acupuncture and sham. Acupuncture and sham effects did have small analgesic effects, but their effects did not significantly differ from one another. It was concluded that acupuncture does elicit acupuncture analgesia, but no different from placebo. Thus, acupuncture effects were significantly less than a DNIC-like effect [133].

Functional MRI

Although acupuncture has been shown to be clinically effective for treating pain, its site-specificity has been questioned. Functional MRI (fMRI) imaging (Fig. 12) has been utilized to show how acupuncture modulates various parts of the brain, including the limbic system [134], periaqueductal gray matter [135], cerebellum [136], motor cortex [137], amygdala [138], hypothalamus [139] basal ganglia, and the brainstem [140]. The effect of acupuncture on brain signaling will be discussed in the following sections.

In 2014, an investigation utilizing a textbook acute pain treatment paradigm [141] on the effect of thermal noxious stimuli was conducted. Functional MRI was used to correlate imaging with behavioral changes when different intensity (optimal versus minimal) electroacupuncture was performed. Heat pain had an excitatory effect on brain areas known for pain processing and perception, and electroacupuncture protocols deactivated these areas, which included the right SI, bilateral SII, bilateral frontal cortices, and bilateral dorsal posterior cingulate cortex (Fig. 13). In

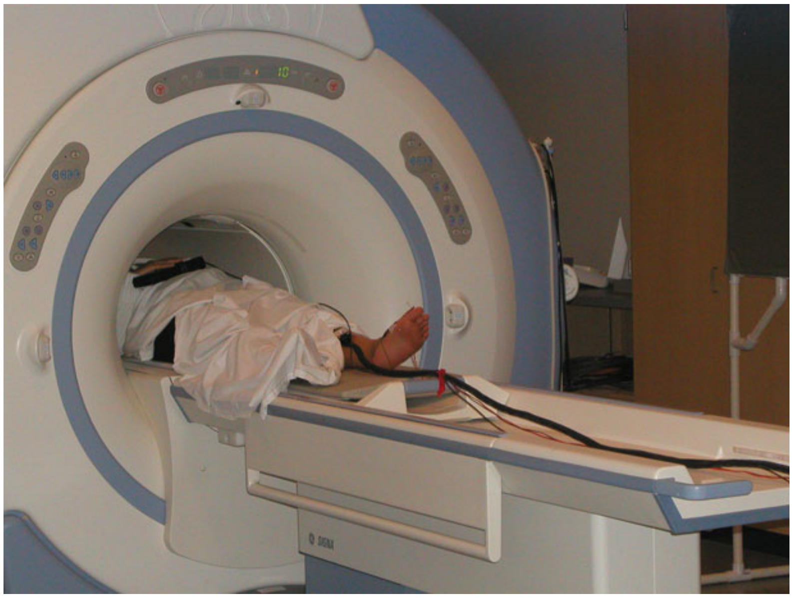


Fig. 12 Functional MRI with acupuncture

addition, optimal intensity electroacupuncture, when compared to minimal electroacupuncture, was found to elicit a more robust supraspinal effect on pain modulation and perception [142].

The same investigators also compared the effect of acupuncture needle combination on the central pain modulation. Eleven healthy subjects were divided into 2 groups that got either: (1) *Ting* points (tendinomuscular meridians used for acute pain, such as LR-1 and SP-1 or SP-2) a combination treatment of *Ting* points (LR-1 and SP-1) with Gathering points (CV-2) (Figs. 14 and 15) [143]. Thermal pain was introduced at the medial aspects of the legs. While electroacupuncture at *Ting* Points alone reduced pain, adding the Gathering Point provided a more sustainable analgesic effect. These results led the investigators to conclude that while both groups had a significant degree of deactivation in the human brain regions related to pain processing, the addition of the Gathering Point stimulation enhanced the inhibitory effect on the ascending spinoreticular pain pathway (Fig. 16) [144].

The supraspinal effect of electroacupuncture has also been compared to manual acupuncture using fMRI. One study observed the differences between subjects that received: manual acupuncture, electroacupuncture at 2 Hz (low frequency) and 100 Hz (high frequency), and tactile control stimulation was set up as sham. All 3 groups received ST-36 (Fig. 17) stimulation. In general, electroacupuncture (low more than high frequency) produced more widespread fMRI signal increases than manual acupuncture which in turn provided more signaling than the sham group. There were also specific findings between the 3 groups. Unlike sham tactile stimulation, both manual and electroacupuncture showed supraspinal activations in the anterior insula, limbic, and paralimbic structures, the cortices of the subgenual and retrosplenial cingulate, as well as the ventromedial prefrontal cortex, frontal, and temporal poles. However, only electroacupuncture produced significant signal increase in the anterior middle cingulate cortex with the 2-Hz electroacupuncture produced signal increase in the pontine raphe area [145].

In an attempt to show that needling same-meridian acupoints have similar effects on the brain, 53 healthy subjects were randomly divided in 6 groups. Two different acupoints of the liver meridians of the foot (LR-3 and LR-6), 2 stomach meridian acupoints (ST-36, ST-43), and 2 nearby sham points were tested (Fig. 18). Each subject received stimulation at one acupoint on the right side of the body. Results of fMRI data

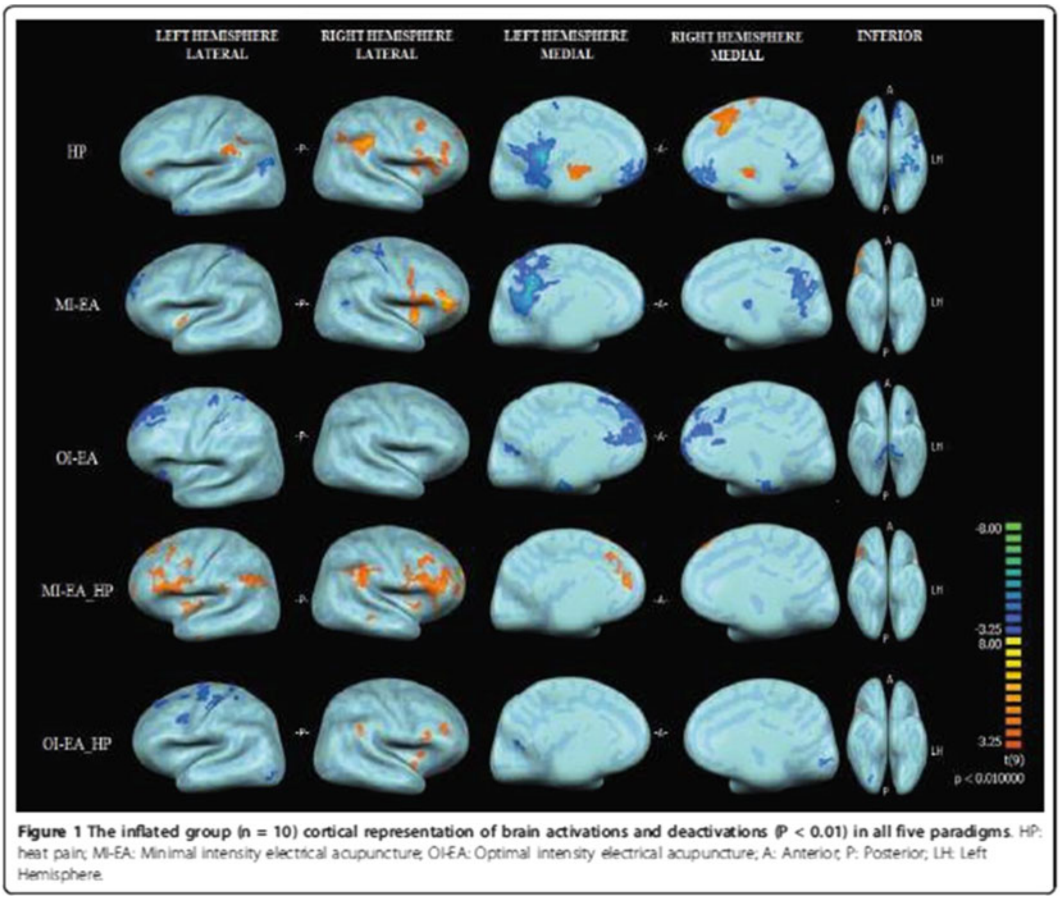
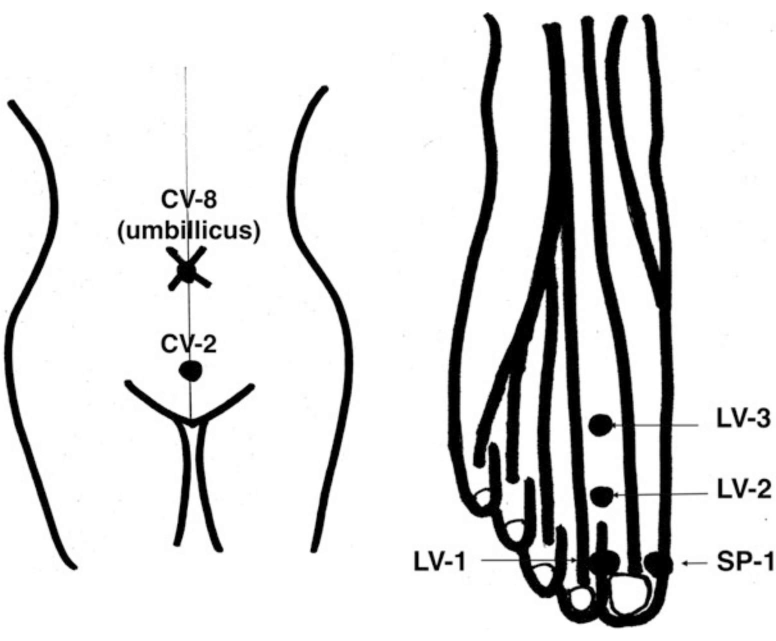


Fig. 13 Inflated cortical representation of identified brain areas of activation and deactivation and deactivation in all 5 paradigms

Fig. 14 CV-2, LR-1, SP-1



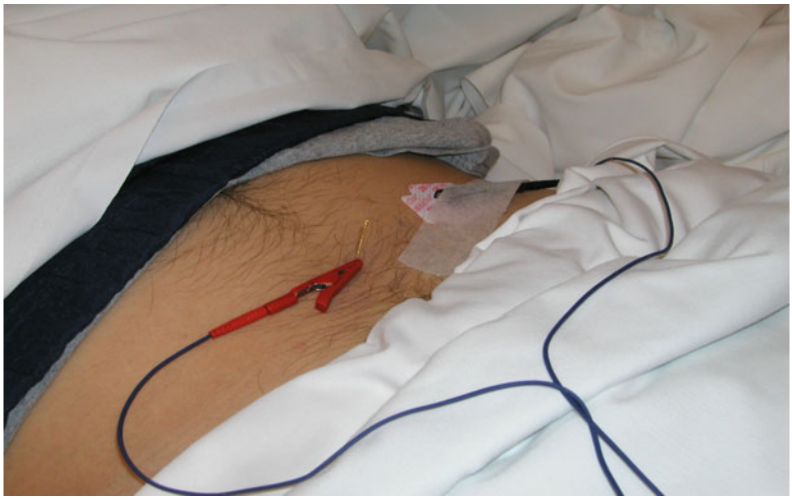


Fig. 15 Gathering point needle placement (CV-2)

analyses showed, that while stimulating both liver points evoked activation at the ipsilateral superior parietal lobe, similar stimulation given at the stomach points activated the ipsilateral middle frontal gyrus. In contrast to the activation of the brain by the sham acupoints, all 4 real acupoints

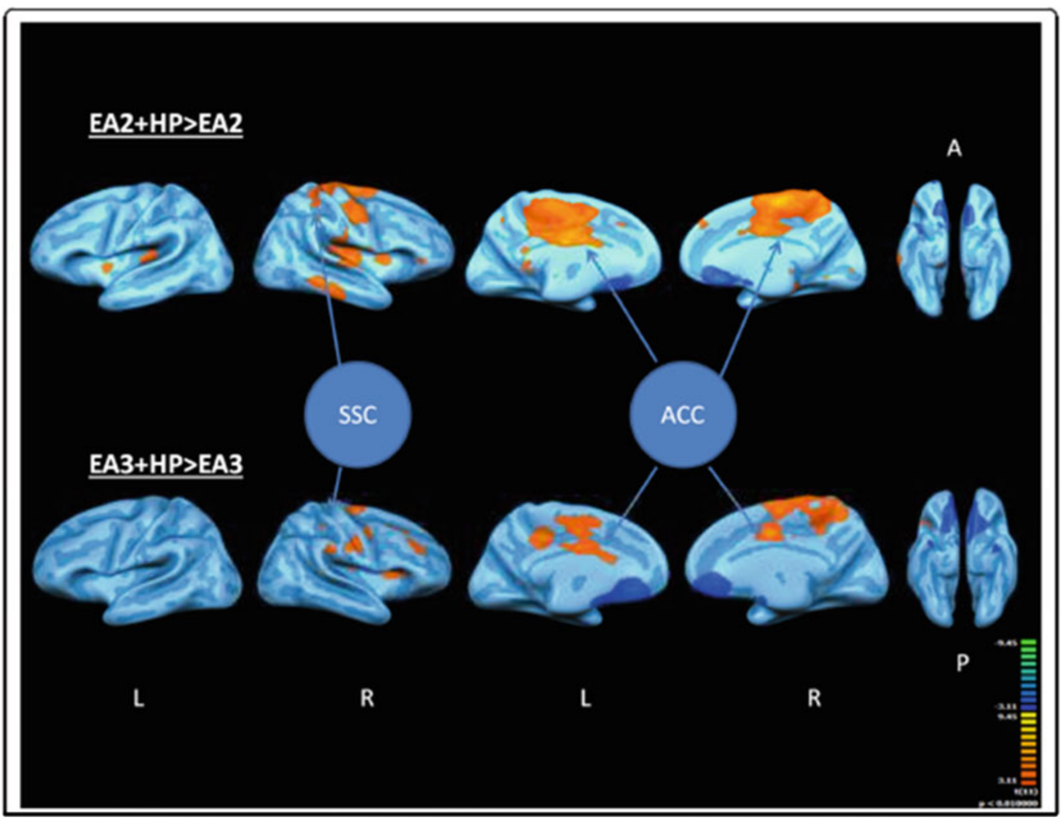


Fig. 16 Effect of Ting and gathering points with heat stimulation [144]

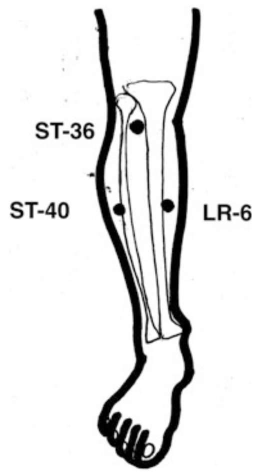


Fig. 17 ST-36

had the common effect of activating 2 specific areas of the brain, the bilateral primary somatosensory area and the ipsilateral cerebellum [146], showing that the pattern of suprapsinal activation from 2 different meridians are somewhat different, even though some brain regions are activated by stimulating either meridian.

Evidence from fMRI imaging has even shown that acupuncture modulates temporal neural responses in widely distributed brain network, which has a large overlap with pain-related areas. It was demonstrated that brain activities could vary at the different stages of acupuncture. During the needling phase, the amygdala and perigenual anterior cingulate cortex exhibited increased activities, and then signals decreased to below baseline. The periaqueductal gray and hypothalamus showed intermittent signaling during the entire fMRI session and even after the acupuncture needling was terminated [147]. The result of the study suggests that the effect of acupuncture on pain perception often outlasts the duration of the stimulation.

Other studies have also shown the site specificities of the acupoints. In one of these studies, twenty-one healthy male volunteers were enrolled into a crossover trial comparing ST-44 to a sham acupoint treatment. ST-44 stimulation affected the inferior parietal and the prefrontal cortex and the posterior insula whereas, the sham acupoint stimulation activated the anterior cingulate cortex and the anterior insula. [148].

In a 2012 systematic review and meta-analysis, the authors aimed to provide an overview of fMRI acupuncture research regarding: (1) sham versus true acupuncture, (2) effects

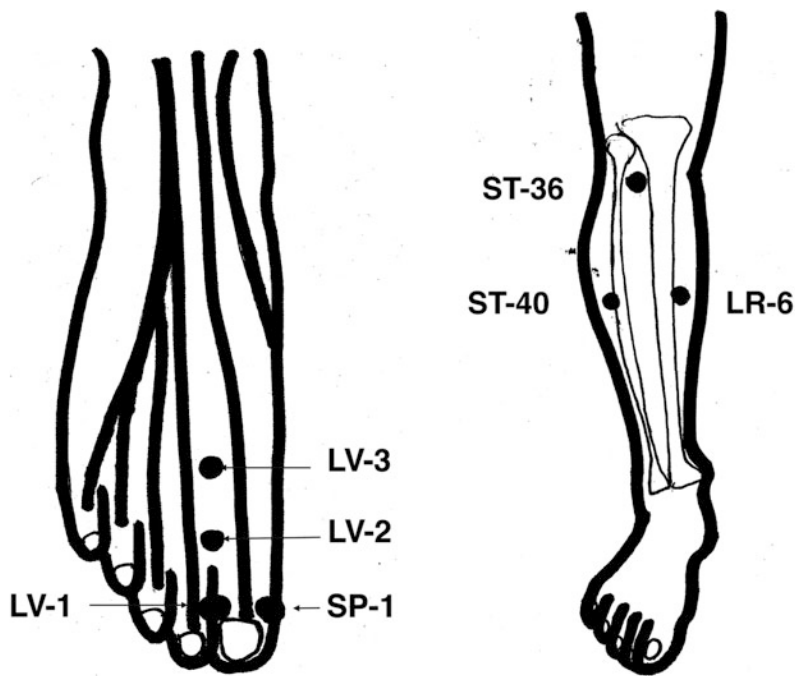


Fig. 18 LR-3 & LR-6

Table 2 Meta-analysis on Acupuncture with fMRI [149]

	Investigated topics	Results
1	Sham versus true acupuncture	Verum acupuncture stimuli confirmed brain activity within many areas of the brain. True versus sham acupuncture differences were noted in the middle cingulate regions. Some heterogeneity was noted, depending on how the meta-analyses was conducted
2	Effects of acupuncture needle manipulation, including electroacupuncture	Increased intensity and duration of needling was also found to increase brain response. Electroacupuncture showed more activation than manual acupuncture with low (2 Hz) versus high (100 Hz) frequencies showing different brain activity
3	Differences between healthy and non-healthy volunteers	Healthy volunteers respond differently to acupuncture compared to non-healthy volunteers
4	Brain effects from different acupuncture points	Brain maps of different acupuncture points differ. However, acupuncture points on the same meridian showed some similarities in brain signaling

of acupuncture needling manipulation, (3) differences between healthy and non-healthy volunteers and (4) the effect of different acupuncture points on the the brain. In this review, 779 papers were identified, 149 met inclusion criteria for analysis, and 34 were eligible for the meta-analysis. The main findings of the analyses are summarized in Table 2. It was concluded that the brain's response to acupuncture was consistent with somatosensory as well as affective and cognitive processing areas [149].

4.4 The Role of the Autonomic Nervous System in Acupuncture Analgesia

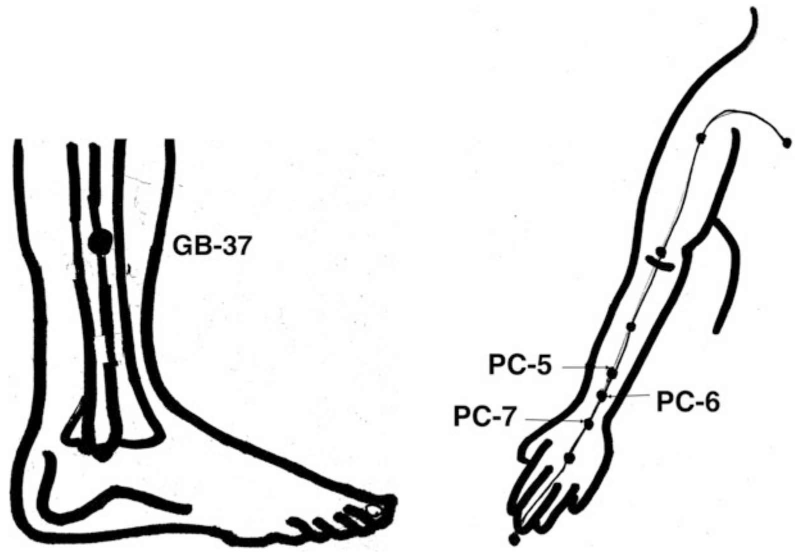
The discovery that cholinergic neurons in the autonomic nervous system inhibit acute inflammation has qualitatively expanded our understanding of how the nervous system modulates immune responses. It is now known that the nervous system can regulate the inflammatory response in real time, just as it controls heart rate and other vital functions. The effect of acupuncture on the ANS is known to occur both centrally and peripherally, and thus providing another line of therapeutic mechanisms related to acupuncture. [150].

Previous studies have shown that the parasympathetic nervous system can be activated by directly stimulating the vagus nerve. Stimulating the ear via acupuncture at *Shenmen* and "Point Zero" [151] in the outer ear has been shown to affect heart rate variability [152]. In addition, these acupuncture points have also been used for treating depression, epilepsy [153], and pain [37, 154–160].

Various ear acupuncture protocols including one by a military physician for pain analgesia have been developed (Fig. 19) [161–166]. Some of these protocols call for the stimulation of the auricular acupuncture "Point Zero," which serves as a conduit for activating the vagus nerve [162].

Fig. 19 Battlefield Acupuncture Protocol for Pain Analgesia using Semi-Permanent Needles

Fig. 20 PC-6,PC-7,GB-37



A different study stimulating the vagus nerve via the ear on patients with chronic pelvic pain due to endometriosis, demonstrated a significant reduction in anxiety, and reduction trend in evoked pain intensity and temporal summation of mechanical pain [167]. Vagal nerve stimulation has also been shown to increase and decrease pain threshold without affecting heart rate and blood pressure [168]. Aside from affecting pain perception, stimulating *Shen Men* in postoperative patients who receive ketamine anesthesia has been shown to reduce hallucinations at the beginning of the emergence period [169].

The vagus nerve can be directly stimulated to activate parasympathetic ANS and induce pain analgesia. However, the parasympathetic activity can also be induced by stimulating distal points in the extremities, without directly stimulating the vagus nerve. Functional MRI studies have been conducted to assess the effect of acupuncture on heart rate variability, and this has been correlated with supraspinal changes. One study showed stimulating ST-36 could induce significant changes in heart rate variability with corresponding supraspinal functional changes in the hypothalamus, the dorsal raphe nucleus, the periaqueductal gray, and the rostroventral medulla. These observations support the assertion that acupuncture needling can affect both central and peripheral autonomic nervous systems [140].

Other studies also showed that distal (i.e., not directly on the vagus nerve) acupoint activation could affect the autonomic nervous system and result in indirect pain analgesic and sedative outcomes. For example, Pericardium 6 (PC-6) is a point that is used in for various conditions, including chest tightness, palpitations, nausea, and carpal tunnel syndrome [139]. Functional MRI with stimulation at the PC-6, a point in the forearm, shows selective responses in the insula, hypothalamus, and flocculonodular lobe of the cerebellum with correlated effect on autonomic regulatory functions and pain. These effects were not observed with stimulation at the control acupoints (PC-7, GB-37) (Fig. 20) [170].

5 Discussion

Although acupuncture has been used clinically over thousands of years, its associated analgesic mechanisms have only been explored in the past few decades. Several aspects of acupuncture research including research tools, study design, choices of control, and subject and practitioner blinding, and overall limitations are worthy of discussion.

Quantitative Sensory Testing (using temporal summation and conditioned pain modulation) and fMRI has vastly improved the current understanding in the analgesic mechanisms of acupuncture. However, challenges still exist even with these advanced research tools. Issues that can affect the outcome of the QST assessment may include: (1) a lack of temporal stability ; (2) an inconsistency in testing methodology; (3) individual variabilities in TS and CPM responses; and (4) subjects' compliance or ability to follow instruction [126, 171]. In the area of fMRI related acupuncture studies, it was noted that not all acupuncture-fMRI studies met the strict methodological requirements including the choice of baseline, issues related to the interpretation of deactivations, problems with attention control and implications of different group statistics [172].

A major issue with in acupuncture study design is the focus on healthy subjects with single-session needling methods. These study treatment approaches do not necessarily reflect the TCM clinical treatment paradigms, in which patients often receive multiple sessions of acupuncture treatments consisting of multiple needles. This difference between study treatment approach and clinical practice somewhat diminishes the translational impact of the study results in the real clinical world, especially in the chronic pain setting. Although recent meta-analyses have shown positive results for acupuncture in managing chronic headache, back, neck, and shoulder pain [10], further research is required to validate the effect of acupuncture on other chronic pain conditions. In addition, treatment paradigms with clinical relevance to a specific diagnosis (e.g., lumbar radiculopathy or lumbar facet arthropathy, as opposed to lumbago) will greatly enhance the translational nature of the study result [126].

Choices of control as well as patient and practitioner blinding continue to be a topic of debate in the world of acupuncture research. TCM providers often believe that stimulating any meridian point, whether with an ear seed (small seeds held in place with adhesive tape) or acupressure (pushing on acupoints with a finger or a tool) can have a therapeutic or physiological effect and research has shown that needling anywhere in the body will elicit diffuse inhibitory control of pain [116, 119]. In addition, expectancy of receiving acupuncture alone has been shown to alter brain function associated with mood and pain perception [116]. Several approaches can potentially minimize the confounding issues of blinding in an acupuncture related RCT may include (1) sedating the research subjects during the treatment; (2) using retractable needles for sham treatments; and/or (3) adopting a blinded personal to conduct the study related assessments.

The Society of Acupuncture Research (SAR) has recently proposed some guidance for future acupuncture related research. One of the proposed ideas is the development of biomarkers that can provide meaningful correlations between animal pain analgesia and patient reported outcomes [173].

6 Conclusion

Acupuncture is an ancient modality within TCM. It continues to be used for acute and chronic pain management. This modality has recently caught the interest of consumers in the United States due to its positive efficacy, and the side effect related limitations in other currently available pain treatment modalities in Western Medicine. To fully expand the practice of this consumer-driven intervention in conventional medical practice will require credible clinical outcome data and a clear understanding in its treatment-related mechanisms. Despite the controversies surrounding acupuncture-related research, high-quality research continues to emerge to explain the effects of acupuncture on the peripheral and central nervous systems, muscle fascia, and neurotransmitter signaling, and to support its clinical efficacy in treating various pain conditions. With ongoing improved outcome measures and research tools such as fMRI and Quantitative Sensory Testing, further research on the mechanisms of acupuncture is warranted to support its clinical application in pain management.

References

1. Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research. Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education, 2011.
2. Prevention CfDCa. Injury Prevention & Control: Prescription Drug Overdose—What the Public Needs to Know about the Epidemic 2015 [updated May 5, 2015]. Available from: http://www.cdc.gov/drugoverdose/epidemic/public.html.
3. Prevention CfDCa. Injury Prevention & Control: Prescription Drug Overdose—Understanding the Epidemic 2015 [April 30, 2015]. Available from: http://www.cdc.gov/drugoverdose/epidemic/index.html.
4. Sita Ananth M. Complementary alternative medicine survey of hospitals—summary of results. Alexandria, VA: Samueli Institute; 2010. p. 2011.
5. White A, Ernst E. A brief history of acupuncture. Rheumatology. 2004;43(5):662–3.
6. Zhang X. Acupuncture: review and analysis of reports on Controlled Clinical Trials World Health Organization; 2003. Available from: http://apps.who.int/medicinedocs/pdf/s4926e/s4926e.pdf.
7. A standard international acupuncture nomenclature: memorandum from a WHO meeting. Bull World Health Organiz 1990;68(2):165–9.
8. Asher GN, Jonas DE, Coeytaux RR, Reilly AC, Loh YL, Motsinger-Reif AA, et al. Auriculotherapy for PAIN management: a systematic review and meta-analysis of randomized controlled trials. J Altern Complement Med. 2010;16(10):1097–108.
9. Usichenko TI, Lehmann C, Ernst E. Auricular acupuncture for postoperative pain control: a systematic review of randomised clinical trials. Anaesthesia. 2008;63(12):1343–8.
10. Vickers AJ, Cronin AM, Maschino AC, Lewith G, MacPherson H, Foster NE, et al. Acupuncture for chronic pain: individual patient data meta-analysis. Arch Intern Med. 2012;172(19):1444–53.
11. Tan JY, Molassiotis A, Wang T, Suen LK. Adverse events of auricular therapy: a systematic review. Evid Based Complement Altern Med eCAM. 2014;2014:506758.
12. Wu J, Hu Y, Zhu Y, Yin P, Litscher G, Xu S. Systematic review of adverse effects: a further step towards modernization of acupuncture in China. Evid Based Complement Altern Med eCAM. 2015;2015:432467.
13. Janssen PA, Demorest LC, Kelly A, Thiessen P, Abrahams R. Auricular acupuncture for chemically dependent pregnant women: a randomized controlled trial of the NADA protocol. Subst Abuse Treat Prev Policy. 2012;7:48.
14. Cochrane S, Smith CA, Possamai-Inesedy A. Development of a fertility acupuncture protocol: defining an acupuncture treatment protocol to support and treat women experiencing conception delays. J Altern Complement Med. 2011;17(4):329–37.
15. Li X, Hu J, Wang X, Zhang H, Liu J. Moxibustion and other acupuncture point stimulation methods to treat breech presentation: a systematic review of clinical trials. Chin Med. 2009;4:4.
16. Neri I, Airola G, Contu G, Allais G, Facchinetti F, Benedetto C. Acupuncture plus moxibustion to resolve breech presentation: a randomized controlled study. J Matern Fetal Neonatal Med (The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet). 2004;15(4):247–52.
17. Zhang X, Cao B, Yan N, Liu J, Wang J, Tung VO, et al. Vagus nerve stimulation modulates visceral pain-related affective memory. Behav Brain Res. 2013;236(1):8–15.
18. IASP Taxonomy. Available from: http://www.iasp-pain.org/Taxonomy.
19. van den Broeke EN, Mouraux A. Enhanced brain responses to C-fiber input in the area of secondary hyperalgesia induced by high-frequency electrical stimulation of the skin. J Neurophysiol. 2014;112(9):2059–66.
20. Schmid J, Langhorst J, Gass F, Theysohn N, Benson S, Engler H, et al. Placebo analgesia in patients with functional and organic abdominal pain: a fMRI study in IBS, UC and healthy volunteers. Gut. 2015;64(3):418–27.
21. Osaka N, Osaka M, Morishita M, Kondo H, Fukuyama H. A word expressing affective pain activates the anterior cingulate cortex in the human brain: an fMRI study. Behav Brain Res. 2004;153(1):123–7.
22. Garza-Villarreal EA, Jiang Z, Vuust P, Alcauter S, Vase L, Pasaye EH, et al. Music reduces pain and increases resting state fMRI BOLD signal amplitude in the left angular gyrus in fibromyalgia patients. Front Psychol. 2015;6:1051.
23. Gosset N, Dietz N. Unlocking pain: deep brain stimulation might be the key to easing depression and chronic pain. IEEE Pulse. 2015;6(2):16–20.
24. Brain scans indicate that depression can increase pain perception. The Harvard Mental Health Letter from Harvard Medical School. 2009;25(9):7.
25. Asghar MS, Pereira MP, Werner MU, Martensson J, Larsson HB, Dahl JB. Correction: secondary hyperalgesia phenotypes exhibit differences in brain activation during noxious stimulation. PLoS ONE. 2015;10(5):e0128640.
26. Asghar MS, Pereira MP, Werner MU, Martensson J, Larsson HB, Dahl JB. Secondary hyperalgesia phenotypes exhibit differences in brain activation during noxious stimulation. PLoS ONE. 2015;10(1):e0114840.
27. Fischer TZ, Waxman SG. Neuropathic pain in diabetes–evidence for a central mechanism. Nat Rev Neurol. 2010;6(8):462–6.

28. Rempe T, Wolff S, Riedel C, Baron R, Stroman PW, Jansen O, et al. Spinal fMRI reveals decreased descending inhibition during secondary mechanical hyperalgesia. PLoS ONE. 2014;9(11):e112325.
29. Kunimoto M. [The peripheral mechanism of physiological pain]. Brain and Nerve = Shinkei kenkyu no shinpo. 2012;64(11):1205–14.
30. Chang S. The meridian system and mechanism of acupuncture—a comparative review. Part 2: mechanism of acupuncture analgesia. Taiwan J Obstet Gynecol. 2013;52(1):14–24.
31. Hanson P, Schumacker P, Debugne T, Clerin M. Evaluation of somatic and autonomic small fibers neuropathy in diabetes. Am J Phys Med Rehabil Assoc Acad Physiatr. 1992;71(1):44–7.
32. Introduction to Pain Pathways and Mechanisms.
33. Schlereth T, Birklein F. The sympathetic nervous system and pain. NeuroMol Med. 2008;10(3):141–7.
34. Abramov R. Lumbar sympathetic treatment in the management of lower limb pain. Curr Pain Headache Rep. 2014;18(4):403.
35. He W, Wang X, Shi H, Shang H, Li L, Jing X, et al. Auricular acupuncture and vagal regulation. Evid Based Complement Altern Med eCAM. 2012;2012:786839.
36. Usichenko TI, Lehmann C, Ernst E. Auricular acupuncture for postoperative pain control: a systematic review of randomised clinical trials. Anaesthesia. 2008;63(12):1343–8.
37. Sator-Katzenschlager SM, Michalek-Sauberer A. P-Stim auricular electroacupuncture stimulation device for pain relief. Expert Rev Med Devices. 2007;4(1):23–32.
38. Psychogenic Pain: Cleveland Clinic. Available from: http://my.clevelandclinic.org/services/anesthesiology/pain-management/diseases-conditions/hic-psychogenic-pain.
39. Kaptchuk TJ. The web that has no weaver. Lincolnwood, Ill.; St. Albans: Contemporary; Verulam [distributor]; 2000.
40. Wiseman N. Fundamentals of Chinese medicine. Southfield, Michigan: Readings for the Blind; 2007.
41. Hayano DS. Measuring Qi Energy Available from: http://www.equilibrium-e3.com/images/PDF/Measuring%20Qi%20Energy.pdf.
42. Hui Lin PD. Overview of the status of Chinese Chi Research International Yan Xin Qigong Association. Available from: http://www.item-bioenergy.com/infocenter/chinesechiresearch.doc.
43. Traditional Chinese Medicine: Wikipedia. Available from: https://en.wikipedia.org/wiki/Traditional_Chinese_medicine.
44. Zhao ZQ. Neural mechanism underlying acupuncture analgesia. Prog Neurobiol. 2008;85(4):355–75.
45. Shi R. Pain according to Chinese Medicine San Gabriel, Texas: Rei Shi Acupuncture Clinic. Available from: http://reishiacupuncture.com/page/pain-according-to-chinese-medicine.
46. Eades W. Ancient Chinese Medicine Meets Modern Anatomy Dissection: Acupuncture Today; 2015. January, 2015, Vol. 16, Issue 01. Available from: http://www.acupuncturetoday.com/mpacms/at/article.php?id=32980.
47. MacPherson H, Asghar A. Acupuncture needle sensations associated with De Qi: a classification based on experts' ratings. J Altern Complement Med. 2006;12(7):633–7.
48. Tian DS, Xiong J, Pan Q, Liu F, Wang L, Xu SB, et al. De qi, a threshold of the stimulus intensity, elicits the specific response of acupoints and intrinsic change of human brain to acupuncture. Evid Based Complement Altern Med eCAM. 2014;2014:914878.
49. Nierhaus T, Pach D, Huang W, Long X, Napadow V, Roll S, et al. Differential cerebral response to somatosensory stimulation of an acupuncture point vs. two non-acupuncture points measured with EEG and fMRI. Front Hum Neurosci. 2015;9:74.
50. Egot-Lemaire SJP, Ziskin MC. Dielectric properties of human skin at an acupuncture point in the 50–75 GHz frequency range A pilot study. Bioelectromagnetics. 2011;32(5):360–6.
51. Ahn AC, Wu J, Badger GJ, Hammerschlag R, Langevin HM. Electrical impedance along connective tissue planes associated with acupuncture meridians. BMC Complement Altern Med. 2005;5(1):10.
52. Leung AY, Park J, Schulteis G, Duann JR, Yaksh T. The electrophysiology of de qi sensations. J Altern Complement Med. 2006;12(8):743–50.
53. Zhu L, Li C, Yang B, Ji C, Li W. The effect of neonatal capsaicin on acupuncture analgesia–to evaluate the role of C fibers in acupuncture analgesia. Zhen ci yan jiu = Acupuncture research [Zhongguo yi xue ke xue yuan Yi xue qing bao yan jiu suo bian ji]. 1990;15(4):285–91.
54. Cao X. Scientific bases of acupuncture analgesia. Acupunct Electrother Res. 2002;27(1):1–14.
55. Li AH, Zhang JM, Xie YK. Human acupuncture points mapped in rats are associated with excitable muscle/skin-nerve complexes with enriched nerve endings. Brain Res. 2004;1012(1–2):154–9.
56. Helms J. The basic, clinical, and speculative science of acupuncture. In: Helms J, editor. Acupuncture energetics a clinical approach for physicians. Berkeley: Medical Acupuncture Publishers; 1995. p. 19–43.
57. Fuiyu Yip L. Tendinomuscular pain treatment with acupuncture. Available from: http://acupuncture-n-herbs.com/tendinomuscular-treatment-for-pain.
58. Leung A, Khadivi B, Duann JR, Cho ZH, Yaksh T. The effect of Ting point (tendinomuscular meridians) electroacupuncture on thermal pain: a model for studying the neuronal mechanism of acupuncture analgesia. J Altern Complement Med. 2005;11(4):653–61.
59. Langevin HM, Churchill DL, Cipolla MJ. Mechanical signaling through connective tissue: a mechanism for the therapeutic effect of acupuncture.

FASEB J: Official Publication of the Federation of American Societies for Experimental Biology. 2001;15(12):2275–82.
60. Langevin HM, Churchill DL, Wu J, Badger GJ, Yandow JA, Fox JR, et al. Evidence of connective tissue involvement in acupuncture. FASEB J: Official Publication of the Federation of American Societies for Experimental Biology. 2002;16 (8):872–4.
61. Yu Bai JW, Jin-peng Wu, et al. Review of evidence suggesting that the fascia network could be the anatomical basis for acupoints and meridians in the human body. Evid-Based Complement Altern Med. 2011.
62. Finando S, Finando D. Qi, acupuncture, and the fascia: a reconsideration of the fundamental principles of acupuncture. J Altern Complement Med. 2012;18(9):880–6.
63. Guo F, Song W, Jiang T, Liu L, Wang F, Zhong H, et al. Electroacupuncture pretreatment inhibits NADPH oxidase-mediated oxidative stress in diabetic mice with cerebral ischemia. Brain Res. 2014;1573:84–91.
64. Bing Z, Villanueva L, Le Bars D. Acupuncture and diffuse noxious inhibitory controls: naloxone-reversible depression of activities of trigeminal convergent neurons. Neuroscience. 1990;37(3):809–18.
65. Chung WY, Zhang HQ, Zhang SP. Peripheral muscarinic receptors mediate the anti-inflammatory effects of auricular acupuncture. Chin Med. 2011;6 (1):3.
66. Mattson MP. Glutamate and neurotrophic factors in neuronal plasticity and disease. Ann NY Acad Sci. 2008;1144:97–112.
67. Zhou W, Fu LW, Guo ZL, Longhurst JC. Role of glutamate in the rostral ventrolateral medulla in acupuncture-related modulation of visceral reflex sympathoexcitation. Am J Physiol Heart Circ Physiol. 2007;292(4):H1868–75.
68. Guo Z, Zhang L, Wu Y, Li M, Yang X, He Z, et al. The role of glutamate transporter-1 in the acquisition of brain ischaemic tolerance in rats induced by electro-acupuncture pre-treatment. Brain Inj. 2015;29(3):396–402.
69. Yang J, Liu WY, Song CY, Lin BC. Through central arginine vasopressin, not oxytocin and endogenous opiate peptides, glutamate sodium induces hypothalamic paraventricular nucleus enhancing acupuncture analgesia in the rat. Neurosci Res. 2006;54(1):49–56.
70. Enna SJ, McCarson KE. The role of GABA in the mediation and perception of pain. Adv Pharmacol. 2006;54:1–27.
71. Xu Q, Yang JW, Cao Y, Zhang LW, Zeng XH, Li F, et al. Acupuncture improves locomotor function by enhancing GABA receptor expression in transient focal cerebral ischemia rats. Neurosci Lett. 2015;588:88–94.
72. McLennan H, Gilfillan K, Heap Y. Some pharmacological observations on the analgesia induced by acupuncture in rabbits. Pain. 1977;3(3):229–38.
73. Pomeranz B, Nguyen P. Intrathecal diazepam suppresses nociceptive reflexes and potentiates electroacupuncture effects in pentobarbital-anesthetized rats. Neurosci Lett. 1987;77(3):316–20.
74. ZHU Lixia YY, MO Xiaorong, JI Changfu. The important role of activation of GABA_B receptors in acupuncture analgesia. Acupunct Res. 2002.
75. Sommer C. Serotonin in pain and analgesia: actions in the periphery. Mol Neurobiol. 2004;30(2):117–25.
76. Takagi J, Yonehara N. Serotonin receptor subtypes involved in modulation of electrical acupuncture. Jpn J Pharmacol. 1998;78(4):511–4.
77. Kim SK, Park JH, Bae SJ, Kim JH, Hwang BG, Min BI, et al. Effects of electroacupuncture on cold allodynia in a rat model of neuropathic pain: mediation by spinal adrenergic and serotonergic receptors. Exp Neurol. 2005;195(2):430–6.
78. Hu WB, Wu ZJ, Wang KM. Progress of researches on involvement of serotonin in the central nervous system in acupuncture analgesia and other effects. Zhen ci yan jiu = Acupuncture research/[Zhongguo yi xue ke xue yuan Yi xue qing bao yan jiu suo bian ji]. 2012;37(3):247–51.
79. Bravo-Hernandez M, Cervantes-Duran C, Pineda-Farias JB, Barragan-Iglesias P, Lopez-Sanchez P, Granados-Soto V. Role of peripheral and spinal 5-HT(3) receptors in development and maintenance of formalin-induced long-term secondary allodynia and hyperalgesia. Pharmacol Biochem Behav. 2012;101(2):246–57.
80. Liu X, Zhu B, Zhang SX. Relationship between electroacupuncture analgesia and descending pain inhibitory mechanism of nucleus raphe magnus. Pain. 1986;24(3):383–96.
81. Treister R, Pud D, Eisenberg E. The dopamine agonist apomorphine enhances conditioned pain modulation in healthy humans. Neurosci Lett. 2013;548:115–9.
82. Potvin S, Grignon S, Marchand S. Human evidence of a supra-spinal modulating role of dopamine on pain perception. Synapse. 2009;63(5):390–402.
83. Millan MJ. Descending control of pain. Prog Neurobiol. 2002;66(6):355–474.
84. Jarcho JM, Mayer EA, Jiang ZK, Feier NA, London ED. Pain, affective symptoms, and cognitive deficits in patients with cerebral dopamine dysfunction. Pain. 2012;153(4):744–54.
85. Wood PB. Role of central dopamine in pain and analgesia. Expert Rev Neurother. 2008;8(5):781–97.
86. Jaaskelainen SK, Lindholm P, Valmunen T, Pesonen U, Taiminen T, Virtanen A, et al. Variation in the dopamine D2 receptor gene plays a key role in human pain and its modulation by transcranial magnetic stimulation. Pain. 2014;155(10):2180–7.

87. Wang HH, Xu SF. Effect of D1 and D2 dopamine receptor antagonists on acupuncture analgesia. Sheng li xue bao: [Acta Physiologica Sinica]. 1993;45(1):61–8.
88. Dai JL, Xu SF. The attenuation effect of chlorpromazine on electro-acupuncture analgesia: involvement of dopamine system. Acupunct Electrother Res. 1991;16(3–4):101–9.
89. Liu XY, Zhou HF, Pan YL, Liang XB, Niu DB, Xue B, et al. Electro-acupuncture stimulation protects dopaminergic neurons from inflammation-mediated damage in medial forebrain bundle-transected rats. Exp Neurol. 2004;189(1):189–96.
90. Gao X, Xin BM, Zhu CB, Wu GC, Xu SF. Effect of intrathecal injection of dopamine receptor agonists/antagonists on pain and acupuncture analgesia in rats. Sheng li xue bao: [Acta Physiologica Sinica]. 1998;50(1):43–8.
91. Wang HH, Zhu YH, Xu SF. The potentiation effect of haloperidol on the binding of etorphine to brain membranes in acupuncture analgesia. Sheng li xue bao: [Acta Physiologica Sinica]. 1994;46(4):313–9.
92. Leung L. Neurophysiological basis of acupuncture-induced analgesia—an updated review. J Acupunct Meridian Stud. 2012;5(6):261–70.
93. Zhang Y, Qu H, Zhou Y, Wang Y, Zhang D, Yang X, et al. The involvement of norepinephrine in pain modulation in the nucleus accumbens of morphine-dependent rats. Neurosci Lett. 2015;585:6–11.
94. Ono H, Nakamura A, Kanbara T, Minami K, Shinohara S, Sakaguchi G, et al. Effect of the norepinephrine transporter (NET) Effect of the norepinephrine transporter (NET) Effect of the norepinephrine transporter (NET) inhibition on mu-opioid receptor (MOR)-induced anti-nociception in a bone cancer pain model. J Pharmacol Sci. 2014;125 (3):264–73.
95. Cao J, Zhou MQ, Wu SB, Wang KM, Zhou YP, Wang YL, et al. Effects of acupuncture on expression of norepinephrine transporter mRNA in the cervical sympathetic ganglion and beta1-AR mRNA in the heart in cerebral-cardiac syndrome rats. Zhen ci yan jiu = Acupuncture research/[Zhongguo yi xue ke xue yuan Yi xue qing bao yan jiu suo bian ji]. 2011;36(4):252–7.
96. Wang H, Jiang J, Can X. Changes of norepinephrine release in rat's nucleus reticularis paragigantocellularis lateralis in acupuncture analgesia. Zhen ci yan jiu = Acupuncture research/[Zhongguo yi xue ke xue yuan Yi xue qing bao yan jiu suo bian ji]. 1994;19(1):20–5.
97. Hackel D, Stolz A, Mousa SA, Brack A, Rittner HL. Recruitment of opioid peptide-containing neutrophils is independent of formyl peptide receptors. J Neuroimmunol. 2011;230(1–2):65–73.
98. Mayer DJ, Price DD, Rafii A. Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. Brain Res. 1977;121(2):368–72.
99. Brissett DI, Whistler JL, van Rijn RM. Contribution of mu and delta opioid receptors to the pharmacological profile of kappa opioid receptor subtypes. Eur J Pain. 2012;16(3):327–37.
100. Wang Y, Gehringer R, Mousa SA, Hackel D, Brack A, Rittner HL. CXCL10 controls inflammatory pain via opioid peptide-containing macrophages in electroacupuncture. PLoS ONE. 2014;9 (4):e94696.
101. Nezhentsev M, Aleksandrov S. Effect of naloxone on the antipyretic action of acupuncture. Pharmacology. 1993;46(5):289–93.
102. Wang Y, Zhang Y, Wang W, Cao Y, Han JS. Effects of synchronous or asynchronous electroacupuncture stimulation with low versus high frequency on spinal opioid release and tail flick nociception. Exp Neurol. 2005;192(1):156–62.
103. Fearon AM, Twin J, Dahlstrom JE, Cook JL, Cormick W, Smith PN, et al. Increased substance P expression in the trochanteric bursa of patients with greater trochanteric pain syndrome. Rheumatol Int. 2014;34(10):1441–8.
104. Teodoro FC, Tronco Junior MF, Zampronio AR, Martini AC, Rae GA, Chichorro JG. Peripheral substance P and neurokinin-1 receptors have a role in inflammatory and neuropathic orofacial pain models. Neuropeptides. 2013;47(3):199–206.
105. Parenti C, Arico G, Ronsisvalle G, Scoto GM. Supraspinal injection of Substance P attenuates allodynia and hyperalgesia in a rat model of inflammatory pain. Peptides. 2012;34(2):412–8.
106. Ebner K, Singewald N. The role of substance P in stress and anxiety responses. Amino Acids. 2006;31 (3):251–72.
107. Lee HJ, Lee JH, Lee EO, Kim KH, Kim SH, Lee KS, et al. Substance P and beta-endorphin mediate electro-acupuncture induced analgesia in mouse cancer pain model. J Exp Clin Cancer Res CR. 2009;28:102.
108. Ma XP, Tan LY, Yang Y, Wu HG, Jiang B, Liu HR, et al. Effect of electro-acupuncture on substance P, its receptor and corticotropin-releasing hormone in rats with irritable bowel syndrome. World J Gastroenterol WJG. 2009;15(41):5211–7.
109. Mackey S. Mechanisms of inflammatory pain: therapeutic implications. J Clin Rheumatol Pract Reports Rheum musculoskelet Dis. 2004;10(3 Suppl):S5–11.
110. Ji RR. Peripheral and central mechanisms of inflammatory pain, with emphasis on MAP kinases. Curr Drug Targets Inflamm Allergy. 2004;3 (3):299–303.
111. Lin JG, Chen WL. Acupuncture analgesia: a review of its mechanisms of actions. Am J Chin Med. 2008;36(4):635–45.
112. Nager AL, Kobylecka M, Pham PK, Johnson L, Gold JI. Effects of acupuncture on pain and inflammation in pediatric emergency department patients with acute appendicitis: a pilot study. J Altern Complement Med. 2015;21(5):269–72.

113. Cao L, Zhang XL, Gao YS, Jiang Y. Needle acupuncture for osteoarthritis of the knee. A systematic review and updated meta-analysis. Saudi Med J. 2012;33(5):526–32.
114. Wang C, de Pablo P, Chen X, Schmid C, McAlindon T. Acupuncture for pain relief in patients with rheumatoid arthritis: a systematic review. Arthritis Rheum. 2008;59(9):1249–56.
115. Levine JD, Gordon NC, Bornstein JC, Fields HL. Role of pain in placebo analgesia. Proc Natl Acad Sci USA. 1979;76(7):3528–31.
116. Atlas LY, Wager TD. A meta-analysis of brain mechanisms of placebo analgesia: consistent findings and unanswered questions. Handb Exp Pharmacol. 2014;225:37–69.
117. Kam-Hansen S, Jakubowski M, Kelley JM, Kirsch I, Hoaglin DC, Kaptchuk TJ, et al. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. Sci Transl Med. 2014;6 (218):218ra5.
118. Vase L, Vollert J, Finnerup NB, Miao X, Atkinson G, Marshall S, et al. Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: a meta-analysis of the individual data from nine industrially sponsored trials. Pain. 2015;156(9):1795–802.
119. Le Bars D, Dickenson AH, Besson JM. Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain. 1979;6(3):283–304.
120. Xiong J, Liu F, Zhang MM, Wang W, Huang GY. De-qi, not psychological factors, determines the therapeutic efficacy of acupuncture treatment for primary dysmenorrhea. Chin J Integr Med. 2012;18 (1):7–15.
121. Chiu YH, Silman AJ, Macfarlane GJ, Ray D, Gupta A, Dickens C, et al. Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study. Pain. 2005;115(3):316–21.
122. Wang XJ, Wang LL. A mechanism of endogenous opioid peptides for rapid onset of acupuncture effect in treatment of depression. Zhong xi yi jie he xue bao = J Chin Integr Med. 2010;8(11):1014–7.
123. Bohren Y, Tessier LH, Megat S, Petitjean H, Hugel S, Daniel D, et al. Antidepressants suppress neuropathic pain by a peripheral beta2-adrenoceptor mediated anti-TNFalpha mechanism. Neurobiol Dis. 2013;60:39–50.
124. Lazzeri L, Vannuccini S, Orlandini C, Luisi S, Zupi E, Nappi RE, et al. Surgical treatment affects perceived stress differently in women with endometriosis: correlation with severity of pain. Fertil Steril. 2015;103(2):433–8.
125. Eshkevari L, Permaul E, Mulroney SE. Acupuncture blocks cold stress-induced increases in the hypothalamus-pituitary-adrenal axis in the rat. J Endocrinol. 2013;217(1):95–104.
126. Kong JT, Schnyer RN, Johnson KA, Mackey S. Understanding central mechanisms of acupuncture analgesia using dynamic quantitative sensory testing: a review. Evid Based Complement Altern Med eCAM. 2013;2013:187182.
127. Olesen SS, van Goor H, Bouwense SA, Wilder-Smith OH, Drewes AM. Reliability of static and dynamic quantitative sensory testing in patients with painful chronic pancreatitis. Reg Anesth Pain Med. 2012;37(5):530–6.
128. Arendt-Nielsen L, Yarnitsky D. Experimental and clinical applications of quantitative sensory testing applied to skin, muscles and viscera. J Pain: Official Journal of the American Pain Society. 2009;10 (6):556–72.
129. Zheng Z, Feng SJ, Costa C, Li CG, Lu D, Xue CC. Acupuncture analgesia for temporal summation of experimental pain: a randomised controlled study. Eur J Pain. 2010;14(7):725–31.
130. Tobbackx Y, Meeus M, Wauters L, De Vilder P, Roose J, Verhaeghe T, et al. Does acupuncture activate endogenous analgesia in chronic whiplash-associated disorders? A randomized crossover trial. Eur J Pain. 2013;17(2):279–89.
131. Le Bars D, Villanueva L, Bouhassira D, Willer JC. Diffuse noxious inhibitory controls (DNIC) in animals and in man. Patologicheskaia fiziologiia i eksperimental'naia terapiia. 1992;4:55–65.
132. Pud D, Granovsky Y, Yarnitsky D. The methodology of experimentally induced diffuse noxious inhibitory control (DNIC)-like effect in humans. Pain. 2009;144(1–2):16–9.
133. Schliessbach J, van der Klift E, Siegenthaler A, Arendt-Nielsen L, Curatolo M, Streitberger K. Does acupuncture needling induce analgesic effects comparable to diffuse noxious inhibitory controls? Evid Based Complement Altern Med eCAM. 2012;2012:785613.
134. Hui KK, Liu J, Makris N, Gollub RL, Chen AJ, Moore CI, et al. Acupuncture modulates the limbic system and subcortical gray structures of the human brain: evidence from fMRI studies in normal subjects. Hum Brain Mapp. 2000;9(1):13–25.
135. Liu WC, Feldman SC, Cook DB, Hung DL, Xu T, Kalnin AJ, et al. fMRI study of acupuncture-induced periaqueductal gray activity in humans. NeuroReport. 2004;15(12):1937–40.
136. Yoo SS, Teh EK, Blinder RA, Jolesz FA. Modulation of cerebellar activities by acupuncture stimulation: evidence from fMRI study. NeuroImage. 2004;22(2):932–40.
137. Jeun SS, Kim JS, Kim BS, Park SD, Lim EC, Choi GS, et al. Acupuncture stimulation for motor cortex activities: a 3T fMRI study. Am J Chin Med. 2005;33(4):573–8.
138. Qin W, Tian J, Bai L, Pan X, Yang L, Chen P, et al. FMRI connectivity analysis of acupuncture effects on an amygdala-associated brain network. Mol Pain. 2008;4:55.
139. Chen Y, Wang Y, Yin Q. The role of paraventricular nucleus of hypothalamus in acupuncture analgesia in rats. Zhen ci yan jiu = Acupuncture

Research [Zhongguo yi xue ke xue yuan Yi xue qing bao yan jiu suo bian ji]. 1991;16(1):32–8.
140. Napadow V, Dhond RP, Purdon P, Kettner N, Makris N, Kwong KK, et al. Correlating acupuncture FMRI in the human brainstem with heart rate variability. Conference proceedings: annual international conference of the IEEE engineering in medicine and biology society IEEE engineering in medicine and biology society annual conference. 2005;5:4496–9.
141. Vargas CA, Helms Medical I. Medical acupuncture for physicians: a pocket clinical reference guide. Berkeley, California: Medical Acupuncture Publishers; 2004.
142. Shukla S, Torossian A, Duann JR, Leung A. The analgesic effect of electroacupuncture on acute thermal pain perception—a central neural correlate study with fMRI. Mol Pain. 2011;7:45.
143. The Eight Influential Points. Available from: http://www.acupuncture.com/education/theory/eightpts.htm.
144. Leung A, Zhao Y, Shukla S. The effect of acupuncture needle combination on central pain processing—an fMRI study. Mol Pain. 2014;10:23.
145. Napadow V, Makris N, Liu J, Kettner NW, Kwong KK, Hui KK. Effects of electroacupuncture versus manual acupuncture on the human brain as measured by fMRI. Hum Brain Mapp. 2005;24(3):193–205.
146. Li L, Liu H, Li YZ, Xu JY, Shan BC, Gong D, et al. The human brain response to acupuncture on same-meridian acupoints: evidence from an fMRI study. J Altern Complement Med. 2008;14(6):673–8.
147. Bai L, Tian J, Zhong C, Xue T, You Y, Liu Z, et al. Acupuncture modulates temporal neural responses in wide brain networks: evidence from fMRI study. Molecular Pain. 2010;6:73.
148. Usichenko TI, Wesolowski T, Lotze M. Verum and sham acupuncture exert distinct cerebral activation in pain processing areas: a crossover fMRI investigation in healthy volunteers. Brain Imaging Behav. 2015;9(2):236–44.
149. Huang W, Pach D, Napadow V, Park K, Long X, Neumann J, et al. Characterizing acupuncture stimuli using brain imaging with FMRI—a systematic review and meta-analysis of the literature. PLoS ONE. 2012;7(4):e32960.
150. Tracey KJ. The inflammatory reflex. Nature. 2002;420(6917):853–9.
151. Xudong G. Clinical study on analgesia for biliary colic with ear acupuncture at point Erzhong. Am J Acupunct. 1993;21(3):237–9.
152. Arai YC, Sakakima Y, Kawanishi J, Nishihara M, Ito A, Tawada Y, et al. Auricular acupuncture at the “shenmen” and “point zero” points induced parasympathetic activation. Evid Based Complement Altern Med eCAM. 2013;2013:945063.
153. La Marca R, Nedeljkovic M, Yuan L, Maercker A, Elhert U. Effects of auricular electrical stimulation on vagal activity in healthy men: evidence from a three-armed randomized trial. Clinical Sci (London, England: 1979). 2010;118(8):537–46.
154. Sator-Katzenschlager SM, Michalek-Sauberer A. P-Stim (TM) auricular electroacupuncture stimulation device for pain relief. Expert Rev Med Devices. 2007;4(1):23–32.
155. Najafi S, Halstead-Kenny J. Applying auricular electroacupuncture device (P-STIM) for chronic lumbar radiculopathy. Am J Phys Med Rehabil. 2014:a33-a.
156. Holzer A, Leitgeb U, Spacek A, Wenzl R, Herkner H, Kettner S. Auricular acupuncture for postoperative pain after gynecological surgery: a randomized controlled trail. Minerva Anestesiol. 2011;77(3):298–304.
157. Sator-Katzenschlager SM, Wolfler MM, Kozek-Langenecker SA, Sator K, Sator PG, Li B, et al. Auricular electro-acupuncture as an additional perioperative analgesic method during oocyte aspiration in IVF treatment. Hum Reprod. 2006;21(8):2114–20.
158. Likar R, Jabarzadeh H, Kager I, Trampitsch E, Breschan C, Szeles J. Electrical point stimulation (P-STIM) via ear acupuncture: a randomized, double-blind, controlled pilot study in patients undergoing laparoscopic nephrctomyX. Schmerz (Berlin, Germany) [Internet]. 2007; 21(2):154–9. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/702/CN-00586702/frame.html, http://link.springer.com/article/10.1007%2Fs00482-006-0519-y.
159. Kager H, Likar R, Jabarzadeh H, Sittl R, Breschan C, Szeles J. Electrical punctual stimulation (P-STIM) with ear acupuncture following tonsillectomy, a randomised, controlled pilot study. Acute Pain. 2009;11(3–4):101–6.
160. Kong KH, Ng WW. Treatment of chronic pain with an auricular acupuncture device (P-Stim) in Singapore. Acupunct Med (Journal of the British Medical Acupuncture Society). 2009;27(4):187–8.
161. Goertz CM, Niemtzow R, Burns SM, Fritts MJ, Crawford CC, Jonas WB. Auricular acupuncture in the treatment of acute pain syndromes: a pilot study. Mil Med. 2006;171(10):1010–4.
162. Niemtzow RC. Battlefield acupuncture. J Acupunct Assoc Chart Physiother. 2010:55–9.
163. Pickett H. Battlefield acupuncture. J Chin Med. 2011;96:14–7.
164. Niemtzow RC, Litscher G, Burns SM, Helms JM. Battlefield acupuncture: update. Med Acupunct. 2009;21(1):43–6.
165. Plunkett A, Turabi A, Wilkinson I. Battlefield analgesia: a brief review of current trends and concepts in the treatment of pain in US military casualties from the conflicts in Iraq and Afghanistan. Pain Manag. 2012;2(3):231–8.
166. Soliman N. Pain: an evidence-based approach through the auricular acupuncture microsystem. Med Acupunct. 2008;20(4):263–7.

167. Napadow V, Edwards RR, Cahalan CM, Mensing G, Greenbaum S, Valovska A, et al. Evoked pain analgesia in chronic pelvic pain patients using respiratory-gated auricular vagal afferent nerve stimulation. Pain Med. 2012;13(6):777–89.
168. Laqua R, Leutzow B, Wendt M, Usichenko T. Transcutaneous vagal nerve stimulation may elicit anti- and pro-nociceptive effects under experimentally-induced pain—a crossover placebo-controlled investigation. Auton Neurosci Basic & Clinic. 2014;185:120–2.
169. Ceccherelli F, Manani G, Ambrosio F, Angel A, Valenti S, Facco E, et al. Influence of acupuncture on the postoperative complications following ketamine anesthesia. The importance of manual stimulation of point R and shen menn. Acupunct Electrother Res. 1981;6(4):255–64.
170. Bai L, Yan H, Li L, Qin W, Chen P, Liu P, et al. Neural specificity of acupuncture stimulation at pericardium 6: evidence from an FMRI study. J Magn Reson Imaging JMRI. 2010;31(1):71–7.
171. Chong PS, Cros DP. Technology literature review: quantitative sensory testing. Muscle Nerve. 2004;29(5):734–47.
172. Beissner F, Henke C. Methodological problems in FMRI studies on acupuncture: a critical review with special emphasis on visual and auditory cortex activations. Evid Based Complement Altern Med eCAM. 2011;2011:607637.
173. Langevin HM, Wayne PM, Macpherson H, Schnyer R, Milley RM, Napadow V, et al. Paradoxes in acupuncture research: strategies for moving forward. Evid Based Complement Altern Med eCAM. 2011;2011:180805.

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