

Antiallodynic Effects of Acupuncture in Neuropathic Rats

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Peripheral nerve injury often results in abnormal neuropathic pain such as allodynia or hyperalgesia. Acupuncture, a traditional Oriental medicine, has been used to relieve pain and related symptoms. However, the efficiency of acupuncture in relieving neuropathic pain is not clear. The aim of this study was to investigate the anti-allodynic effects of acupuncture through behavioral and electrophysiological examinations. Male Sprague-Dawley rats were subjected to neuropathic surgery consisting of a tight ligation and transection of the left tibial and sural nerves, under pentobarbital anesthesia. The acupuncture experiment consisted of four different groups, one treated at each of three different acupoints (Zusanli (ST36), Yinlingquan (SP9), and a sham-acupoint) and a control group. Behavioral tests for mechanical allodynia and cold allodynia were performed for up to two weeks postoperatively. Extracellular electrophysiological recordings were made from the dorsal roots using platinum wire electrodes. Mechanical and cold allodynia were significantly reduced after acupuncture treatment at the Zusanli and Yinlingquan acupoints, respectively. Electrophysiological neural responses to von Frey and acetone tests were also reduced after acupuncture at the same two acupoints. These results suggest that acupuncture may be beneficial in relieving neuropathic pain.

Key Words: Neuropathic pain, acupuncture, acupoint, allodynia, electrophysiology

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INTRODUCTION

Peripheral nerve injury frequently results in the development of chronic neuropathic pain characterized by a spontaneous burning sensation, hyperalgesia, and allodynia.¹ It has been shown that neuropathic pain is often unresponsive to conventional analgesics such as morphine.² Therefore, complementary and alternative medicine, like acupuncture, is often used in patients who cannot find appropriate treatment to relieve pain.

Acupuncture involves stimulation of skin regions called meridians by a variety of techniques, including insertion of small, thin needles through the skin surface followed by manual or electrical manipulation.³ Acupuncture has long been used as a therapeutic treatment in Oriental medicine and is known to be effective in relieving chronic pain.⁴⁻⁸

Systematic studies on the efficacy of acupuncture in treating neuropathic pain are rare, consisting of only a few electroacupuncture studies.⁹⁻¹² In one of these studies, Dai et al.⁹ showed that electroacupuncture effectively relieved mechanical and heat hyperalgesia, but not allodynia, in rats with chronic constriction injuries. Mechanical allodynia, on the other hand, could be suppressed by electroacupuncture in rats, after a spinal nerve ligation¹⁰ or superior caudal trunk resection.^{11,12} According to Sung et al.,¹² electroacupuncture treatment at the Zusanli acupoint reduced mechanical allodynia in the rat tail model of neuropathic pain. In spite of these studies, it is not clear how potent manual acupuncture is in relieving

neuropathic pain. Previously, we revealed that arthritic pain can be inhibited by manual acupuncture at both the Yinlingquan and the Zusanli acupoints.¹³ Similarly, manual acupuncture at the Zusanli or Yinlingquan acupoint may inhibit one of the symptoms of neuropathic pain. Therefore, we conducted the present study to determine any effects that acupuncture at the Zusanli and Yinlingquan acupoints have on pain relief. We used behavioral and electrophysiological examinations in an animal model of neuropathic pain to assess any effects.

MATERIALS AND METHODS

Subjects

Experiments were performed on adult male Sprague-Dawley rats (200-250g). Animals were housed in plastic cages (four/cage), with soft bedding, a 12h-12h light-dark cycle (light cycle: 08:00-20:00), constant temperature ($22 \pm 2^\circ\text{C}$), and constant humidity ($50 \pm 10\%$). Laboratory animals in this experiment were cared for and used according to the "Guidelines and Regulations for Use and Care of Animals in Yonsei University."

Neuropathic surgery

Neuropathic pain was induced as described by Lee et al.¹⁴ Briefly, while under sodium pentobarbital anesthesia (50 mg/kg, i.p.), a segment of the sciatic nerve was exposed between the mid-thigh and the popliteal fossa by skin incision and blunt dissection through the biceps femoris muscle. The three major divisions of the sciatic nerve (tibial, sural, and common peroneal nerves) were clearly separated based on individual perineuria. The tibial and sural nerves were tightly ligated then transected, meanwhile the common peroneal nerve was left intact. Complete hemostasis was confirmed and the wound was closed with muscle and skin sutures.

Behavioral test in neuropathic rats

To measure mechanical allodynia, rats were placed on a metal mesh floor under a custom-

made transparent plastic dome ($8 \times 8 \times 18$ cm). Innocuous mechanical stimuli were applied to the sensitive area of each hind paw with a von Frey filament every 3-4 s (8 mN bending force, 10 repetitions). To quantify cold sensitivity of the foot, brisk withdrawal in response to acetone applied to each paw every 5 min (5 repetitions) was observed. In both tests, the frequency of foot withdrawal (expressed in percentage) was used as the mechanical/cold allodynia index.

Acupunctures performed at two acupoints that are equivalent to specific human acupoints were used. These points are the Zusanli (ST36) and Yinlingquan (SP9) acupoints. Animals were divided into four treatment groups, those receiving acupuncture at the Zusanli, Yinlingquan, sham-acupoint and a control group (no acupuncture). The Zusanli point is located near the knee joint, 5 mm lateral to the anterior tubercle of the tibia. The Yinlingquan point is in a depression between the posterior border of the tibia and gastrocnemius muscle, located near the knee joint on the inferior border of the medial condyle of the tibia. A lipid tissue located along the border of the body trunk at the thigh on the contralateral side was selected as a sham-acupoint. A stainless steel needle (0.3 mm in diameter and 30 mm long) was used for the acupuncture at Zusanli or Yinlingquan acupoint. Under 2% enflurane (in 95% O₂ / 5% CO₂) anesthesia, the acupuncture needle was inserted vertically, through the skin, to a depth of about 5 mm, and then manually rotated right and left three times per second with twirling. Manipulation persisted for 1 min at 10 min intervals during a 30 min treatment period. No treatment and treatment at a sham-acupoint were performed as controls. The behavioral examiner was blind to experimental groups.

Electrophysiological recording in neuropathic rats

Immediately following the last behavioral test (14 days p.o.), the rats were anesthetized with 50 mg/kg sodium pentobarbital (i.p.). A tracheotomy was performed, and the sciatic nerve was exposed from the mid-calf to the ischium, with the sciatic nerve site midway between the two points. A laminectomy was performed between the L1 and L5 vertebrae. The remaining skin was used to

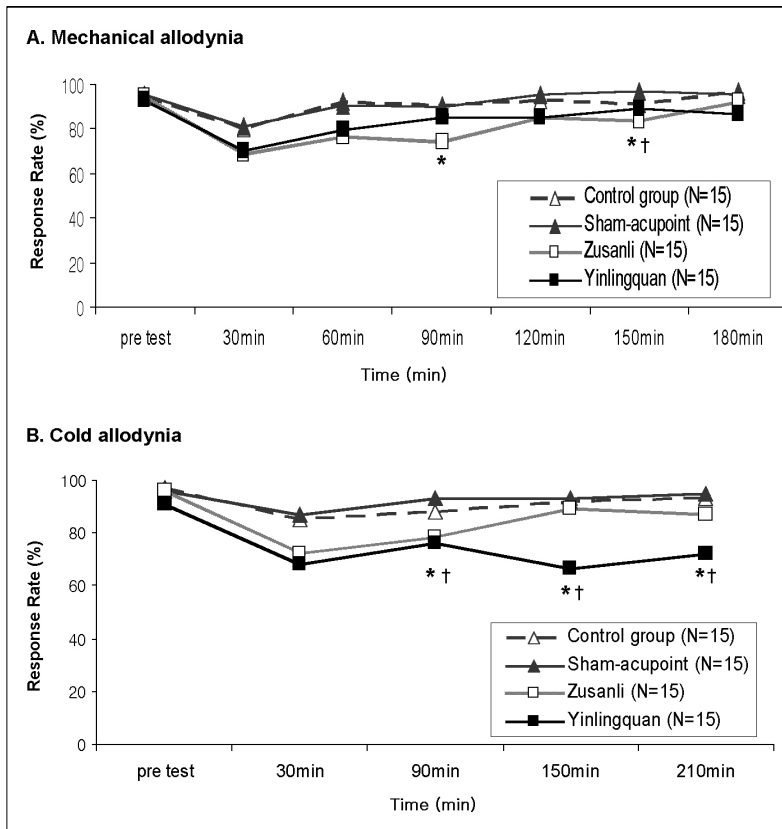


Fig. 1. Effects of acupuncture at the Zusanli, Yinlingquan and sham-acupoints on neuropathic pain. A: Mechanical allodynia. There were statistically significant differences in the responses to von Frey filament between the Zusanli acupuncture group and the control/ sham acupoint group at 90 and 150 min after termination of acupuncture. B: Cold allodynia. There were statistically significant differences in the responses to acetone application between the Yinlingquan acupuncture group and the no-acupuncture control/sham-acupoint group at 90, 120 and 150 min after termination of acupuncture. The data are expressed as the changes in the mean response rates. Statistical analysis was done using a one-way ANOVA followed by Dunnett's (2-sided) post-hoc multiple comparison test. A * denotes $p < 0.05$ as compared with control group. A † denotes $p < 0.05$ as compared with sham-acupoint group. N = 15 in each group.

form a pool to hold warm mineral oil. The dorsal roots innervating the receptive field which were determined previously during behavioral testing were teased with fine forceps and a nerve fiber could be separated and placed on a platinum wire recording electrode. The responses to von Frey filament and acetone stimulation at a single dorsal root fiber in each animal were recorded.

Animals were divided into two acupoint groups (Zusanli and Yinlingquan) and one control group (no acupuncture). Acupuncture was performed blindly as in the behavioral study above. Following electrophysiological recording, the sciatic nerve was stimulated electrically to measure the conduction velocity of the recorded fiber.

Statistical analysis

Data are presented as the mean \pm standard error of the mean (S.E.M). Differences between groups either in behavioral or electrophysiological results were analyzed using one-way ANOVA followed by Dunnett's post-hoc pair wise com-

parisons. A p value < 0.05 was considered significant.

RESULTS

Effects of acupuncture on neuropathic pain behaviors

Behavioral changes in mechanical or cold allodynia were observed before treatment and at 30, 90, 150 and 210 min after acupuncture treatment. In the acupuncture group, a marked decrease in the response to painful stimuli was observed (Fig. 1). Mechanical allodynia (Fig. 1A) was significantly reduced after acupuncture at the Zusanli acupoint as compared to both the no-acupuncture control and sham-acupoint groups ($p < 0.05$). Acupuncture at the Yinlingquan acupoint, however, did not significantly reduce the mechanical allodynia at any time point.

In contrast, cold allodynia (Fig. 1B) was significantly reduced after acupuncture at the Yinling-

quan acupoint as compared to both the non-acupuncture control and sham-acupoint groups ($p < 0.05$). Acupuncture at the Zusanli acupoint did not significantly reduce the cold allodynia at any time point.

Effects of acupuncture on neuronal responses to external stimulation

Changes in the electrophysiological responses of the dorsal roots to mechanical (von Frey filament) or thermal stimulation (acetone) were recorded before treatment and at 30, 60, 90 and 150 min after acupuncture treatment. As shown in Fig. 2, the dorsal root responses to von Frey and acetone stimulation were significantly reduced following acupuncture at the Zusanli and Yinlingquan acupoints.

Fig. 3 shows the summarized data recorded from the neural filaments. As shown in Fig. 3A,

the dorsal root responses to von Frey filament stimulation were significantly reduced after acupuncture at both the Zusanli and Yinlingquan acupoints as compared to the control group (no-acupuncture) ($p < 0.05$). The dorsal root responses to acetone application (Fig. 3B) were reduced significantly after acupuncture at both the Zusanli and Yinlingquan acupoints ($p < 0.05$). Therefore, acupuncture at both Zusanli and Yinlingquan were effective in reducing the dorsal root responses to von Frey and acetone application. Mean conduction velocities of the nerve fibers were 52.41 ± 4.61 (mean \pm S.E.M., range: 32.00-66.47), 49.42 ± 4.82 (33.55-66.30) and 56.25 ± 4.51 (27.94-75.33) m/sec in no-acupuncture control, Zusanli and Yinlingquan groups, respectively. Overall values belong to A β fiber range. Differences in conduction velocities were not significant ($p > 0.05$).

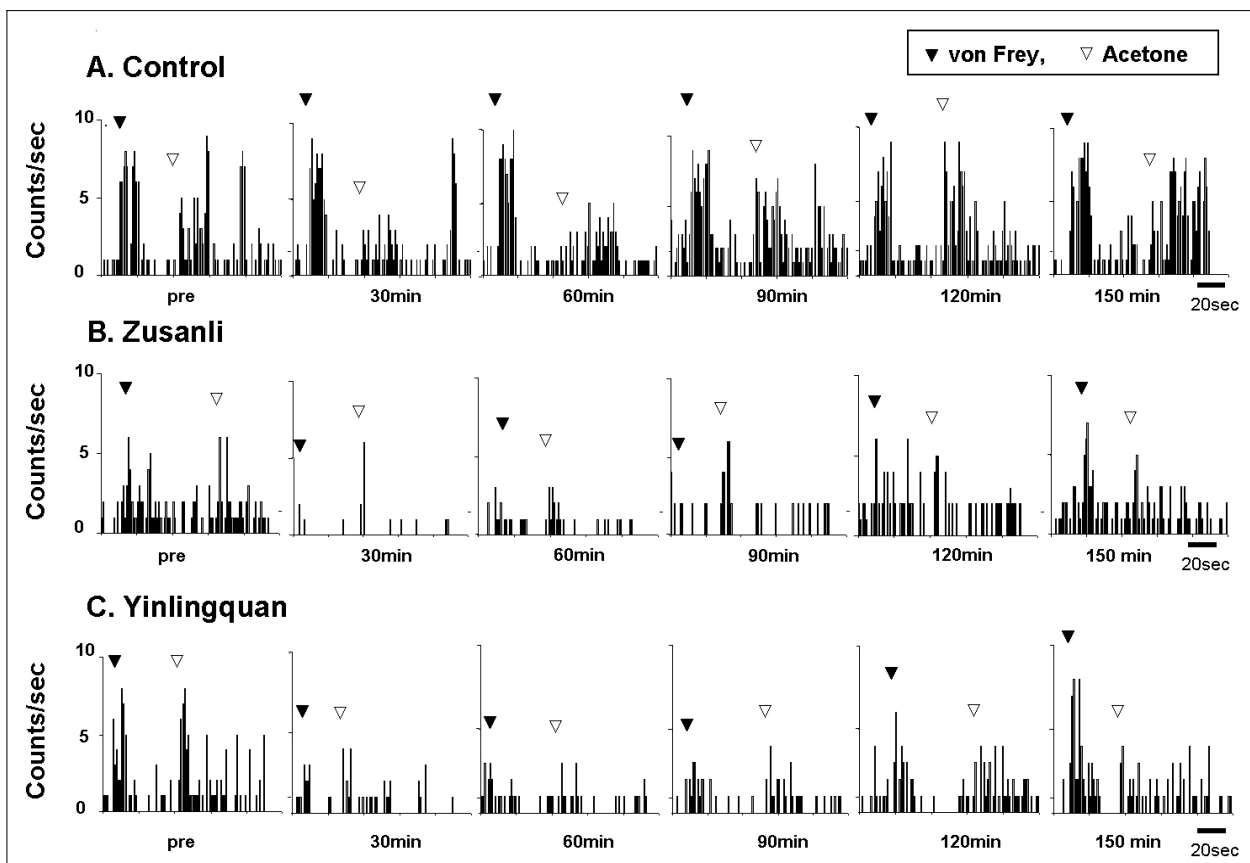


Fig. 2. Representative responses of dorsal root filaments to mechanical and cold stimulation following acupuncture at different acupoints. A shows the no-acupuncture group. B shows the Zusanli group. C shows the Yinlingquan group. A \blacktriangledown denotes von Frey stimulation, and a \triangledown denotes acetone application.

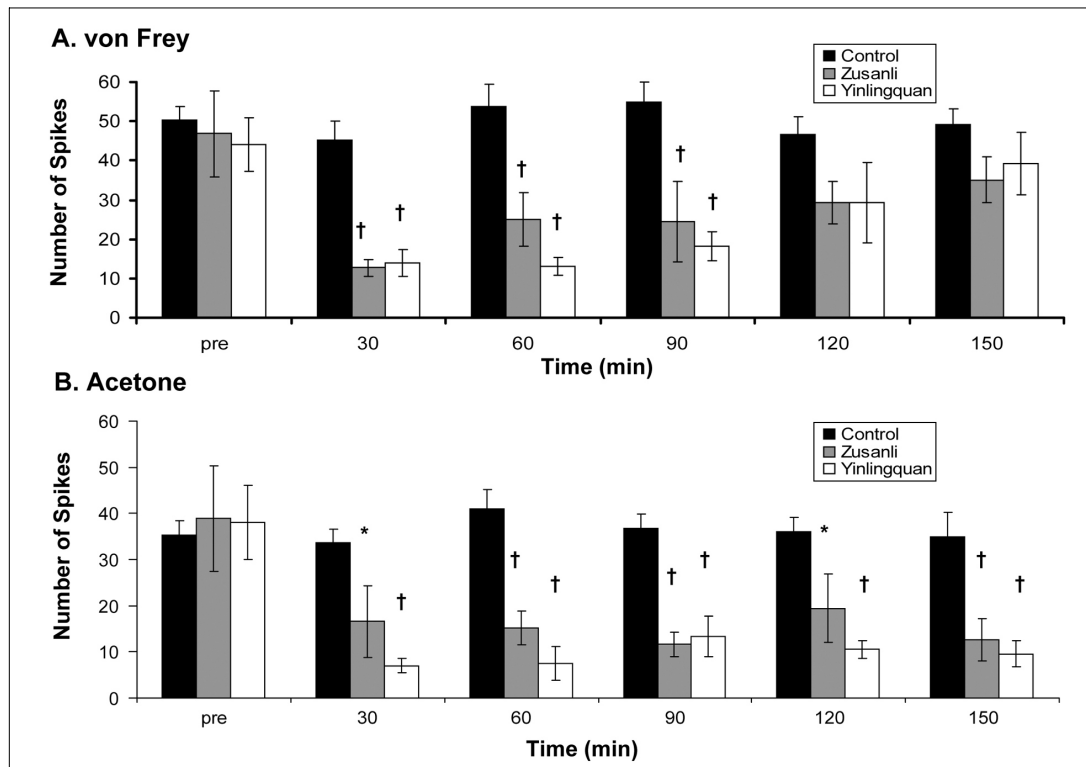


Fig. 3. Neural responses of the dorsal root filaments to von Frey and acetone stimulation after acupuncture at the Zusanli or Yinlingquan acupoint, and no-acupuncture. A shows the responses to von Frey stimulation, and B the responses to acetone stimulation. Data are expressed as the mean \pm S.E.M. Statistical analysis was done using a one-way ANOVA followed by Dunnett's (2-sided) post-hoc multiple comparison test. A * denotes $p < 0.05$ and a † denotes $p < 0.01$. N = 9 for each group.

DISCUSSION

Neuropathic pain is a complex phenomenon, possibly involving several independent pathophysiological mechanisms in both the peripheral and central nervous systems. The precise mechanisms of neuropathic pain and the relationships between these mechanisms, signs and symptoms are not fully understood.^{15,16} Currently, there is no consensus on the optimal management of neuropathic pain.¹⁷ Therefore, neuropathic pain is a very difficult form of chronic pain to treat.

Acupuncture, derived from ancient Oriental medicine, has evolved into a pain treatment in current Western medicine. Some hypotheses associate 'meridians' with the autonomic nervous system.^{18,19} In some cases, a 'trigger point' has been hypothesized to be the optimum site for acupuncture.²⁰ Very recently, Li et al.²¹ investigated acupoints in an animal study. The findings suggested that acupoints might be excitable muscle/

skin/nerve complexes with a high nerve ending density.

Following insertion of the needle, numerous 'manipulation' techniques are carried out to increase the efficacy of acupuncture. These manipulations include twisting the inserted needle, pressing down on the needle, applying a ball of herbs at the base the needle and igniting the ball, and electrical stimulation. Despite all of these manipulations, the site of insertion appears to be the most important factor in successful treatment.

This study used manual manipulation (twisting the inserted needle) to investigate the efficacy of acupuncture as an alternative and complementary treatment for neuropathic pain. In the behavioral study, mechanical allodynia was significantly reduced by acupuncture treatment at the Zusanli but not at the Yinlingquan acupoint. Cold allodynia was inhibited by acupuncture at the Yinlingquan but not at the Zusanli acupoint. These results indicate that the efficacy of acu-

puncture on neuropathic pain is dependent on the characteristics of the pain. In the electrophysiology study, the A β fiber dorsal root responses to von Frey filament (mechanical stimulation) and acetone (cold stimulation) were reduced by acupuncture at either the Zusanli or the Yinlingquan acupoint. These data indicate that allodynia, a symptom of neuropathic pain, may be inhibited by either acupoint.

According to our results, acupuncture treatment can be an effective treatment for the relief of neuropathic pain. There is, however, a discrepancy between the behavioral and electrophysiological studies. Behaviorally, the efficacy of acupuncture was dependent on the pain characteristics but not electrophysiologically. Currently, there is no adequate explanation for this observation. It appears that electrophysiological responses of the dorsal roots may reflect only the peripheral mechanisms of neuropathic pain and/or acupuncture. Rat overt behavioral responses, however, may reflect both peripheral and central mechanisms. These mechanistic differences may, at least in part, explain the discrepancy between behavioral and electrophysiological results. Nevertheless, acupuncture at specific acupoints may be able to confidently inhibit neuropathic pain. Our results are consistent with previous studies using electro-acupuncture.⁹⁻¹²

Although acupuncture is increasingly available for pain management, there is inconclusive evidence that acupuncture is more effective than a placebo (sham acupuncture).²² The main reasons for such inconclusive results, despite the wide use of acupuncture, are a lack of a sufficient number of objective studies demonstrating an analgesic effect and a poor understanding of the physiological mechanisms of acupuncture analgesia. The data produced in this study may provide further evidence that acupuncture is an effective method for relieving neuropathic pain.

Currently, a detailed mechanism of acupuncture analgesia in relieving neuropathic pain has not been described. The analgesic properties of acupuncture are thought to be mediated by activation of the descending modulatory system.^{23,24} The two major components of this endogenous descending antinociceptive system, the intrinsic opioidergic system and a descending monoaminergic (i.e.,

serotonin and adrenaline) system in the brainstem, have been implicated in the inhibition of nociceptive input at the level of spinal cord.²⁵ We have shown that activation of descending opioidergic system, by stimulation of the periaqueductal gray, inhibits neuropathic pain.²⁶ Similarly, activation of this opioidergic system by acupuncture may produce analgesia in neuropathic pain. In addition, serotonergic and noradrenergic systems of pain inhibition also play an important role in mediating the analgesic effects of acupuncture.²⁷⁻³¹ It has been proposed that the antinociceptive effect induced by acupuncture is mediated by different neuronal mechanisms depending on the type of stimulation that is applied to an acupoint.^{32,33} If this is true, the mechanisms involved in acupuncture analgesia must be complex.

In addition to mechanisms involving the central nervous system, the peripheral nervous system may also be involved in acupuncture analgesia. For example, inserting the acupuncture needle results in depolarization of a single or a group of muscle fibers, inducing micro-twitches.³⁴ These micro-twitches are capable of producing micro-stretch effects on adjacent shortened muscle fibers that are undergoing varying stages of denervation, thereby producing pain relief. Several studies have suggested that changes in local blood flow may also be induced by acupuncture.^{35,36} All of the aforementioned central and peripheral mechanisms may be combined to produce all the pain-relieving effects that are felt with acupuncture. For example, Cao³⁷ suggested that needling an acupuncture point could activate afferent peripheral nerves fibers eliciting a De-Qi sensation (acupuncture sensation in traditional Chinese medicine). The afferent nerves ascend, primarily, through the ventro-lateral funiculi, which conducts pain and temperature sensations to the brain, where they activate the antinociceptive system. The nuclei involved in this system induce analgesia through activation of the descending inhibitory pathway. Cao also suggested that endogenous opiate peptides participate in mediating acupuncture analgesia signals from the presynaptic neuron to the inhibition receptor sites.

Despite little knowledge of the precise mechanisms of acupuncture-induced analgesia, the use

of acupuncture in neuropathic pain treatment is continually increasing. For example, Brunelli and Gorson³⁸ reported a high prevalence of complementary and alternative medicine (CAM) use in patients with neuropathy. The most common reason for CAM use was the lack of adequate pain control. Similarly, Phillips et al.³⁹ reported that pain and peripheral neuropathy symptoms in persons with HIV were also reduced when acupuncture therapy was delivered in a group setting. A better understanding of the neurobiological mechanisms that mediate acupuncture analgesia may help to improve its effectiveness.

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