Acupuncture's neuroanatomic and neurophysiologic basis

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Abstract: Ever since acupuncture's tenets were first delineated in the *Huangdi Neijing (Neijing)* treatise ~200 BCE, theorists and researchers have sought to define the anatomic and physiologic bases for acupuncture's beneficial clinical effects in treating pain and non-pain medical conditions. In the last century, technical advances in both the basic biomedical sciences (including anatomy, biochemistry, pharmacology, electrophysiology, and radiology) and also clinical research methodologies have led to publication of an extensive body of basic science and clinical research publications on the topics of acupuncture anatomy, physiology, and clinical effects. This body of literature demonstrates that the beneficial clinical effects of acupuncture derive from the activation of peripheral nerves by needling, with resulting secondary modulatory effects on the peripheral nervous system, the central nervous system (CNS) (including the limbic system), the autonomic nervous system, and the immunologic and endocrinologic systems. A neuroanatomic and neurophysiologic model of acupuncture's mechanisms and effects is the only theory that can be reconciled with research findings of the efficacy of laser acupuncture and the positive randomized clinical trial results in studies that used non-penetrating or minimally penetrating "sham" needle control interventions, and this model is also consistent with anatomic and physiologic descriptions contained in the *Neijing*. This review article summarizes the anatomic, basic science, and clinical evidence that demonstrates acupuncture signaling and its myriad clinical benefits can be understood as arising from and transduced by neural mechanisms.

Keywords: Acupuncture; anatomy; meridians; nerves; neurophysiology

Introduction

Bian stones ("stone needles") dating to the New Stone Age (10000–40000 BCE) are believed to have been used clinically to incise abscesses, perform bloodletting, and regulate *Qi* circulation (1,2). Inscriptions on bones and tortoise shells dating to the Shang Dynasty era (1556–1046 BCE) illustrate acupuncture and moxibustion practice (1,2). The *Huangdi Neijing (Neijing)* treatise, dating from the Warring States period in China (475–221 BCE), first compiled the foundations of Traditional Chinese Medicine

(including acupuncture) that reflect thousands of years of accumulated clinical knowledge and experience (3).

Though the *Neijing* does not describe an anatomic basis for the Primary Channels and the Classical acupuncture points that exist on them, it does provide a clue in Article 3.1.3: "… the twelve main channels run latently in the muscles… they are deep and invisible… what can be seen is usually where the foot Greater Yin-Spleen Channel passes the medial malleolus… it is not hidden there" (3). Other historical evidence comes from ten Rhijne's 1683
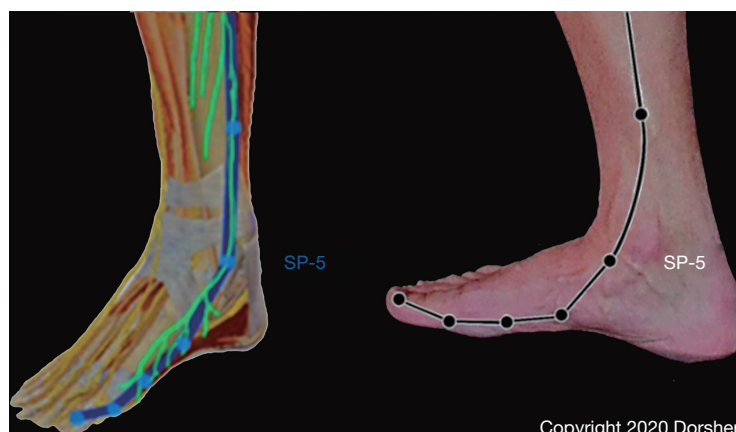
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Figure 1 Spleen Channel anatomic relationship to the distribution of the great saphenous vein and the accompanying saphenous nerve in the calf and foot regions.

dissertation on his observations of acupuncture practice in Nagasaki in which he noted Chinese and Japanese acupuncturists used the terms artery, vein, and nerve interchangeably when discussing the acupuncture channels—this description is consistent with the anatomic fact that arteries, veins and nerves course through the body together as neurovascular bundles in the intermuscular fascial layers (4). At the medial ankle region, the great saphenous vein, which is accompanied by the saphenous nerve, is visible (5,6). The distribution of the Spleen Channel in the distal lower leg and foot mirrors the distribution of the saphenous nerve there (*Figure 1*), consistent with the *Neijing* description of the visible portion of the Spleen Channel at the ankle (3,5,6).

In the last century, technical advances in both the basic biomedical sciences (including anatomy, biochemistry, pharmacology, electrophysiology, and radiology) and clinical research methodologies have led to publication of an extensive body of basic science and clinical acupuncture research on the topics of acupuncture anatomy, physiology, and clinical effects. Indeed, acupuncture research publications have grown exponentially over the past two decades (7). This scientific literature demonstrates that the beneficial clinical effects of acupuncture derive from the activation of peripheral nerves by needling, with resulting secondary modulatory effects on the peripheral/central nervous (including limbic and autonomic structures), immune, and endocrinologic systems.

Theories of acupuncture mechanisms

Over the millennia since the *Neijing* was published, a

number of different theories of what structures/mechanisms underlie acupuncture's beneficial clinical effects have been proposed. These theories can be broken down into two major categories: anatomic and non-anatomic mechanisms (*Table 1*).

The basic science literature serves to exclude proposed acupuncture mechanisms that involve circulatory and/or humoral systems (8,13,14,20-22). Simply, a tourniquet of an extremity does not affect the efficacy of its acupuncture points for analgesia in humans or animals (23-25). Further, Lu *et al.* showed that isolation of circulation to Zusanli (ST-36) acupoint from the general circulation does not affect its clinical analgesic effects (24). These studies demonstrate that acupuncture's afferent signaling mechanisms do not involve the vascular system or humoral factors. Bonghan circulatory system, hypodermic interstitial fluid migration channel, perivascular space, and vascular signaling mechanisms are not plausible anatomic or physiologic mechanisms for acupuncture signaling as none of these mechanisms can be reconciled with the tourniquet studies' results—all of these anatomic, afferent signaling pathways for acupuncture would be obliterated/blocked by proximal tourniquet application (8,13,14,20-22).

The interstitial fascia model of acupuncture mechanisms also is inconsistent with the above cited tourniquet studies, as the fascia model experimental studies' results showed that estimated perimuscular connective tissue displacements 4–6 cm from the needle stimulation site were only ~5 micrometers (<1/10 the width of a human hair) and measured torques along the interstitial fascial plane with needling were only 200 μN-m (~2×10^{-5} kg-m)

Table 1 Theories of acupuncture mechanisms

Anatomic theories	Non-anatomic theories
Bonghan circulatory system (8)	Biophotons (9)
Cutaneous intrinsic visceral afferent nervous system (10)	Electromagnetic field (11,12)
Hypodermic interstitial fluid migration channels (13)	Neuroimmune-endocrine (14)
Perimuscular interstitial connective tissues (15)	
Peripheral nerve (16-19)	
Perivascular spaces (20)	
Vascular system (21,22)	

maximum, which would be of insufficient magnitude to pass the high interstitial tissue compression forces at the proximal limb locations (far distant from the acupuncture needle insertion site) where the tourniquet studies applied those circumferential limb forces (15,23-27). Second, the perimuscular interstitial fascia model of acupuncture cannot explain the results from large, scientifically rigorous acupuncture clinical trials that showed clinically and statistically significant positive results in their control groups that utilized non-penetrating "needling" or minimal superficial needling at the acupoints examined in those studies—these trials' "sham" needles were not inserted near perimuscular fascia and neither study utilized needle rotation that would "wind" that fascia around their "sham" needles (15,28,29). Finally, the interstitial fascia model also cannot explain the clinical benefits seen with laser acupuncture, as laser energy produces no displacement of the perimuscular fascia (30).

The non-anatomic models of acupuncture mechanisms, specifically biophoton and electromagnetic field acupuncture signaling, also cannot be reconciled with acupuncture basic science and clinical studies (9,11,12). Anesthetic blockade of nerves suppling acupuncture points abolished their pain and non-pain clinical effects (23,31,32). Anesthetic blockade of the brachial plexus eliminates typical brain fMRI activity produced by Hegu (LI-4) stimulation (33). Sectioning the peroneal or sciatic nerve (but not sectioning the femoral or tibial nerve) eliminated or nearly eliminated the analgesic effect of stimulating ST-36 in rats (24). Sectioning the sciatic or femoral nerve in rats abolishes the increased pyloric motility induced by hindpaw stimulation, whether acupuncture stimulation occurs at skin and/ or muscle tissue level (34). Anesthetic nerve blockade or nerve sectioning would not eliminate biophoton or

electromagnetic field generation, so those two theories are not plausible explanations for acupuncture's afferent signaling mechanisms.

Thus, the acupuncture basic science and clinical trial literature by itself demonstrates that the only mechanism of acupuncture's afferent signaling that is consistent with its basic science and clinical trial literature is neurologic (10,16-19). There is overwhelming basic and clinical scientific evidence supporting a neuroanatomic/ neurophysiologic model of acupuncture's mechanisms, which will now be detailed in this review.

Anatomic evidence of acupuncture's neural based mechanisms

There is microscopic and macroscopic anatomic evidence that peripheral nerves are stimulated at Classical acupoints to produce acupuncture's clinical effects. Histologic studies of acupuncture points in humans and animals demonstrate the presence of small neurovascular bundles containing A-delta (Aδ) and C nerve fibers penetrating through pores formed by bone, muscle, and/or fascia (35-37). Antidromic sensory nerve stimulation studies in rats demonstrated that the receptive fields of Aδ and C nerve fibers were concentrated either at the sites of acupuncture points or along the course of acupuncture channels, indicating that peripheral anatomic sites demonstrating a high density of nerve endings (Aδ and C fiber nerve terminals) are closely associated anatomically with Classical acupoint locations (38).

Macroscopically, analysis utilizing all major print anatomic references including those of Clemente, Netter, Gray, Grant, and Chen as well as multiple contemporary 3D digital anatomic references demonstrate that Classical acupoint locations are anatomically proximate to cranial
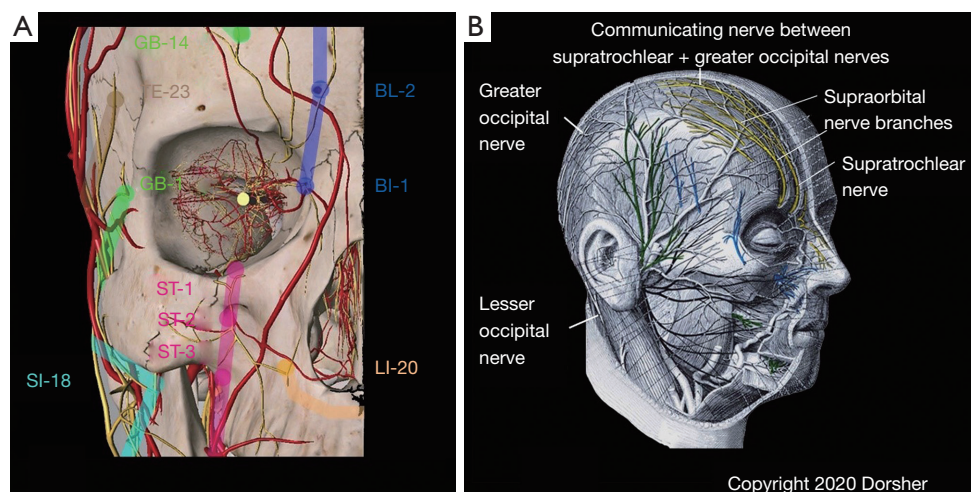
Figure 2 Anatomic relationships of Classical acupoints and their Primary Channels to spinal and cranial nerves in the human head: (A) frontomaxillary region and (B) anastomosis of supratrochlear and greater occipital nerves near the vertex.

or peripheral nerves, or their branches (5,6,39-47). These anatomic references include acupoint—specific anatomic analyses with Chen's anatomic dissection based acupoint anatomy reference atlas that covers the anatomy of all Classical acupoints, plus the anatomy for acupuncture digital 3D anatomy reference—a digitized human cadaver demonstrates acupuncture needle 3D trajectory for 88 commonly used Classical acupoints (41,43). The Shanghai College of Tradition Medicine acupuncture reference on page 111 documents that in 1960 its Anatomical Teaching and Research Group in a study of 324 acupuncture points, found that 323 were supplied by nerves with "microscopy showing all layers of skin and muscle tissues at acupuncture sites contained numerous and varied nerve branches, plexi, and endings" and this reference documents as well "a particularly close relationship between the paths of the channels on the limbs and the pathways of peripheral nerves" (19). Examples of these relationships demonstrated on a body region basis are as follows.

Figure 2 shows the anatomic relationship of Classical acupoints and Primary Channels in the head region to cranial and spinal nerve branches there. *Figure 2A* shows that for the frontomaxillary region, Classical acupoints are proximate to trigeminal nerve branches there, with the Bladder Channel distribution mirroring that of the supratrochlear nerve, the Gallbladder Channel distribution mirroring that of the supraorbital nerve, and the Stomach Channel distribution mirroring those of infraorbital nerve branches. Meltz and Chiang confirmed these anatomic

relationships by cadaveric and electrical stimulation analysis for 26 classical and 10 "extra" head region acupoints located in the trigeminal nerve distribution, as does Chen's acupoint cross-sectional anatomy atlas (41,48). *Figure 2B* shows anatomic evidence of anastomosis of the supratrochlear nerve (a cranial nerve branch) with the greater occipital nerve (a spinal nerve branch) near the vertex—note the combined distributions of these two nerves replicates the distribution of the Bladder Channel from the medial eyebrow over the medial scalp to the upper cervical spine (5).

The close anatomic relationship of Classical acupoints and the Primary Channels to the peripheral nervous system (spinal nerve branches) in the trunk region is likewise evident from print and digital anatomic references, including the acupoint cross-sectional anatomy atlas of Chen, as shown in *Figure 3* (41).

Figure 3B demonstrates the relationship of the Bladder Channel acupoint locations in the posterior trunk to spinal nerve branches, with inner Bladder Channel acupoint locations being anatomically proximate to intermediate branches of the dorsal rami of the spinal nerves, and outer Bladder Channel acupoint locations being anatomically proximate to lateral branches of the dorsal rami. *Figure 3A* demonstrates the close anatomic relationship of anterior trunk Classical acupuncture point locations to branches of the ventral rami of the spinal nerves for Spleen, Stomach, Kidney, and Conception Vessel Classical acupoints. Conception Vessel acupoints (white) receive bilateral innervation and Kidney acupoints (brown) ipsilateral
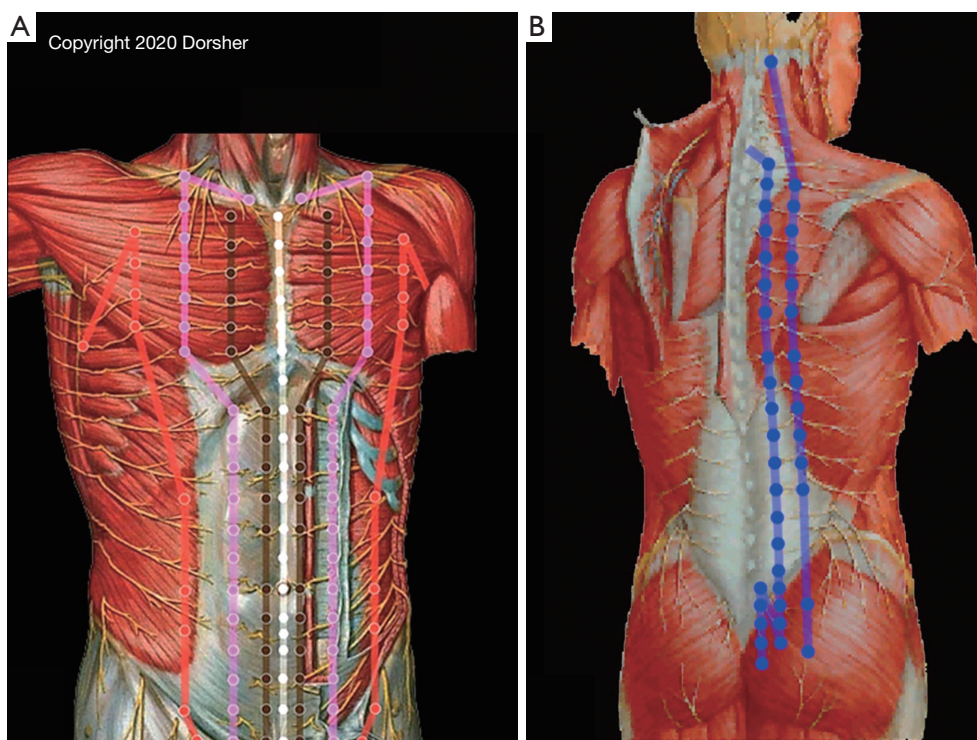
Figure 3 Anatomic relationships of Classical acupoints and their Primary, Governing Vessel, and Conception Vessel Channels to spinal nerve branches in the human torso: (A) anterior trunk and (B) posterior trunk regions.

innervation from branches of the anterior cutaneous branches of the spinal nerves' ventral rami, where they penetrate the fascia in the medial anterior trunk to provide cutaneous innervation (5,6). Stomach acupoints (pink) receive innervation from more lateral branches of the anterior cutaneous branches of the spinal nerves' ventral rami, while Spleen acupoints (orange) receive innervation from anterior branches of the lateral cutaneous branches of the spinal nerves' ventral rami.

The thorax is (normally) anatomically larger than the abdomen, which along with the presence of the sternum in the midline, anatomically leads to more lateral locations of the anterior cutaneous branches of the spinal nerves' ventral rami in the thorax compared to those in the abdominal region (5,6). Consistent with that anatomic finding, *Figure 3A* also demonstrates that Kidney and Stomach Classical acupoints' described locations are more laterally positioned in the thorax than the abdomen (19,49). Note the Primary, Conception, and Governing Vessel Channels' distributions course perpendicular to the transverse orientation of the spinal nerves in the trunk, which likely relates to the differences in embryologic development of the

trunk, extremity, and head/neck regions (50-52).

The bilateral innervation of the midline in the anterior and posterior trunk may provide an anatomic basis for the Conception Vessel Channel being considered the "Yin of the Yin" and the Governing Vessel Channel the "Yang of the Yang" (19,49).

The close anatomic relationship of Classical acupoint locations and Primary Channels to peripheral nerves in the upper and lower extremities is also confirmed by standard and digital anatomy resources, including the acupoint cross-sectional anatomy atlas of Chen and *Anatomy for Acupuncture*, as shown in *Figure 4* (41,43). Recent cadaveric confirmation of Lung and Kidney acupoints' relationships to peripheral nerves has provided even further anatomic evidence of acupoint-nerve correspondences (16,53).

Figure 4A demonstrates the clear anatomic correspondences of Lung Channel acupoint locations and the Lung Channel distribution itself to the distribution of the lateral cord of the brachial plexus and its distal branches (the musculocutaneous and lateral antebrachial cutaneous nerves) in the upper extremity from the anterior pectoral region all the way to the base of the thumb. There is similar
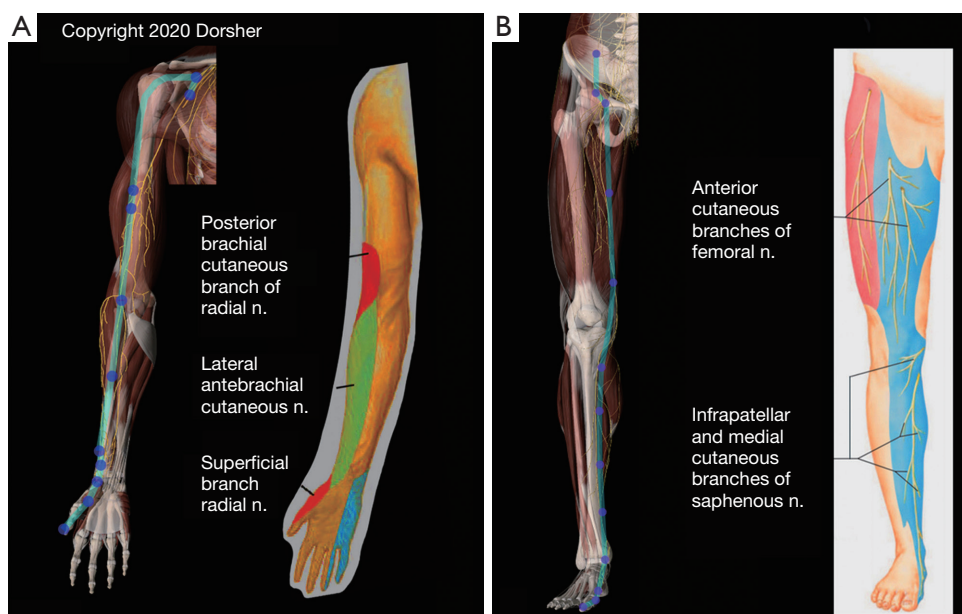
Figure 4 Anatomic relationships of Classical acupoints and their Primary Channels to peripheral nerves and their branches in the extremities: (A) Lung Channel and lateral cord of the brachial plexus nerve and its branches and (B) Spleen Channel and the femoral/ saphenous nerve and its branches.

compelling overlap of the distribution of the femoral nerve and its distal saphenous nerve sensory branch to the distribution of the Spleen Channel and Spleen acupoint locations from the groin all the way to the base of the great toe, as shown in *Figure 4B*. Further, the Spleen Channel (dark blue) in the lower extremity has 6 directional changes of 10–40 degrees (mean 20 degrees) along its described course from the groin to the great toe. These directional changes accurately reflect those of the femoral and saphenous nerve as shown in *Figure 4B*. The statistical odds that the Spleen Channel would coincidentally follow the femoral/saphenous nerve directional changes throughout the lower extremity is ~1 in 34 million, further evidence that these close Classic acupoint to peripheral nerve anatomic relationships are not due to chance.

The close relationship of many Classical acupuncture point locations to peripheral nerves had been documented decades ago in acupuncture references including the Shanghai College of Traditional Medicine text, but the development of 3D anatomic software in the last 15 years markedly enhances to the ability to confirm these anatomic relationships. Primal Picture's 3D software "*Anatomy for Acupuncture*" (based on a digitized human cadaver) shows the anatomic trajectory of 88 commonly used Classical acupoints in clinical practice (19,43). This

digital acupuncture anatomy model demonstrates the close anatomic proximity of these Classical acupoints to peripheral nerve branches, whose distributions also mirror those of these acupoints' Primary Channels (43).

da Silva has shown the anatomic proximity of head and neck acupuncture points to the Vagus nerve and its branches, as well as their physiologic/clinical similarities (54). Dimitrova found in randomized controlled trials of acupuncture in treating neuropathies, the acupoints used in those trials were all closely anatomically related to peripheral nerves and those points' acupuncture indications were consistent with treating neuropathic pain (55).

Physiologic evidence of acupuncture's neural based mechanisms

Beyond the comprehensive evidence outlined above of the anatomic correspondence of Classical acupoints and peripheral nerves and their branches, the acupuncture literature also provides overwhelming physiologic evidence of the fundamental involvement of the nervous system in transducing acupuncture's clinical effects.

The physiologic importance of the Aδ and C nerve fibers, which are anatomically present at acupuncture point locations as previously discussed, in transducing
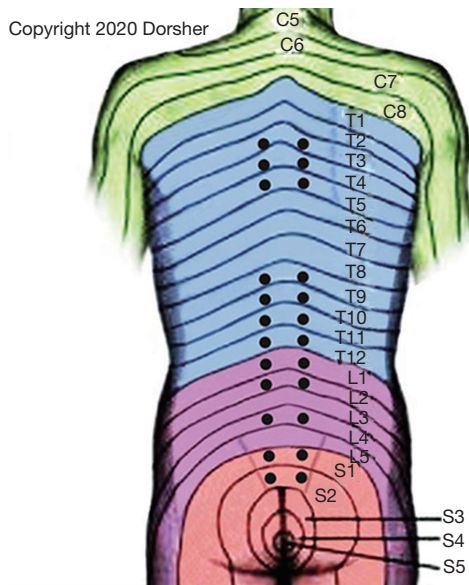
Figure 5 Back-Shu points: segmental acupuncture needling to effect visceral function.

acupuncture's clinical effects is well documented in the literature. Optimal acupuncture stimulates both Aδ and C nerve fibers in producing its analgesic effects. Experimental evidence demonstrates that *in vivo*, Aδ nerve fiber stimulation is required to produce analgesia outlasting the needle stimulation, while C-fiber stimulation is required to achieve descending pain inhibition (56,57). Analgesia produced by manual acupuncture is similar to that evoked by activation of the diffuse noxious inhibitory control (DNIC) system, which is mediated by Aδ and C-type afferents (58,59). Electrical stimulation of acupuncture needles stimulates C-fibers; and while sufficient electrical stimulation intensity to activate Aβ fibers produces some degree of acupuncture analgesia, more potent analgesia occurs if the stimulation intensity is sufficient to activate Aδ afferent fibers (60,61).

The physiologic importance of peripheral nerves in afferent acupuncture signaling is also well documented in the acupuncture literature. Clinically, acupuncture is ineffective when applied to areas of skin affected by postherpetic neuralgia, where pinprick sensation (subserved by Aδ and C fibers) is usually absent (62,63). Capsaicin application to nerves selectively blocks conduction in Aδ and C fibers—capsaicin applied to the bilateral sciatic nerves before manual acupuncture stimulation of ST-36 completely abolished its analgesia effects in rats (59). In humans, anesthetic block of the nerves innervating the

location of LI-4 abolishes its physiologic effect for pain reduction, while median nerve anesthetic block abolishes the anti-emetic effect of Neiguan (PC-6) (31,32). Anesthetic blockade of the brachial plexus abolishes the patterns of brain activation induced by electroacupuncture (EA) at LI-4 (33). Sectioning the peroneal or sciatic nerve (but not sectioning the femoral or tibial nerve) eliminated or nearly eliminated the analgesic effect of stimulating ST-36 in rats (24). Sectioning the sciatic and femoral nerves in rats abolishes the increased gastric motility produced with hindpaw acupuncture-like stimulation (34).

Historical experience has suggested that achieving *deqi* ("arrival of *qi*") sensation when inserting a needle at an acupuncture point is important to achieve optimal therapeutic results from acupuncture treatment (23,64-66). Hui *et al.* scientifically examined this *deqi* sensation, and determined that the majority of the *deqi* sensations, such as aching, soreness, dull pain, and warmth involve the slower conducting Aδ and C fibers (67). Gu *et al.* demonstrated that the BOLD signal of the thalamus on fMRI correlated significantly with acupuncture (*deqi*) sensation score during EA at Hegu (LI-4), and that specific brain fMRI changes noted in the bilateral thalamus, basal ganglia, cerebellum and left putamen regions with LI-4 stimulation were eliminated by ipsilateral brachial plexus anesthetic block (33). This experimental data is consistent with afferent Aδ and C fiber neural signaling with acupoint stimulation, with the degree of neural stimulation of those fibers proportional to the needle (*deqi*) sensation achieved.

The other essential component of the neuroanatomic basis of Classical acupuncture points is their sympathetic autonomic nervous system (SANS) innervation. Postganglionic sympathetic nerve fibers from thoracolumbar sympathetic ganglia (prevertebral or paravertebral) compromise 20% or more of spinal nerve fibers and also invest the adventitial layers of the arteries that accompany spinal nerves and their branches to the extremities (39,68,69). The sympathetic innervation of the arteries, however, only appears to regulate vascular tone of the vessel it invests (69). There is somatotopic organization of nerve fibers within distal peripheral nerve fascicles, which particularly in smaller fascicles contain a bundled organization of sympathetic nerves (70,71). This provides a plausible anatomic basis for acupoints' differing effects on autonomic (visceral) functions.

The neuroanatomy/neurophysiology of the Back Shu points (*Figure 5*) also corroborates the neural basis of acupuncture mechanisms.

Table 2 Back-Shu points, sympathetic autonomic nervous system segmental innervation, and osteopathic spine levels manipulated manually to treat function of specific organs

Organ	Shu point	Spinal level	Sympathetic segmental innervation per Bonica (72) + Beal (73)	Osteopathic level
Lung	BL-13	T3	T2-T7 (T2-T5)	T3-T9
Pericardium	BL-14	T4	T1-T4 (T1-T5)?	C8, T1-T8?
Heart	BL-15	T5	T1-T4 (T1-T5)	C8, T1-T8
Liver	BL-18	T9	T6-T9 (T5-T10)	T6-T11
Gallbladder	BL-19	T10	T5-T9 (T7-T10)	T6-T11
Spleen	BL-20	T11	T6-T10 (T5-T11)	T7-T10
Stomach	BL-21	T12	T6-T9 (T5-T11)	T7-T10
Triple heater (?adrenal)	BL-22	L1	Cortex T6-L2, medulla T11-L1	
Kidney	BL-23	L2	T11-L1 (T10-L2)	T9-L2
Large intestine	BL-25	L4	Proximal 2/3 T10-L1 (T6-L1), distal 1/3 L1-L2 (T6-L2), (white-afferent S2-S4)	T9-L1
Small intestine	BL-27	S1	T6-T11 (T6-T12)	T6-T11 duodenum + jejunum
Bladder	BL-28	S2	T11-L2 (white-afferent S2-S4), S2-S3 parasympathetic	

Each of these Back-Shu Classical acupoint locations is innervated by the corresponding dorsal ramus of the spinal nerve at its segmental level. As shown in *Table 2*, the Back-Shu acupoints exist at the same spinal segmental levels as the known anatomic segmental SANS outflow to their respective Organs for 9 of the 12 Back-Shu points (19,49,72,73).

The Back-Shu points of the Stomach and Large Intestine Organs are near (one and two spinal segments caudal, respectively) to their described SANS innervation (72,73). The Back-Shu point of the Small Intestine Organ is located at the S1 level and the Bladder Organ at S2, far caudal to the described SANS outflow to this Organ (*Table 2*). Note the Bladder Back-Shu point is at the spinal level of its known parasympathetic outflow, however. Given the 14 potential spinal levels involved in SANS innervation (12 thoracic, 2 lumbar) of the trunk organs, the statistical odds that these anatomic/physiologic correspondences would occur by chance is ~1 in 5 billion ($1/14^9$). Note these Back-Shu points are the same spinal levels that manual medicine practitioners mobilize clinically to selectively influence internal organ function (73).

Thus, the acupuncture basic science literature provides compelling anatomic and physiologic evidence that Classical acupuncture points are neurologically based.

Acupuncture's central nervous system (CNS) mechanisms

The acupuncture basic science literature also documents the essential involvement of CNS ascending/descending pathways and central processing of afferent neural signaling from acupuncture points in producing acupuncture's clinical effects.

Acupuncture analgesia requires intact spinal cord ascending pain pathways in its ventrolateral funiculus. Needling the affected side in hemiplegic or below level of injury in paraplegic patients has no analgesic effect on painful stimulation of unaffected limbs (31). In patients with syringomyelia, when the anterior commissure and dorsal horn of the spinal cord are damaged, pain and temperature sensation deficits are accompanied by reduced or abolished acupuncture effects and ability to feel *deqi* sensation (74). Damage to the posterior columns experimentally (or clinically as in tabes dorsalis) has little effect on acupuncture analgesia, while unilateral sectioning of the ventrolateral funiculus of the spinal cord (carrying pain and temperature information rostrally) nearly eliminates acupuncture analgesia in the contralateral (but not ipsilateral) limb (75).

Spinal cord and brain activation of endogenous descending pain inhibition mechanisms also contribute to acupuncture analgesia. Acupuncture produces analgesia in non-segmental

fashion likely through C-fiber mediated activation of descending pain inhibition including activation of the diffuse noxious inhibitory control (DNIC) system, which is mediated by Aδ and C-type afferents (56,58,59,76). Toda *et al.* documented that stimulation of forelimb paw point LI-4 in rats reduces experimentally induced dental pain, and Kim *et al.* have demonstrated that stimulation of a forelimb acupoint SI-6 in rats reduces lower limb dorsal horn neuronal activity (pain) caused by experimental pain from ankle sprain (60,77). Acupuncture also produces both ipsilateral and contralateral analgesia experimentally in humans (78). Intact central nervous pathways (spinal cord and brain) are necessary for these analgesic effects to occur (77,78).

These spinal cord and brain pathways are involved in the mechanisms of acupuncture's non-pain effects as well. In rats, sectioning the bilateral femoral and sciatic nerves, or sectioning the bilateral Vagus nerves, abolishes the increased pyloric motility induced by hindpaw stimulation, whether acupuncture stimulation occurs at skin and/or muscle tissue level (34). Noguchi and Hayashi demonstrated in rats that increased gastric acid secretion produced by EA of the hindlimb was abolished by sciatic nerve denervation or by Vagus nerve sectioning (79). These studies illustrate that afferent acupuncture point stimulation in the hindlimb is processed in the CNS, with clinical effect on gastric motility and acid secretion occurring through the descending Vagus nerve pathway.

Cheng and Pomerantz demonstrated that acupuncture stimulation causes release of endorphins and enkephalins that are fundamentally important in acupuncture's analgesic response, as naloxone blocks or significantly attenuates acupuncture analgesia (80). The release of these endogenous opioids results from corticotropin-releasing hormone (CRH) release from the hypothalamus that in turn releases pro-opiomelanocortin (from which endorphins and enkephalins derive) from the anterior and central pituitary gland (80). Lesions of arcuate nucleus of the hypothalamus abolish acupuncture analgesia, and experimental reduction of pituitary endorphin suppresses acupuncture analgesia (81,82). Endorphin levels rise in blood and cerebrospinal fluid (CSF) during acupuncture analgesia - this acupuncture analgesia can be transmitted to a second animal by CSF transfer and blocked by intra-ventricular opiate antagonist administration (31,83-86). In human experiments, acupuncture analgesia produces bilateral analgesia consistent with these central mechanisms including pituitary release of endorphins and enkephalins (78).

Acupuncture also modulates hypothalamic pituitary adrenal (HPA) axis activity in inflammatory pain states. EA at Huantiao (GB-30) in an experimental rat paw inflammation study produced a [5–10]-fold increased plasma cortisol levels compared to sham EA controls and also reduced paw inflammation (87). Adrenalectomy eliminated EA inflammation improvement but not its anti-hyperalgesia effect (87). The observed increase in plasma cortisol levels is produced via EA activation of CRH neurons of the hypothalamus' paraventricular nuclei, which in turn increases ACTH secretion from the anterior pituitary gland two-fold to stimulate the adrenal gland (88).

Functional magnetic resonance imaging studies confirm that stimulation of peripheral Classical acupoints selectively modulates brain structures to produce acupuncture's analgesic effects consistent with the above physiologic experiment findings. Wu *et al.* found that LI-4 and ST-36 EA stimulation (but not sham electroacupuncture) produces activation of somatosensory cortex areas subserving pain sensation and localization as well as the hypothalamus (where the process of release of endogenous opioids is initiated) while simultaneously inhibiting limbic system structures including anterior cingulate gyrus and amygdala that subserve the behavioral reaction to pain (89). Manual acupuncture at these points also modulated brain fMRI activity in areas including thalamus, anterior cingulate, insula, and cerebellum, which are also part of the reported neuromatrix of pain (89). Hui *et al.* found similar results with stimulation of LI-4; and additionally noted that if pain was produced rather than *deqi* when stimulating LI-4, then the limbic system structures were not inhibited (no reduction of behavioral response to the painful stimulus) (90). This means that proper acupuncture reduces the behavioral reaction to a painful stimulus without interfering with ability to perceive the painful stimulus. Hui *et al.* further demonstrated acupuncture stimulation produces deactivation of the medial prefrontal, medial parietal and medial temporal lobes and activation of regions in the sensorimotor and paralimbic structures, in a pattern consistent with acupuncture modulating the default mode network and the anti-correlated task-positive network to produce its analgesic effects (91).

Neural basis of acupuncture's observed clinical (efferent) effects

Acupuncture's analgesic effects

As previously discussed, the work of Cheng and Pomerantz

demonstrated acupuncture stimulation causes release of endorphins and enkephalins from the pituitary, which are experimentally proven to be fundamentally involved in acupuncture analgesia, including the bilateral analgesia produced by unilateral acupuncture (78,80-85). Acupuncture also activates descending spinal cord and brain pain pathways (including the DNIC system) and brain anti-nociceptive networks as described in the previous section (56,75,77,89-91).

Acupuncture's anti-inflammatory effects

Neurogenic inflammation is defined as inflammation arising from the local release of inflammatory mediators (including substance P, calcitonin gene-related peptide and nitrous oxide) in peripheral nerve terminals of afferent neurons caused by antidromic nerve activity after those afferent neurons are stimulated (92,93). Release of these neuropeptides alters local vascular permeability and helps to initiate pro-inflammatory and immune reactions. Animal models demonstrate acupuncture reduces peripheral inflammation and neurogenic inflammation, producing central and peripheral inhibition of capsaicin-induced inflammation by reducing substance P release in peripheral nerve terminals of nociceptive neurons (94). This appears to be mediated by both serotonergic and endogenous opioid systems (95).

Acupuncture modulation of Vagus nerve efferent activity can regulate local and systemic inflammatory responses. Clinical and experimental evidence demonstrate a negative feedback loop between the autonomic nervous system and the innate immune system called the cholinergic anti-inflammatory pathway (CAP) (96). CAP inhibits the immune system inflammatory response by suppressing cytokine synthesis through the release of acetylcholine in the reticuloendothelial system organs, which include the lungs, spleen, liver, kidneys and gastrointestinal tract (96). Acetylcholine release causes down regulation of pro-inflammatory cytokines by macrophages and other cytokine producing cells to prevent tissue damage (97). Electrical stimulation of the Vagus nerve inhibits macrophage activation and inhibits production of pro-inflammatory cytokines including tumor necrosis factor, IL-1β, IL-6, and IL-18 (98). Vagal nerve stimulation also reduces systemic inflammatory response to endotoxins in sepsis via this peripheral mechanism as well as afferent stimulation of the HPA axis (98). Thus, stimulation of appropriate auricular and/or Channel acupoints can produce local and systemic

parasympathetic autonomic nervous system (PANS) modulation that reduces local and systemic inflammation (thus also reducing inflammatory pain).

Acupuncture also modulates HPA axis activity in inflammatory pain states through its effects on ACTH/cortisol secretion, as discussed in the prior section to produce a systemic anti-inflammatory effect (87,88).

Acupuncture's visceral effects

The relationship of the Back-Shu points to the known segmental SANS outflow of the thoracolumbar spine and the bundled, segmental organization of SANS fibers in distal peripheral nerve fascicles, as previously outlined, are both mechanisms for the selective visceral effects of Classical acupoints seen in clinical practice (68,70,71). Acupuncture selectively modulates efferent Vagus nerve (PANS) visceral activity as well. Animal experiments showed the effects of acupuncture hindlimb stimulation to increase gastric acid secretion and motility is eliminated by vagotomy (34,79). In cats, EA at Pericardium Channel points PC-5 to PC-6 (near volar wrist) has been demonstrated to activate cholinergic Vagal preganglionic neurons in the nucleus ambiguus, at least in part through an enkephalinergic mechanism (99). Human heart rate variability studies demonstrate that stimulation of Hegu (LI-4) produces a statistically significant increase in SANS and PANS activity along with a significant decrease of heart rate (70). Laser stimulation of Taichong (LR-3) in humans significantly lowers blood pressure, heart rate, and heart rate variability compared to sham laser (100).

Neuroanatomic model of acupuncture: implications for needle sensation and the positive randomized clinical trial results seen with "sham" needles

Historical experience has suggested that achieving *deqi* sensation (subserved by A and C fiber signaling) during acupuncture point needling is important to achieve optimal therapeutic results from acupuncture treatment, though contemporary acupuncture clinical trials have not been able to definitively demonstrate this (23,65-67). Of interest, Gu *et al.* demonstrated that the intensity of BOLD signal of the thalamus on fMRI correlated significantly with the acupuncture (*deqi*) sensation score during EA at Hegu (LI-4), suggesting an acupuncture "dose" dependent response of afferent neural signaling to the intensity of needle sensation
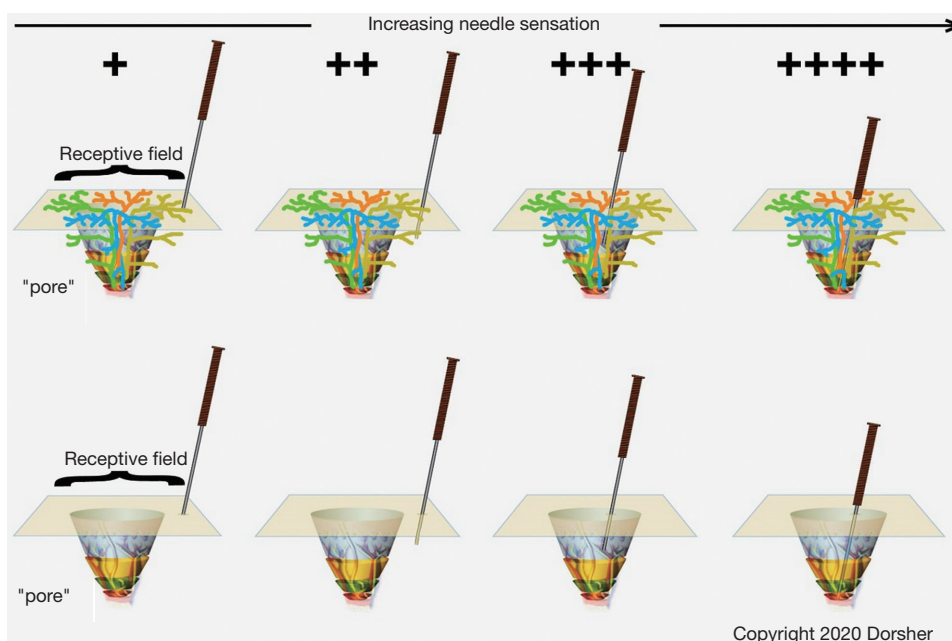
Figure 6 Neuroanatomic anatomic acupuncture model for afferent acupuncture signaling "dose". Bottom graphics demonstrate acupuncture point "pore" and neurovascular bundles passing through this pore. Top graphics demonstrate 4 different nerve branch distributions (gold, orange, green and blue) to subcutaneous tissue and cutaneously across the receptive fields of these nerve branches on the skin surface (represented by the plane).

achieved (33).

Figure 6 shows a neuroanatomic model of acupuncture signaling, that is consistent with the above findings as well as human and canine acupoint histologic studies which demonstrate small neurovascular bundles containing Aδ and C nerve fibers penetrating through pores formed by bone, muscle and/or fascia (35-37). This model is also consistent with Kim *et al.*'s findings that cutaneous neurogenic inflammatory spots on the skin associated with visceral disorders corresponded to traditional acupuncture points (101).

The top portion of *Figure 6* illustrates four such nerve fibers (gold, orange, green and blue) at one acupoint "pore". Though the fibers give some innervation to the subcutaneous tissues as shown, these Aδ and C fibers mostly innervate their cutaneous receptive fields as shown. The higher density of nerve branches cutaneously fits with skin being more sensitive to needling than subcutaneous tissues. As shown in *Figure 6A*, cutaneous pressure from acupressure or a non-penetrating "sham" needle will produce some degree of afferent neural signaling from stimulation of the "gold" nerve terminals. With needling into the subcutaneous tissue locally as shown in *Figure 6B*

, deeper sensory nerves will also be stimulated producing a larger afferent neural signal. If, as in *Figure 6C*, the acupuncture needle is inserted closer to the acupuncture "pore", other nerve fascicles (orange and blue) will be stimulated leading to a much larger afferent neural signal. Finally, *Figure 6D* shows that if the acupuncture needle tip reaches the "true" acupoint at the actual pore opening, then all 4 nerve fascicles are activated producing the maximal afferent neural signaling. This model is consistent with the results of Gu *et al.* showing an increase in thalamus activation with increasing needle sensation score, as well as the animal study of Kim *et al.* showing greater expression of GAP-43 and upregulation of phospho-Erk1/2 signals in dorsal root ganglia sensory neurons with Zusanli (ST-36) stimulation compared to control point stimulation 5–10 mm away (33,102).

This neuroanatomic model provides a plausible explanation for the unexpected clinically and statistically significant positive results of "sham" acupuncture in large randomized clinical trials (though subjects receiving verum acupuncture had somewhat better outcomes). Cherkin *et al.*'s acupuncture for lumbar pain trial used non-penetrating "needling" (toothpick in a guide tube) at acupoints as the

sham intervention, which would in the neuroanatomic model (*Figure 6A*) produce Aδ and C fiber afferent stimulation at the acupoint with a resulting physiologic effect for pain reduction (28). Haake *et al.*'s GERAC acupuncture for lumbar pain randomized controlled trial used "minimal" superficial needling at non-acupoints, most of which were along lumbar and sacral dermatomes/myotomes (29). Per *Figure 6B*, this minimally penetrating needling would be anticipated to produce greater afferent nerve stimulation than the non-penetrating needle of Cherkin *et al.*'s study and thus greater physiologic effect for pain reduction (28,29).

Acupuncture point stimulation using laser has demonstrated clinical efficacy in treating pain and other non-pain conditions- this cannot be explained by fascial acupuncture mechanisms, as the light energy does not displace tissue (30). Infrared low level laser energy has been shown to be able to depolarize nerve axons, again consistent with a neural basis of laser acupuncture's mechanism (103,104).

Discussion

For any proposed theory of acupuncture's anatomy and/or physiology, the putative mechanism(s) must be compatible with all prior basic and clinical acupuncture research results. The only acupuncture mechanism that is able to do so is a neuroanatomic/neurophysiologic mechanism. Print and digital anatomic references confirm Classical acupoint and Primary Channel anatomic relationships to neural structures. Histologic, neurophysiologic and fMRI studies provide compelling evidence of the fundamental involvement of the peripheral nervous system in transducing and the CNS in processing acupuncture needle stimulation into its efferent (clinical) effects. Acupuncture's clinical effects ultimately occur through modulation of the innate immunologic, endogenous opioid, hypothalamic-pituitary axis, autonomic, and CAP systems. This in turn results from acupuncture needle stimulation of peripheral nerves, which modulate neurogenic inflammation (via peripheral and central mechanisms) and multiple neural systems including the DNIC network, the Vagus nerve, the autonomic nervous system, and the CNS including its default mode and anti-correlated task-positive networks. Acupuncture influence on viscera can be understood through the segmental innervation of the Back-Shu points, the somatotopic/bundled organization of sympathetic nerve fibers in distal peripheral nerve fascicles, and acupuncture's

modulation of autonomic nervous system (including Vagus nerve) activity/balance.

The neuroanatomic/neurophysiologic model of acupuncture mechanism serves to reinforce the clinical brilliance of the founders of acupuncture and traditional Chinese medicine 2200+ years ago—these acupuncture scientist/clinicians described essential aspects of human neurophysiology despite not having 20th century technology available to them to be able to study autonomic, peripheral, and CNS functions. This neuroanatomic and neurophysiologic model of acupuncture suggests that Classical acupoints and the Channels they exist on offers a mapping of the human autonomic nervous system in the head, trunk, and extremities that is very non-linear compared to the dermatome and myotome distributions. This autonomic mapping of the human nervous system has largely yet to be "discovered" (rediscovered) by allopathic medicine some 2 millennia later, though there have been contemporary clinical introductions of "seasickness" wrist bands stimulating the Neiguan (PC-6) region for treatment of nausea/vomiting, as well as the PTNS (posterior tibial nerve stimulator) device currently used to treat urge incontinence (105,106). This PTNS device electrically stimulates the medial leg near San Yin Jiao (SP-6), whose acupuncture clinical indications include difficult urination, incontinence, and enuresis (19,49). The Cefaly device for headache stimulates scalp over Yintang, Cuanzhu (BL-2) and Yangbai (GB-14), which are all used to treat headaches in the acupuncture tradition (19,49,107). All these devices are clearly "rediscovering" the clinical benefits of acupuncture described 2000+ years ago.

"Nothing is new".

Conclusions

The acupuncture literature provides overwhelming anatomic and physiologic evidence that all of acupuncture's beneficial analgesic and non-analgesic effects can be explained through neuroanatomic and neurophysiologic mechanisms—that is, acupuncture stimulation of specific peripheral nerve locations (acupoints) produces its clinical effects. A neural based model of acupuncture is the only model that is consistent with acupuncture basic science and clinical literature.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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