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ORIGINAL PAPERS

Neuroimaging Acupuncture Effects in the Human Brain

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ABSTRACT

Acupuncture is an ancient East Asian healing modality that has been in use for more than 2000 years. Unfortunately, its mechanisms of action are not well understood, and controversy regarding its clinical efficacy remains. Importantly, acupuncture needling often evokes complex somatosensory sensations and may modulate the cognitive/affective perception of pain, suggesting that many effects are supported by the brain and extending central nervous system (CNS) networks. Modern neuroimaging techniques such as functional magnetic resonance imaging, positron emission tomography, electroencephalography, and magnetoencephalography provide a means to safely monitor brain activity in humans and may be used to help map the neurophysiological correlates of acupuncture. In this review, we will summarize data from acupuncture neuroimaging research and discuss how these findings contribute to current hypotheses of acupuncture action.

INTRODUCTION

Acupuncture is currently gaining popularity in the West as an "alternative" or "complementary therapy," and there is growing interest in determining its neurophysiologic correlates in humans. Although animal research clearly supports a role for antinociceptive limbic, hypothalamic, and brainstem networks in acupuncture analgesia (for review see[1–3]), it is difficult to interpret these studies in the context of more complex human cognition. One leading investigatory approach includes mapping or localizing acupuncture-associated changes in the brain function. Functional neuroimaging technologies such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG) provide a means to monitor the neurophysiologic effects of acupuncture in the human brain.

Importantly, recent neuroimaging data in humans suggest that therapeutic acupuncture may modulate activity in many cortical and subcortical (i.e., somatosensory, brainstem, limbic, cerebellum) brain areas (Fig. 1). This includes endogenous antinociceptive limbic networks as well as higher-order cognitive and affective control centers within the prefrontal cortex and medial temporal lobe. Figure 1 shows some basic brain anatomy related to the present review. The brain has two hemispheres, each of which has four lobes: the frontal, temporal, parietal, and occipital lobes. The frontal lobes (Fig. 1A) are often termed the executive center and are implicated in working memory, planning, and cognitive evaluation. The temporal lobes are involved in evaluative processing and memory. The parietal lobes are most often implicated in spatial processing, whereas the occipital lobe mainly supports vision. The cortical brain area most important for sensing touch is the primary somatosensory cortex (SI). It is located within the parietal lobe just posterior to the central sulcus. Medially within the brain are other structures thought to participate in acupuncture (Fig. 1B). The anterior cingulate cortex (ACC) is part of the limbic system, which supports pain, attention, memory, and affective processing. The brainstem contains the periaqueductal gray (PAG) and raphe nuclei, both of which may participate in endogenous opioidergic and nonopioidergic

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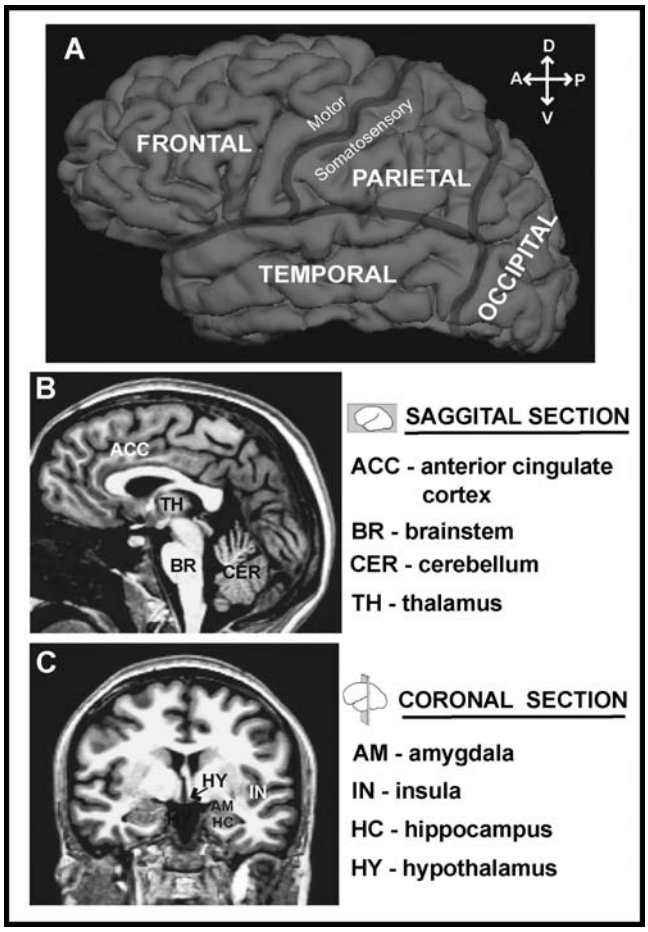


FIG. 1. Basic brain anatomy: **A.** Lateral view of the left hemisphere of the brain. The arrowed cross in the upper right corner exemplifies directional naming convention. Anterior (A) and posterior (P) are used to describe relative position along the horizontal axis, whereas dorsal (D) and ventral (V) are used to describe relative position along the vertical axis. Each brain hemisphere has four lobes called the frontal, temporal, parietal, and occipital lobes. The primary somatosensory (SI) cortex is located in the parietal lobe posterior to the central sulcus. The primary motor cortex (MI) is located anterior to the central sulcus within the frontal lobe. **B.** Midsagittal section: In this medial view of the brain, it is easy to see the anterior cingulate cortex (ACC), which is part of the limbic system. The brainstem (BR) and cerebellum (CER) are also visible. **C.** Coronal section: Both hemispheres can be seen and there is bilateral symmetry of all structures. Structures are only labeled in the left hemisphere here. The insula is a key player in pain perception and may also relay somatosensory information to more medial limbic brain regions. The hippocampus (HC) and amygdala (AM) are located within the medial temporal lobe and are both components of the limbic system. The thalamus (TH) and hypothalamus (HY) are both located centrally within the brain.

antinociception, respectively. The cerebellum helps control postural reflexes but may also participate in higher-order cognitive functions and affect. The insula (Fig. 1C), which is located within the perisylvian fissure, is part of the "pain neuromatrix" (i.e., brain areas commonly activated in response to experimental pain), which also includes the ACC and the amygdala. The hippocampus and amygdala are both located in the medial temporal lobe. These structures are also part of the limbic system and support memory and affect (emotion). The thalamus and hypothalamus are both located centrally within the brain. The thalamus plays a large role in relaying sensory information from the periphery to higher areas located within the cortex. The hypothalamus is a key player in maintaining homeostasis through autonomic and neuroendocrine regulation.

This paper briefly reviews modern functional neuroimaging techniques and discusses recent data regarding the neurophysiologic mechanisms of acupuncture. Although most acupuncture neuroimaging studies have been conducted in normal subjects, the potential for acupuncture therapy in chronic disease populations has prompted neuroimaging research in carpal tunnel syndrome (CTS), fibromyalgia, and even chronic stroke patients. Chronic pain has previously been correlated with maladaptive neuroplasticity, and it is possible that therapeutic acupuncture modifies such maladaptive states, leading to pain reduction. Furthermore, neuroimaging the specific versus nonspecific (placebo) effects of acupuncture may promote its acceptance as a viable clinical treatment. Finally, we suggest future directions for neuroimaging research, which may elucidate mechanisms of acupuncture action further.

NEUROIMAGING MODALITIES

Currently, there are multiple neuroimaging techniques that allow us to observe structure and/or function within the living brain. For example, magnetic resonance imaging (MRI) may be used to acquire high-resolution images of brain structure noninvasively.[4,5] A special version of this technique, functional magnetic resonance imaging (fMRI), may be used to assess which areas of the brain are active. PET, like fMRI, makes use of hemodynamic (i.e., blood flow) measures to monitor brain function and is minimally invasive because of its use of radioactivity. Both fMRI and PET have been consistently used to understand "where" processing occurs in the brain. Techniques such as EEG and MEG are used for mapping the brain's electrical activity on a millisecond timescale and thus can tell us "when" during task performance brain areas may be most active. Together, all of these technologies may be used to investigate which areas of the brain are active and when they are active, thus providing us with valuable insight into the functional mechanisms by which acupuncture exerts its effects.

MRI/fMRI and PET

fMRI is the most commonly applied method of functional neuroimaging (Fig. 2A). It relies on the hemodynamic blood oxygenation level dependent (BOLD) effect, which reflects the ratio between oxygenated and deoxygenated hemoglobin.[6,7] The BOLD contrast is used to infer which areas of the brain are active and may be used to map response within superficial

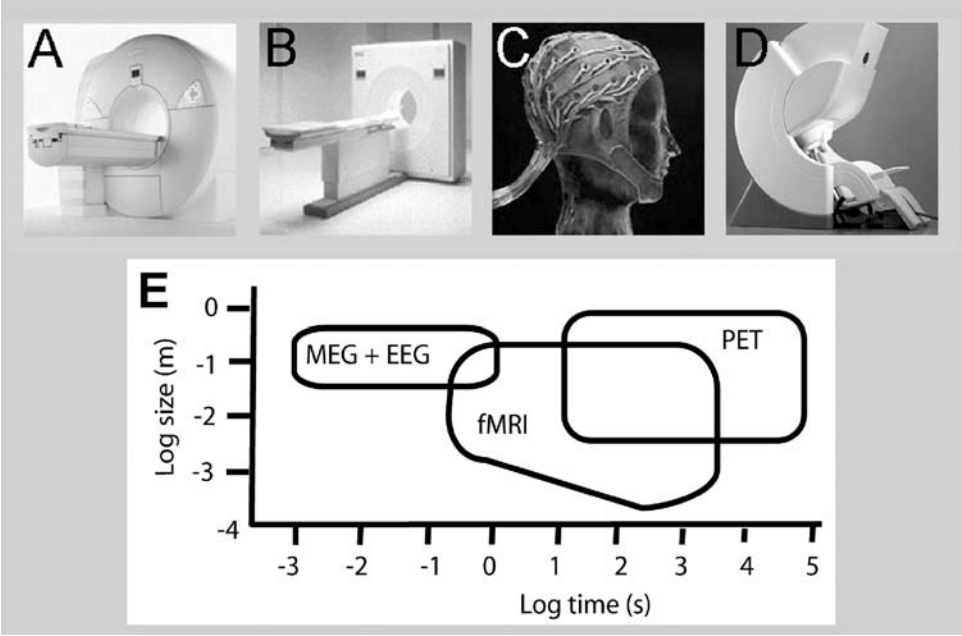


FIG. 2. Modern neuroimaging modalities. **A.** Magnetic resonance imaging (MRI) scanner: The subject lies on the table, which slides into the magnet bore. This system allows for both high-resolution structural imaging of the brain and functional MRI (fMRI) scanning to monitor brain activity (pictured: Siemen's 3T Magnetom Trio, Erlangen, Germany). **B.** Positron emission tomography (PET) scanner: Subjects are intravenously administered radiolabeled markers while lying on the scanner bed. Blood flow within the brain is monitored by mapping the movement of radiolabeled markers. **C.** Electroencephalography (EEG) cap: The cap has multiple electrodes to measure differences in electrical potentials at the scalp generated by currents within the brain. **D.** Magnetoencephalography (MEG) scanner: A subject sits in the chair and places their head in the helmet. SQUID sensors in the helmet are used to measure the small magnetic fields around the head that are generated by neurons in the brain (306 channel Elekta-Neuromag, Elekta AB, Stockholm, Sweden). **E.** The different modalities vary in their relative spatial and temporal resolution (adapted from "FSL" software manual). fMRI and PET are most often used to localize brain activity, whereas procedures such as MEG and EEG display high temporal resolution.

as well as deep areas of the brain. This includes limbic, cerebellar, and even brainstem areas all putatively involved in therapeutic acupuncture. BOLD fMRI has high spatial resolution (1–3 mm^3) and does not involve harmful radiation. However, it has limited temporal resolution because of the delay and temporal spread of the hemodynamic response, which is thought to peak 4–5 seconds after neuronal activity.[8]

Another imaging tool, PET (Fig. 2B), (and a similar method, single photon emission computed tomography; SPECT), may be used to monitor regional cerebral blood flow (rCBF), regional cerebral blood volume, and regional cerebral metabolic rate using radionuclides. PET may also be used to map specific neuroreceptors using radiopharmaceuticals such as ^{18}F-fluoroethylspiperone for dopaminergic D2 receptors and ^{11}C-carfentanil for opioid receptors, both of which may play a role in therapeutic acupuncture. Unfortunately, the use of such radioactive tracers limits the number of scans an individual may have at any given time. Furthermore, although the spatial resolution in PET can be as good as 8 mm^3, the temporal resolution, being on the order of minutes, is too low to investigate neuronal mechanisms of the brain in real-time.[9]

EEG and MEG

EEG monitors changes in electrical potentials measured at the scalp surface (Fig. 2C). These potentials may be generated by cortical as well as deep structures within the brain and may arise from either neuronal and/or glial cell populations.[10] MEG, however, is used to evaluate changes in weak magnetic fields measured just outside of the head (Fig. 2D). The recorded field mainly reflects postsynaptic potentials in dendrites of pyramidal cells within the neocortex.[11] MEG is more sensitive to superficial compared to deep sources of synaptic activity because the strength of the neuronal magnetic field decreases as a function of the distance from the source. Although EEG and MEG are good for determining "when" cells may be active, they have relatively limited spatial resolution (>1 cm) because of an ill-posed inverse problem.*

Most EEG and MEG somatosensory studies utilize paradigms in which trials of sensory stimuli are given repeatedly. Thus, when averaging trials, brain responses that are time-locked to the stimulus (i.e., occur at the same time after each stimulus event) become visible against background

*The EEG/MEG inverse problem involves formulating a mathematical model for locating sources of electrical activity inside the brain through the use of data collected from electrodes/sensors placed outside of the head. The problem is ill-posed because of insufficient constraints. Thus, there are multiple source configurations inside the brain that can produce the same externally recorded signal.

noise. These averaged responses are called somatosensory evoked potentials (SEPs) when recorded with EEG and somatosensory evoked fields (SEFs) for MEG studies. Signals occurring ~0–20 milliseconds indicate signal transmission in the spinal cord and subcortical structures (for review see[12]). By ~20 milliseconds, the sensory signal has reached contralateral primary somatosensory cortex (SI) appearing as a negative deflection at parietal electrode sites, often referred to as the EEG N20 (or N1). It is followed by a positive peak at ~30 milliseconds termed the P30 or P1 also believed to have SI generators. In MEG data, these components are often called the M20 and M30, respectively. Later components, at ~40–60 milliseconds, may have strong contributions from secondary somatosensory cortex (SII), while longer latency components may have even more distributed sources including prefrontal areas. Spectral analysis is another common EEG/MEG analysis method that is often used to quantify signals on the basis of the amount of "frequency power" present in different frequency bands (i.e., alpha, beta, gamma, theta, delta, etc.). However, even today the precise functional significance of these oscillatory bands remains debatable. Alpha oscillations were among the first "brain waves" to be characterized and can be modulated even by the simple act of opening and closing one's eyes.[12] Data suggest that alpha activity may in some cases be related to attention.[14] Studies recording gamma-band activity within visual cortical areas suggest that oscillations in this frequency range may support local coordination of neuronal activity.[15] Activity within the beta and alpha frequency ranges has also been linked to somatomotor function.[16]

Summary of neuroimaging modalities

Modern neuroimaging technologies allow us to spatiotemporally map brain networks supporting acupuncture effects in humans. Techniques such as fMRI and PET are most useful for revealing which brain networks are activated and are better for localizing subcortical (e.g., limbic, cerebellar, and brainstem) activity. However, because of their excellent temporal resolution, EEG/MEG are best suited for determining the temporal sequence of activity within active brain networks.[17] Figure 2E summarizes the relative spatiotemporal resolution of these different neuroimaging modalities.

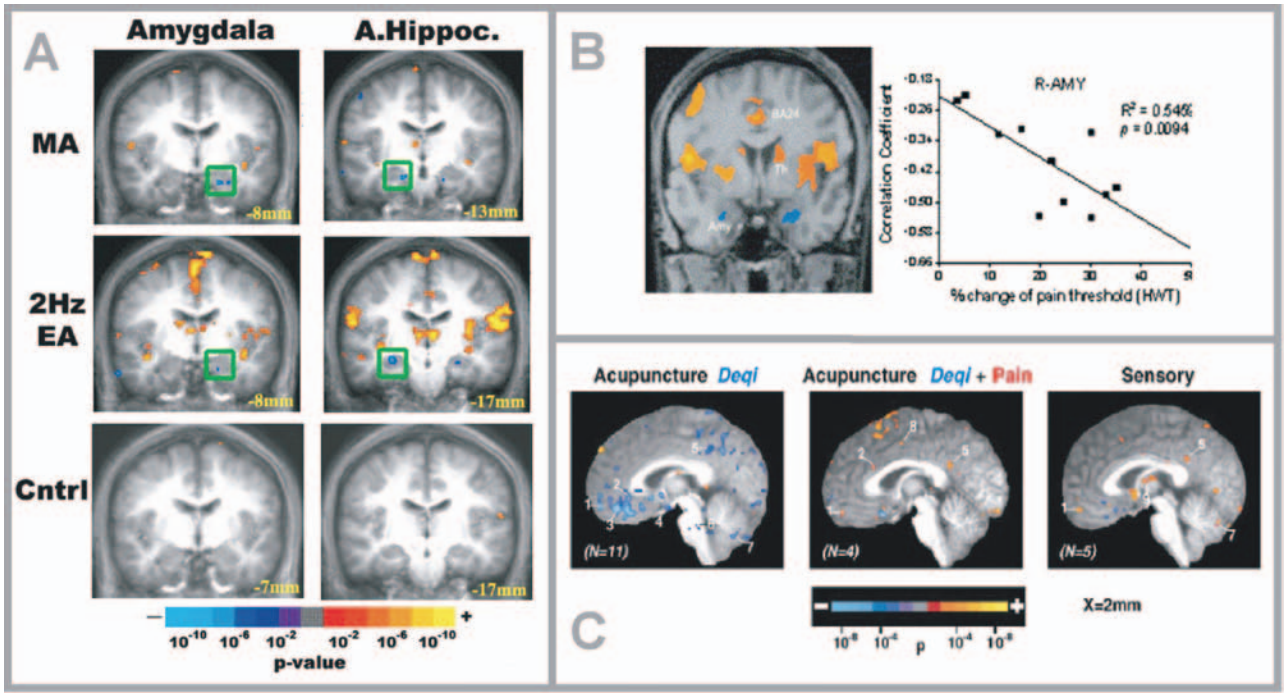
NEUROIMAGING ACUPUNCTURE EFFECTS IN THE BRAIN

The brain exerts control over many functional subsystems within the body (e.g., cardiorespiratory, renal, musculoskeletal, gastrointestinal, reproductive, and endocrine) and helps regulate homeostatic balance. The wide range of physical effects exerted by acupuncture and its purported efficacy for a compendium of clinical pathologies suggest that the brain may be responsible for transducing the needle stimulus into signals aimed at maintaining homeostatic balance within and across functional subsystems. Noninvasive functional neuroimaging provides a means to observe acupuncture effects within the human brain and better understand how multiple bodily functions may be modified simultaneously.

In general, acupoint specificity lies at the core of traditional acupuncture theory. The most likely form of acupoint specificity lies in the somatotopic response[18] in the primary somatosensory cortex (i.e., the SI homunculus). In addition, some fMRI data suggest that acupuncture given at traditional "vision-related" acupoints elicits activity primarily within the visual (occipital) cortex,[19,20] whereas other data suggest that multiple brain areas may support acupoint specificity.[21] However, such acupoint specificity has been controversial and difficult to replicate.[22–26] Other studies suggest that modulation of the pain neuromatrix is specific to acupoints compared to nonacupoints.[27] However, which locations on the body are considered acupoints, and which are considered non-acupoints, has been ever-changing in the 2000+-year history of acupuncture. Many of the acupoints investigated in acupuncture fMRI studies (e.g., LI-4, ST-36, GB-34, LV-3) have been chosen because they are consid-

FIG. 3. Acupuncture-related functional magnetic resonance imaging (fMRI) activity decreases in limbic areas. **A.** Both manual and electroacupuncture at ST-36 induces fMRI signal decrease in the amygdala and anterior hippocampus. This decrease was not seen for superficial tactile control stimulation (adapted from ref. 37). **B.** Studies have also found that amygdala deactivations correlate with decreased pain ratings. 100-Hz transcutaneous electrical acupoint stimulation (TEAS) at ST-36 induced fMRI signal decrease in the amygdala. A negative correlation was found between TEAS response in the amygdala and post-TEAS analgesia (adapted from ref. 47). **C.** Data also suggest that decreased brain response within limbic structures is more pronounced when *de qi* sensation is induced, versus when *de qi* is mixed with sharp pain or with somatosensory control stimulation (adapted from ref. 40).

FIG. 4. Effects of acupuncture treatment on patients with carpal tunnel syndrome (CTS). **A.** In CTS, the brain demonstrates hyperactivation to innocuous stimulation of the third finger (median nerve innervated) of the affected hand. This hyperactivation occurs within the contralateral hemisphere in primary somatosensory cortex (SI) and precentral gyrus (PreCG). After a 5-week course of acupuncture treatment, patients with CTS demonstrated less hyperactivation, and more focused SI finger representation (adapted from Napadow et al., 2007a). **B.** Compared to healthy adults, CTS patients demonstrated more closely separated somatotopic representations for the 2nd and 3rd fingers (both median nerve innervated). After acupuncture treatment, the 2nd and 3rd finger representations moved further apart, similar to the degree of separation seen in healthy adults (adapted from ref. 60).


A
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-7mm
-17mm
p-value
B
R-AMY
R² = 0.548
p = 0.0094
Correlation Coefficient
% change of pain threshold (HWT)
Acupuncture Deqi
Acupuncture Deqi + Pain
Sensory
(N=11)
(N=4)
(N=5)
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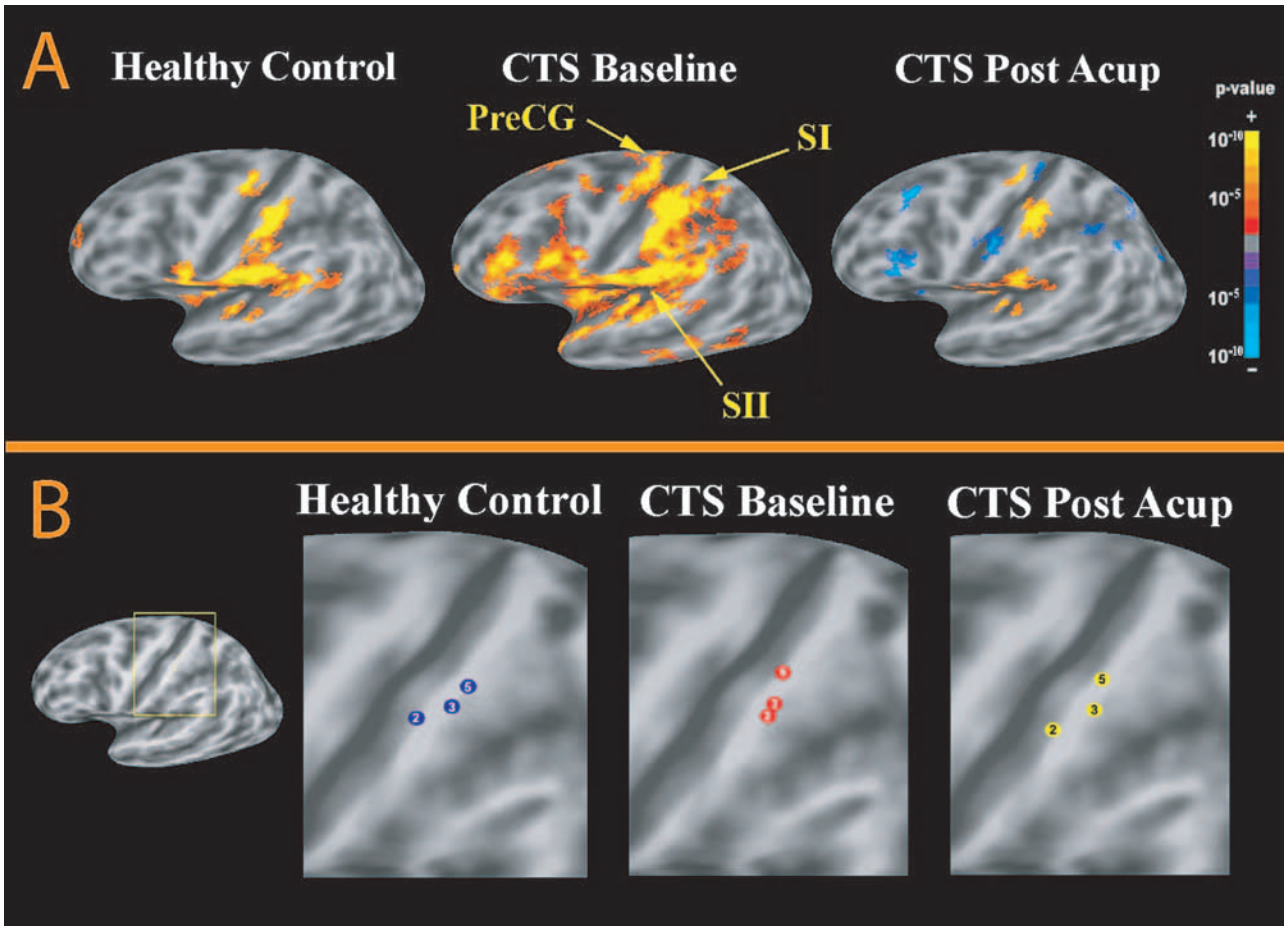
X=2mm

FIG. 3.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Healthy Control
CTS Baseline
CTS Post Acup

FIG. 4.

ered potent and have a wide clinical applicability. However, acupoints may also be locations with increased somatosensory innervation[28;for discussion29]) and thus, more efficient locations to induce *de qi*[†30] sensations (and sensory brain activation). EEG studies investigating SEPs at acupoints versus nonacupoints also suggest that although responses are largely similar, existing amplitude and latency differences may be caused by increased innervation at acupoints.[31,32] Thus, differences in brain response for stimulation at different points on the body may be caused by variation in both sensory perception as well as cognitive/affective processing.

Acupuncture modulates a distributed network of brain areas

Human neuroimaging studies suggest that stimulation of different acupoints can elicit overlapping response within multiple cortical, subcortical/limbic, and brainstem areas.[33–38] This includes primary and secondary somatosensory cortices (SI, SII), which support initial localization and early qualitative characterization of somatosensory stimuli. Limbic brain regions (e.g., hypothalamus, amygdala, cingulate, hippocampus) are also recruited. The hippocampus and amygdala putatively support learning and memory, whereas the amygdala may also play a dominant role in affective encoding (i.e., mood).[39] Both structures are directly connected to the brainstem as well as the hypothalamus, which modulates neuroendocrine and homeostatic function. Coordinated interaction between the amygdala/hippocampus and the hypothalamus may affect arousal and motivational state within the nervous system. Interestingly, Hui et al. have elaborated on an integrated limbic system downregulation in response to acupuncture,[35,37,40] specifically if *de qi* sensation is induced (Fig. 3A and C). This hypothesis stems from the observed BOLD fMRI signal decrease in response to acupuncture needle stimulation and has been at least partially corroborated by other investigators as well.[34] Furthermore, many acupuncture studies have demonstrated modulation of anterior and posterior insula, and the prefrontal cortex (PFC). The insula has been implicated in the sensory-discriminative dimension of visceral pain[41] and may also play a role in therapeutic acupuncture.[38,42] Finally, the prefrontal cortex, which has multiple distributed connections with the limbic system, is likely to play an important role in expectancy-related modulation of pain processing.[43]

Collectively, neuroimaging data strongly suggest that acupuncture modulates many distributed cortical and subcortical (i.e., brainstem, limbic, cerebellum) brain areas. Limbic and brainstem areas within these networks have also been demonstrated to support endogenous antinociceptive mechanisms and are part of the "pain neuromatrix." The primary somatosensory cortex (SI), which is also activated during acupuncture, has been shown to play a role in pain perception. Long-term modulation of SI activity by acupuncture may foster reversal of the maladaptive plasticity seen in chronic pain states (see below). Acupuncture-related modulation of activity in other brain areas including the brainstem, hypothalamus, and amygdala may contribute to stress reduction by shifting autonomic nervous system (ANS) balance and altering the affective and cognitive dimensions of pain processing. Finally, acupuncture has been demonstrated to modulate prefrontal and cingulate areas, which in addition to affective processing may play a role in directed attention. Thus, acupuncture may exert its therapeutic effects on pain by modulating a distributed network of brain areas involved in sensory, autonomic, and cognitive/affect processing. Neuroimaging evidence for effects of acupuncture in the brain is discussed in detail in the sections below.

Acupuncture modulates corticolimbic and brainstem networks supporting endogenous antinociception

Data from animal research suggest that acupuncture analgesia may be largely supported by endogenous opioidergic and/or monoaminergic "antinociceptive" networks.[44] Endogenous analgesia manifests at least partially through inhibition of afferent pain signaling by brainstem modulation.[45] Specifically, the PAG may activate "off cells" in the rostroventral medulla, which inhibits afferent pain signaling at the level of the dorsal horn.[46] In humans, PAG activity may be triggered or facilitated by "top-down" pain signaling from higher centers including the PFC and ACC. These areas, along with limbic regions including the hippocampus and amygdala, are activated during pain and are associated with the pain neuromatrix. Importantly, brainstem activity may also modulate opioidergic and/or monoaminergic transmission within the pain neuromatrix, thereby decreasing the subjective/conscious experience of pain.

Neuroimaging data demonstrate that multiple areas supporting endogenous antinociception are also modulated by acupuncture. For instance, decreased amygdala activity may correspond to decreased affective pain processing. An fMRI study of transcutaneous electrical acupoint stimulation (TEAS) found greater limbic deactivation in high compared to low acupuncture responders (Fig. 3B).[47] However, TEAS is different from insertive electroacupuncture in many ways, and the results from these studies may not apply to acupuncture. EEG data also support possible limbic involvement in acupuncture. High-frequency TEAS at LI-4 was associated with processing in the ACC and decreased theta frequency power.[48] Unfortunately, neither EEG nor fMRI studies have shed light on whether acupuncture's analgesic effects are supported by opioidergic and/or monoaminergic neurotransmission.

Although many of the above studies have mapped brain response during acupuncture stimulation, other studies have

[†]*De qi* corresponds to a multitude of different painlike and nonpain sensations experienced by a needled subject and may be a correlate of effective treatment.

explored the effects of acupuncture after stimulation (e.g., how brain response to a pain stimulus is altered by prior acupuncture stimulation. For example, Harris et al. have demonstrated that both verum and sham acupuncture reduce fMRI pain responses in the thalamus and insula of patients with fibromyalgia. PET data using carfentanil in this same population also support μ-opioid receptor involvement in acupuncture and/or sham analgesia.[49,50] Studies in healthy adults demonstrate similar fMRI signal reduction to pain within the sensory thalamus, ACC, and premotor cortex after acupuncture stimulation at either real or sham (nonclassical) acupoints.[51]

In general, acupuncture analgesia that occurs in immediate response to needling may be supported by spinal gating mechanisms and/or diffuse noxious inhibitory control (DNIC).[52] With respect to nonpainful needling at the affected site, the gate-control theory proposes that incoming somatosensory signals carried by large-diameter Aβ-fibers can inhibit transmission of pain signals carried by smaller-diameter pain fibers (Aδ and C) at the level of the spinal cord.[53] Furthermore, EEG studies have demonstrated that EA may result in modulation of median nerve SEPs because of sensory interference.[31,54] In contrast, the DNIC hypothesis proposes that painful acupuncture needling may serve as a counterirritant that attenuates perception of the original pain sensation (i.e., pain inhibiting pain).[55,56] Intentionally painful acupuncture is less common in clinical practice (especially in Western countries) and DNIC effects are not likely to play a major role in clinical acupuncture efficacy (see ref. 52 for discussion). Furthermore, the time course of both DNIC and sensory gating effects is relatively short lived (minutes), whereas clinically relevant acupuncture analgesic effects have been found to peak hours, if not days, after stimulation.[57]

Acupuncture alters somatomotor cortex processing and cortical somatotopy in patients with chronic pain and stroke

Pain is often accompanied by maladaptive plasticity (i.e., reorganization) in the SI associated with the affected body part.[58–60] The reasons for this are not fully understood but may be correlated with decreased movement and increased pain and/or paresthesias arising from the affected area. For example, in a study of phantom-limb pain, Lotze et al. (61) used a myoelectric prosthesis to provide normalized sensory, motor, and visual feedback. Intensive use of this myoelectric prosthesis was positively associated with both less phantom-limb pain and less cortical reorganization in comparison to controls. It is possible that the myoelectric prosthesis provided relevant and correlated sensory input, driving beneficial plasticity in the brain. It is also possible that similar mechanisms are at play in chronic pain syndromes treated by acupuncture.

Studies with patients who have CTS demonstrate that pain coincides with sensorimotor hyperactivation and an overlapping or blurred representation of adjacent fingers within the primary somatosensory cortex.[62] Furthermore, after a 5-week course of acupuncture treatment, there was clinical improvement, partial release from hyperactivation, and more somatotopically separated finger representations (Fig. 4A and B).[60] Improvement in SI finger separation was correlated with improvement in peripheral median nerve electrophysiologic measures. Other studies investigating acupuncture effects on populations with chronic pain have also demonstrated (using SPECT) acupuncture-associated modulation of somatosensory brain regions.[63] Because maladaptive neuroplasticity may contribute to the maintenance of a centrally mediated chronic pain state, future studies should explore acupuncture's role in correcting maladaptive plasticity in the brain.

Another disease population that has received attention from acupuncture neuroimaging groups has been chronic stroke. Although preliminary, the results of these investigations have found that both acupuncture and somatosensory stimuli to the contralesional side produce hyperactivation in ipsilesional primary sensorimotor cortex and SII.[64] Another fMRI study by Schaechter et al.[65] revealed that after acupuncture intervention (verum or sham), patients exhibited changes in motor cortex activity associated with the stroke-affected hand that were positively correlated with changes in somatosensory-motor function of the affected upper limb. There was a trend toward greater increases in motor cortex activity in patients treated with verum acupuncture than sham acupuncture ([65], also reviewed in Napadow et al.[50]). A SPECT study found contralesional acupoint stimulation increased rCBF in regions surrounding the ischemic lesion.[66] Although these studies are preliminary, they do suggest potential mechanisms for acupuncture efficacy in chronic stroke.

Acupuncture may modulate brain regions supporting ANS activity

Therapeutic acupuncture may also modulate ANS function. In general, it is hypothesized that enhanced parasympathetic (or reduced sympathetic) activity may decrease stress responses and promote immunologic homeostasis through altered brainstem and hypothalamic–neuroendocrine function.[67] Previous data have demonstrated that acupuncture may be associated with an immediate stimulus-induced and/or a poststimulation sympathovagal shift toward parasympathetic dominance as assessed by heart-rate variability (HRV).[68–71] On the other hand, skin sympathetic nerve activity has been found to shift toward the sympathetic during stimulation.[72] Again, the strength of stimulation may play a significant role in how noxious the stimulus is perceived and in what direction the sympathovagal system shifts. Furthermore, sympathetic outflow is organ specific; thus, acupuncture may modulate sympathetic tone to the skin differently from sympathetic outflow to the heart.

Increased vagal stimulation by therapeutic acupuncture may also initiate fast "neural" and slow "diffusible" components of the cholinergic anti-inflammatory pathway.[73] In general, the cholinergic anti-inflammatory pathway is driven by brainstem and hypothalamic activity, which may downregulate macrophage activation and suppress synthesis of tumor necrosis factor and other peripheral pro-inflammatory cytokines. It is possible that this pathway plays a role in acupuncture efficacy.[73,74] However, this theoretical assertion requires experimental substantiation. Although neuroimaging studies have noted hypothalamic response to acupuncture stimulation in healthy adults,[34,35] recent fMRI data support greater response in the hypothalamus for patients with CTS (Fig. 5A).[75] It remains to be seen whether this hypothalamic response to acupuncture is concomitant with autonomic modulation and whether this modulation plays a role in acupuncture efficacy for CTS. A preliminary study found that activity in hypothalamic and brainstem regions correlated with modulation of HRV parameters by electroacupuncture (EA) at ST-36 in healthy adults.[76] Thus, neuroimaging coupled with ANS activity monitoring and inflammatory marker sampling could aid the evaluation of these potential mechanisms in inflammatory pain models. Similarly, recent studies have found correlations between wide-band EEG spectral power and HRV[77] suggesting that brain activity during acupuncture may be indicative of broader autonomic modulation.

Acupuncture intervention may modulate activity within brain networks supporting attention and higher cognition

Acupuncture modulates multiple areas of cortex including PFC, ACC, and insula. These areas have also been demonstrated to support higher-order cognition including attention,[78] but their precise role in acupuncture analgesia remains unclear. Some investigators have suggested that acupuncture analgesia may be supported by attentional mechanisms (see below). In relation to this, EEG studies have tested the effects of acupuncture versus anesthetics on experimental pain stimuli. For example, one study compared the effects of fentanyl, nitrous oxide (NO), and low-frequency EA stimulation on experimental pain and found that all three treatments decreased the amplitude of the P250 pain component.[79] The authors thus suggested that acupuncture analgesia may be based on attentional mechanisms. However, a more recent study comparing low-frequency EA with desflurane anesthesia on noxious abdominal stimulation was unable to find any significant effects of EA.[80] Such variability in findings may be caused by differences in the acupoints stimulated and the pain model used. Another EEG study compared effects of verum versus sham EA in subjects given propofol anesthesia and found a significant decrease in the P260 pain SEP after real but not sham EA.[81] The authors argued that acupuncture analgesia is not related to changes in attention because both groups were sedated. Thus, results are somewhat conflicting, and whether modulation of these areas is related to acupuncture-specific analgesia mechanisms remains questionable. Furthermore, acupuncture analgesia that occurs in the context of acute experimental pain may be mediated by different mechanisms than when it occurs in the clinical pain setting (i.e., chronic pain treated with multiple intervention sessions).

CHOOSING THE APPROPRIATE SHAM/PLACEBO FOR ACUPUNCTURE NEUROIMAGING

Choosing an appropriate control for neuroimaging studies is challenging and although several control modalities are available, it is unclear which ones most effectively mimic verum treatment. One approach is to use a "placebo needle" to enact sham acupuncture. Placebo needles mimic the sensation of needle *insertion* and appear to penetrate the skin but actually consist of a blunt tip that retracts into a hollow shaft, like a stage-dagger.[82,83] Placebo needles are certainly necessary when subjects are able to view the procedure taking place. In PET and fMRI studies, where subjects lie supine in the scanner and cannot see the intervention performed, sham acupuncture may just as easily consist of simulating an insertion with any sharp-tipped object (e.g., a toothpick in a guidetube[84]) and inducing poking sensations with any blunt-tipped object (e.g., von Frey monofilament). This latter approach has been taken by several research groups.[35,36,37,40] Unfortunately, how well placebo needles or any other sham treatments actually mimic the sensory experience of verum needle *manipulation* (e.g., twisting, lifting-and-thrusting, as opposed to just insertion) remains uncertain, and the intensity of *de qi* sensations is not likely equivalent between verum acupuncture and any sham intervention (for discussion see ref. 85). In general, however, studies should be consistent in their use of control and use only one form of placebo/sham throughout.

NEUROIMAGING ACUPUNCTURE SPECIFIC VERSUS PLACEBO EFFECTS IN THE BRAIN

Before acupuncture can be widely established as a treatment for pain management, the neural correlates of its specific and nonspecific (e.g., placebo) effects may need to be dissociated.[86] However, finding an appropriate placebo or sham intervention for acupuncture is complicated by a lack of understanding of the "verum" mechanisms of acupuncture.[87]

Research on the brain circuitry underlying the placebo effect has yielded some interesting results (for a more thorough review see ref. 88). Early work with naloxone suggested that placebo analgesia is partially mediated by

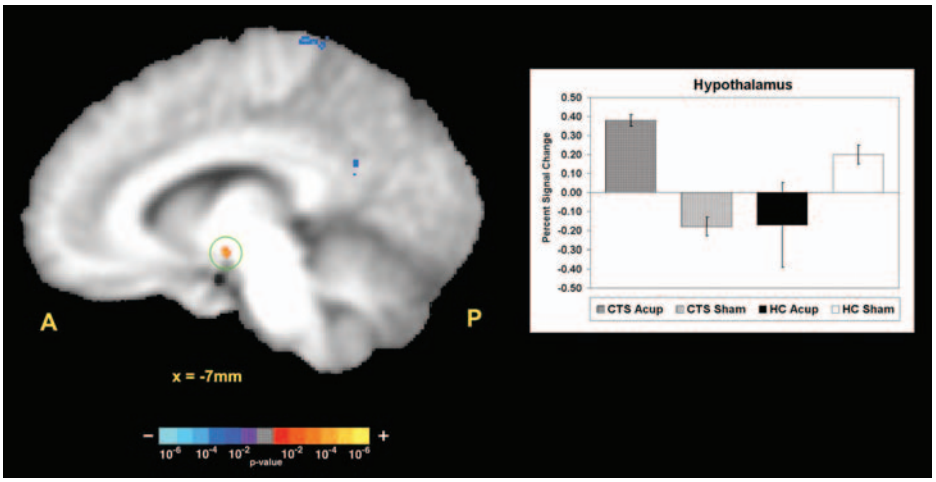

FIG. 5. Differences in acupuncture brain processing between patients with chronic pain and healthy subjects. Functional magnetic resonance imaging analysis of brain response to verum acupuncture at LI-4 for patients with carpal tunnel syndrome (CTS) and healthy controls (HC), controlling for effects of sham acupuncture: (CTS.acup—CTS.sham)—(HC.acup—HC.sham). A positive interaction was found in the hypothalamus. Bar plots demonstrated that the greatest percent signal change in the interaction was by the subgroup: patients with CTS with verum acupuncture stimulation (adapted from ref. 75).

opioidergic[89] limbic and brainstem networks,[88] which may be activated during sustained pain and modulated by both sensory and affective dimensions of pain perception.[90,91] In a recent fMRI investigation of experimental pain, Wager et al.[92] explored how expectancy for pain relief modulated the cortical and subcortical pain neuromatrix. Decreased pain rating during covert placebo (i.e., subjects were given an "analgesic cream") was accompanied by *decreased* brain activity in the insula, ACC, and thalamus, whereas the anticipation of pain was associated with increased activity in the prefrontal cortex. The authors hypothesized that placebo analgesia may arise from changes in the expectation of pain within higher cognitive centers such as the prefrontal cortex and ACC. A similar study with PET used noxious thermal stimuli with covert placebo (intravenous saline) and active treatment IV (opioid receptor agonist remifentanil).[93] In both conditions, analgesia was accompanied by changes in rostral ACC activity that correlated with activity in the brainstem periaqueductal gray (PAG) and pons. Increased activity was noted in orbitofrontal regions. The authors suggested that the prefrontal cortex and ACC may support top–down regulation of pain. Although both studies supported involvement of limbic regions in placebo analgesia, there were some differences. For example, ACC response during placebo analgesia resulted in decreased fMRI activity[92] but increased rCBF.[93] Such discrepancies are hard to explain but may be caused by differences in task conditions and/or simply the imaging modality used.

Overall, the data demonstrate that placebo analgesia recruits subcortical and cortical opioid-sensitive brain regions including the PAG, rostral ACC, thalamus, insula, amygdala, and in some studies PFC. However, to understand how acupuncture-specific effects differ from placebo, it is necessary to study expectancy in the context of both verum

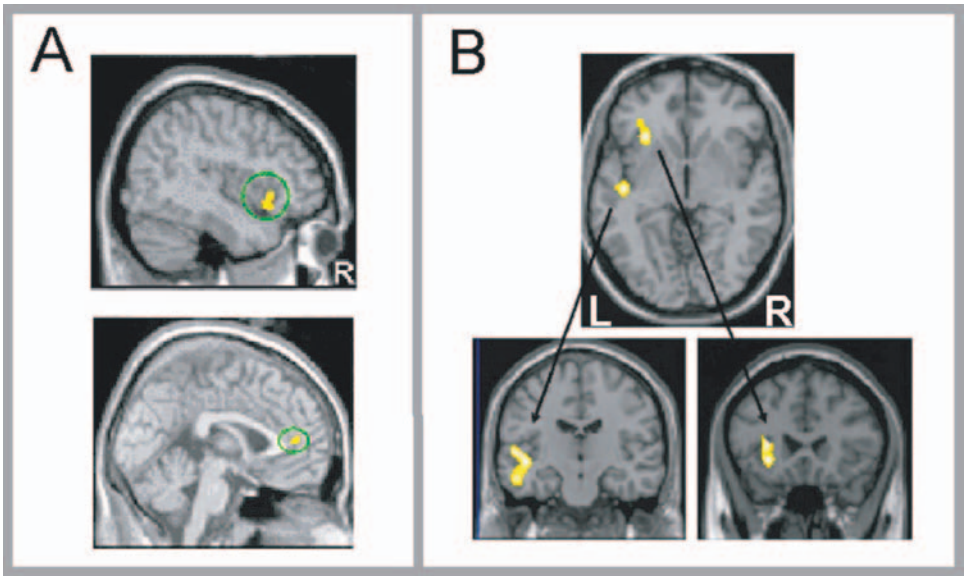

FIG. 6. Neuroimaging pain and placebo analgesia in the brain. **A.** Top image: Brain regions representing differential response as revealed by the contrasting post-treatment and pretreatment differences (post minus pre) on the control side subtracted from the same difference on the placebo side [placebo (post − pre)—control (post − pre)]. **A.** Bottom image: shows activation in right anterior insula (46, 20, −4), and C shows activation in bilateral rostral anterior cingulate cortex (2, 44, 10). Adapted from ref. 95. **B.** Comparison of verum acupuncture and placebo (Streitberger needle). Greater response was seen within ipsilateral posterior insula/SII. Adapted from ref. 38).

(real) and sham acupuncture. Recently, Pariente et al. used PET to explore brain response to verum, covert (Streitberger needle) and overt (subjects were told it was a placebo) sham needling.[38] They found that verum acupuncture induced greater brain response in the ipsilateral insula than either covert or overt sham. Furthermore, subjects were reportedly unable to distinguish between verum and covert sham interventions. Verum acupuncture and covert sham both differed from overt sham in dorsolateral PFC (DLPFC), rostral ACC (rACC), and midbrain activation. The authors hypothesized that activity within the insular cortex may support acupuncture-specific effects, whereas modulation of the DLPFC, rACC, and midbrain may be related to expectancy. However, there were no analgesic effects of any treatment on experimental or ongoing pain.

In a study of experimental pain processing, Kong et al. found that analgesia induced through the use of a placebo acupuncture needle (Streitberger needle) was associated with *increased* activity in response to a pain stimulus within multiple brain regions including bilateral rostral ACC, lateral PFC, right anterior insula, supramarginal gyrus, and the left inferior parietal lobe (Fig. 6).[94,95] The authors concluded that placebo needling may evoke different types of brain responses than those evoked by more conventional placebos, such as creams or pills. Clinical trials further support the idea that sham acupuncture has different effects on pain than a placebo pill.[96]

Differences between verum and sham acupuncture may also occur in the temporal domain, which may be resolved by neuroimaging modalities such as MEG. For example, preliminary data suggest that evoked responses for EA and sham acupuncture (noninsertive tapping) both localize to the contralateral SI cortex.[97,98] However, initial response to sham acupuncture peaked at longer poststimulus latencies (~35 milliseconds) than verum EA (~20 milliseconds). This may have resulted from temporal dispersion caused by sham acupuncture's mechanical (versus electrical) mode of stimulation. It remains to be seen whether there are any downstream consequences of these temporal differences.

In general, investigation of specific and nonspecific effects of acupuncture may require mapping dissociations between positive and negative expectancy conditions for both verum and placebo treatments in clinical pain populations. If verum acupuncture in the guise of "placebo acupuncture" is found to produce significantly greater analgesia than placebo/sham needling, this would lend strong support for the existence of acupuncture-specific analgesic effects.

FUTURE DIRECTIONS FOR ACUPUNCTURE NEUROIMAGING RESEARCH

There are a number of challenges that acupuncture neuroimaging researchers must overcome in order to understand the therapeutic mechanisms of acupuncture. First, research studies have mostly investigated the effects of stimulating one to two acupoints simultaneously; however, an actual treatment session typically involves needling at many acupoints. Furthermore, variability in needling technique, *de qi* sensations, stimulation paradigm as well as scanner and data analysis parameters may all account for many of the reported differences in brain response. Thus, it may be useful to devise a standardized reporting system to describe details of needling depth, manipulation style (lift-thrust, rotation, etc.), and stimulus duration. This could be extended to include qualitative ratings of individual *de qi* sensations (the questionnaire adopted by the Massachusetts General Hospital neuroimaging group can be found at www.nmr.mgh.harvard.edu/acupuncture/PPG/resources/index.php). Recently, efforts to standardize the reporting of research clinical trials were made with the publication of "Standards for Reporting Interventions in Controlled Trials of Acupuncture" (STRICTA).[99] Similar standardization should be incorporated to neuroimaging studies. Studies would then be able to be more readily compared by meta-analyses. Facilitating data sharing can only benefit the field of acupuncture research by increasing access to information from around the world. The Biomedical Informatics Research Network (BIRN) (www.nbirn.net) has established a working infrastructure for the uploading and sharing of neuroimaging data and associated clinical meta-data. In the near future, BIRN should be used to facilitate acupuncture neuroimaging data sharing.

Collectively, neuroimaging studies demonstrate that acupuncture modulates a widely distributed network of brain areas including limbic, prefrontal, and brainstem regions. Future studies involving PET may help determine whether modulation is linked to opioidergic and/or monoaminergic transmission within these areas. Ongoing studies with MEG may also shed light on the time course of SEFs and oscillatory activity occurring during acupuncture intervention.[97,98] Concurrent physiologic measurements (e.g., electrocardiography, pupilometry, and electrodermal activity) during neuroimaging may help correlate acupuncture-related changes in ANS function to brain activity, because acupuncture efficacy may be related to downstream regulation imparted by a change in brain activity. Finally, peripheral effects close to the needle site should also be explored in conjunction with physiologic monitoring and neuroimaging. Thus, future studies that evaluate both central and peripheral effects of needle stimulation, in a well-chosen disease model, may help determine specifically which acupuncture effects are most important to clinical efficacy.

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GLOSSARY OF NEUROIMAGING AND ACUPUNCTURE RELATED TERMS

Acupoint specificity—This is the existence of markedly distinct effects by different acupoints. In the context of this review, we refer to distinct neurophysiologic effects.

Antinociceptive—This is related to decreasing the sensation of pain.

Blood oxygenation level dependant (BOLD)—BOLD effect reflects the ratio between oxygenated and deoxygenated hemoglobin in blood. Mapping BOLD effects in the brain allows for inference of which areas are most active during a task.

Diffuse noxious inhibitory control (DNIC)—This is a decrease in pain brought about by activation of endogenous antinociceptive systems following persistent noxious stimulation (i.e., one pain diminishes another pain).

Electroencephalography (EEG)—This is a neuroimaging technique with very good temporal resolution that monitors changes in neuronal electrical activity by measuring changes in electrical potentials measured at the scalp

Functional magnetic resonance imaging (fMRI)—This is a neuroimaging technique with very good spatial resolution that monitors brain activity by measuring changes in BOLD signal

Magnetoencephalography (MEG)—This is a neuroimaging technique with very high temporal resolution and adequate spatial resolution. MEG monitors neuronal electrical activity by measuring changes in the magnetic field at sensors located just outside the head.

Pain neuromatrix—This is comprised of areas of the brain that respond to and process pain stimuli.

Positron emission tomography (PET)—This is a neuroimaging technique that can be used to monitor changes in blood flow (rCBF), blood volume (rCBV), or metabolism (rCMR) in the brain. PET may also be used to map specific neuroreceptors using radiopharmaceuticals.

Regional cerebral blood volume/flow (rCBV/F)—This is the amount of volume or flow of blood in a specific region of the brain; constitutes an indirect marker for brain activity.

Somatotopy—This is the mapping of touch, vibration, and heat signals coming from *different* parts of the body to distinct and specific locations in the brain's primary somatosensory cortex (SI). This somatotopic organization of SI is sometimes described as the homunculus, or "little man" in the brain.

Somatosensory evoked potential (SEP)—This is a change in EEG signal occurring after the presentation of a somatosensory stimulus; in MEG this is called a somatosensory evoked field (SEF).

Single photon emission computed tomography (SPECT)—This is a 3-dimensional imaging technique that uses a gamma ray camera to measure photon emission from intravenously administered radiopharmaceuticals.

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