The Evidence and the Promise of Brain Imaging in Acupuncture Research

By Vitaly Napadow, PhD, LAc

Abstract

Application of the scientific method to acupuncture therapy can and should test different hypotheses about how acupuncture impacts patients with various diseases. One relatively recent approach to evaluate mechanisms of acupuncture action in humans is termed “neuroimaging” and is applied to study brain response to acupuncture. Many neuroimaging technologies are non-invasive and can be readily applied in both healthy human subjects and different patient populations. Furthermore, technologies such as functional MRI (fMRI) can evaluate short-term brain responses, as well as longer-term effects. While experimental designs have, to date, been mostly reductionist, gradually, neuroimaging designs will also incorporate more naturalistic acupuncture interventions and may better inform clinical practice. However, using neuroimaging technologies, we have already learned a substantial amount about human brain response to acupuncture stimulation. Multiple studies have shown that acupuncture does not just activate somatosensory areas, but modulates many distributed cortical and subcortical (i.e., brainstem, limbic, cerebellum) brain areas. Unfortunately, the relationship of this brain response to clinical outcome measures has been less readily studied, an important question future studies need to address. Additionally, brain imaging has significantly impacted the way acupuncture is perceived within the mainstream community. Thus, it is important to keep in mind that while such scientific research might not always find what proponents of acupuncture want it to find, a solid research base for acupuncture mechanisms will be paramount if this therapy is ever to be incorporated seriously into our mainstream health care system.

Key Words: functional MRI, fMRI, neuroimaging, acupuncture, limbic, somatosensory

Introduction

If acupuncturists wish to gain greater access to patients and broader acceptance by the mainstream healthcare system, then acupuncture mechanisms of action must be better identified. Application of the scientific method to acupuncture therapy can and should test different hypotheses about how acupuncture produces clinically relevant outcomes for patients with various diseases.

Since acupuncture has been applied to so many different disorders, it is tempting (and logical) to think that acupuncture somehow taps into an overarching system in the body, which holistically mediates and regulates proper homeostasis in all the body’s different organs. Thus, when disease subverts this homeostasis, acupuncture can be used to restore proper bodily function. From decades of scientific research, the leading (but, of course, not only1) candidate for such an overarching system of homeostasis is in fact the nervous system, which permeates or influences every organ and tissue in our body. We know that the executive control of our nervous system is managed by the “central” nervous system – specifically the brain. From the very early days of acupuncture research, the brain was a prime target of investigators. Thus, while some of the methods are evolving, in many ways the target remains the same, even as we dig deeper and understand more and more about how acupuncture works.

One relatively recent approach to evaluate mechanisms of acupuncture action in humans is termed “neuroimaging.” Different technologies have been applied to produce images of brain structure and function. These images can be used to quantitatively changes in the brain, and proper experiment designs can be employed to connect these changes to acupuncture therapy2. One of the most exciting aspects of many neuroimaging technologies is that they are non-invasive and can be readily applied in both healthy subjects and different patient populations. This review updates and attempts to better explain the neuroimaging evidence for acupuncture effects. Particular focus is placed on functional MRI (fMRI), which is the technology most often applied to study human brain response to acupuncture.

Brain Imaging Technology

Different technologies have different strengths and weaknesses. Our lab has been primarily focused on using magnetic resonance imaging (MRI), which is a very rich and flexible technology and may be used to non-invasively acquire high-resolution images of both brain structure and function. Images of structure can be used to assess gray matter thickness and white matter integrity. Additionally, a special version of MRI, dubbed fMRI, may be used to assay brain activity. fMRI is sensitive to brain activity because the MRI signal is made sensitive to the oxygen content of blood—when brain areas are activated, oxygen is consumed and blood flow increases to the activated area in order to bring in fresh oxygenated blood, carry away metabolic by-products, etc.

One very important aspect of fMRI is that it is typically a comparative technique—you don’t image “the brain on acupuncture.” Instead, the brain can be imaged during needle stimulation (mechanically, electrically, etc.), and these data are compared (typically in the same scan experiment) to brain activity when the needle is not being stimulated. Positron

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emission tomography (PET), like fMRI, can make use of hemodynamic (i.e., blood flow) measures to monitor brain function. PET can also be used to monitor the response of specific neurotransmitter systems, such as endorphins, to acupuncture. However, due to its use of radioactive contrast agents, PET is limited by dosage to the number of times it can be applied in any one individual.

Both fMRI and PET have been consistently used to understand “where” processing occurs in the brain. Techniques such as electroencephalography (EEG) and magnetoencephalography (MEG) are used for mapping the brain’s electrical activity on a millisecond timescale and can tell us “when” brain areas may be active. Interestingly, EEG was one of the earliest brain imaging technologies to be applied in acupuncture research, while MEG has been the most recent. EEG and MEG are less sensitive to deeper brain areas and have mainly been applied to evaluate activity in brain regions closer to the scalp. Collectively, all of these technologies have their advantages and limitations (for an updated review see ).

and limitations (for an updated review see ) and may be used to investigate which areas of the brain are active and when they are active, thus, providing us with valuable insight into potential brain mechanisms by which acupuncture exerts its effects.

The Application of fMRI to Study Acupuncture

Acupuncture and fMRI have enjoyed a fruitful but difficult relationship. Certain aspects of acupuncture therapy make it challenging to study with scientific approaches, particularly with fMRI, while certain technical aspects of fMRI make it difficult to apply to the study of acupuncture mechanisms. Just a flavor of these challenges is enumerated below:

(1) Acupuncture is a complex intervention whose so-called “specific effects” are not well understood. Thus an agreed-upon control intervention has been difficult to implement in both clinical and basic research. Current thinking suggests that an adequate comparison group controls for all the aspects of acupuncture you do not wish to study. Thus different controls are acceptable, to ask and answer different research questions. However, pragmatic approaches, which may be sensitive to synergistic aspects of a complex intervention, do not use placebo controls and are also of interest.

(2) fMRI is inherently a low “signal-to-noise” ratio technology, meaning that the typically reported changes in brain activity range from only 0.5 to 4%, depending on the strength of the stimulus. Thus, the brain is far more actively engaged in ongoing intrinsic activity than in responding to anything we do at LI-4, for example. Moreover, clinically-relevant acupuncture stimulation (i.e., acupuncture without intense sharp pain) is relatively weak and induces brain response changes on the lower range of the scale above. The consequence of this is:

(3) Stimuli typically need to be repeated multiple times in order to improve statistical significance in fMRI data analysis. Unfortunately, while we don’t strictly know the washout period of any acupuncture stimulation effects, we do know that acupuncture sensation persists long after needle stimulation has ceased. This fact makes it difficult to ensure that the brain reaches some “pure” baseline state before the next stimulus is delivered. While longer and longer rest periods can be used between stimuli, there is a problem:

(4) Noise in the fMRI signal has a classic 1/frequency relationship—the longer you wait between stimuli, the lower your frequency, and the more noise you have to fight to pick out the true signal representing what you want—brain response to acupuncture.

(5) Acupuncture needles are typically magnetic. While stainless steel is nominally non-magnetic, the material used for acupuncture needles is commonly doped with nickel alloys, making different brands of needles more or less magnetic and potentially dangerously inappropriate for fMRI use. Our lab has obviated this problem by using pure silver and/or pure titanium needles ensuring the safety of our subjects and acupuncturists, who work near the MRI scanner’s strong magnetic field (1.5 – 9.4 Tesla).

(6) Finally, the fMRI environment does not approximate the clinical environment very well. While subjects are typically lying supine, they have their head in a confined cage-like “head coil.” Moreover, during the fMRI scan, the noise level can vary from 100 to 130dB (depending on the pulse sequence and model of scanner)—for comparison, standing 3 feet from a power saw subjects you to about 110dB, while pain begins at about 125dB). This latter problem can be mitigated by having subjects wear earplugs to suppress fMRI noise.

While this partial laundry list of challenges presents hurdles to the application of fMRI for acupuncture research, these hurdles are certainly not insurmountable. Technical advances such as open magnets, “silent” fMRI pulse sequences, custom head coils, etc. continue to advance the field and address some of the concerns enumerated above.

Furthermore, research groups have come up with innovative experiment designs also aimed to work around some of the above issues. For instance, instead of imaging during the acupuncture intervention itself, groups have imaged brain response to a “task” before versus after acupuncture stimulation. Such “tasks” range from the innocuous (e.g., resting brain states) to noxious (e.g., pain). Such approaches can investigate both short-term responses, as well as longer term effects, by embedding neuroimaging evaluation within a clinical trial framework. These advances represent a natural evolution in a still very young field. Gradually, neuroimaging experimental designs will incorporate a more naturalistic acupuncture intervention and will better inform clinical practice.

The Evidence—what have we learned about acupuncture from neuroimaging?

Studies to date have focused on evaluating acupuncture needle stimulation and have partially converged on some consistent findings. Human fMRI studies suggest that stimulation of different acupoints can elicit overlapping response within multiple cortical, subcortical/limbic, and brainstem areas. This includes primary and secondary somatosensory cortices (SI, SII), which support initial localization and early qualitative characterization of somatosensory stimuli. While it is nice to see that acupuncture can affect brain response, this result is not very surprising, as any tactile stimulus over the skin should produce activation in these areas.

However, brain regions rarely function in isolation and other brain networks have also been found to be modulated by acupuncture stimulation. Limbic brain regions (e.g., hypothalamus, amygdala, anterior and posterior cingulate cortex (ACC and PCC), hippocampus) are recruited. The hippocampus and amygdala putatively support learning and memory while the amygdala may also...
play a dominant role in affective encoding (i.e., mood). Both structures are directly connected to the brain stem 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 reported an integrated limbic system down-regulation in response to acupuncture, specifically if "deqi" sensation is induced. This hypothesis stems from the observed fMRI signal decrease in response to acupuncture needle stimulation and has been at least partially corroborated by other investigators.

Furthermore, many acupuncture studies have demonstrated modulation of anterior and posterior insula, and the prefrontal cortex. The anterior insula has been implicated in the emotional-affective dimension of pain and may also play a role in therapeutic acupuncture. Finally, the prefrontal cortex, which has multiple distributed connections with the limbic system, is likely to play an important role in higher, executive and expectancy-related modulation of pain processing. Response in dorsomedial and dorsolateral prefrontal cortex has been specifically related to deqi sensation, and may support increased attention to needle stimulation, which we have hypothesized increases internal bodily awareness. This enhanced connection between the patient and their own body, something anecdotaly common with patients in my own clinic, may in fact be a mechanism for clinically relevant analgesia in a subset of chronic pain patients. Another potential mechanism comes from the evaluation of resting brain states before versus after acupuncture stimulation. We found that the so-called “default mode network” (DMN) in the brain has greater resting connectivity to pain (ACC), emotion (amygdala), and anti-nociceptive (PAG) brain regions after real, but not sham, acupuncture. This result suggests that the DMN may act as a substrate to functionally connect pain processing with anti-nociceptive (pain down-regulatory) regions of the brain.

Collectively, neuroimaging data strongly suggest that acupuncture does not just activate somatosensory areas, but 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 anti-nociceptive mechanisms and are part of the “pain neuromatrix.” In fact, 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 neuroplasticity seen in chronic pain states.

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 balance toward greater parasympathetic outflow, thus 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. In sum, human neuroimaging studies have shown that acupuncture may exert its therapeutic effects on pain by modulating a distributed network of brain areas involved in sensory, autonomic and cognitive/affective processing.}

The Promise—future goals for acupuncture neuroimaging

The main problem with most acupuncture neuroimaging studies to date is actually not that “true” acupuncture has or has not been incorporated into the study design, but that we don't know whether the brain response patterns that have been reported have any relevance to clinical pathology in patients. In fact, brain response to needle stimulation, no matter how innovatively assessed and how interesting the potential mechanisms suggested, may just be an “epi-phenomenon” without any relevance to clinical outcome. The only way to address this question is to correlate acupuncture neuroimaging assessment to clinical outcomes. Such so-called “translational” approaches (which connect basic science to clinical outcomes) require neuroscientists and experimentalists to work collaboratively with clinicians and acupuncturists who can assess patient-centered outcomes. Several preliminary studies have taken this approach with stroke, fibromyalgia patients, and carpal tunnel syndrome patients, and I am sure that even more studies will be reported in the coming years.

Brain imaging has significantly impacted the way acupuncture is perceived within the mainstream community in the United States. For example, our lab's imaging findings have been featured in newspaper stories and on popular television programs such as Good Morning America. In addition, acupuncture neuroimaging results have been relayed to Congress in testimony by the National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM), which funds acupuncture research. In short, scientific research might not always find what proponents of acupuncture want it to find, but a solid research base for acupuncture mechanisms will be paramount if this therapy is ever to be incorporated seriously into our mainstream health care system.

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Vitaly Napadow is an assistant professor at Harvard Medical School and the Department of Radiology at Massachusetts General Hospital, Boston, MA. He received his PhD in biomedical engineering from the Massachusetts Institute of Technology in 2001. In 2002 Vitaly graduated from the New England School of Acupuncture. He practices acupuncture at Brigham & Women’s Hospital Pain Management Center. His research interests focus on evaluating brain processing of chronic pain states and brain response to potential therapies such as acupuncture. Dr. Napadow has more than 30 publications in leading peer-reviewed journals, with over 20 publications specifically related to acupuncture neuroimaging. He may be reached at vitaly@nrm.mgh.harvard.edu.