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Review

# Investigating Acupuncture Using Brain Imaging Techniques: The Current State of Play

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We have systematically researched and reviewed the literature looking at the effect of acupuncture on brain activation as measured by functional magnetic resonance imaging and positron emission tomography. These studies show that specific and largely predictable areas of brain activation and deactivation occur when considering the traditional Chinese functions attributable to certain specific acupuncture points. For example, points associated with hearing and vision stimulates the visual and auditory cerebral areas respectively. Pain, however, is a complex matrix that is intimately intertwined with expectation. Acupuncture clearly affects this matrix in both specific and non-specific manner that is consistent with its specific clinical effects, as well as the effects of expectation on pain relief. This article summarizes the current imaging literature.

**Keywords:** acupuncture – imaging – review

## Introduction

Interest in investigating acupuncture with various imaging techniques have been growing since the mid 1990s. The development of imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have opened a 'window' into the brain that allows us to gain an appreciation of the anatomy and physiological function involved during acupuncture in humans and animals non-invasively. Researchers such as Alavi (1) and Cho (2) were among the first to publish in this area. Their initial observations have subsequently been enhanced and further developed in relation to point specificity, effects in hearing, nausea and more generalized analgesic effects in both animal models and human experimental pain.

This review is not systematic but it is a comprehensive narrative review of the available literature with respect to imaging and acupuncture with the aim of defining both the current state of play and a future research strategy. One of the major problems within the field of acupuncture and neuroimaging is the necessity for very careful and thoughtful trial design so that the researcher only asks one question at a time. With these two techniques (PET and fMRI), brain images are acquired while a subject/patient is performing a task. Brain images of each individual are then transformed to 'brain activation maps' using statistical software such as Statistical Parametric Mapping (3). Maps of individuals across the group are then collated and compared to another group or another task in the same group. Maps of 'difference of activation' are thus created enabling researchers to evaluate difference between tasks in a group of subjects or differences in activation between groups performing the same task. Differences of activation may be produced by both relative activation and deactivation of specific areas of the brain.

The advent of fMRI and PET allows us to see brain activation in a variety of clinical conditions, but it is often difficult to interpret these images and relate them to specific neurology when the non-specific effects of the treatment process also seem to influence brain activation and may be of great clinical relevance. While there has been some correlation with clinical outcome in experimental pain, there are no publications that to date have correlated clinical outcome in pathological conditions (such as osteoarthritis) with definitively induced acupuncture changes in brain activation. However, imaging

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offers us the potential for a far greater understanding of the neurophysiology of acupuncture, but its interpretation and clinical relevance remains problematic. Furthermore, experiments with imaging must be firmly grounded in a very thorough understanding of the sensations elicited by acupuncture as well as the neurophysiology and biochemistry that underpins the treatment. They must also be conducted in conjunction with clinicians who understand the modality and in association with clear clinical outcome criteria. This work was in its infancy when it was previously reviewed by Joannie Shen (4) some 5 years ago and our review summarizes and incorporates recent important advances.

## Identification of the Literature

The papers, and therefore the literature, reviewed in this article have been derived from a combination of systematic searching within the common databases (EMBASE, PubMed, AMED, CINAHL, MEDLINE and CISCOM), as well as the use of personal contacts within the field simply to make sure that we have not omitted any major publication. However, we are only too aware that this is a rapidly changing field, and while we believe that this paper summarizes our current knowledge of brain imaging within acupuncture and draws out some of the important principles, we may not have been able to identify every single publication in this area.

## Traditional Chinese Medicine Revalidated: The Effect of Specific Acupuncture Points

Cho *et al.*'s (2) work was the first to identify that specific areas of the visual cortex appeared to be activated in response to acupuncture points in the foot in the same way as it would respond to a stimulation from a light source shone into the eyes. The main point used to stimulate visual cortex was UB67; Cho and co-workers claimed that a difference in character of the subjects (i.e. Yin or Yan) accounted for variations in the pattern of response. This was point-specific and so could not be reduplicated through similar stimulation in a non-acupuncture point. A number of other visually active acupuncture points were manipulated and produced a similarly predictable response in accordance with traditional Chinese principles. The stimulation of auditory-related points similarly produced activation of the auditory cortex (5). Although the studies only involved small numbers of volunteers, the science appeared convincing. Further reduplication by others (6,7) and also continuing work by Cho and co-workers seems to support this hypothesis. Siedentopf *et al.* (8) suggests similar phenomena to needle puncture may be elicited by soft laser acupuncture, a finding supported by Litscher *et al.* (9). However, Gareus *et al.* (10) throws some doubt on Cho's findings. Therefore, while it appears that it is probable that acupuncture-like stimulation of UB67 triggers specific activation of the occipital cortex, it is by no means a uniform and consistent finding.

Li *et al.* (11) looked at the possibility that a similar phenomenon may be elicited by using points specific to language in 17 healthy Mandarin speaking Chinese volunteers. They suggest that there is stronger activation in the left hemisphere and that electrical stimulation of two acupuncture points (implicated in languages, i.e. SJ8 and Du15) produced significant activation in an appropriate area of the brain, the right inferior frontal gyrus and in the left and right superior temporal gyrie. However, activation was not seen in the left inferior frontal gyrus and it is also clear that not all acupuncturists would agree that these points are related to language. Non-acupuncture points did not produce significant brain activation, so these researchers concluded that specific acupuncture points may have language-specific effects. Yoo *et al.* (12) noted that PC6 produces a well documented clinical response to acupuncture in nausea. They were able to demonstrate consistently that acupuncture-specific neural substrates are selectively activated in the left superior frontal gyrus, the anterior cingulate gyrus and the dorsomedial nucleus of the thalamus as well as nausea-specific substrates in the cerebellum. This did not occur with penetrating sham needling at a non-acupuncture point, thus suggesting a PC6-specific effect that potentially correlates with proven clinical effectiveness. Yan *et al.* (13) have demonstrated point-specific patterns using fMRI in 37 healthy volunteers while needling LI4 and Liv3 as compared to sham points. Common activation areas for LI4 and Liv3 were in the middle temporal gyrus and cerebellum, along with deactivation areas in the middle frontal gyrus and inferior parietal lobule when compared with sham points. Acupuncture at Liv3 evoked specific activation in the post-central gyrus, posterior cingulated, parahippocampal gyrus, BA 7, 19 and 41, but deactivation at the inferior frontal gyrus, anterior cingulated, BA 17 and 18 when compared with sham. LI4 evoked specific activation in the temporal lobe but deactivation in the precentral gyrus, superior temporal gyrus, pulvinar and BA 8, 9 and 45 when compared with sham. They suggest that these different patterns may be related to specific therapeutic effects, although it is difficult to justify this based on data obtained from healthy volunteers receiving one acupuncture treatment.

## Pain Processing

A variety of imaging studies have been published that look at the whole mechanism behind pain processing. A number of cortical areas have been shown to be involved in pain processing, these include the primary somatosensory cortex, the secondary somatosensory cortex, the insula, the anterior cingulate and the prefrontal cortex (14) as well as the hypothalamus and periaqueductal gray (PAG); the pain matrix. Derbyshire *et al.* (15) looked at 12 healthy volunteers using PET and subjected them to experimental pain with a $CO_2$ laser. The pain was classified as: 'just painful', 'mildly painful' and 'moderately painful'. Again a wide range of active regions were shown to be responsive to pain, including the prefrontal inferior parietal and premotor cortices as well as the thalamus insula, primary somatosensory cortex and the ipsilateral perigenual cingulate cortex (15). Tracey *et al.* (16) have clearly defined the distraction techniques that may modulate clinical pain and activate the PAG. Petrovic *et al*. (17) have demonstrated that placebo analgesia involves the rostral anterior cingulate cortex and brainstem, again suggesting (through the use of PET) that both opiate and placebo analgesia are associated with increased activity in these endorphin-rich regions. Wager *et al*. (18) have found that placebo analgesia is related to decreased brain activity in pain-sensitive regions and that the effect of placebo analgesia is associated with expectation. The regions involved are the thalamus, insula and anterior cingulate cortex. These demonstrated increased activity during the anticipation of pain and diminished activity in the expectation of pain relief delivered by placebo. Fuente-Fernandez *et al*. (19) have also demonstrated that dopamine release in the nucleus accumbens is related to the expectation of reward, this may be involved in the placebo response to pain.

## The Modulation of Pain with Acupuncture

Studies in this area have been conducted in both animal and human environments with experimental pain in healthy subjects. Chiu *et al*. (20) used three acupuncture points in rats to induce analgesia. They noted increased brain activity in the hypothalamus which was dependent on the extent of the stimulation. Liu *et al*. (21) also noticed a dramatically increased acupuncture-induced activation of the PAG in humans with both Li4 and a non-acupuncture point. It appeared PAG activation, while present as a consequence of non-acupuncture point stimulation, was substantially enhanced by stimulation of a true acupuncture point. Wu *et al*. (22) argues that acupuncture designed to provide analgesia involves the pain-related neuromatrix; this investigative group employed fMRI to evaluate the effects of electroacupuncture, mock electroacupuncture, minimal acupuncture and sham electroacupuncture on either real acupuncture points or non-acupuncture points in human healthy volunteers. Stimulation of real acupuncture points with electroacupuncture elicited significant activation over the hypothalamus, primary somatosensory motor cortex and rostral anterior cingulate cortex. The superior temporal gyrus and medial occipital cortex seemed to respond to minimal electroacupuncture, sham electroacupuncture and real electroacupuncture. Wu *et al*.'s group concluded that the hypothalamus and limbic system modulated the effects of electroacupuncture as an analgesic in a fairly non-specific manner. A similar conclusion was arrived at by Zang *et al*. (23), Wu *et al*. (24), Hui *et al*. (25), Kong *et al*. (26) and Hsieh *et al*. (27).

Fang et al. (28) looked at the method of needle stimulation to see if different areas were activated or de-activated in response to the nature of the stimulation. While they demonstrated similar areas of general activation in healthy subjects using Liv3 and G40, they were unable to demonstrate that specific needle manipulation techniques modified the response in the appropriate neuronal substrates. Biella *et al*. (29) also showed similar areas of general activation from acupuncture, which correlate closely with a wider pain matrix that have already been identified as modulating and managing expectation, placebo and pain. These papers and their main findings are summarized in Table 1.

It appears that there are substantial overlaps between the pain matrix that have already been identified within the brain and its response to placebo acupuncture and pain. There is also considerable overlap between the areas of placebo response and expectation and acupuncture, although a recent study of brain activation with PET involving patients in pain, by Pariente *et al*. (30), have clearly identified different areas of activation in response to touch with a needle, the expectation of acupuncture and real acupuncture, suggesting that real acupuncture not only activates areas associated with expectation and placebo response but also the ipsilateral insula that may represent a specific response to acupuncture in patients presenting with osteoarthritis pain. However, it does appear that there is a relatively 'plastic' pain matrix within the brain that is equally responsive to placebo and acupuncture with many overlapping areas. This might correlate quite closely with the large non-specific effects observed from many analgesic treatments, including acupuncture, in a clinical context (31,32).

## Discussion

Lewith and Vincent (33) have previously suggested that it may be appropriate to consider different underlying mechanisms behind the observed effect of acupuncture in different types of conditions. The preliminary data from neuroimaging would tend to support this observation in that specific neural substrates may be activated by the use of specific acupuncture points associated with widely acceptable traditional Chinese medical, non-painful, indications. However, in pain a far less specific response emerges containing overlapping neural substrates activated by both placebo and expectation.

These studies generally involve small numbers of subjects because of economic and practical situations and also raise a number of quite different specific issues. Should we be considering studies using imaging with respect to non-painful conditions in a different context to those looking at imaging in either experimental or clinical pain? The vast majority of studies on imaging and pain have been conducted in experimental pain, can we legitimately generalize from experimental pain into the clinical arena of chronic benign painful conditions? Imaging may allow us to differentiate between expectation, placebo and real acupuncture as Pariente et al. (30) suggest. However, considerable further investigation will be needed if we are to be anything more than tentative about these suggestions. Both technology and our understanding of neuroimaging are very much 'in development'. We must accept that this is a rapidly evolving field which is difficult to interpret with clarity.

It is quite possible that specific acupuncture points for non-painful conditions, such as PC6 in the treatment of nausea, may activate or inhibit very specific neuronal substrates. This

**Table 1.** Summary of imaging studies, their subjects and conclusions (in date order of publication)

| Author | Type | *n* | Subject type | Finding | Condition | Intervention |
|---|---|---|---|---|---|---|
| Alavi *et al*. (1) | PET | 5 | Pain | Reduction of thalamic asymmetry | Pain | RA |
| Cho *et al*. (2) | fMRI | 12 | HV | Point-specific effect for vision-related acupoint | NP | RA |
| Wu *et al*. (24) | fMRI | 9 | HV | Activation of pain matrix (primary and secondary somatosensory cortex, insula, anterior cingulate prefrontal cortex, hypothalamus and PAG) | Pain | RA |
| Cho *et al*. (5) | fMRI | ? | HV | Point-specific effect for auditory-related acupoint | NP | RA |
| Hui *et al*. (25) | fMRI | 13 | HV | Activation of pain matrix | Pain | RA |
| Hsieh *et al*. (27) | PET | 16 | HV | Both activate insula, anterior cingulated, cerebellum. Hypothalamus only activated by RA | Pain | RA versus sham |
| Biella *et al*. (29) | PET | 13 | HV | Anterior cingulate cortex activated by RA | Pain | RA versus sham |
| Lee *et al*. (7) | fMRI | 24 | Rats | cFos expression in visual cortex in response to stimulation of vision-related acupoint | NP | RA |
| Siedentopf *et al*. (8) | fMRI | 18 | HV | Point-specific effect for vision-related acupoint | NP | Laser |
| Gareus *et al*. (10) | fMRI | 21 | HV | No point-specific effect for vision-related acupoint | NP | RA |
| Wu *et al*. (22) | fMRI | 15 | HV | EA activated the pain matrix more than sham EA | Pain | EA versus MEA versus Sham EA versus Mock EA |
| Kong *et al*. (26) | fMRI | 11 | HV | Both activate pain matrix | Pain | RA versus EA |
| Li *et al*. (6) | fMRI | 18 | HV | Point-specific effect for vision-related acupoint | NP | RA versus EA |
| Li *et al*. (11) | fMRI | 17 | HV | Point-specific effect for 'language'-related acupoint | NP | RA |
| Chiu *et al*. (20) | fMRI | 38 | Rats | EA produced a greater activation of pain matrix than other interventions | Pain | Sham versus Sham EA versus EA |
| Zhang *et al*. (23) | fMRI | 48 | HV | Activation of pain matrix | Pain | EA |
| Litscher *et al*. (9) | fMRI | 1 | HV | Increased activity of visual cortex on use of vision-related acupoint | NP | Laser |
| Yoo *et al*. (12) | fMRI | 12 | HV | Point-specific effect for nausea | NP | RA |
| Liu *et al*. (21) | fMRI | 7 | HV | Activation of PAG | Pain | RA |
| Fang *et al*. (28) | fMRI | 15 | HV | Point-specific effect from RA | Pain | RA versus sham |
| Pariente *et al*. (30) | PET | 14 | OA | Specific effect for RA. Expectation elicits non-specific physiological effect | Pain | RA versus SN versus OP |
| Yan *et al*. (13) | fMRI | 37 | HV | Specific effects for Liv3 and LI4 | | |

HV, healthy volunteer; OA, patient with Osteoarthritis; NP, non-pain; RA, real acupuncture; Sham, needling at a non-acupoint; EA, electroacupuncture; MEA, minimal (penetration) electroacupuncture; SN, Streitberger needle; OP, overt placebo.

may support, as Cho suggests, the assumptions inherent within traditional Chinese medicine. The effects of acupuncture in pain and possibly also in addiction may be far less point-specific as has been previously suggested from the available clinical evidence (33). To date, the limited work available from brain imaging would suggest that this might provide a reasonable series of hypotheses through which to investigate the effects of acupuncture using fMRI and PET.

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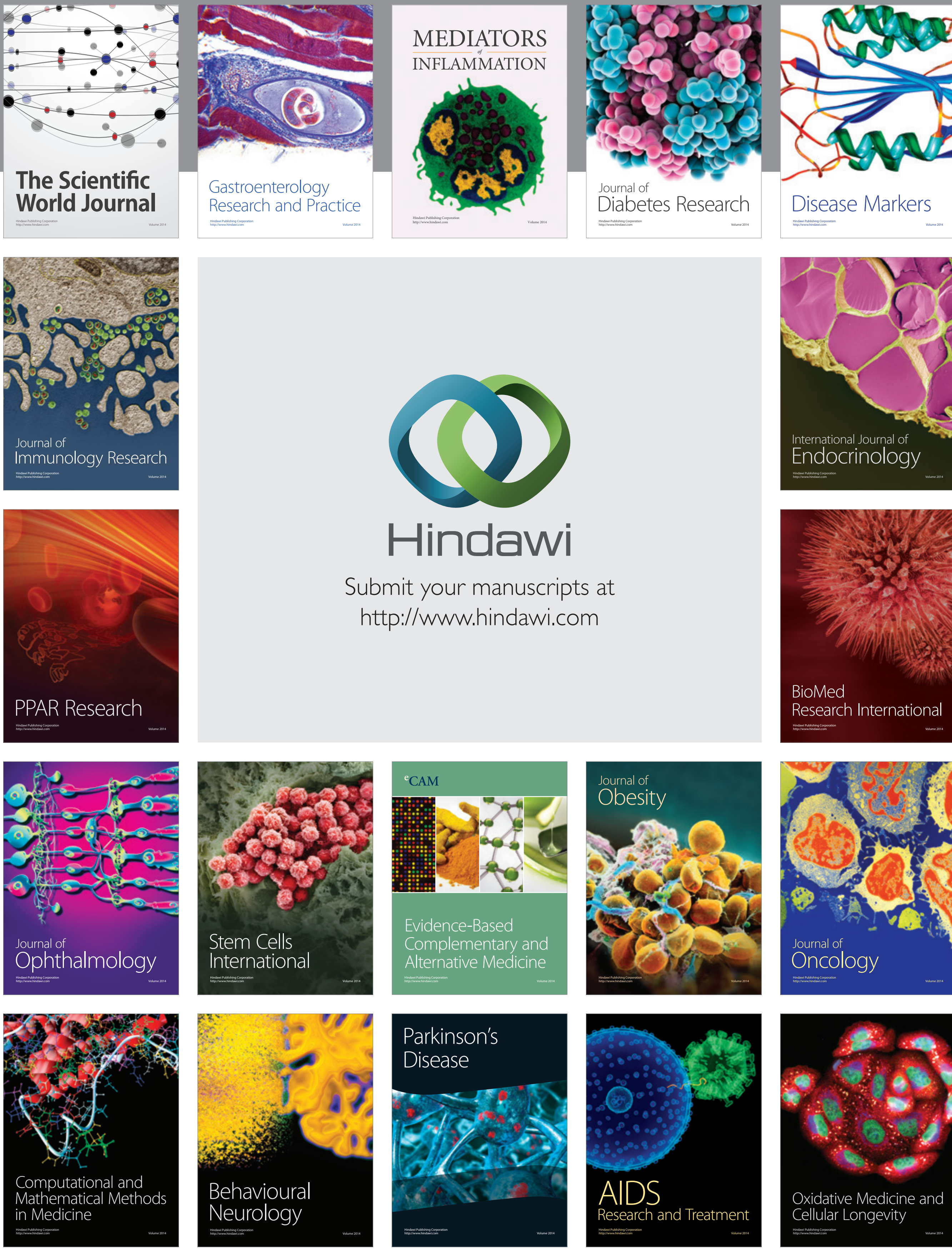
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