The limbic system and default mode network—how does acupuncture affect it?

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The past 30 years has seen an explosion in research in the physiology of acupuncture from all regions of the world. Much of the research has focused on the response to pain in the nervous system to acupuncture. This is an extremely difficult system to study due to the vast number and variability of transmitters and reflexes involved. Through advances in the technology of neurologic studies, acupuncture is gaining credibility in the medical world and today many highly regarded medical institutions are actively involved in further study and employment of this ancient art. This article explores some of the highlights of the evolving understanding of acupuncture by use of functional magnetic resonance imaging (fMRI) of the limbic system and associated brain responses.

The limbic system basically deals with three main functions: emotions, memories, and arousal. It sits above the brainstem and connects the primitive part to the higher cerebral centre. Three major parts include the thalamus (detects and relays information from the senses); the hypothalamus (regulates autonomics, respiration, metabolism, and endocrine functions); and the amygdala (responds to smell, processes fear, stores memories, and involves sexual arousal). Homeostasis, self-preservation, and procreation are the key functions of the limbic systems activities.

From the time of Pavlov to the 1960s, a dog's behaviour was judged to be a simple response to punishment or reward cues. However, neuroscience research has shown that dogs and all mammals experience emotions much as we do. Professor Christine Zink of the Department of Molecular and Comparative Pathobiology at Johns Hopkins School of Medicine has written (www.examiner.com/article/the-dogs-limbic-system-and-brain): "dogs experience emotions such as happiness, enjoyment, pride, confusion, affection, embarrassment, anxiety, anger, surprise, depression, and even emotions such as resignation and distrust. Through their positive emotions, dogs build enduring personal resources such as coordination, problem-solving, and social relationships with dogs, other species, and people. Through negative emotions dogs are protected from situations that may be dangerous." Although other mammals have more or less intelligence we recognise the same emotions expressed by their behaviour, once their behaviour is understood.

An important distinction to keep in mind between humans and animals is the ratio of the limbic system to the higher centres; the animal's limbic system is a greater proportion of its brain and their behaviour is therefore much more emotion based; their limbic system connections with the higher centres modulate instinct and survival mechanisms. One hopes humans continue to improve the handling and keep of animals by better understanding their emotions. Animal behavioural studies improve our understanding of their body language – especially important for veterinarians.

One recent example is from Italy: "Asymmetric tail-wagging responses by dogs to different emotive stimuli," by Quaranta, Siniscalchi and Vallortigara published in Current Biology.

Although there is some debate over which structures and functions are included in the Limbic System, a landmark study was performed on rhesus monkeys having their hippocampus and amygdala removed (Kluver & Bucy,1939). The result was an immediate loss of fear or anger. Science has not come close to a full understanding of the integration and functional roles of the limbic system or the rest of the brain – understandable as it contains over 70 billion nerve cells, each with approximately 1000 connections and enormous plasticity capacity.

Josephine C. Moore, Ph.D. (Professor Emeritus of Neuroanatomy, University of South Dakota School

1–5. Acupuncture is much more than needle stimulation: voice, touch, empathy, posture, respect – elements of the treatment before the 1st needle is applied. Animal response is often immediate – signs of acceptance, tranquility, tolerance, sleepiness. One suspects a great deal of the animal response to acupuncture is via the limbic system.

of Medicine, 1966–1993), was a pioneer in the field of childhood development & occupational therapy. She reported: "animal research seemed to provide a great deal of insight into the complexities of the limbic system in relation to man's behavioural mechanisms. Limbic is a descriptive term, meaning border or the outside edge of a structure. If one examines the medial view of the human brain, the limbic cortex forms an almost complete ring or border of grey matter around all of the deeper structures of the brain."

Professor Moore noted that excessive emotional stress producing fear causes the loss of homeostatic balance and exhausts the entire nervous system if not resolved in time (this is a concept clearly recognised in Chinese Medicine for thousands of years). She also stated that in all gregarious animal species the most important emotional drive is "to love and to be loved, to touching, fondling, communicating, and acceptance". Early environment in the young is clearly critical to the establishment of the limbic responses & memories that lead to successful coping and a balanced (Yin/Yang) life. The relationship of acupuncturist to patient involves trust, touching, acceptance to the needle, affection, empathy and I dare say, love between the two.

One striking feature of the limbic structures is the complexity of the fibre connections within the system and to adjacent parts of the brain. Compared to other brain regions it has a circular circuitry causing feedback and reverberation, leading to long lasting reactions that are reinforcing. Given that the limbic system and the brain is very complex and still poorly understood, let us examine the acupuncture role from a relatively simplified point of view. I think we can all appreciate the relevance of the emotions in association with homeostatic functions.

The first papers (of approx. 300) on the studies of acupuncture and the limbic system start in 1976 (Jacobs et al). These experiments relied on the use of invasive brain implants and selective lesions in discrete areas of the brain and spinal cord. This work led to the conclusion that acupuncture responses include reducing the affective (emotional) component of pain. This is very often made very obvious by animal responses.

Through the 1980–1990s many studies focused on the neurotransmitters operating at various levels in the brain, especially those involved in acupuncture analgesia. A huge leap forward came about in the late 1990s from the use of fMRI studies of subjects during acupuncture and first published on the limbic system responses in 2000 (Hui et al).

A closely linked brain system identified by fMRI and also heavily involved in acupuncture responses is called the *Default Mode Network* (DMN). The DMN includes the prefrontal cortex, precuneus, lateral parietal and temporal regions (Otti A,

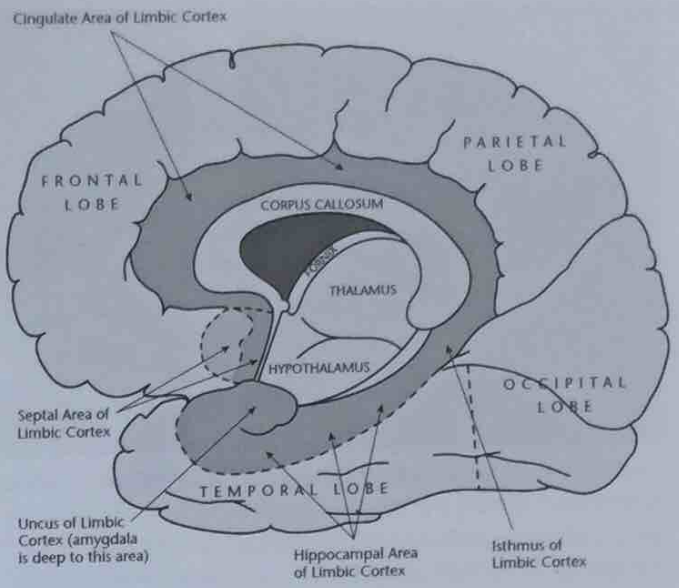
Noll-Hussong M. 2012). This integrates several aspects of inner life matters like body states, emotions, and memory and is intimately linked with the Limbic system. The DMN is a "task negative" network, i.e. is inactive when the mind is occupied with tasks; it is active in resting states and is contemplative, reflecting on one's emotions, moral and social evaluations, and empathy to others. This is a very recent concept in brain studies – prior to 2007 there were only 12 publications on the DMN and from 2007–2014 there were 1384. It has much relevance to studies of mental illness and chronic pain and has become recognised as an important, even a core aspect of acupuncture responses.

Resting fMRI in male adolescents with Conduct Disorder (persistent antisocial and aggressive behaviour) as well as patients with chronic depression and chronic pain, shows decreased functional connectivity in the DMN correlated to social cognition, as well as perceptual network systems (Lu et al. 2015). The intensity of chronic pain is highly correlated with abnormal neural plasticity causing changes in the functional connectivity of brain areas. Acupuncture can restore this functional connectivity. One can relate this to the common experience in veterinary acupuncture of resolving anti social and aggressive behaviours, and restoring signs of well being, often in animals presented as having purely behavioural rather than undetected chronic pain issues.

I wish to review some of the findings of these studies and how they contribute to present day understanding of acupuncture. First, it is helpful to visualise the technique of fMRI of acupuncture responses to understand the opportunities as well as limitations of this very advanced neurologic investigation. A video was produced by leading researchers of this procedure at the Harvard Medical School & made available online (Hui K et al, 2010 http://www.jove.com/details.php?id=1190).

Clearly this fascinating and informative imaging holds many promises, but also requires caution in interpretations. Some of the highlighted concerns include:

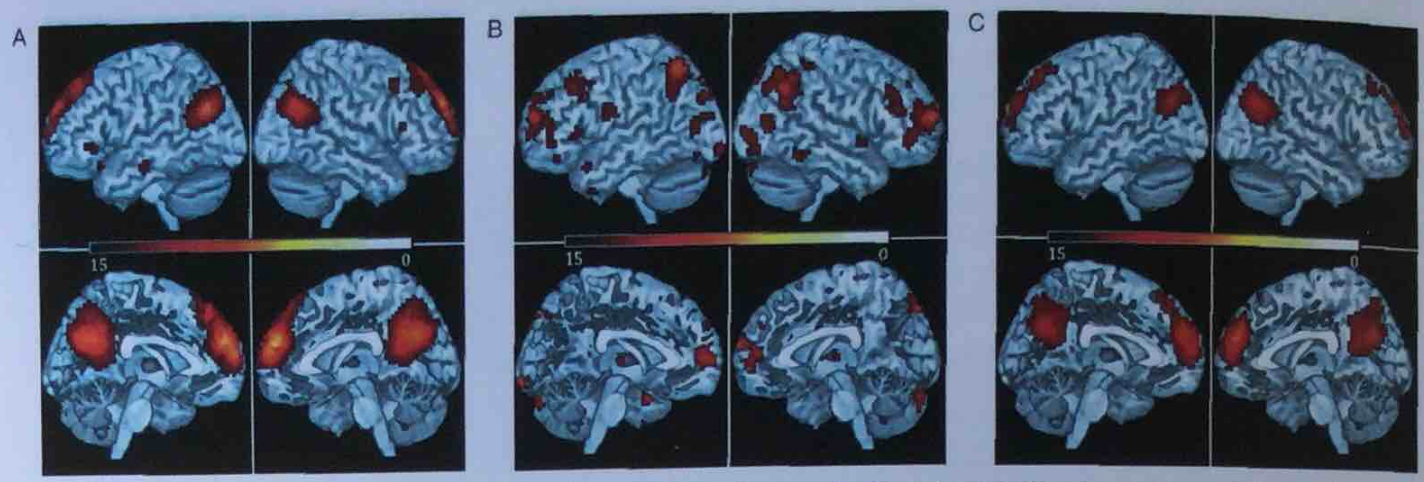
- Structures such as the amygdala, hippocampus, and ventral medial prefrontal cortex are particularly susceptible to artefacts.
- Head movement, swallowing, and respiration cause motion artefacts
- Differences in loss of signals between scanner models with similar field strength and with a similar MRI sequence for data collection.
- Subjects must relax and remain still and comfortable for extended periods during scanning at pre-treatment, during acupuncture, and some period after (total ~ 2 hrs).
- Rats, monkeys and dogs have been trained to lie still in MRI, but this still requires head & body restraints and may affect responses due to stress from immobilisation as well as interventions.
- Spatial resolution limits: e.g. the amygdala has over 20 discrete areas which cannot be delineated.



6. Limbic System Figure 1: Schematic of Limbic Structures – Moore JC. Behavior, Bias, and the Limbic System; Am J of Occupational Therapy, 1976.

To examine more closely the functional connectivity effects of acupuncture, Egorova, Gollub, & Kong (2015) at Harvard Medical School looked at the brain patterns in chronic pain patients with knee osteoarthritis and their responses to acupuncture. They found that chronic pain is associated with increased attention to pain, emotional rumination, nociceptive memory and avoidance learning, resulting in brain connectivity changes, specifically affecting the *periaqueductal gray* (PAG), *medial frontal cortex* (MFC) and bilateral *hippocampus* (Hpc). They also demonstrated that the PAG–MFC and PAG–Hpc connectivity in patients with chronic pain correlated with clinical severity scores and further show that verum (true) acupuncture-induced improvement in pain scores (compared to sham) is related to the modulation of PAG–MFC and PAG–Hpc connectivity in the predicted direction.

In this study patients had either unilateral or bilateral knee pain and were randomly assigned to one of 3 groups: 1) verum acupuncture at 6 acupoints, 2) verum at 2 acupoints, or 3) sham at 6 acupoints with a Streitberger needle. There were 2 treatments per week in weeks 1 & 2, then 1 per week for a total of six treatments. After a



7. Acupuncture treatment of chronic low back pain reverses an abnormal brain default mode network in correlation with clinical pain relief. Lie et al. 2014 Acupunc in Med.

(A) The default mode networks (DMNs) of the healthy volunteers during rest comprised the inferior parietal lobule, posterior cingulate cortex and medial areas of the inferior, middle and superior frontal gyri, and the precuneus.

(B) The DMN connect ivities in patients with chronic low back pain (cLBP) before treatment were reduced in the dorsolateral prefrontal cortex, medial prefrontal cortex, anterior cingulate gyrus, and precuneus compared with the control group.

(C) After treatment the DMNs of the patients with cLBP were almost identical to those of the control group.

pre-treatment brain scan, they were subsequently scanned during treatments at week 1, 3, & 6. The verum 2 point acupuncture was performed at ST35 & Xiyan with added GB34 & 39, SP6 & 9 in the 6 point group. The sham group received Streitberger stimulation at 6 non points in the lower limb located off any classical channels. All treatments lasted about 25 minutes and deqi was elicited in both verum groups; patients were blinded to which treatment they received and received no other treatment during the trial.

PAG–Hpc connectivity was negatively correlated with baseline pain scores (the lower the connectivity, the better the pain score) and this connectivity decreased following repeated verum acupuncture, resulting in pain score improvement. PAG–MFC connectivity was positively correlated with knee function scores (the lower the connectivity, the worse the function score), and it decreased in subjects who received sham acupuncture, also resulting in minor worsening in the function score. In contrast, the verum group had improved PAG–MFC connectivity level together with increased function scores. These results suggest that repeated verum acupuncture might reverse chronification and the associated abnormal functional connectivity in patients by interrupting persistent nociception and reducing attention to pain.

Chronic pain has been conceptualised as a type of long-term learning characterised by accumulation of nociceptive memory and the inability to extinguish negative emotional associations like anxiety, in which both Hpc and mPFC are involved. The repeated aspect of the acupuncture treatment could be crucial for this process of pain-related re-learning, possibly through the immediate pain relief with each verum acupuncture session boosting expectation and introducing positive re-assessment of the pain state. As verum acupuncture was associated with stronger deqi sensations, it is possible that it activated the descending pain modulation system, initiating the release of endogenous opioids and inhibiting nociceptive signalling from the periphery, maintaining subjects' expectancy and leading to pain improvement as the treatment progressed. In contrast, high PAG–Hpc connectivity level in the sham group could indicate that no prediction or pain behaviour update took place, as subjects did not experience pain relief from session to session, apart from the non-specific treatment effects — expectation and "placebo" that decreased over the course of treatment. This speculation is further corroborated by the decrease in the PAG–MFC connectivity (associated with declining joint function) in the sham group. Based on these findings, pain reduction during repeated verum acupuncture in patients reverses chronification by updating nociceptive memory, while sham acupuncture, relying on expectation alone, fails to maintain this expectation effect in the absence of actual pain relief.

Another key aspect of pain chronification related to pain learning is increased attention to pain and aberrant default mode network (DMN) connectivity in chronic pain conditions, suggesting an inability to disengage from attending to painful sensations (emotional rumination). This study did not find a distinction between the verum 2

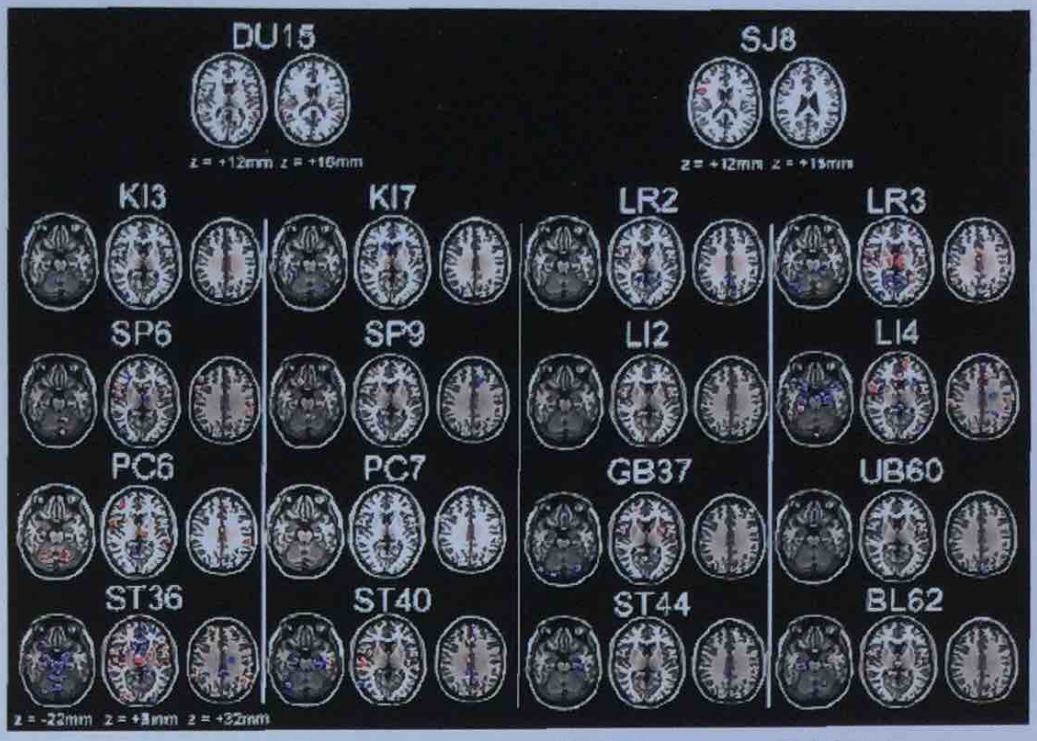
points acupunctured vs 6 points acupunctured treatment groups in the connectivity analysis, or in behavioural differences in the clinical outcome between the two groups. In this trial a chronic local problem was effectively treated with simple minimal local points acupuncture. Might we be over-complicating our acupuncture treatments in similar conditions?

On the comparison of sham vs true acupuncture one must be very careful in drawing conclusions due to the variety of sham acupuncture controls used (e.g. non penetrating vs penetrating; near vs distant to the "real point"), and a lack of consensus on what constitutes a suitable sham (or placebo). Even the ethics of administering sham procedures involving needle penetration are a questionable matter, or an outright unethical matter in clinical trials as discussed by Miller & Kaptchuk (2004).

As an example of a sham acupuncture study of brain responses – 80 rats were divided into a healthy control group and a group with induced Alzheimer's disease. The aim of the study was to observe brain responses in an untreated group, a ST36 needled group and a sham point (placed 5mm lateral and distal to ST36) group. The brain areas that were activated in the sham-point group were primarily centred on the bilateral limbic system, the right frontal lobe, and the striatum, whereas the activated areas in the ST36 group were primarily centred on the bilateral limbic system (pyriform cortex), the bilateral temporal lobe (olfactory cortex), the right amygdala and the right hippocampus. The authors concluded that needling at a sham point or ST36 can increase blood perfusion and metabolism in certain brain areas, and thus may have a positive influence on the cognition of Alzheimer's disease patients (Lu et al, 2014). In this case the sham point was in close proximity, the same spinal segment, and same fascia. Had the sham point been placed in the forelimb or on the trunk an entirely different conclusion may have resulted. Too often, a sham controlled acupuncture study produces misleading results due to inappropriate sham designs fostered by traditional beliefs regarding acupoint and channel specificity.

In a systematic review of studies investigating brain responses from acupuncture with fMRI there were 149 publications (from English, Chinese, Korean, & Japanese databases up to the year 2009) that met the criteria for descriptive analysis. The common brain responses recorded were modulation of the somatosensory cortex, limbic system, basal ganglia, brain stem, and cerebellum. Compared to sham, acupuncture was associated with more

deactivation in the limbic system. One variable cannot be over stated: patients with disease also show stronger responses than healthy volunteers (Huang et al, 2012). Studies performed on healthy volunteers are extremely limited in explaining the therapeutic benefits of acupuncture. This review also covers comparisons of deep versus superficial needling, different intensities of stimulation, electro-acupuncture, different sham treatments, different acupuncture points, different time points, and more.



8. Huang W, Acupoint Brain Scans Figure 2: Map of brain responses to 18 different acupuncture points. Red: activation; Blue: deactivation. PLoS ONE, 7(4): e32960. Doi:10.1371/journal.pone.0032960.

The quantity of details in these reviews cannot be covered in this article and the reader is urged to study this in greater depth on line, especially as many of these papers are now free to access via the internet. Here is an example of the detail found in fMRI scans in imaging different points.

Other important factors include the duration of needle stimulation, frequency of needle manipulation before scanning and the interval between acupuncture cessation and scanning. One study demonstrated clearly that sequential scans over 45 minutes of needle retention at ST36 with 4 minutes of manipulation followed by a 10 minute break period repeated 3 times leads to an habituation process. The first block responses were strongest and were activations of the thalamus, somatosensory cortex, and correlated areas. Subsequent responses to repeat stimulation were progressively attenuated to become deactivations at the end. Cumulative effects during an acupuncture session of 20–40 minutes reflect habituation and explains why some studies have reported more in brain activations while others report deactivations (Li et al, 2014).

Many different forms of acupuncture stimulation exist, from superficial to deep needling, minimal to strong needle manipulation, electro-acupuncture, mild to strong deqi, and so on. Thus far, it has been shown that acupuncture that elicits deqi without causing sharp pain or very strong deqi is required to achieve the desired deactivations in limbic-paralimbic-neocortical network, comprised of the default mode network, amygdala and hypothalamus – otherwise this is attenuated or reversed. Hui et al (2010) found that 71% of acupuncture and 24% of tactile stimulation (tapping by von Frey filament on the point used as sham) elicited deqi, with differences noted between the acupoints tested (mainly LI4/hegu, ST36/zusanli, and LR3/taichong). LI4 showed the most prominent response in human subjects and the amount of needle manipulation to cause deqi varies hugely between individuals. They also noted acupuncture but not tactile stimulation caused deactivations of the amygdala and hypothalamus central to the regulation of emotion, cognition, endocrine and autonomic functions.

The fMRI studies during acupuncture fosters a greater understanding of the holistic well being effects from acupuncture. Past research focused primarily on endogenous opioids and descending inhibition mechanism producing analgesia, but with advancing technology researchers are able to fill in more pieces of the puzzle. This has lead to the greater use of acupuncture within the conventional medical environment. The Evidence Based Medicine criteria is mounting for the use of acupuncture in many chronic disease conditions.

The ancient Chinese understanding of health and disease embraced the inclusiveness of all the emotions, senses, activities and the "functional connectivity" that is increasingly appreciated through the application of modern technology. Indeed, Hui et al (2010) added in their summary this statement: "With the demonstration of the

naturally occurring anti-correlated systems in the brain that interact to maintain normal functions and a state of health, it may be possible to draw analogies between yin and the deactivation of the task-negative default mode network, yang and the activation of the task-positive network, and the flow of qi and functional connectivity."

Thus far only very few traditional acupuncture points have been studied in relatively few diseases using brain imaging with much more to assess. This is likely to not only continue to foster greater use of acupuncture but also to help refine and modify how acupuncture is best used.

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