



Acupuncture, the limbic system, and the anticorrelated networks of the brain

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ARTICLE INFO

Keywords:

Acupuncture

fMRI

Limbic–paralimbic–neocortical network

Default mode network

Deqi

Amygdala

ABSTRACT

The study of the mechanism of acupuncture action was revolutionized by the use of functional magnetic resonance imaging (fMRI). Over the past decade, our fMRI studies of healthy subjects have contributed substantially to elucidating the central effect of acupuncture on the human brain. These studies have shown that acupuncture stimulation, when associated with sensations comprising *deqi*, evokes deactivation of a limbic–paralimbic–neocortical network, which encompasses the limbic system, as well as activation of somatosensory brain regions. These networks closely match the default mode network and the anti-correlated task-positive network described in the literature. We have also shown that the effect of acupuncture on the brain is integrated at multiple levels, down to the brainstem and cerebellum. Our studies support the hypothesis that the effect of acupuncture on the brain goes beyond the effect of attention on the default mode network or the somatosensory stimulation of acupuncture needling. The amygdala and hypothalamus, in particular, show decreased activation during acupuncture stimulation that is not commonly associated with default mode network activity. At the same time, our research shows that acupuncture stimulation needs to be done carefully, limiting stimulation when the resulting sensations are very strong or when sharp pain is elicited. When acupuncture induced sharp pain, our studies show that the deactivation was attenuated or reversed in direction. Our results suggest that acupuncture mobilizes the functionally anti-correlated networks of the brain to mediate its actions, and that the effect is dependent on the psychophysical response. In this work we also discuss multiple avenues of future research, including the role of neurotransmitters, the effect of different acupuncture techniques, and the potential clinical application of our research findings to disease states including chronic pain, major depression, schizophrenia, autism, and Alzheimer's disease.

Published by Elsevier B.V.

1. Introduction

The limbic system is a group of limbic, paralimbic and neocortical brain regions that together play a concerted role in the regulation and integration of cognition, affect, sensory perception, biological behavior, and autonomic, immunological and endocrine functions. The advent of functional magnetic resonance imaging (fMRI) enabled *in vivo* investigation of brain function and definition of additional brain networks. The activity of the resting brain, in particular, when challenged with a task, appears to be organized into two anti-correlated networks that regulate each other to maintain balance (Fransson, 2005; Fox et al., 2005). These networks are termed the task-positive network, which shows activation during a task relative to rest, and the task-negative network, which shows deactivation

during a task relative to rest. The regions comprising these networks are task-specific.

The default mode network is an instance of a task-negative network showing extensive deactivation when an attention-demanding task is engaged. It is described in the literature as comprising of clusters of regions in the medial prefrontal cortex, posterior medial parietal cortex and medial temporal lobe that are highly active in the awake and conscious resting state but become deactivated when exposed to external stimuli such as cognition and conceptual tasks (Binder et al., 1999; Buckner et al., 2008; Fransson, 2005; Golland et al., 2008; Gusnard and Raichle, 2001; Shulman et al., 1997). The task-positive network is comprised of the sensorimotor and attention-related cortices that become activated during goal-directed tasks (Corbetta and Shulman, 2002). Although not as extensively engaged as in the task-negative system, a few paralimbic structures such as the anterior middle cingulate, right insula and dorsal division of the posterior cingulate Brodmann area 23 constitute core regions in the anticorrelated system.

Our fMRI studies of the effect of acupuncture on the brain in normal human subjects have led us to define a task-negative network

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for acupuncture that is centered on the limbic system. We have named this network the limbic–paralimbic–neocortical network (Hui et al., 2005; Fang et al., 2008; Wang et al., 2007). Inspection of the patterns of response of this network during acupuncture stimulation reveals a striking similarity to the default mode network during attention-demanding tasks (Hui et al., 2009). The task-positive network that is anticorrelated to the default mode network in the resting brain shares a few common regions with the activation network in acupuncture, such as the sensorimotor cortex and paralimbic structures.

In this review we summarize our research, discuss the brain networks involved in acupuncture, and describe their relationships. We then discuss future research directions, including the role of neurotransmitters in acupuncture action, the difference between acupuncture methods, and the selection of and differences among acupuncture control stimulation. We then conclude with a summary of the potential clinical application of our research findings given what is currently known about several common disease states that affect the brain.

2. Our research

Over the past decade, we have built a database of fMRI scans of the brain response to traditional Chinese acupuncture at multiple acupoints in healthy adults. We have focused on three classical acupoints that are commonly used clinically for their analgesic and regulatory clinical effects, namely LI4 (*hegu*) on the hand, ST36 (*zusanli*) on the leg, and LV3 (*taichong*) on the foot (Hui et al., 2000, 2005, 2009). In our studies we have compared four minutes of acupuncture needling to five minutes of the acupuncture needle at rest, in a standard ten-minute paradigm, excluding the first minute of scanning during the first rest period to allow for baseline equilibration of the fMRI machine, (Fig. 1).

We first described the coordinated signal decreases in the limbic system in fMRI of the brain during acupuncture at LI4 in Hui et al. (2000). This partial brain imaging encompassed cortico–limbic and sensorimotor regions of special interest to the study. Our observation of decreased signal represented decreased blood flow during acupuncture needling in brain areas including the nucleus accumbens, amygdala, hippocampus, parahippocampus, hypothalamus, ventral tegmental area, anterior cingulate gyrus, caudate, putamen, temporal pole, and insula. These decreases were found in patients experiencing the constellation of sensations termed *deqi*, but were absent or markedly attenuated in patients experiencing sharp pain (Figs. 2 and 3). In contrast, signal increases in the somatosensory cortices were present during both acupuncture and sensory control. In this early paper we first showed evidence for the coordinated signal decreases during BOLD fMRI, representing decreased cerebral blood

flow due to suppressed neuronal metabolic activity within the limbic and paralimbic systems.

In Hui et al. (2005) we extended our fMRI findings to ST36, showing with whole brain imaging that manual acupuncture at this point also led to coordinated decreased signal throughout the limbic system. We also described the central effect of acupuncture on the cerebellum, showing that the cerebro–cerebellar system also demonstrated signal decreases in concert with the limbic system. Again, the pattern of hemodynamic response depended on the psychophysical response to needle manipulation, with *deqi* sensations leading to signal decrease, while inadvertent sharp pain led to signal increase. Tactile stimulation as control elicited signal increases, predominantly in the somatosensory areas. Based on these findings, we argued that the cerebro–cerebellar and limbic system responds in an integrated manner in correlation with the psychophysical response to acupuncture stimulation at ST36.

In our most recent study (Hui et al., 2009), we described our analysis of 201 acupuncture runs and 74 tactile stimulation control runs in 48 healthy subjects at all three acupuncture points. The large size of this data set provides a foundation for comparison of neuroimaging findings in health and disease and between acupuncture and tactile stimulation controls. We again described clusters of decreased activity in limbic and paralimbic regions including the medial prefrontal, medial parietal and medial temporal lobes, along with increased activity in the sensorimotor cortices and select paralimbic structures. To better analyze and characterize this large fMRI dataset, we used a general linear model and cross-correlation analysis to identify the activation and deactivation networks and their functional connectivity during acupuncture administration (Fig. 4).

The temporal and spatial features of the activation and deactivation networks were compared with descriptions in the resting brain literature to explore their relationships as well as additional effects that acupuncture might evoke. We found that the extensive regions of deactivation and activation observed during acupuncture showed substantial overlap with both the default mode network and the anti-correlated task-positive network in response to stimulation (Fig. 5). However, during acupuncture, the amygdala and hypothalamus—structures not commonly reported as involved in the default mode literature—were found to be a central part of the activation response of the brain to acupuncture.

A second reproducible finding of our research has been that the signal increase observed in the somatosensory regions during acupuncture needling, an invasive procedure, is less than the signal increase seen during the control superficial tactile stimulation. Tactile stimulation, as has been previously described, induced greater activation in the somatosensory regions but less extensive involvement of the default mode network and limbic-associated regions of the anti-correlated task-positive network. Moreover, even short periods of inadvertent pain can attenuate or reverse the deactivation of the default mode network that occurs during acupuncture. Such effects indicate that deactivation of the default mode network during acupuncture cannot be completely explained by the demand of attention, as is commonly proposed in the literature. Together, these results strongly suggest that acupuncture engages extensive functionally organized intrinsic systems of the brain as mediators of its diverse effects.

To provide a single terminology for the network of brain regions involved in the acupuncture response, we have defined the limbic–paralimbic–neocortical network, comprised of the default mode network, amygdala and hypothalamus (Figs. 6 and 7). Our findings show that acupuncture mobilizes these anti-correlated functional networks of the brain to mediate its actions, and that the effect is dependent on the psychophysical response to acupuncture stimulation. Functional MRI studies from other groups have also shown generalized deactivation of the limbic–paralimbic–neocortical network across multiple levels of the brain, along with activation of the sensorimotor system, during acupuncture stimulation (Fang et al.,

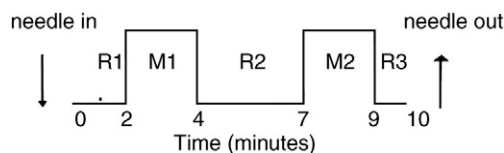


Fig. 1. Time course of acupuncture needling. The acupuncture needle was inserted and the sensitivity of the subject to manipulation was pre-tested and adjusted to tolerance prior to starting functional MRI scanning. The needle remained at rest for 2 min after the start of MRI scanning before bidirectional rotation at 1 Hz for 2 min. The needle was not manipulated for 3 min, then manipulation was repeated for 2 min, followed by a third period of rest for 1 min. The needle was removed after MRI scanning was complete. Data analysis compared the blood oxygenation level-dependent (BOLD) MRI signal intensity of the two needling periods with the three rest periods, with the first minute of scanning excluded from analysis to allow for MRI signal equilibration.

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