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The Effect of General Anesthesia on Acupuncture: A Functional MRI Study

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The Effect of General Anesthesia on Acupuncture: A Functional MRI Study

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THE EFFECT OF GENERAL ANESTHESIA IN ACUPUNCTURE STIMULATION: A FUNCTIONAL MRI STUDY

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We performed a study to examine brain activity as assessed by functional-MRI when acupuncture is administered to awake volunteers as compared to acupuncture administered to volunteers under general anesthesia.

Healthy, acupuncture-naive volunteers were recruited for this cross-over study. Volunteers underwent two experimental sessions that included a sequence of 4-20 seconds of on and off manual acupuncture stimulation for a period of 3 minutes while awake *and* while under propofol general anesthesia. The acupuncture intervention was performed at left stomach 36. General anesthesia was induced and maintained with propofol. *BOLD* signal images were obtained in a 1.5 T MRI scanner in both experimental conditions. The primary single subject analysis for each study utilized a GLM to examine the response to the stimulus, and a spatially varying autoregressive model for the temporal errors.

f-MRI imaging obtained during acupuncture stimulation in awake volunteers revealed: (1) *Activation foci* at bilateral primary and secondary somatosensory cortices, hypothalamus, contralateral substantia nigra, nucleus accumbens, bilateral hippocampal formations, and bilateral superior colliculi; (2) *Deactivations* at bilateral posterior lobes of cerebellum and contralateral posterior temple lobe. In contrast, *f*-MRI imaging obtained during acupuncture stimulation in volunteers under general anesthesia revealed: (1) *Activation foci* at the limbic orbitofrontal cortex, ipsilateral putamen, contralateral temple lobe and bilateral primary visual cortices; (2) *Deactivation* at the ipsilateral primary and secondary somatosensory cortices. Statistical analysis revealed significant differences at the following areas: ipsilateral primary and secondary somatosensory cortices, hypothalamus, posterior lateral thalamus, and contralateral head of caudate ($p<0.005$).

We found significant differences in brain *f*-MRI images when comparing acupuncture while awake to acupuncture given under propofol general anesthesia.

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INTRODUCTION

History of Acupuncture

Acupuncture has been used for analgesia for thousands of years. While an exact mechanism has not been elucidated, the traditional explanation of its powers is based on the theory of Qi, an energy that flows through the body. As acupuncture transitioned from the realm of traditional Chinese medicine towards its role as an adjunct to Western medicine, scientists have tried to determine its mechanism of action and delineate the pathologies for which it is effective.

Acupuncture originated in China as long ago as 6000 B.C. The first document that describes the use of acupuncture in its present form dates to 100 B.C. This text, entitled *The Yellow Emperor's Classic of Internal Medicine,* describes a concept that at the time was already well established involving the energy Qi that flows within meridians. While the principle of Qi has persisted to the present day, acupuncture as a practice, like all medicine, did not remain a static technique. Over years, it has developed and evolved into a standard treatment modality in Chinese medicine. (1)

The practice of acupuncture that is most akin to that of the modern day may have been in the Ming Dynasty. The publication from that era, *The Great Compendium of Acupuncture and Moxibustion,* holds a description of the acupuncture points and channels of Qi. Like many trends in medicine, interest in acupuncture subsequently waned, and by the 17th century it was removed from the practice of the Imperial Medical Institute. Despite losing its official stature, individuals and rural healers continued to use the skill in their medical practice. Acupuncture was actually outlawed in China in 1929, only to be reinstated in 1949 under the new Communist government that strove to increase nationalism and saw in acupuncture a way to provide inexpensive health care to the masses. Acupuncture began to regain its official status in the 1950's, when research institutes were opened, and departments developed even within western-medicine based hospitals. As the popularity of acupuncture grew again, the search for a scientific explanation for its efficacy and mechanism began. (1)

The history of acupuncture in the West began as early as the 17th century. For a short-lived period in the early 19th century, it was featured in scientific journals. In one Lancet publication in 1823, the author discusses its uses and offers a brief description of the variations of technique available that depend on the patient's habitus and the disease at hand. He also reports observing first hand the hasty recovery it produced for a sailor crippled by vomiting at sea. (2) American interest in the use of acupuncture for surgical analgesia was jumpstarted in 1971 when a US Press Corps member reporting on a Chinese-US Ping-Pong tournament received it for post-operative pain following an emergent appendectomy in China. His publication of a report in the New York Times entitled "Now about my operation in Peking" in 1971 fueled subsequent research trips to China. (1)

Practices and Techniques

The current term "acupuncture" encompasses both two different types of practice systems, as well as a vast array of techniques and functions. All subsets are based on an ancient Chinese practice which involved the insertion of sharp objects in the specific sites in the skin that were held to have the power to prevent or alleviate illness in other parts of the body. Acupuncture stimulation produces a sensation, DeQi, that indicates that the acupuncture is taking effect. The DeQi sensation can be described as a constellation of sensations that includes aching, pressure, soreness, fullness, distension, numbness, tingling, warm or cool sensation, dull pain and spreading of sensation. (3)

The two primary practices of acupuncture are traditional Chinese body acupuncture, and Microsystem acupuncture. The traditional Chinese body acupuncture is based on the ancient Chinese view that the human body is connected through a network of channels that are three-dimensional passages. Through these channels the Qi and blood flow. In this practice, there are 14 prominent channels, twelve of which are bilaterally oriented in the body as extensions of the twelve Yin and Yang organs, while the remaining two are midline, one on the back, the other on the front. While the numbers vary based on reference, there are a total of 656 acupuncture points on the skin surface, between 25-52 midline acupoints, and 136-309 bilateral points. (4) (Table 1), (Figure 1)

Channel	Notation	
Arm greater Yin lung	Lu	Bilateral
Arm Yang Ming large intestine	LI	Bilateral
Leg Yang Ming stomach	ST	Bilateral
Leg greater Yin spleen	Sp	Bilateral
Arm Less Yin heart	H	Bilateral
Arm greater Yang small intestine	SI	Bilateral
Leg greater yang bladder	BI	Bilateral
Leg les Yin kidney	Ki	Bilateral
Arm absolute Yin pericardium	Pc	Bilateral
Arm less Yang triple burner	TB	Bilateral
Leg lesser Yang gall bladder	GB	Bilateral
Leg absolute Yin Liver	Li	Bilateral
Governing	Gv	Back
Conception	Co	Front

Table 1: Acupoint channels.

Figure 1a

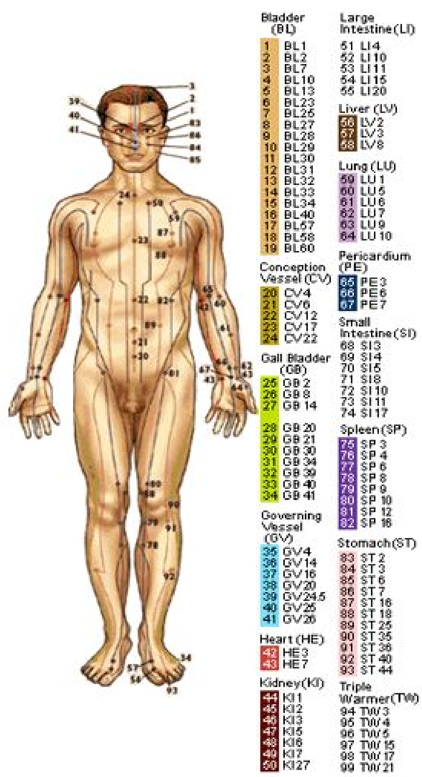

Figure 1b

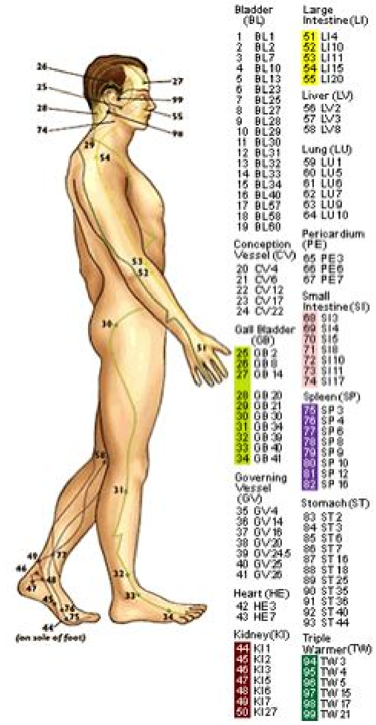

Figure 1c

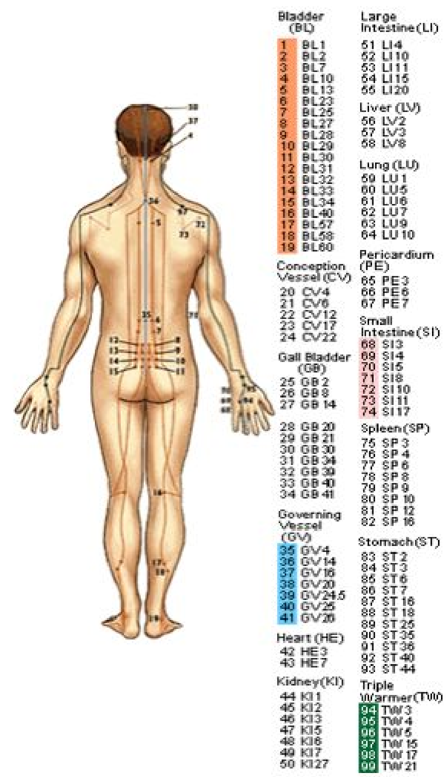

Figure 1: Map of acupoints.

The other main practice of acupuncture is Microsystem acupuncture, which is similar to reflexology. The Microsystem practice is based on the principle that the human is derived from a single cell (zygote) that develops through differentiation and forms multiple organs and tissues. Since all differentiated cells have the same origin, they can still communicate with one another through an internal signal. The Microsystem is based around a local organization center that represents the entire body. If there is a pathological change in one organ, the reflex point of that local control center is activated. By then stimulating an active reflex point at another part of the body, the distant pathology will be resolved and function will be restored. The recognized organization centers include hand, foot, scalp, tongue, nose, ear and pulses. Microsystems can also be used to diagnose pathology, or for feedback about the effects of therapeutic practices on the organism. The most commonly used Microsystems are Korean Hand acupuncture, Yamamoto Scalp acupuncture, Nogier Auricular acupuncture, and Chinese Ear and Scalp acupuncture. (5)

Within the practice of Traditional Chinese Body Acupuncture, several techniques are used. These include: acupressure, acupuncture, moxibustion, electrical stimulation, laser acupuncture, cupping, and acupoint injection. Each modality is preferred in one setting or another, and the practitioner determines which technique would best suit the pathology. For example, acupressure, which involves direct massage of the acupoints with the finger or with magnetic beads, is used either for an acute problem such as a fainting spell or for mild disturbances such as nausea. Needle acupuncture, the most common technique, involves the direct insertion of a disposable filiform steel needle that ranges in size from 2mm to 10cm long, and from 26-36 gauge. The insertion and rotation of the needle is used to either tonify the Qi or to remove excess Qi, and thus regulate its flow. In place of needles, electrical stimulation can be used at acupoints by applying an electrode (either on the surface or through needles) on the acupoints. This method is frequently used for postoperative pain management. Moxibustion, in which acupoints are heated by burning dried leaves of Vulgaris, is used to tonify and enhance the Qi for conditions caused by weakness or deficiency. It is often used in conjunction with needle acupuncture. Laser acupuncture is performed with a Helium Neon Laser light of low intensity in either the red visible range (632 nm) or in the infared range (904nm), or with a diode laser (780nm), and is often used for skin problems or on children who are afraid of needles. A mode of acupuncture that differs largely from the traditional known techniques is cupping. In this technique, which is often used to treat diseases of congestion, a partial vacuum is created in a jar that is applied to the skin. This vacuum draws up the underlying skin and tissue and creates blood stasis in the area. This treatment can involve only a single site, or cover a larger area by moving the jar over large flat body areas. When used in combination with acupuncture it is effective for treatment of rheumatism. Lastly, injections of solutions into acupoints have been used. Saline and glucose injected into acupoint P6 is used to decrease post-operative nausea and vomiting, and injection of Vitamin K3 into Spleen 6 has been used to decrease menstrual cramps. (4) (Table 2)

Technique	Method	Tools		Utilization
Acupressure	direct massage to acupoints	Finger or magnetic beads		Mild disturbances
Acupuncture	Direct needle insertion	Disposable, sterilized steel needles; size 26-36 gauge, 2mm-10cm		
Moxibustion	Heating of acupoints by burning dried leaves of vulgaris		Often used in combination with acupuncture	Conditions caused by weakness (deficient, Xu); tonification and enhancement
Electrical	Electrode applied to acupoint	Surface electrodes or needles	Similar to transcutaneous electrical nerve stimulation	Pain treatment/ postoperative analgesia/PONV
Laser	Laser applied to acupoint	Helium neon laser light in red visible range (632 nm), infared (904nm), diode laser (780 nm)	Used in children afraid of needle; substitute for moxibustion	Skin problems
Cupping	Partial vacuum placed over skin – single site or moving technique for larger site	Jar to create vacuum – draws up the underlying tissues and forms blood stasis	Can be combined with acupuncture	Often used for rheumatism Heat stroke Acute psychosis
Injection	Injection of solution into acupoint P6	Saline, glucose, medications e.g. Vitamin K3		Nausea and vomiting menstrual cramps

Table 2: Acupuncture techniques and uses.

With the rise in use of acupuncture, concern for adverse effects has been addressed. The complications that have been seen with some of these treatments are mostly psychological in nature, including: anxiety, agitation, tearfulness, fatigue and depression. There are also reports of light-headedness and syncope, as well as local irritation and infection at acupoints. According to recent reviews, the rates of complications related to acupuncture remain very low (around 0.13%) and there was no evidence of serious complications in a cohort of over 34000. (6) Most of these complications were mild and transient in nature including failure to remove the needle, pain, dizziness, nausea and vomiting, fever, and contact dermatitis. Compared to complication rates from adverse drug reactions or prescribing errors, which vary from 0.5- 6% in community pharmacies, acupuncture seems to be a very safe technique. (7)

Acupuncture in Western Medicine

Acupuncture gained acceptance despite the lack of a known mechanism, when the 1997 NIH Consensus meeting concluded that acupuncture was a safe treatment that had the potential to decrease the use of pharmacological analgesics and antiemetics. (8) The consensus felt that there was conclusive evidence of its efficacy for the control of nausea, vomiting and post-operative dental pain, as well as probable efficacy in other settings when used alone or in combination with other treatments. (9)

Since the rekindling of interest in acupuncture in 1971, the skill has been considered as a possible adjunct to perioperative analgesia regimens. Acupuncture has been shown to be effective in randomized controlled trials, especially in the setting of post-operative nausea and vomiting both in adult and pediatric populations. In 2001, Kotani et al. conducted a controlled, double-blinded study that showed that pre-operative intradermal acupuncture served to reduce post-operative pain, as well as nausea and vomiting. In this particular setting, the decrease in nausea and vomiting was speculated to be due to decreased pain and opioid requirement. (10) The P6 antiemetic acupoint has long been a recognized point for control of post-operative nausea and vomiting. Dundee et al. used preoperative acupuncture (both manual and electrical) and showed a marked improvement over controls in post-operative nausea and vomiting up to 6 hours after women underwent minor gynecologic procedures. (11) A Cochrane review in 2004 also concluded that stimulation of acupoint P6 on the wrist is effective for the control of post-operative nausea, but not of post-operative vomiting. Many studies have focused on establishing whether acupuncture or acupressure is effective in controlling post-operative nausea and vomiting in the pediatric population, because of the reluctance to use medications that may have other side-effects. Wang demonstrated that injections at the P6 acupoint surpassed control, and were equal to droperidol, in controlling early post-operative nausea and vomiting, but that neither was effective in preventing delayed symptoms. (12) Another randomized prospective study showed that transcutaneous electrical acupoint stimulation (TEAS) was better than control and as effective as ondansetron in preventing post-operative nausea and vomiting following pediatric tonsillectomy. The authors of this study chose to use TEAS rather than traditional acupuncture because they recognized the potential risks of using needles in the pediatric population, as well as the contradictions to their use as in the setting of unstable spines, clotting disorders or neutropenia. (13)

However, not all studies have shown an efficacy of acupuncture either in the control of post-operative nausea and vomiting, or as an adjunct to pharmacologic analgesics. Most studies have been conducted under different conditions and at various times in relation to the administration of general anesthesia. In 2002, Morioka et al looked at whether electroacupuncture could decrease the anesthetic requirement of desflurane needed to prevent movement in response to noxious stimulation. They concluded that there was no decrease in the mean requirement of desflurane. (14) Subsequently, Kvorning et al. demonstrated that electroacupuncture not only did not reduce, but in fact increased the requirement of sevoflourane needed to prevent movement in response to initial incision in a surgical operation. (15) These studies have apparent discrepancies, including different anesthetic agents used, different types of stimuli, and different experimental designs. The key factor that seems to recur in most of the studies conducted is that conflicting evidence has arisen in the setting of general anesthesia, and the timing at which acupuncture is performed in relation to the induction of general anesthesia.

Proposed Mechanisms of Acupuncture

While researchers are still trying to demonstrate efficacy of acupuncture, there has been a continued effort to determine its mechanism. One theory regarding the anti-emetic effect of acupuncture and acupressure is that the stimulation, especially at P6 along the median nerve, may cause an increase in beta-endorphins in the CSF.

This overflow of beta-endorphins may desensitize chemoreceptors in the trigger zones, or perhaps the emetic center in the medulla oblongata. (13) Most of the leading theories for the analgesic effect involve an effect on an endogenous opioid or humoral system. Dopamine, which plays a large role in the modulation of the limbic system and can be normally induced by pain, cocaine and alcohol, was shown to undergo decreased synthesis in animal models following acupuncture stimulation. (3) The same research group reported a similar effect on serotonin, which is involved in controlling the release of glutamate. (3) Another proposed mechanism is one similar to Cognitive Behavioral Therapy, in which acupuncture works to induce the neurophysiologic system to self-regulate and thus restore balance internally. (3) Other studies have shown that acupuncture stimulates large, myelinated A-delta nerves, which in turn cause a decrease in transmission along the slow, unmyelinated pain transmitting C-fibers. (16) The classical "gate control" theory has been offered, in which acupuncture needles produce sensory stimulation that activates large nerve fibers which in turn cause changes in pain perception in the spinal cord. The decreased pain perception in the spinal cord thus decreases signals from pain stimulation that would normally be transmitted by smaller fibers. (10) Other hypotheses have associated the mechanism of acupuncture analgesia with low-frequency stimulation of nerves, or with long-term depression of excitatory synapses that in turn induce long-term synaptic depotentiation and depression. (17) Another proposed theory is that acupuncture functions by sending conflicting messages into the pain neuromatrix, thus causing a unbalanced setting and therefore altered perception of pain. (17)

Pain Pathway and Neuromatrix

A major factor in the understanding of the mechanism of acupuncture is the delineation of the pain pathway. The neurologic pathways involved in pain perception have been well established in functional studies. The basic structure of the nociceptive system begins at peripheral nociceptors in the dorsal horn of the spinal cord and flows cranially via A, delta (thinly myelinated) and C (unmyelinated) fibers. Signals cross the midline, and ascend in the spinothalamic tract to the thalamus. (16) Specific areas of the cortex are involved in pain processing, including the anterior cingulate cortex, which is involved in the modulation of sensory and cognitive signals of tonic persistent as well as acute pain; the insula, a focal node for the pain intensity circuits, and the raphe nuclei, which initiates the signals for descending pathways that control nociceptive inputs. (17) One of the most frequently demonstrated pathways of the descending antinociceptive system includes the arcuate nucleus of the hypothalamus, the nucleus accumbens, periaqueductal gray and raphe nuclei, as well as areas of the limbic system. (18) Areas known to be activated in nociception processing also have been seen to be activated in acupuncture. (17)

A theory about pain perception and modulation that has been slowly evolving over several years is one proposed by Melzack, involving a pain "neuromatrix." Melzack and collaborators first proposed a gate control theory for pain in 1965, which emphasized the CNS modulation of inputs that ascend from the dorsal horns. He also first described the different aspects of pain sensation: sensory-discriminative, motivational-affective, and evaluative. (19) His concept of a pain neuromatrix involves a widespread network of neurons throughout the CNS that is composed of loops of connections and pathways. These connections run between the thalamus and cortex, and between the cortex and the limbic system. While the basic plot of connections is genetically determined, according to his model, it is molded later by sensory inputs. This network is traversed by “cyclical processing and synthesis” in a characteristic pattern of connections that makes up a “neurosignature.” Thus it is the output of the neuromatrix, and not the individual sensory inputs, that make up an individual neurosignature pattern. (19)

The limbic system plays an important role in this neuromatrix theory. The limbic system consists of: septal and pre-optic regions, amygdala, hippocampus, the posterior parahippocampus, anterior thalamus, entorhinal cortex, and the cingulate gyrus in the telencephalon; the pineal gland, habenulam hypothalamus and zona incerta in the diencephalons; and the periaqueductal gray, reticular formation, and raphe nucleus. (3) While not entirely understood, the limbic system is believed to be involved in the affective and cognitive aspects of pain perception, (18) in addition to its sensorimotor, autonomic, endocrine and immunologic functions. (3) The network entirely encompasses the limbic system. The limbic system has been shown to control an aversive drive to pain. The thalamus is involved in a fear response and escape function, and the hippocampus, fornix, and amygdala also function in escape and defense, as demonstrated by electrostimulation on mouse models. Excising the amygdala and overlying cortex in mice led to decreased responsiveness to noxious stimuli, and blocking the cingulum bundle, which connects the posterior frontal cortex to the hippocampus, induced analgesia. (19)

The Role of fMRI

Recently, the aim of most acupuncture research has been to demonstrate functional change in brain activation rather than to attempt to prove clinical efficacy or elucidate exact mechanisms. To this end, researchers have employed state-of-the-art neuroimaging modalities, most commonly functional magnetic resonance imaging. Changes is tissue blood oxygenation occur in brain regions when they are involved in any task or control functions, and the functional MR image is able to measure this change in blood flow to the vasculature and thus localize these regions. The contrast used in fMRI studies is the blood oxygenation level dependent effect (BOLD) which is produced as the net result of oxygen consumption (CMRO2, cerebral metabolic rate of O2 consumption) and the hemodynamic response to changes in O2 demand. (3) This effect is based on the difference in magnetic susceptibility of oxygenated versus deoxygenated blood. Oxy-hemoglobin is diamagnetic, and has nearly the same magnetic property as brain parenchyma. Deoxyhemoglobin, on the other hand, is paramagnetic and has a magnetic property very different from brain parenchyma. Deoxyhemoglobin thus alters the local magnetic field within capillaries and surrounding tissues, leading to spin dephasing and a low-signal intensity on T2 weighted gradient echo MR images. Thus upon neuronal activation, regions of cortical tissue are flooded with oxygenated blood in an amount that is in excess of what can be metabolized. This leads to an increased difference between oxy and deoxyhemoglobin, and thus an increased signal intensity that is detected by the BOLD based fMRI.

During fMRI data acquisition, a series of images of the brain are obtained in quick succession, and then are analyzed for differences among them. Usually, a series of baseline images are captured at rest, and then a subject will perform a task, and a second series is taken. For analysis, the first set of images is subtracted from the second, and the remaining areas that are most visible are considered to have been activated. The challenge with analysis is that there are many physiological changes that occur that can affect the signal intensity and thus confound results. Different techniques exist to enhance contrast due to one parameter over another, and thus BOLD signal changes based on cerebral blood flow mapping and gradient echo planar imaging have been used to differentiated BOLD signal changes due to neuronal activity versus purely physiological changes. (20)

fMRI has become a widely used neuroimaging modality due to its ability to relate anatomy with function, such as seen in the functional neuronal changes that are detected by fMRI, PET, and EEG as a result of cognitive and emotional changes. (3) Additionally, fMRI detects these changes with a resolution that is better than other functional imaging modalities. The other benefits of using fMRI over other tools to assess function include the lack of need for radioactive isotopes and the brief scanning time.

Previous studies have employed fMRI to localize the neuronal activation produced by acupuncture stimulation. These studies have used a variety of different acupuncture methods, locations and study designs, and most use the sensation of DeQi to indicate that an appropriate response to acupuncture had occurred. One of the pioneer studies that studied the use of fMRI to assess the effect of acupuncture was conducted by Wu et al. in 1999. Recognizing that the ability of fMRI to detect changes in regional blood oxygenation as an indication of neuronal activity had been used successfully in mapping brain functions, Wu hypothesized that the imaging modality would be useful to characterize the CNS pathways involved in acupuncture. Additionally, Wu hypothesized that the areas of activation would involve the hypothalamus and limbic system. (18) This innovative study looked at two acupoints, ST 36 and LI 4, as well as two types of control stimulations (minimal acupuncture and superficial pricking) performed on healthy subjects. Their endpoint to indicate successful acupuncture was the DeQi sensation rather than any analgesic effect, because the patients were pain-free initially. (18)

In 2000, Hui et al. again showed that fMRI was useful to assess the neuronal activation effect from acupuncture at LI 4. They also found activity changes in the limbic system and subcortical structures. (21) Once fMRI became a well established modality for determining location of activation, studies focused on more specific aspects of acupuncture stimulation. Zhang et al. used fMRI to determine the effects of different levels of electro-acupuncture stimulation on neuronal activation and analgesic effect. (22) More recently, specific locations have become targets of study, as researchers attempt to elucidate the exact pathways involved in acupuncture as a path to understand its analgesic effects. Liu et al. looked at activation induced specifically in the periaqueductal gray area, a brain stem location associated with processing noxious stimulation, and an area that had not yet displayed activation in prior acupuncture studies. (23) In 2005, Hui et al examined the integrated responses between the limbic system and the cerebellum and they continued their in depth examination of the reaction associated with acupuncture stimulation at ST 36 and the resultant sensations of DeQi, pain + DeQi, or pain alone. (3)

Some studies have also used other modalities such as PET, SPECT, EEG and emission tomography to assess acupuncture effect, but while often effective, these have not provided the same level of resolution as fMRI. Hsieh et al. successfully used PET imaging to localize activation to the hypothalamus, and their findings on PET correlated to earlier findings by fMRI. (24) Biella et al. also used PET to evaluate rCBF (regional Cerebral Blood Flow) changes as an indication of neuronal activation in response to acupuncture stimulation. (17)

PURPOSE OF STUDY

The purpose of this study is to demonstrate that general anesthesia has an effect on the level of neuronal activation produced by acupuncture stimulation. The results from this demonstration would serve as a stepping-stone in the process of determining the efficacy of acupuncture in the operative setting, and eventually determining whether it is a valuable method of reducing the amount of pharmacologic analgesia used during surgery. The long-term goal, that of reducing the amount of pharmacologic agents used during and after surgery, would serve to decrease post-operative complications such as pain, nausea and vomiting, the cost of peri-operative care, and time spent in the post anesthesia care unit.

Hypothesis

Our hypothesis is that acupuncture will produce a pattern of activations and deactivations of various brain regions that differs depending on whether the subject is awake or under general anesthesia.

MATERIALS AND METHODS

Study Design

This is a double blinded, controlled study that examines a sample of 11 subjects who are all subjected to the same protocol of treatment. The acupuncturist is aware of the patients state, but the radiologist reading the fMRI is blinded to awake and anesthetized conditions.

Subjects

The study enrolled a cohort of 11 healthy, right-handed volunteers who were assessed to be American Society of Anesthesiologists (ASA) physical status 1. The Human Investigation Committee at the Yale School of Medicine approved the study and all subjects signed informed consent documents. The volunteers were financially compensated for their participation. The group consisted of nine males and two females, aged 28 $\pm$ 2 years. The volunteers had no recent history of acute illness, no history of substance abuse, and the two females were not pregnant. The volunteers also did not have any prior experience with acupuncture. Eligibility of study subjects was first assessed by telephone interview, and subjects were then assigned dates for the studies. During the telephone interview, they were instructed to follow the ASA recommended NPO guidelines for anesthesia, as well as to avoid caffeine and alcohol for at least 24 hours prior to the study. On the day of the experiment, the attending anesthesiologist performed a standard pre-anesthesia history and physical examination and pregnancy test. A standard metal screening questionnaire was completed as well.

Experimental Protocol.

Subjects were studied in two separate fMRI scanning sessions on different days, one while awake, and one while anesthetized with propofol. The sessions were performed on different days in order to avoid carry-over or memory effects in the results, and the order was randomized among subjects.

The acupuncture sequence consisted of: 4-20 seconds on and off, 1 rotation/second of pushed, pulled, and twisted manual stimulation, repeated 3 times during each session. The acupuncture was performed with sterile, single use, individually wrapped needles (0.3mm x 3 cm; SEIRIN, OMS Medical Supplies Inc., Braintree, MA, USA). To ensure uniform stimulation across subjects, the exact timing of the acupuncture was projected on a screen.

Acupuncture stimulation was performed at the left ST36 acupoint (Zusanli acupoint), which is located below the head of the tibia, 1.5 “cun” (Chinese equivalent of inch) lateral to the head of the tibia. This site was chosen both because it is one of the most frequently used and one of the most well studied acupoints used for acupuncture analgesia, and because of its location, on the tibia, is far enough away from the MRI machine to avoid interference with the magnet. (Figure 2)

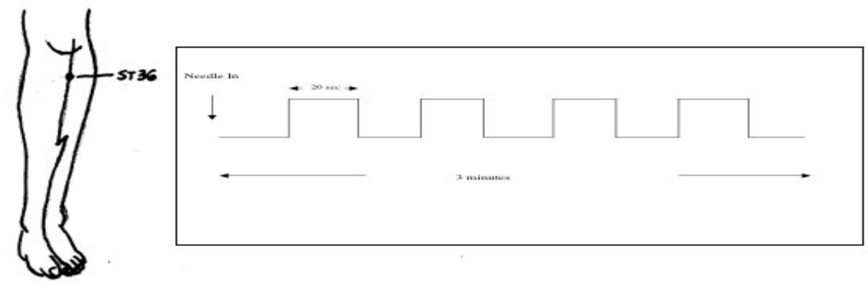

Figure 2: The location of acupuncture point ST 36 and the timing of acupuncture stimulation per cycle.

During the awake-session, the subject walked to the MRI scanner, was positioned with his head within the magnet, and instructed to lie still for the duration of the experiment. During the anesthesia-session, the subject first went to a holding room where an intravenous cannula was placed, and MRI compatible ASA monitors were attached. In addition, a BIS monitor was applied to the forehead in order to standardize anesthesia depth among all the subjects. (Aspect, Boston, MA). General anesthesia was induced by an infusion of 1-2mg/kg IV propofol over 3 minutes. The goal level of anesthesia was a BIS number of 40±10. (Normal level for surgery is 40-60.) Following induction, a continuous propofol infusion of 120-150 μg/kg/minute was initiated. Subjects continued to breathe spontaneously, and O2 saturations were monitored and maintained at a level of ≥ 95% on room air. No subjects required airway intervention. Subjects were monitored for 15 minutes in the holding room to establish stable vital signs and a BIS number consistent at 40-60. The BIS monitor was then removed and subjects were transported to the MRI scanner. The subjects were maintained on continuous propofol infusion and constant ASA monitoring.

Imaging Data Acquisition

Images were obtained with a Siemens Sonata, 1.5T field strength, whole-body MRI scanner (Erlangen, Germany). Each study followed the same imaging protocol. First, a preliminary 3-plane localizer scan of 20 seconds was taken to localize the brain within the scanner. Next a sagittal localizer of inversion recovery T1-weighted scan ((TI/TE/TR=800/11/1800, 256x192x2nex) 3mm thick, skip 0.5mm, FOV=22cm, 16 slices) was obtained to define the ac-pc line for the following series of anatomic T1 and functional images. Finally axial-oblique T1-weighted images were obtained for use as basic anatomic reference images that were later registered with the 3D high-resolution acquisition obtained at the end of the study (TI/TE/TR=800/11/1800msec, 256x192x2nex, 5mm thick, skip 0mm, FOV=22cm, 22 slices). During the acupuncture stimulation, functional MRI images were recorded using gradient echo EPI blood oxygenation level dependent contrast. The EPI imaging parameters were: flip angle = 80 degrees, TE = 45msec, TR=1800msec, matrix 64 x 64, 108 images per slice.

Analysis of fMRI Data

The collected data were motion corrected using SPM-99 and blurred using Gaussian blurring function with FWHM 6.25mm. Data recorded from each subject underwent primary single-subject analysis using a General Linear Model (GLM) to examine the response to the stimulus, and a spatially varying autoregressive model (AR(p)) for the temporal errors. The minimum variance estimator of the parameters **b** of the GLM (**Y** = **Xb** + **e**), were obtained by least squares after pre-whitening the errors. The pre-whitening was achieved by multiplying the measurement vector **Y** and the model matrix **X** by a matrix **A** such that the variance of the resulting errors was proportional to the identity matrix. As described in Worsley et al., modeling the errors as an AR(p) process makes the computation of the whitening matrix **A** efficient. Contrasts between the **b** parameters can then be tested for the null hypothesis that there is no effect of anesthesia. Beta maps are stored, converted into the multi-subject data space using registration software. (25) Correction for multiple comparisons was performed using the cluster-size threshold approach described by Forman et al. and similar to that implemented in AFNI (http://afni.nimh.nih.gov/afni/). (26) We have implemented a modified QUIPSSII sequence (27) to allow quantitative assessment of direct baseline flow changes between the awake and anesthetized conditions. All activations recorded were reported using Broadman's area definitions and Talairach coordinates, as defined for the common brain space images. The paired t-test was used to compare the maximum beta maps on a voxel by voxel basis across conditions.

Activation maps that were determined during the awake condition were used to define regions of interest (ROI). ROI were those areas that were significantly activated ($p<0.05$) by acupuncture stimulation. These functionally defined ROI's were then used to assess the overall activation across both awake and anesthetized conditions.

RESULTS

All 11 right-handed volunteers completed two study sessions as described above. None of the volunteers experienced oxygen saturation below 95%, all maintained end tidal CO_2 values of 40±5 mmHg and none required airway intervention while under propofol. There were no significant changes in arterial blood pressure and heart rate between pre-intervention baseline, acupuncture stimulation, and post-intervention settings (p=ns).

Functional MRI Findings

The functional MRI images recorded and analyzed showed significant differences in BOLD activations between the awake subjects as compared to anesthetized subjects receiving acupuncture. In the awake subjects, the areas of activation included: bilateral postcentral gyri corresponding to the primary and secondary somatosensory cortices (SI & II), left superior temporal gyrus, thalamus, left posterior insula, left pallidum, left inferior temporal gyrus, mescencephalon, red nuclei, substantia nigra, and right basis of pedunculi (cluster 100, $P<0.01$). (Table 3), (Figure 3) In contrast, in the general anesthesia setting, areas of activation included: right precentral gyrus corresponding to motor cortex, left frontal pole and right occipital gyrus. Images of subjects in the general anesthesia setting also displayed areas of deactivation, including: left postcentral gyrus corresponding to SI &SII, right cerebellar hemisphere and right inferior temporal gyrus (cluster 100, $p<0.01$). (Figure 4)

Region	Side	Signal Intensity (during awake acupuncture)	Talairach Coordinates
Thalamus	Left	Increase	-16,-23,+16
Insula	Left	Increase	-39,-7,-1
Aquaductus	Left	Increase	-1,-33,-8
Primary somato-sensory	Left	Increase	-55,-19,+36
Red Nucleus		Increase	
Basal Temporal	Left	Increase	-49,-43,-8
Retrosplenial cortex	Left	Decrease	-6,-45,18
Retrosplenial cortex	Right	Decrease	7,-46,20

Table 3: The Talairach coordinates of BOLD signal changes in the regions of interest in the awake condition.

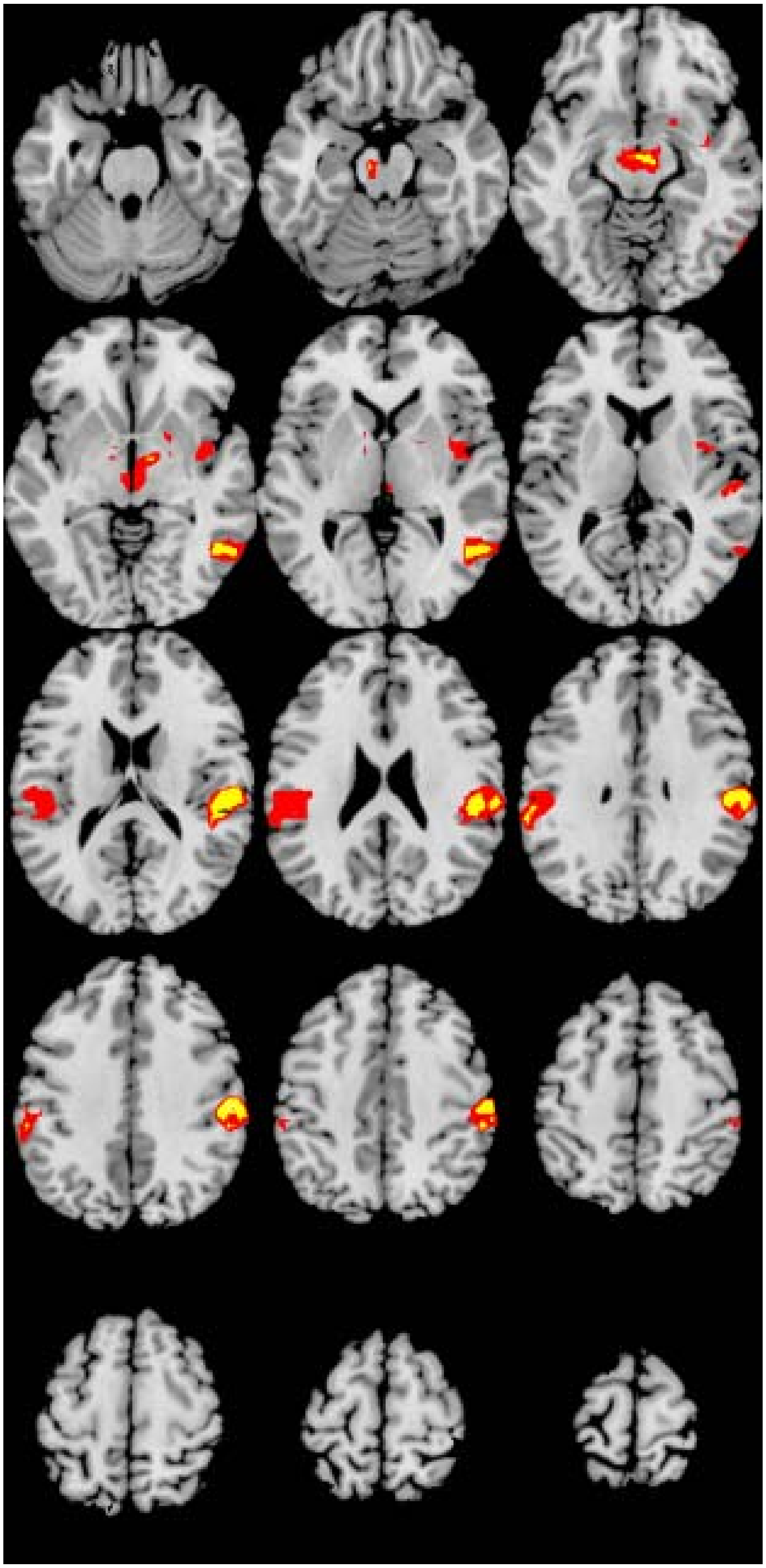

Figure 3: The acupuncture induced BOLD signals in awake condition (cluster 100, p<0.01).

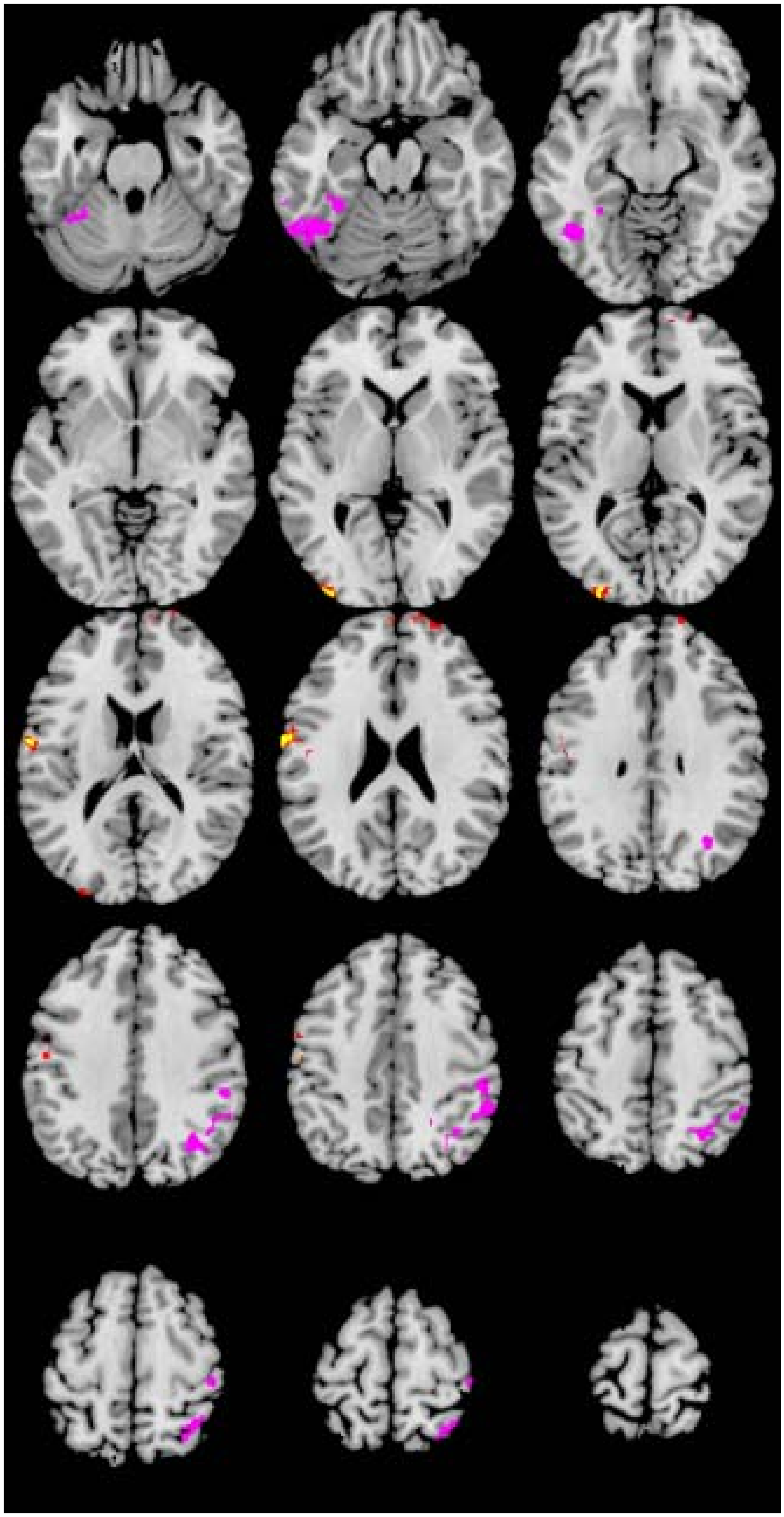

Figure 4: The acupuncture induced BOLD signals in general anesthesia condition (cluster 100, $p<0.01$).

Significant differences between awake and anesthetized conditions were determined through paired t-test analysis. These included: bilateral postcentral gyri, cingular gyrus, left inferior frontal gyrus, retrosplenial area, left posterior insula, bilateral precunes, thalamus, red nuclei, substantia nigra, right basis pedunculi, left middle temporal region (cluster 100, $p<0.01$). (Figure 5)

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

Figure 5: The differences of acupuncture induced BOLD signals between awake and general anesthesia (cluster 100, $p<0.01$).

We conducted a second level analysis that allowed us to distinguish the influence of baseline flow change due to propofol, external stimuli, or normal physiologic changes and isolate the signal due to neuronal activation. Through this secondary analysis, we are able to see the discrepancy between CBF and BOLD signal that arises between the awake and anesthetized conditions due to acupuncture stimulation alone, broken down by brain region. In the thalamus, the CBF showed a slight decrease from the awake to anesthesia state, but was relatively high in both settings. The BOLD signal in the thalamus displayed a greater decrease from awake to anesthesia state than would be expected from the decrease in CBF. In the red nucleus, CBF was approximately equal in the two states, but BOLD signal was greatly decreased in the anesthesia setting compared to the awake setting. The insula actually had a higher CBF in the anesthesia setting compared to awake, but then the BOLD signal showed a dramatic decrease in signal under anesthesia. Similarly, the periaqueductal gray showed a slight increase in CBF under anesthesia, but a large decrease in the BOLD signal under anesthesia. The both the inferior temporal gyrus and retrosplenial cingular gyrus had decreases in CBF with anesthesia, but showed a contrasting increases in BOLD signal. (Figure 6)

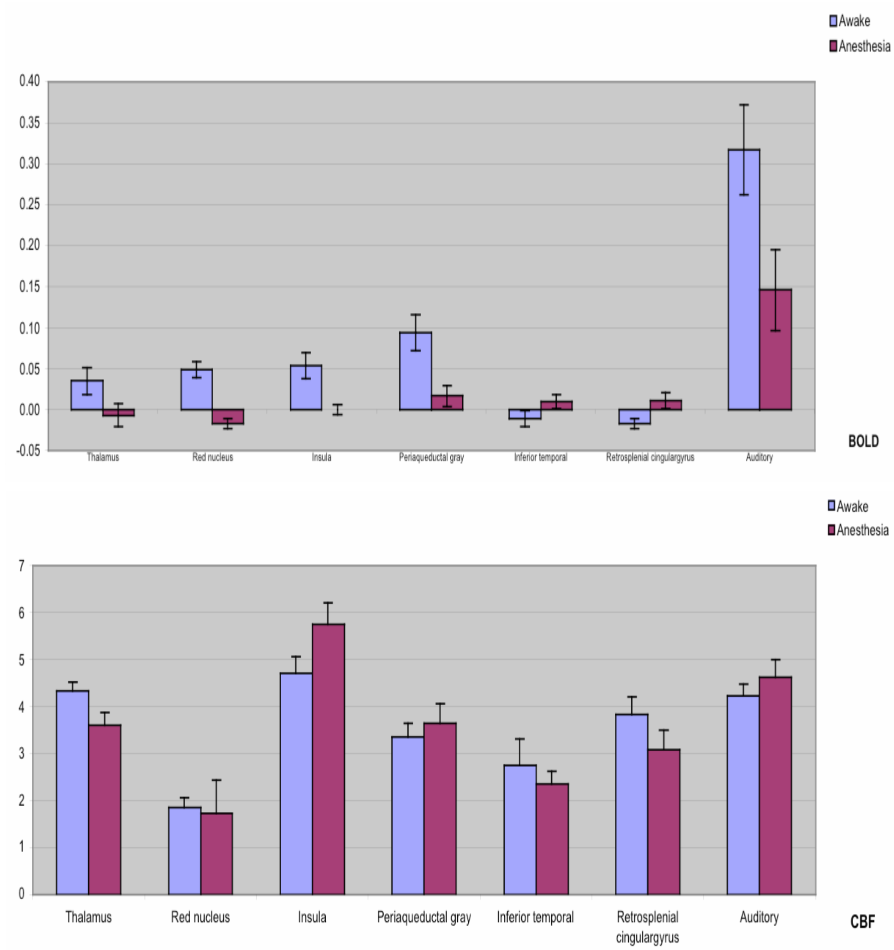

Figure 6: Contrast graphs for CBF and BOLD signals in isolated regions.

We also examined our data to determine which areas of the brain were affected by acupuncture stimulation at ST36. In the awake setting, we found BOLD signal activation foci in the posterior insula and periaqueductal gray, and deactivation foci in the retrosplenial area, right cerebellar hemisphere and inferior temporal region (no cluster, $P<0.05$). These findings were significantly diminished in the subjects after propofol general anesthesia. (Figure 7)

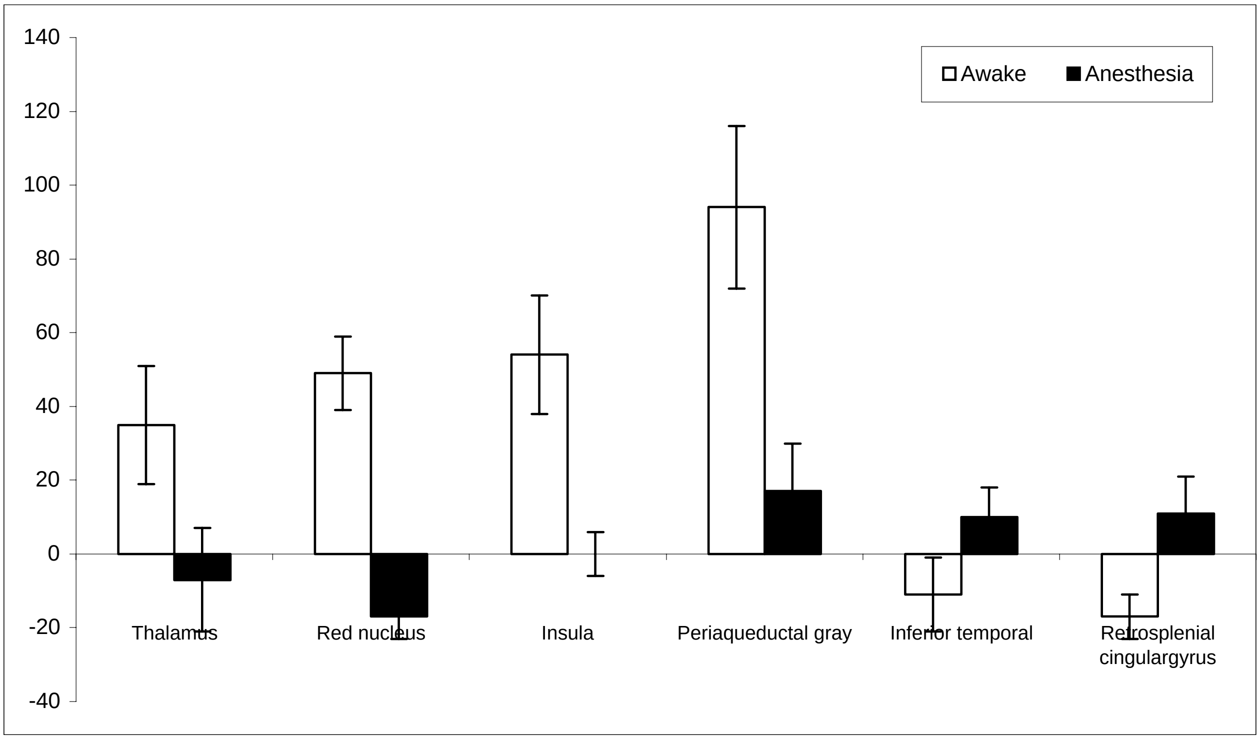

Figure 7: The acupuncture induced BOLD signals in regions of interests between awake and general anesthesia ($p<0.05$).

DISCUSSION

With this experiment, we confirmed our hypothesis that acupuncture produces a pattern of activations and deactivations that is different depending on whether the subject is awake or under general anesthesia. We found that there is a significant difference in acupuncture-induced BOLD signals detected by fMRI in each setting. Many areas that are activated by acupuncture in awake subjects are not activated in the anesthetized subject, and there are several regions that are actually deactivated by acupuncture in the anesthetized setting.

It is well established that acupuncture causes alterations in neuronal activity and our results corroborate this fact. Our findings also will begin to explain the discrepancy seen in earlier research regarding the efficacy of acupuncture in the operative and perioperative period. While our results are not geared toward clinical or functional endpoints, by demonstrating an underlying difference in activation when patients are under general anesthesia, we can understand the reason for conflicting data and begin to design studies that will account for this difference.

Our results also confirmed previously published data about activation of the periaqueductal gray area. (23) This finding supports the suspicion that acupuncture stimulates pathways involved in the pain "neuromatrix" as described by Melzack. (19)

Additionally, corresponding to data in previous studies, our results show that acupuncture induces significant deactivations in the limbic system. This pattern is consistent with the neuromatrix theory of pain sensation. Acupuncture-induced deactivation of the limbic system was shown as early as 1977 by Jacobs, who demonstrated a down-regulation via microelectrodes implanted in the squirrel monkey. More recently, Hui et al noted marked deactivations in the limbic system, with activations present only in the somatosensory cortex and dorsal raphe nucleus. (21)

Another area of significant activation by acupuncture is the insula. The insula is generally associated with higher functions of pain perception, a function that corresponds to its anatomic location and synaptic connections, as it receives input from the thalamus which in turn receives input from the spinal-thalamic tract that carries nociceptive input. The function of the insula has also been demonstrated in studies where brain injury in the superior-posterior portion of the insula led to decreased pain perception. The function of the posterior insular cortex is most well studied and is known to process both noxious and innocuous somaesthetic stimuli. The anterior insula is thought to be associated with the expectation of painful stimuli. (28) Our results indicate activation in the posterior insula in the awake-acupuncture setting, which is consistent with its function in processing noxious and somaesthetic stimuli. The lack of activation in the anterior insula also indicates that there was not a confounding factor of anticipation in the subjects that would bias the results. One reason for this lack of anticipation may be that the subjects were all acupuncture naïve.

We chose to perform this study at the acupoint Stomach 36, on the lower leg. This acupoint is widely used for analgesia to treat various conditions and is one of the most well studied acupoints. We analyzed our results to determine the areas of the brain activated by acupuncture at this point specifically. We included this analysis in an effort to continue to clarify data that has been published about neuronal activation in response to acupuncture. In 2005 Hui looked at the effects of acupuncture at ST 36 on the cerebro-cerebellar and limbic systems. Hui's data showed a predominance of deactivations, while only minimal in magnitude, when acupuncture induced DeQi. Our findings of deactivation in the retrosplenial cortex, right cerebellar hemisphere and inferior temporal cortex correspond with their data that specifically demonstrates activations in many regions. However, we saw activation in the insula while they saw deactivation, and we also saw activation in the periaqueductal gray, while Hui did not record that data point. (3) The activation we saw in the periaqueductal gray does correlate with a finding by Liu et al. that acupuncture at LI4 activates the periaqueductal gray, while non-acupoint stimulation actually causes a deactivation. (23)

We used propofol as an anesthetic agent for this study because of its safety profile as well as for its easy delivery and titration. Propofol has been shown to produce metabolic depression of the CNS, with a greater effect on cortical metabolism than subcortical, and perhaps a more marked decrease in rCBF in the thalamus and cingulate cortex. However, despite the generalized depression, autoregulation is maintained in humans and mammals. (29) Propofol is also known to cause BOLD signal depression on fMRI. Several mechanisms have been proposed for this depressed BOLD signal, including the impaired processing of stimuli or a propofol-induced uncoupling of oxidative metabolism and reduction in cerebral hemodynamics that would decrease the BOLD signal regardless of neuronal activity. (29) However, we have found that the magnitude of the BOLD signal difference between the awake and general anesthesia states can not be explained solely by the effect of propofol induced changes in cerebral blood flow. Thus our findings suggest that the BOLD signal changes present between awake and general anesthesia states most likely reflect that the effect of acupuncture stimulation was inhibited the general anesthesia and not by the changes of regional cerebral blood flow caused by propofol.

Our data represent the foundation for subsequent studies. We have shown that there is a difference in the activation pattern in awake versus anesthetized conditions. Hence we will need to determine why this difference occurs. Although our results are corrected for the effects that propofol may have on activation or BOLD signals, in future studies we may compare propofol with other general anesthetic agents to determine if the specific agent alters activation differently. In later studies we may also trial different levels of sedation, as assessed by the BIS monitor.

Studies on acupuncture, whether aiming to determine its clinical effects or its basic mechanism, are very difficult to conduct. This is due to the numerous confounding factors that are inherently present when dealing with a practice that has so many variables. In a review of the difficulties that arise when conducting clinical acupuncture research, Ernst reviewed several trials that aimed to show the clinical efficacy of acupuncture, and through these examples delineated the obstacles that are present at every step. These included the presence of specific and non-specific effects, difficulties in setting up a randomized controlled trial, the vast variety of treatments and individual techniques, and the ambiguity in establishing endpoints. (30) Every factor of the experimental design may affect the outcome as well. These include: order of experimental arms (awake then asleep, vs. asleep then awake), seasonal effects, variation between male and female or left-handed vs. right-handed subjects, or the difference in effects on subjects who are in pain or who are pain-free. Variation in experimental design also can skew data, including bias of the acupuncturist and the fMRI reader, study size, and standardization of acupuncture stimulation.

A large problem with acupuncture studies has been options for the control group. Controls can be handled either with sham acupuncture (involving needles that are placed in real acupoints, but are not manipulated in the proper way), minimal acupuncture (needles are placed near, but not at an acupoint, or are placed at a real acupoint but more superficially and not manipulated as aggressively), or superficial pricking. (18) Our study avoids this very common limitation that results from inconsistent control groups because we performed real acupuncture in both arms of the study and only compared the different states of the patient. In addition, our data was also corrected for artifact, changes in CBF due to propofol and changes due to hemodynamic states.

In conclusion, we have found that acupuncture performed when subjects are awake activates and deactivates a number of CNS areas. However, as we hypothesized, activation in the majority of these CNS areas is suppressed once the volunteers undergo general anesthesia with propofol. We now need to elucidate the impact of various levels of consciousness on the acupuncture-induced BOLD signal changes in selective areas of the CNS as well as determine the clinical implications of these findings.

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