Title
fMRI shows specific brain areas activated with acupuncture (large intestine 4 acupoint) in patients with myofascial pain of the jaw muscles

Author
Shen, Yoshi Fun-Zu

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fMRI shows specific brain areas activated with acupuncture (Large Intestine 4 Acupoint) in patients with myofascial pain of the jaw muscles: A Pilot Study

by

Yoshi F. Shen

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INTRODUCTION/ BACKGROUND

Myofascial pain, one of the tempromandibular disorder (TMD), is a frequently encountered pain syndrome of muscle/connective tissue that is characterized by localized, hypersensitive spots in one or more palpable taut bands of skeletal muscle fiber, also known as myofascial trigger points. The etiology of trigger points is said to involve muscle overload either from trauma or repetitive activities placing abnormal stresses on specific muscle groups.[1] Trigger points develop at the motor end plates, where sensitization of sensory and autonomic nerve endings lead to excessive release of acetylcholine, preventing normal functioning of the calcium pump mechanism and resulting in sustained contraction of sarcomeres.[1] This motor endplate irritability results in an energy crisis with a relative loss of sufficient quantities of high-energy phosphates to allow the calcium-dependent lengthening of the myofibril unit. This leads to decreased capillary flow into the muscle secondary to the increased muscle tension, lowering of the local pH, and release of sensitizing substances into the muscle that can cause activation of muscle nociceptors and pain. Sensitization of peripheral nociceptors ensues, leading to increased local tenderness and referred pain. The sensitization can also take place at the spinal level, where dorsal horn neurons develop increased responsiveness as well as expanded receptive fields.[2] Some clinical features of myofascial pain disorder include localized tenderness in a taut band of muscles, headaches, restricted movement, stiffness of muscles, weakness of muscles, and autonomic dysfunction.[3]

Several treatment modalities for myofascial pain, including the stretch and spray technique, trigger point injection, Botulinum toxin injection, dry needling, acupuncture, pharmacological agents, massage, self-management, relaxation therapy, stress management, physical therapy, heat, ultrasound, exercise, electrical stimulation, transcutaneous electric nerve stimulation, biofeedback, and splint therapy, have gained varying degrees of acceptance.[4,5,6,7,8,9,10,11,12,13] Unfortunately, the therapeutic effect of these treatments has been poorly quantified, and the mechanisms underlying these treatments are not well understood. Thus, definitive treatment protocols for myofascial pain have not been emerged.

Acupuncture is becoming increasingly widespread in the United States. The U.S. Food and Drug Administration estimated that 9-12 million acupuncture treatments are provided each year and at least 80 private insurers and Medicaid programs in some states cover acupuncture for certain disorders.[14] In 1996, the U.S. Food and Drug Administration promoted acupuncture needles from the investigational and experimental medical device category to the regular medical-device category,[15] and the following year the U.S. National Institutes of Health (NIH) consensus statement on acupuncture supported the treatment efficacy of acupuncture for specific conditions such as pain, nausea, and vomiting control.[16] Despite this increased recognition of acupuncture as a treatment for pain, evidence for its efficacy has been largely anecdotal or based on poorly designed studies.[17] Appropriate controls, sample sizes, and blinding are often lacking in a dynamic, patient-centered study milieu.[18]

Acupuncture has been used in the treatment of disease or pain for thousands of years. Traditional acupuncturists believe that every disease or complaint is caused by an imbalance of energy flow ("chi") throughout the body and that this imbalance can be corrected by inserting needles into specific acupoints that are mapped along meridians on the human body.[19] Such philosophical concepts are not compatible with modern Western medicine understanding of physiology; and. modern acupuncturists have attempted to explain acupuncture in terms of Western science. They suggest that the mechanical action of needling causes receptors to send neural impulses to the spinal cord to act on ascending pathways to the brain and cause the release of neurotransmitters that subsequently modulate pain processing in the brain. This alternative theory of the mechanism of acupuncture is based on studies that have used acupuncture to treat head and neck pain. [20,21,22,23,24,25,26,27,28] It has also suggested that acupuncture-induced analgesia is mediated by the release of endogenous opioids.[29] Results from human and animal studies, with the help of positron emission tomography and functional MR imaging, support these suggestions.[30,31,32,33] Acupuncture at acupoints Stomach.36 (on the leg) and Large intestine 4 (on the hand), in healthy subjects demonstrated activation of the anterior cingulate cortex, hypothalamus, and somatosensory cortex, thus implicating endogenous pain modulation circuits in the brain.[34, 35] Manual needle manipulation at Hegu large intestine 4 acupoint produced prominent decreases of fMRI blood oxygen level dependent (BOLD) signals in the posterior cingulate, superior temporal gyrus, putamen/insula.[36] Another study found that the anterior cingulate cortex and thalamic areas were activated as a result of noxious stimulation. [37] Decreased activation in these areas was noted following both meridian acupuncture and sham acupuncture, indicating that acupuncture appears to inactivate the brain regions involved in the transmission and perception of pain. These findings, however, have raised questions as to whether the effect of acupuncture is due to a placebo effect,[38,39] since studies have established a physiological basis for placebo analgesia.[27, 30, 40] Therefore, it is important to distinguish these possibilities.

Although laboratory evidence supports a physiological basis for acupuncture analgesia, the efficacy of acupuncture for chronic pain relief in humans remains in question. The purpose of this study was to assess the short term effects of acupuncture on myofascial pain and to examine the effects of acupuncture on brain activations through the use of functional magnetic resonance imaging (fMRI), a technique that detects changes in regional blood oxygenation as an index of neuronal activity.[41] Functional MRI has been used with wide success in the mapping of human brain functions.[42] I hypothesized that acupuncture at Hegu large intestine 4 (LI4) would reduce pain and decrease of fMRI BOLD signals in the anterior cingulate cortex and thalamus, brain areas known to be associated with nociception. LI4 acupoint was chosen because it has been associated with analgesic effects. [26, 43,44,45,46] Since few studies of acupuncture have correlated clinical outcome with changes in brain activation, such could help in understanding the neural basis of acupuncture analgesia.

MATERIALS/METHOD

Target Population

Patients seeking treatment from the UCSF TMD Center were considered for participation in this study. All adult subjects diagnosed with chronic myofascial pain who met the following criteria were invited to participate.

To be included, participants must:

1. Be at least 18 years of age.

2. Have a diagnosed chronic myofascial pain syndrome of the masticatory muscles
3. Have had chronic pain (at least 4 times/week) in the jaw muscles for at least twelve weeks
4. Have pain severity of at least 4 on a 0 to 10 numerical scale lasting at least 1 hour per day
5. Have pain in the jaw, temples, face, pre-auricular area, or in the ear at rest or during function

Individuals meeting the following criteria were excluded from participation:

1. Claustrophobia evolved by confinement in MRI scanner.
2. Pregnancy
3. Current opioid use.
4. Existence of metabolic disease (e.g., diabetes, hyperthyroidism), coagulopathies (e.g., hemophilia, anti-coagulants), neurologic disorders (e.g., dyskinesia, trigeminal neuralgia), vascular disease (e.g., migraine, hypertension), or neoplasia

Experiment Location/Approval

All experiments were conducted at the UCSF China Basin Landing Radiology Department. Approval for clinical research was obtained by the UCSF Committee on Human Research. (CHR#H9237-23642-01A) Funding was provided by the UCSF Osher Center for Alternative and Integrative Medicine.

Experimental Design

Randomization

The treatment (ie. acupuncture or sham acupuncture) was randomly assigned to study subjects based on order of involvement. Twenty subjects were screened for participation. Of these, eight failed to qualify; the remaining twelve subjects completed the study.

Blinding

Because this study involved acupuncture, it was not possible to blind the acupuncturist to the treatment (ie. acupuncture or sham acupuncture); therefore an independent observer, who was blinded to the treatment, collected the data from the study subjects, who were also blinded to the treatment.

Materials

Acupuncture needles (Seirin 30 gauge) were used for all subjects. To apply sham acupuncture, the needles were shortened by 10 mm and blunted to avoid actual piercing of the skin. To maintain blinding to the study subjects and the data collector, the needles were inserted through a poly foam paid, 10 mm x 10 mm x 10 mm thick (Ace weather strip, Oak Brook, Illinois 60521 USA).

Hegu Large Intestine 4 Acupoint

LI4 acupoint is located at the highest point of the adductor pollicis muscle between the thumb and index finger. The radialis nerve innervates this site. This acupoint is commonly used for head and neck pain. A neuroimaging study of this acupoint observed that stimulation of this acupoint activated jaw and face projection areas of the brain, suggesting that this acupoint might be appropriate for treatment of head and neck pain.[47] A single needle acupuncture treatment modality was used for this study because past studies have shown this to be enough to obtain a clinical result. [48,49,50]

PROCEDURES

Clinical Protocol

All subjects were asked to discontinue any analgesic medication 24 hours prior to the study. Informed consent to participate in the study was obtained from all subjects. All experiments were performed by a state certified dental acupuncturist, who was instructed not to discuss the treatment during interventions.

Psychophysical responses were recorded before and after treatment. Each subject rated severity of jaw and face pain, jaw and face tightness, headache, neck pain, and tooth pain on a 10-point numerical analog scale (NAS). A mechanical stimulus was applied with a pressure algometer placed on the right masseter muscle at the angle of the right mandible. A sticker dot was placed onto each subject's right masseter to mark the placement of the algometer. With the subject comfortably supported and relaxed, the stimulus was applied directly over the right masseter, at a rate of 1 lb./min until the subject raised his/her hand at maximal tolerable pain. The pressure algometer reading was recorded and the subject was asked to rate his/her pain to the mechanical stimulus on a visual analog scale (VAS).

Prior to the treatment of each subject, the skin at the LI4 acupoint was wiped with alcohol pads, air dried, and then covered with the foam pad [Figure 1]. The subject was positioned supine altitude and instructed to close the eyes and relax throughout the imaging session. To reduce motion artifact, subjects' heads were immobilized with foam support cushions and adhesive strips. The MRI technician signaled commencement of a run. After an initial baseline scanning for two and a half minutes, the acupuncturist tapped the foot of the subject to begin teeth clenching for 2 minutes. The subjects were instructed to clench at maximal force. After a thirty second rest, following the clench, the acupuncturist performed the acupuncture/sham protocol by inserting the needle through the foam pad. The acupuncturist used a clear guide tube to insert the needle through the foam pad to ensure accurate penetration depth.

Actual acupuncture consisted of needle insertion through the sterile foam pad into the left hand LI4 acupoint to a depth of 10-20 mm. The depth of the needle into tissue was estimated by subtracting the 10 mm thickness of the foam pad from the 30 mm length of the needle. Sham acupuncture consisted of a blunted needle insertion through the sterile foam pad, positioned 1 cm distal to LI4 acupoint, until the needle touched and did not penetrate the skin [Figure 1]. Other studies have used similar control methods that were found to be valid. [51,52]

The acupuncture needle was left in place for five minutes, after which time re-stimulation was performed by quick quarter turns of the needle for 5 seconds. The needle remained in place for another ten minutes. After a total of fifteen minutes, the subject was removed from the MRI tube and the acupuncturist removed the needle and foam pad. The time course of the entire scan was twenty minutes [Figure 2]

After the acupuncture procedure and the fMRI scan were completed, subjects were re-evaluated for general jaw and face pain, jaw and face tightness, headache, neck pain, and tooth pain on a NAS pain rating scale. Mechanical stimulation with the algometer was repeated, using the same pressure at the same location determined at the beginning of the experiment. Finally, subjects were asked whether they believed they received real or sham acupuncture.

Magnetic Resonance Imaging

All brain imaging was performed with a 3.0 Tesla GE Signa MRI System [GE Medical Systems, Milwaukee,Wisconsin) equipped for echo planar imaging. The first five subjects were scanned with a 2 channel head coil; remaining subjects were scanned after the headcoil was upgraded to 8 channels.

The imaging protocol: First, a 3-plane spoiled gradient echo scout localizer image (7.8 /1.7 repetition time msec/echo time msec; 30 degree flip angle, 24 cm field of view, 256 x 256 matrix, 1 mm through-plane resolution, 5mm thick with 1.5 mm skip), consisting of axial, coronal, and sagittal plane images, was obtained. To orient for subsequent acquisitions, 25 contiguous axial sections along the anterior commissure-posterior commissure line covered both cerebral hemispheres. This localizer image also was used as the structural image for transformation to Talairach coordinates of the imaging data.

An automated shimming technique was used to optimize B_0 (constant magnetic induction field) homogeneity. This was followed by acquisition of a 2-plane pulse sequence axial echo gradient localizer scan (3,000/35, 90 degrees flip angle, 3 mm x 3 mm in plane resolution, 5 mm thick with 0 mm skip, 24 cm field of view, 128 x 128 matrix, 25 slices), for use as the structural scan for Talairach transformation.

Lastly, a gradient T2*-weighted sequence was performed. Twenty-five contiguous axial slices (5 mm thick with 0 mm skip) parallel to the anterior and posterior commissure covering the entire brain were imaged with 3,300 ms repetition time, 40/80 ms echo time, 90 degree flip angle, 24 cm field of view, 2 x 2 x 5 mm voxel resolution, 256 x 256 matrix, and 20 x 20 cm in-plane spatial resolution. This sequence, which is sensitive to signal changes that arise from small changes in blood oxygenation, was used for measurements of brain activation.[46]

The entire brain scan repeated once every 3 seconds for twenty minutes. Each functional scan session generated 400 sets of images.

Image Processing

fMRI data were analyzed using Matlab 7.2 (Math Works Inc, Natick, MA) and statistical parametric mapping (SPM2) software (Wellcome Department of Cognitive Neurology, London, UK).

Motion Correction/Realignment- The data were pretreated by removing the first three images to eliminate non-equilibrium effects of magnetization. All volumes of functional images were spatially realigned to the first image to correct for movement using a ratio-variance minimization algorithm (called "automatic image registration"). A mean image created from the realigned volumes was co-registered with the subject's individual structural T1-weighted volume image.

Normalization- Both morphologic and functional imaging data for each subject were transformed to correspond to the Talairach stereotactic system. The structural volumes were spatially normalized to the standardized Talairach coordinates template.[53] Talairach-transformed functional data were intensity scaled so that all mean baseline raw

MR signal intensities were equal. Group data for each stimulation paradigm were obtained by averaging the Talairach-transformed functional data across the grouped subjects.

Smoothing- Spatial smoothing was by 12 mm. Temporal smoothing was carried out by using the Gaussian kernal high-pass filter to reduce noise that cycled every 1,024 seconds. These were performed to decrease the spatial noise and smooth adjacent voxels in order to increase signaling and contrasts of activated/deactivated sites.

Statistical Analysis

Ninety-five percent confidence intervals were compared for mean outcome per group and used to perform significance tests at the 5% level of significance ($\alpha = 0.05$). Fisher's Exact Test was used to determine whether what the subjects thought they received had a relationship with what they actually received. A t-test assuming equal variances was used to determine whether age, baseline facial pain, baseline neck pain, and baseline headache were significant variables between real and sham acupuncture groups. To determine if there were significant differences between groups or between pre-treatment and post-treatment measures, two-way repeated measures ANOVAs with one within subjects factor (time) and one between subjects factors (group) were performed for each dependent variable measured (ie. face pain, headache, neck pain, pain with mechanical stimulation). To answer the question of whether the subject's belief that he/she received acupuncture is a more important predictor for improvement in pain than whether or not they actually received real acupuncture, the same ANOVAs were performed except that the between subjects factor consisted of those who believed they had received acupuncture and those who believed they had received sham acupuncture. Since this study involved multiple comparisons, (face pain, headache, neck pain, and masseter muscle tolerance), the alpha-level was set at 0.0125 (ie. 0.05 ÷ 4) for a Bonferroni-type correction.

Image Analysis

Talairach coordinates-transformed imaging data were averaged for a group analysis. Voxel-by-voxel statistical mapping and anatomic localization was performed. Stimulation-induced changes in functional MR imaging signal intensity were assessed by using Kolmogorov-Smirov statistical maps constructed from these averaged data sets. A high pass filter of 1,024 seconds to control for the long duration of the scans.

A contrast map was calculated to compare cerebral activations after clenching with before clenching and after clenching with during acupuncture. Group data were analyzed by using Bonferroni-uncorrected fixed effects analysis, and all reported volumetric activations showed *P* values <0.01. All maps had a threshold at $P<0.01$ (uncorrected, two-tailed) with a minimum cluster of 84 voxels. Kolmogorov-Smirov maps for group results were created for significant changes in signal intensity established with a P value of less than 0.01. Brain areas with increased signal intensity during the stimulation period were defined as activated areas, and those with decreased signal intensity during the stimulation period were defined as deactivated areas. An increased signal reflects an increased cerebral blood flow while a decreased signal reflects a decreased cerebral blood flow resulting from suppression of neuronal metabolic activity. Statistical maps were superimposed on conventional T1-weighted images that also had been transformed into the Talairach domain.

The time courses of signal intensity changes were evaluated for each putative activation or deactivation identified on statistical maps derived from averaged data. These signal intensity vs. time determinations were assessed to ascertain that the changes in signal intensity did not precede stimulus presentation and that the changes specifically followed performance of the stimulation paradigm. All activations and deactivations had to follow these two criteria. All blood oxygen level dependent (BOLD) related signal contrasts were made between the rest period after clenching and the first five minutes of acupuncture treatment.

RESULTS

Psychophysical Assessments

A total of twelve subjects participated in the study. All twelve (one male and eleven female) subjects completed the study. There were no significant differences in demographic characteristics between acupuncture and sham acupuncture groups. [Table 1]

Half of the subjects correctly identified as having received acupuncture. A majority of the subjects that received sham acupuncture believed the treatment modality to be acupuncture. [Table 2] The subjects were not able to predict which experimental condition they received. [Fisher's Exact Test; $p = 0.242$]

Because many of the subjects reported no toothache, there was insufficient data to analyze, so toothache was omitted from analysis. Face tightness was also dropped from analysis because subjects rated facial tightness the same as facial pain, indicating a lack of differentiation between the two variables. For the other general symptoms of myofascial pain, acupuncture and sham acupuncture were not significant for decreasing masseter muscle tolerance pain, facial pain, headache, and neck pain. [Table 3, Table 4, Graph 1] For facial pain, the ANOVA showed that neither the main effect of time ($F(1,10)=4.747$, $p=0.054$), the main effect of group ($F(1,10)=0.409$, $p=0.537$), nor the time (x) group interaction ($F(1,10)=1.709$, $p=0.220$) were significant [Diagram 1]. For headache, the ANOVA showed that neither the main effect of time ($F(1,10)=0.286$, $p=0.604$), the main effect of group ($F(1,10)=0.055$, $p=0.820$), nor the time (x) group interaction ($F(1,10)=1.934$, $p=0.195$) were significant [Diagram 2]. For neck pain the ANOVA showed that neither the main effect of time ($F(1,10)=0.754$, $p=0.406$), the main effect of group ($F(1,10)=2.249$, $p=0.165$), nor the time (x) group interaction ($F(1,10)=0.138$, $p=0.718$) were significant [Diagram 3]. For masseter muscle pain to mechanical pressure, the ANOVA showed that neither the main effect of time ($F(1,10)=0.070$, $p=0.797$), the main effect of group ($F(1,10)=0.039$, $p=0.847$), nor the time (x) group interaction ($F(1,10)=1.579$, $p=0.237$) were significant [Diagram 4].

The effect of the perception of treatment was also considered. When subjects believed that real acupuncture was received, there was a significant decrease in facial pain and headache [Table 5, Table 6, Graph 2]. For facial pain, the ANOVA showed that the time (x) group interaction ($F(1,10)=10.787$, $p=0.008$) was significant, however the main effect of time ($F(1,10)=2.697$, $p=0.132$) and the main effect of group ($F(1,10)=2.307$, $p=0.160$) were not significant, indicating that the belief of receiving acupuncture significantly reduced facial pain after treatment [Diagram 5]. For headache, the ANOVA showed that the time (x) group interaction ($F(1,10)=6.755$, $p=0.027$) was significant, however the main effect of time ($F(1,10)=0.072$, $p=0.793$) and the main effect of group ($F(1,10)=2.519$, $p=0.144$) were not significant, indicating that within the group of individuals believing they received acupuncture, headache was significantly reduced after treatment [Diagram 6]. For neck pain, the ANOVA showed that neither the main effect of time ($F(1,10)=0.151$, $p=0.706$), the main effect of group ($F(1,10)=1.095$, $p=0.320$), nor the time (x) group interaction ($F(1,10)=2.411$, $p=0.152$) were significant [Diagram 7]. For masseter muscle pain to mechanical pressure, the ANOVA showed that the main effect of group ($F(1,10)=7.954$, $p=0.018$) was significant, however the main effect of time ($F(1,10)=0.755$, $p=0.405$) and the time (x) group interaction ($F(1,10)=3.271$, $p=0.101$) was not significant, indicating that between the groups, the individuals that believed they received acupuncture significantly increased the pain tolerance of the masseter muscle [Diagram 8].

Functional MR Imaging Findings

Midway through the study, the MR imaging system was upgraded from a 2-channel head-coil to an 8-channel head-coil system, thereby rendering the pre-upgrade data (5 subjects) incompatible with the post-upgrade data (7 subjects) because of differences in resolution between the two techniques. There were 3 sham acupuncture and 2 real acupuncture subjects in the pre-upgrade group, and 3 sham acupuncture and 4 real acupuncture subjects in the post-upgrade group.

Group results were emphasized in this study because not all subjects showed activation in the foci determined from the group results, which may reflect the clinical observation that individual variation is common in the treatment response of acupuncture therapy.[40,54,55] The foci determined are based on clusters of voxels; each voxel is sized 2 mm x 2 mm x 2 mm. The small size of the voxels can present the same brain region as being both activated and deactivated, even though the precise location of the voxels within the region is actually different.

Prior to clenching during the baseline scanning, there was significant activation of the middle frontal gyrus, lingual gyrus, and superior occipital gyrus [Figure 3]. Immediately after clenching, there was significant activation of the nucleus caudalis [Figure 4]. Both treatments commonly activated the precentral gyrus and deactivated the middle frontal, parietal lobule, and temporal gyrus. Acupuncture induced significant activation (signal intensity increased during acupuncture stimulation period as compared with during the rest period) of the primary sensory cortex [Figure 3] and significant deactivation (signal intensity decreased during acupuncture stimulation period as compared with that during the rest period) of the limbic system [Figure 4]. Sham acupuncture significantly activated the primary sensory cortex and activated and deactivated specific parts the limbic system. All detailed results are shown in Table 7.

Contrasts between acupuncture and sham acupuncture showed that both acupuncture [Figure 4] and sham acupuncture [Figure 5] significantly deactivated the primary somatosensory cortex, middle frontal gyrus, parietal lobule, and temporal gyrus were deactivated in both groups.

Contrasts between subjects that believed they received acupuncture and subjects that believed they received sham acupuncture showed that those that believed they received acupuncture yielded a significantly greater activation of the primary somatosensory cortex and limbic system [Figure 7]. Subjects that believed they received sham acupuncture significantly deactivated the somatosensory cortex [Figure 8].

Contrasts between subjects that actually received acupuncture and subjects that believed they received acupuncture showed significant deactivation of the limbic system in both groups. The comparison of subjects that actually received sham acupuncture with subjects that believed they received sham acupuncture showed no commonality for activated and deactivated sites.

DISCUSSION

The functional MR imaging findings were insufficient to support the hypothesis that acupuncture significantly deactivated the thalamus and anterior cingulate cortex to reflect the CNS pathways that mediate the acupuncture effect in previous studies.[56, 57] The anterior cingulate cortex is known as a modulator of the internal emotional response to pain[58] and has been associated with pain effect.[59,60,61] If there was deactivation at these sites, the intensity of BOLD fMRI signals during acupuncture were equivalent to the intensity of BOLD fMRI signals after clenching. Clenching significantly activated the nucleus caudalis, indicating that it was a valid pain stimulus. The results were consistent with the findings of past studies that found significant cerebral processing of alternative sites to support the CNS pathway that mediates acupuncture analgesia. Further, the findings in this study showed that the belief of receiving acupuncture significantly established a greater analgesic effect, also known as the placebo effect, than actual acupuncture.

Pre-Treatment Effect

All subjects had a baseline at moderate pain level prior to clenching [Table 1]. During baseline, there was significant activation of the middle frontal gyrus, lingual gyrus (occipital lobe), and superior occipital gyrus, which have been associated with a tendency for activation patterns of these sites in chronic pain individuals.[62] After clenching, there was significant activation of the nucleus caudalis, an anatomical site that has been associated with jaw muscle pain.[63, 64] Activation of this site had a positive correlation with the increased pain level subjects felt after clenching [Table 1]. This validates that clenching was a sufficient pain stimulus.

Actual Treatment Effect

Acupuncture treatment did not demonstrate efficacy beyond sham acupuncture in any of the outcome measures, similar to the findings of previous studies that showed a lack of significant effect from acupuncture in the treatment of acute pain.[65, 66, 67, 68] The face and neck pain of the chronic myofascial pain patients did reduce with real acupuncture, but these were not statistically significant effects, perhaps because the effect size was too small to detect with the number of participants. Both electroacupuncture[69] and dry needling[70] have been shown to provide significant myofascial pain relief in studies with larger sample sizes and more treatment sessions.[71,72] Sham acupuncture had an even greater reduction of the outcome measures, but these were also not statistically significant.

During acupuncture, there was positive brain activation of the primary sensory cortex. The primary sensory cortex has commonly been found to be activated with real acupuncture. [61, 73, 74, 75] Activation of the primary sensory cortex connects with the cerebral cortex for control of fine movements in the face. If explained by Eastern medicine philosophy, acupuncture needles placed along the LI4 meridian of the body elicits a "de qi" sensation from the hand to the face. By Western medicine terms, "de qi" sensations are micro-twitches that stimulate A-delta fibers[76,77,78] to inhibit C- fibers by activating dorsal horn interneurons and inducing a cascade of endorphins and monoamines to activate mu receptors to effectively alleviate pain. [66, 67,79, 80, 81, 82, 83,84]

Activation of the primary sensory cortex corroborates this acupuncture theory because of the positive correlation with the reduction of face pain and neck pain in subjects that received acupuncture.

Acupuncture deactivated sites of the limbic system, which were the subcallosal gyrus, cingulum (cingulate cortex), precuneus, tapetum (insular cortex), and major forceps (corpus callosum). The limbic system is suggested to participate in the affective cognitive aspect of pain perception.[85,86] By deactivating the limbic system, there is a decrease in pain perception by decreasing sympathetic autonomic responses through the crossed spinothalamic-cortico-limbic pathway. [75,87,88,89,90] Past studies on humans and animals have suggested that acupuncture acts as a neuromodulating input in the CNS that can activate multiple analgesia systems and stimulate pain modulation systems to release neurotransmitters such as endogenous opioids.[39,40,91,92,93,94] This deactivation shows a positive correlation with the reduced face pain, neck pain, and pain to mechanical pressure of subjects that received acupuncture.

Sham acupuncture induced a significant increase in neural activity of both the limbic system and primary somatosensory cortex. The limbic system involved the lateral pallidus globule (basal ganglia), nucleus caudalus (basal ganglia), insular cortex (fornix), thalamus (dorsomedial nucleus), cingulum, and parahippocampal gyrus. As discussed earlier, the limbic system participates in pain perception and has been activated by placebo analgesia.[95] Modulation of activity in these deeper brain regions are more likely mediated by axons ascending in the spinothalamic, spinoreticular, and spino-mesencephalic tracts; which relay sensory information to the somatosensory cortex. Activation of the limbic system would have demonstrated an increase in pain perception, however there was a negative correlation with the psychophysical response because subjects that received sham acupuncture felt a reduction in face pain, headache, and neck pain. Activation of the somatosensory cortex during sham acupuncture may have been due to the same reason as during acupuncture, where the pricking sensation from the blunted needle then triggers A-delta fibers to block C-fiber pain signals and induce an analgesic effect.

Interestingly, other parts of the limbic system, specifically the lateral pallidus globule (basal ganglia), putamen (basal ganglia), and insular cortex, were deactivated by sham acupuncture. The insular cortex is activated during the experience of pain, [85, 96, 97, 98] and by decreasing its activity, the pain sensations are reduced. Because deactivation of the putamen and insular cortex has been found with real acupuncture at LI4 acupoint[105], the placebo effect is evident here. This has a positive correlation with the reduced psychophysical pain levels of the sham acupuncture group.

The precentral gyrus of the somatosensory cortex was significantly activated for acupuncture and sham acupuncture conditions, suggesting that the neural pathway for tactile perception was commonly engaged. The somatosensory system mediates the sense of touch, temperature, and pain via the dorsal columnal medial lemnisscal pathway and the spinothalamic tract. The penetration of the acupuncture needle may have possibly activated this structure. Although sham acupuncture did not penetrate through the skin, activation over the somatosensory cortical areas were found.[61, 99] Because this was commonly engaged in both groups, the sham acupuncture may also have triggered acupuncture analgesia. This shows a positive correlation with the psychophysical response of sham acupuncture subjects feeling a decrease in facial pain, headache, and neck pain.

The middle frontal gyrus, parietal lobule, and temporal gyrus (middle and superior) were deactivated during acupuncture and sham acupuncture. The middle frontal gyrus is associated with the prefrontal cortex, which carries the functions of expectation, prediction, decision-making, and social "control." The parietal lobe has a somatosensory association with movement, orientation, and perception of stimuli. Activation of these sites may not be an acupoint-specific phenomenon, but a somatic-visceral sensory stimulation. The temporal lobe is associated with the auditory cortex and visual processing. Deactivation of these auditory-related areas may be associated with the decreased cognitive attention given to the rhythmic scanner noise of the MRI machine over time.

Perceived Treatment Effect

Precisely half of the subjects that received acupuncture treatment believed their treatment modality to be sham acupuncture. Some of the reasons could have been the subject did not feel a prick, the subject did not feel anything at all, or the subject did not recognize the "de-qi" sensation. This reduction in tactile sensation is evidenced by the significant decrease in the postcentral gyrus of the primary somatosensory cortex region in subjects that believed they received sham acupuncture but actually received acupuncture. The questionnaire did not ask about the "de-qi" sensation because the subject group consisted of volunteers who were acupuncture naïve. Therefore, these subjects would not know the sensations of true acupuncture and were less able to differentiate between the treatments. It has also been observed that the "de qi" needle sensation is an "unusual" experience that is difficult to describe, which leaves subjects uncertain about the sensation they feel or are supposed to feel when asked about the "de-qi" sensation. [100]

In this study, a majority of the subjects that received sham acupuncture believed the treatment modality to be acupuncture because the administration of sham acupuncture closely mimicked acupuncture. The blunted needle may cause a pricking sensation that simulates a needle penetrating the skin, therefore significantly activating the postcentral gyrus of the somatosensory cortex. The postcentral gyrus corresponds with the primary somatosensory cortex that is concerned with the initial cerebral processing of tactile and proprioceptive information. Another finding was that the subject's perception of the sham treatment as acupuncture treatment improved all pain levels, specifically the facial pain and headache significantly. Subjects that believed their treatment was sham acupuncture felt greater pain after treatment at all pain levels. Since the sham needles were placed away from the acupoint and non-penetrating, this decreased the possibility that the manual stimulation of the blunted acupuncture needle stimulated acupuncture-like effects and therefore, it is more likely that perception of acupuncture had an isolated analgesic effect, or also known as the placebo effect.

A contrast between subjects that believed they received real acupuncture and subjects that actually received acupuncture showed the commonality of deactivating the limbic system. The subjects that believed they received real acupuncture had a significant decrease in activity of the subcallosal gyrus, while the subjects that actually received acupuncture had a significant decrease in activity of the cingulum, subcallosal gyrus, and precuneus. These deactivated sites have a positive correlation with their psychophysical results of feeling some relief of the face and neck pain. Although there is evidence that modulation of the limbic system activity from acupuncture analgesia may relieve pain, [38,48,73,75] so can the belief of receiving acupuncture. [36,101,102] The significance of this is that the placebo effect is evident here.

The results of this study strongly suggest that acupuncture is possibly a uniquely effective method in the activation of positive placebo effects. The effects of placebos may reflect the capacity of an individual to recruit the endogenous opiate peptide system to release endorphins. [100,103,104] Several subjects had asked whether acupuncture has been used to treat myofascial pain before and the response that acupuncture has been used for myofascial pain may have been positive information that induced stronger expectations rather than neutral information. There has been evidence that expectations have been the stimulus for the generation of placebo analgesia.[105,106,107] There is also evidence that beliefs about complementary and alternative medicine have outcomes that are mediated through a placebo effect with subjects improving because they expect to do so.[108,109] This suggests that cognitive elements are involved in Pavlovian conditioning on the basis of the information that the conditioned stimulus provides about the unconditioned stimulus.[110,111,112] In other words, the conditioning procedure used in this study unintentionally produced increased expectations of benefit.

The overall change in face pain, headache, neck pain, and masseter muscle pain tolerance may actually be greater than statistically analyzed because of the pain stimulus used in this study. By clenching for 2 minutes, the prolonged activation of masseter muscles may have briefly exacerbated the pain of the facial muscles. This would cause myofascial pain to be elevated towards the level of allodynia or hyperalgesia, where nonpainful or normally painful stimulus would become even more painful. By elevating to the state of allodynia or hyperalgesia, detection of the true effect of acupuncture is limited because of the further increase in the subject's pain level prior to treatment. This may be why the subjects that actually received acupuncture seemed to have a lower masseter muscle pain tolerance and greater headache after clenching, when there is the possibility that if the subject's didn't clench, acupuncture may have reduced pain levels even more. In this study, all subjects continued to suffer low grade to moderate grade level of pain after treatment. This may be due to the continued excitability in peripheral tissues or central neural areas which may contribute to the persistence of jaw muscle tenderness. [113]

The psychophysical results of this study had several limitations. To understand in further detail the behavioral influence of pain with perception, the patients should have been asked to describe their "de qi" sensation and the reason for their perception. The importance of this is that often the presence of the de-qi state indicates the clinical acupuncture effect. [57,114] All subjects should also have been asked their prior expectations and beliefs towards acupuncture. To further exaggerate the acupuncture effect, the subjects should have received bilateral acupuncture treatment at Hegu L.I. 4. Further, an NAS and VAS should have been used for subjects to rate their facial pain and headache immediately after clenching. Without this data, detection of the true effect of acupuncture after clenching could not be analyzed. Besides testing the masseter muscle threshold, the functional capacity after acupuncture treatment should be tested as well. Measuring the range of motion in opening the jaw is of more importance to the subjects because at times, this is limiting with myofascial pain. Having a larger subject pool would increase the power of the study.

The functional MRI results of this study had its limitations. The Talairach map used to identify brain structures was based on a general template. This runs the risk of the misidentification of structures between subjects when all subjects are matched to this general template. Also, the scanned images were extremely sensitive to any head movement, which may increase the motion artifacts. With the long duration of 15 minutes of acupuncture treatment, only the initial five minutes of acupuncture treatment could be analyzed because there would be an accumulation of too much activation that would make the individual structures unidentifiable after fifteen minutes. Furthermore, the general conclusions drawn from this study is underpowered and activated sites may have been due to chance because with only twelve subjects in total, scans for each individual yielded some varied patterns of activation. This was expected as a pilot study.

CONCLUSION

In summary, acupuncture activated the primary sensory cortex and deactivated the limbic system. Sham acupuncture activated the primary sensory cortex and limbic system. There was also psychophysical evidence that the belief of receiving acupuncture elicited a placebo effect that had a significantly stronger analgesic effect than actual acupuncture treatment. Acupuncture and the belief of receiving acupuncture deactivated the limbic system, suggesting that acupuncture and a placebo effect can decrease the activity of brain sites related to pain.

TABLE 1: Subject Demographics

	Acupuncture (average)	Sham Acupuncture (average)	Total (average)	Paired t-test *p*-value
Age (yrs)	37.33 ± 12.97	44.5 ± 13.7	40.92 ±13.3	0.93
Male/Female	0/6	1/5	1/11	
Baseline Facial Pain (NAS)	5.5 ±1.52	7.17 ± 2.32	6.33 ± 2.06	0.17
Baseline Neck Pain (NAS)	4.0 ± 1.67	6.5 ± 2.59	5.25 ± 2.45	0.075
Baseline Headache (NAS)	3.67 ± 2.42	5.17 ± 3.6	4.42 ± 3.03	0.42
Pain to Mechanical Pressure (NAS)	7.8 ± 0.58	7.25 ± 0.86	7.53 ± 0.8	0.25
Pain After Clench	8.56 ± 0.73	6.06 ± 2.6	7.31 ± 2.4	0.1

TABLE 2: Actual Treatment vs. Perceived Treatment

	True Treatment		
Perceived Treatment	Real	Placebo	total
Real	3 subjects	5 subjects	8 subjects
Placebo	3 subjects	1 subjects	4 subjects
total	6 subjects	6 subjects	12 subjects

TABLE 3: Real Acupuncture Group Pain Readings

	Avg Pre-treatment Pain Level	Avg Post-treatment Pain Level	Average Change in Pain Level
Facial Pain (NAS)	5.5 ± 1.5	5.0 ± 3.7	-0.5
Headache (NAS)	3.7 ± 2.4	4.3 ± 3.6	0.667
Neck Pain (NAS)	4.0 ± 1.7	3.7 ± 4.1	-0.33
Mechanical Press. Pain (VAS;cm)	7.8 ± 0.6	7.3 ± 2.4	-0.533

* A negative number indicates a decrease in pain level. A positive number indicates an increase in pain level

TABLE 4: Sham Acupuncture Group Readings

	Avg Pre-treatment Pain Level	Avg Post-treatment Pain Level	Average Change in Pain Level
Facial Pain (NAS)	7.2 ± 2.3	5.2± 2.6	-2
Headache (NAS)	5.2 ± 3.6	3.7 ± 3.7	-1.5
Neck Pain (NAS)	6.5 ± 2.6	5.7 ± 2.4	-0.83
Mechanical Press. Pain (VAS;cm)	7.25 ± 0.9	8.1 ± 1.2	0.817

* A negative number indicates a decrease in pain level. A positive number indicates an increase in pain level

GRAPH 1: Actual Treatment Effect on Pain Readings

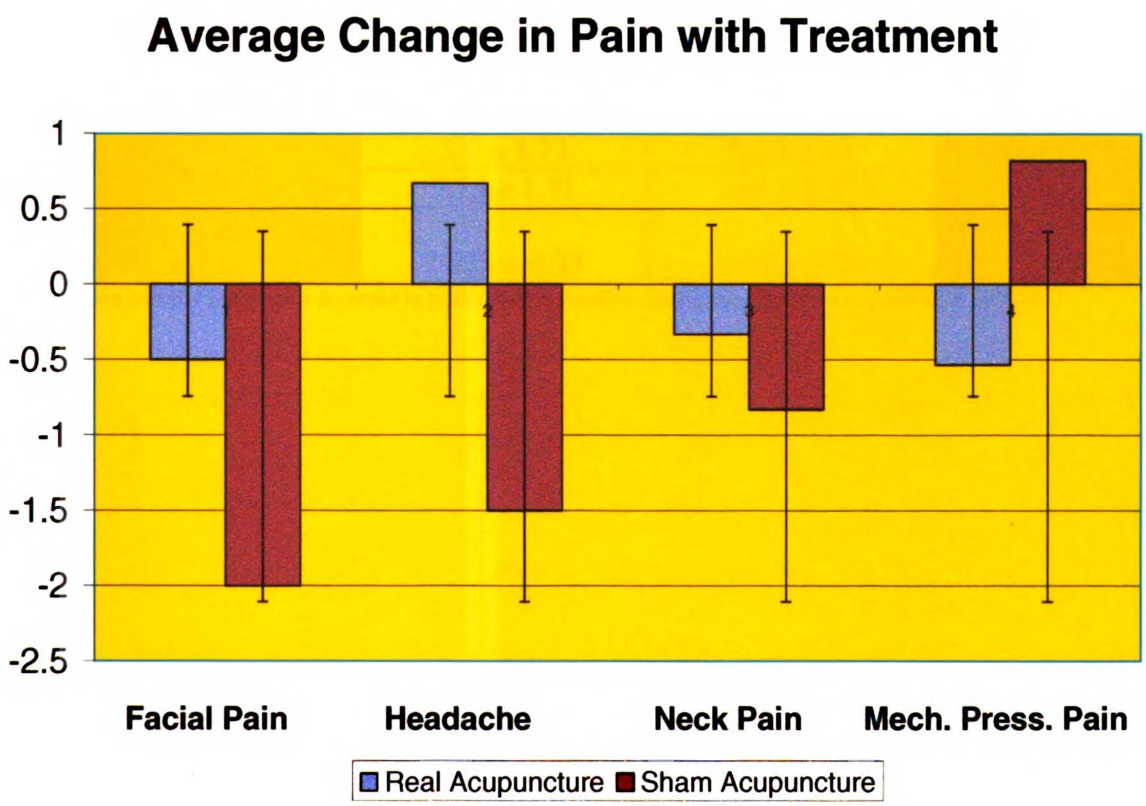


TABLE 5: Perceived Acupuncture Treatment

	Avg Pre-treatment Pain Level	Avg Post-treatment Pain Level	Average Change in Pain Level
Facial Pain (NAS)	6.125 ± 2.36	3.875 ± 2.42	-2.25
Headache (NAS)	4.125 ± 3.64	2.5 ± 2.78	-1.625
Neck Pain (NAS)	5.0 ± 2.82	3.75 ± 2.96	-1.25
Mechanial Press. Pain (VAS;cm)	7.375 ± 0.95	6.875 ± 1.71	-0.588

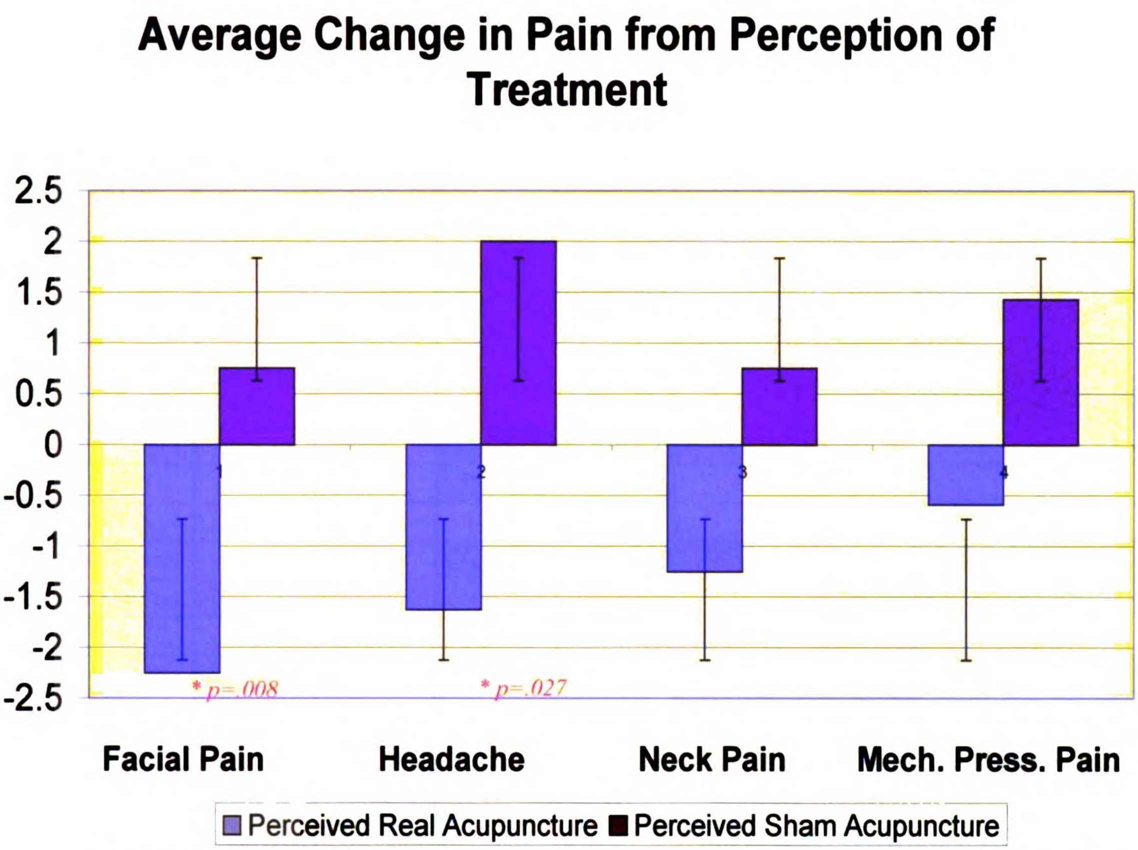
* A negative number indicates a decrease in pain level. A positive number indicates an increase in pain level

TABLE 6: Perceived Placebo Acupuncture Treatment

	Avg Pre-treatment Pain Level	Avg Post-treatment Pain Level	Average Change in Pain Level
Facial Pain (NAS)	6.75 ± 1.5	7.5 ± 3.11	0.75
Headache (NAS)	5.0 ± 1.73	7.0 ± 2.94	2
Neck Pain (NAS)	5.75 ± 1.71	6.5 ± 3.87	0.75
Mechanical Press. Pain (VAS;cm)	7.825 ± 0.25	9.25 ± 0.74	1.43

* A negative number indicates a decrease in pain level. A positive number indicates an increase in pain level

GRAPH 2: Perceived Treatment Effect on Pain Readings



* A negative number indicates a decrease in pain level. A positive number indicates an increase in pain level

TABLE 7: Functional MR Imaging Findings

	Individual Group of Average Significant Activations/Deactivations									
	Acupuncture		**Sham Acupuncture**		**Perceived Acupuncture**		**Perceived Sham Acupuncture**		**After clench**
BRAIN SITES	First 5 Subjects	Last 7 Subjects	First 5 Subjects	Last 7 Subjects	First 5 Subjects	Last 7 Subjects	First 5 Subjects	Last 7 Subjects	ALL subjts
Frontal Gyrus									
Superior	+/—	+		+	+	+	+	+	
Middle	+/—	—	+	+/—					+
Inferior			+/—	+/—			+	+	+
Temporal Gyrus									
Superior	+/—		—				+	+	+
Middle	—		+	—	+	+			+/—
Inferior	+	—							
Transverse			—						
Fusiform Gyrus	+/—	+/—	—	+	+	+	+	+	—
Occipital Gyrus									
Superior		+			+	+			—
Middle	+	+					+	+	
Inferior	—	+		+	+	+			
Cuneus			+						
Lingual Gyrus	—	—			+	+			—
Parietal Lobule									
Superior		—	—		+	+			+
Inferior			+	—	+	+			+
Somatosensory Cortex									
Primary (precentral gyrus/premotor cortext)	+	+	+/—	+/—					
Paracentral Lobule (primary cortex)	+		—						
Postcentral gyrus				+	+	+	+	+	
Cingulate Gyrus			+						
Visual System									
Optic Radiation	—	+							
Optic Tract			—						

* A "+" indicates a Bonferroni uncorrected significant activation. A "—" indicates a Bonferroni uncorrected significant deactivation. A highlighted box indicates the site as significant in contrast to another group.

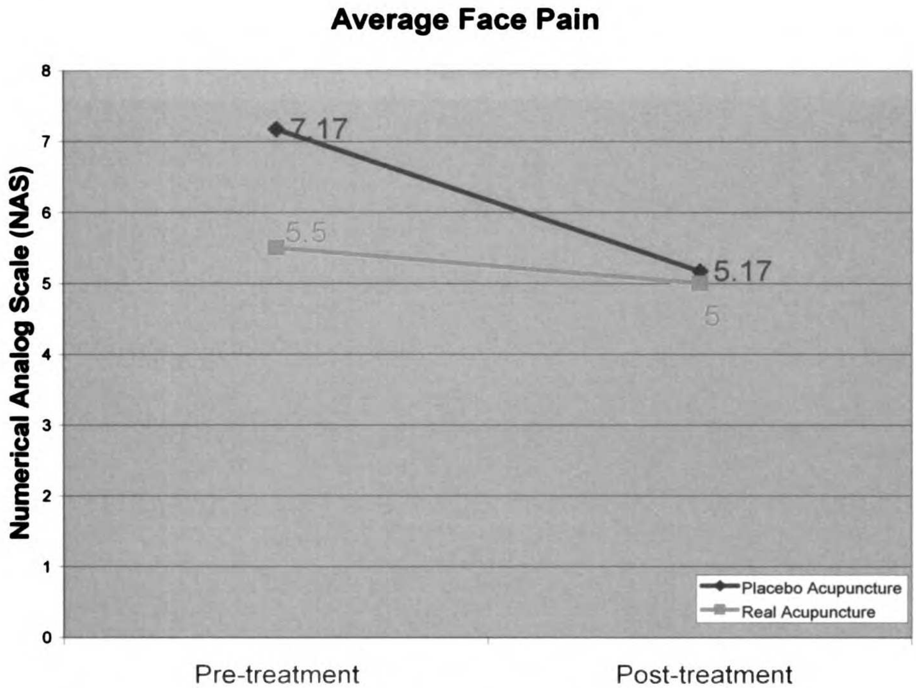
TABLE 7 (continued)

	Individual Group of Average Significant Activations/Deactivations								
	Acupuncture		Sham Acupuncture		Perceived Acupuncture		Perceived Sham Acupuncture		After clench
BRAIN SITES	First 5 Subjects	Last 7 Subjects	First 5 Subjects	Last 7 Subjects	First 5 Subjects	Last 7 Subjects	First 5 Subjects	Last 7 Subjects	ALL subjts
Limbic System									
Precuneus	—								
Cuneus									—
Basal Ganglia									
Lateral Pallidus Globule			+/—						
Nucleus caudalis				+					+
Putamen			—						
Lateral Ventricles	+	+							—
Insular Cortex	—								
Insula				—					
Fornix			+		+	+			
Tapetum	—								
Major forceps	—								
Cingulate Cortex									
Cingulum		—		+					
Subcallosal Gyrus	—						+	+	
Parahippocampal gyrus				+					
Thalamus/ Hypothalamus									
Dorsomedial Nucleus			+						
Inferior Logitudinal Fasciculus			—						

* A "+" indicates a Bonferroni uncorrected significant activation. A "—" indicates a Bonferroni uncorrected significant deactivation. A highlighted box indicates the site as significant in contrast to another group.

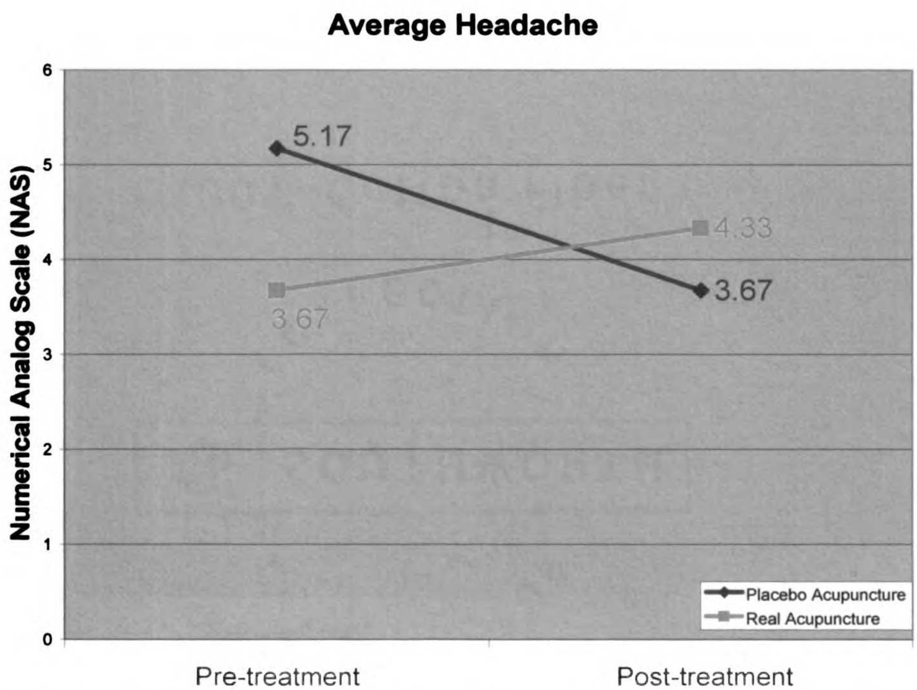
Yellow	Sites significantly activated/deactivated during acupuncture
Blue	Sites significantly activated/deactivated during sham acupuncture
Pink	Sites significantly activated/deactivated during perceived acupuncture
Green	Sites significantly activated/deactivated during perceived sham acupuncture
Orange	Sites significantly activated/deactivated after clenching

DIAGRAM 1: Acupuncture Treatment Effect on Face Pain



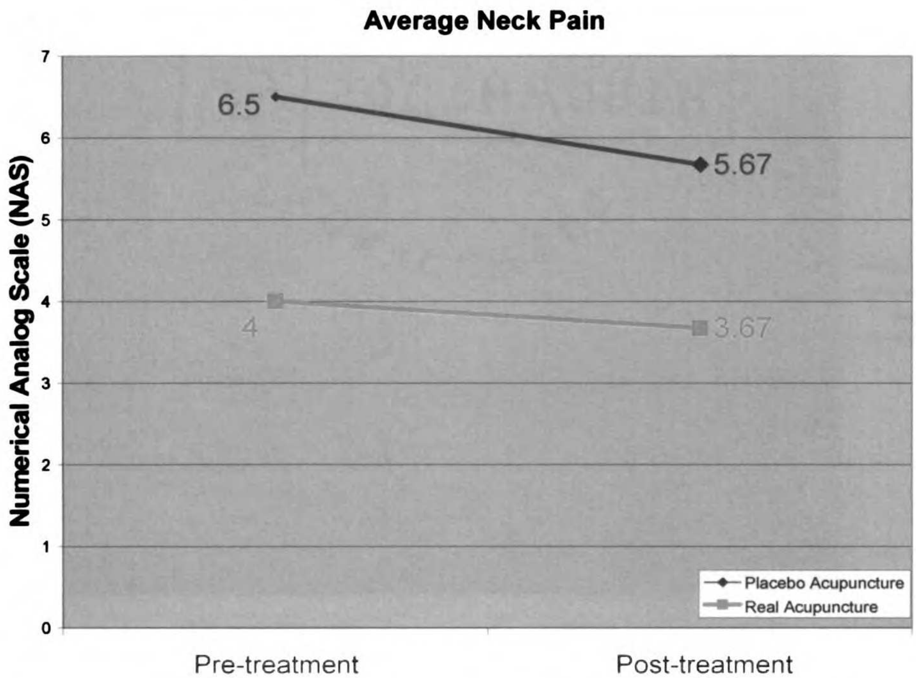
Average facial pain of subjects pre-acupuncture and post-acupuncture grouped by actual treatment given.

DIAGRAM 2: Acupuncture Treatment Effect on Headache



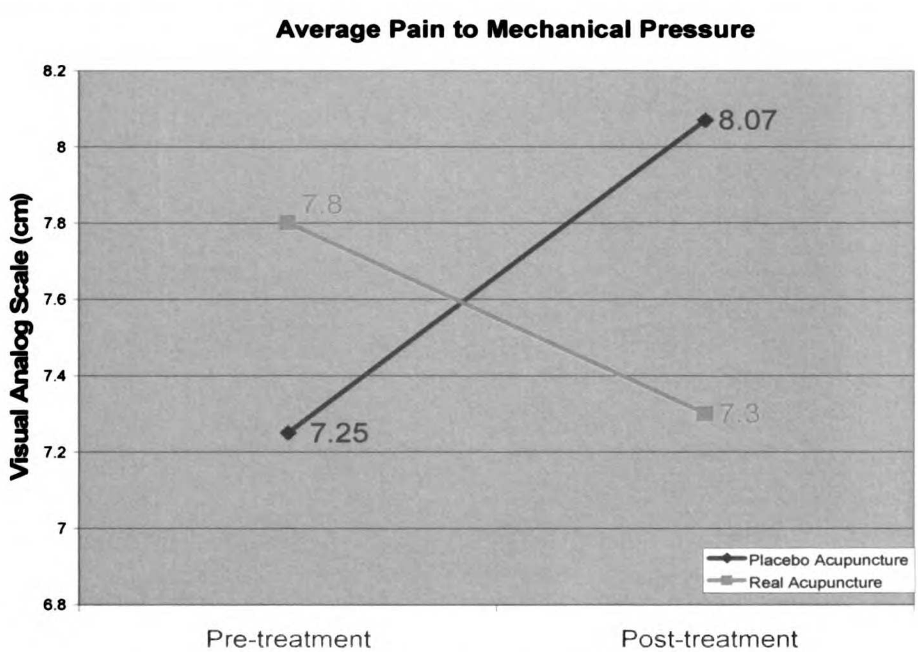
Average headache of subjects pre-acupuncture and post-acupuncture grouped by actual treatment given.

DIAGRAM 3: Acupuncture Treatment Effect on Neck Pain



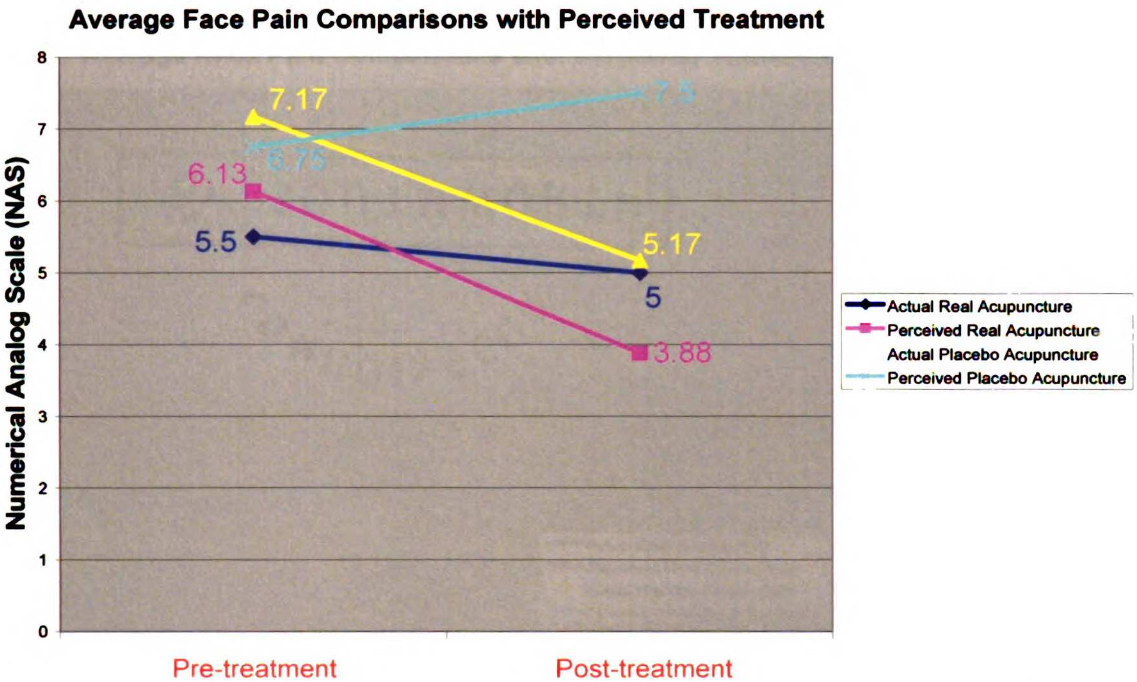
Average neck pain of subjects pre-acupuncture and post-acupuncture grouped by actual treatment given.

DIAGRAM 4: Acupuncture Treatment on Mechanical Pressure Pain



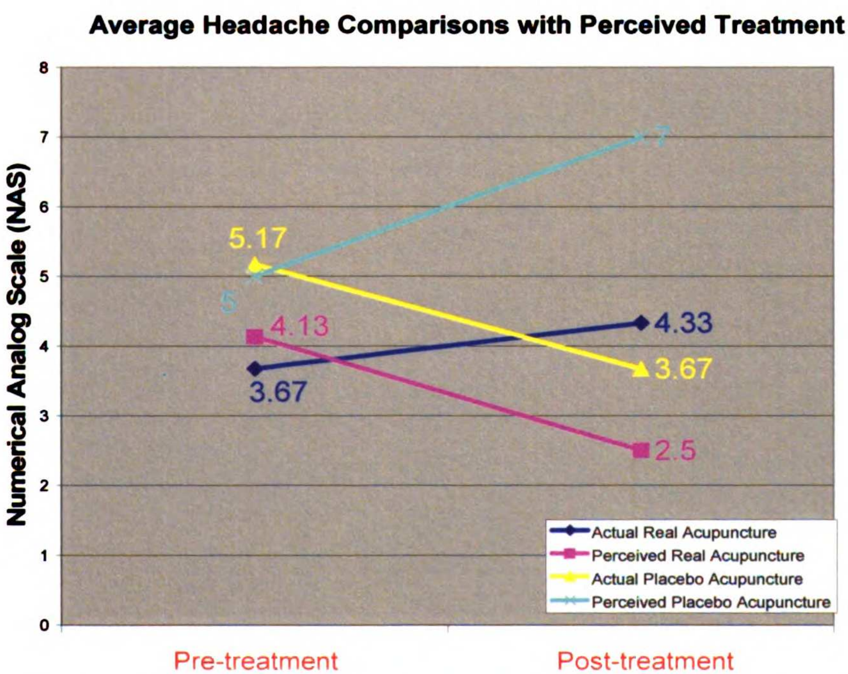
Average pain to mechanical pressure of subjects pre-acupuncture and post-acupuncture grouped by actual treatment given.

DIAGRAM 5: True Treatment vs. Perceived Treatment on Face Pain



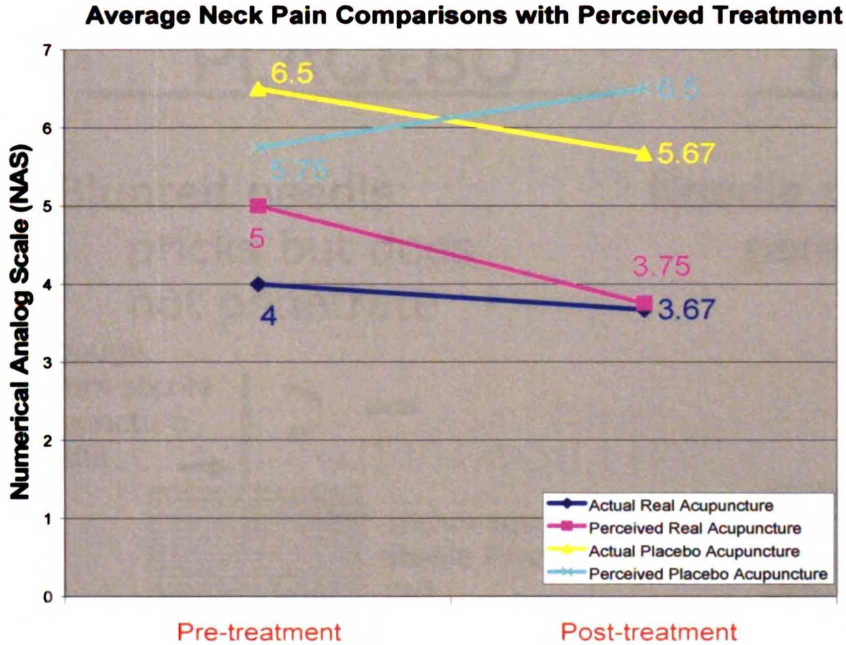
Comparison of treatment effect on facial pain between subjects that actually received acupuncture and subjects that believed they received acupuncture.

DIAGRAM 6: True Treatment vs. Perceived Treatment on Headache



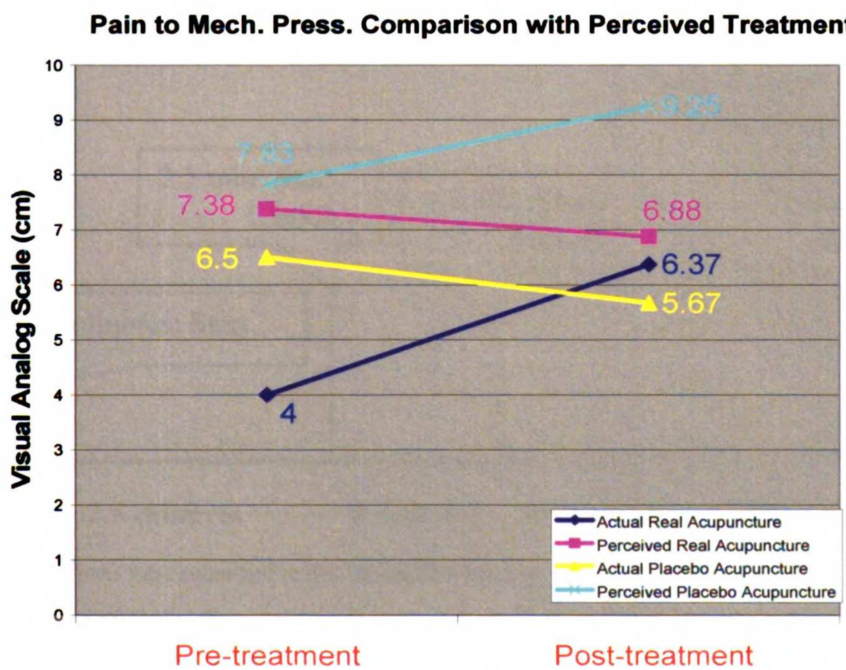
Comparison of treatment effect on facial pain between subjects that actually received acupuncture and subjects that believed they received acupuncture.

DIAGRAM 7: True Treatment vs. Perceived Treatment on Neck Pain



Comparison of treatment effect on neck pain between subjects that actually received acupuncture and subjects that believed they received acupuncture.

DIAGRAM 8: True Treatment vs. Perceived Treatment on Mechanical Pressure Pain



Comparison of treatment effect on pain to mechanical pressure between subjects that actually received acupuncture and subjects that believed they received acupuncture.

FIGURE 1: Acupuncture Method

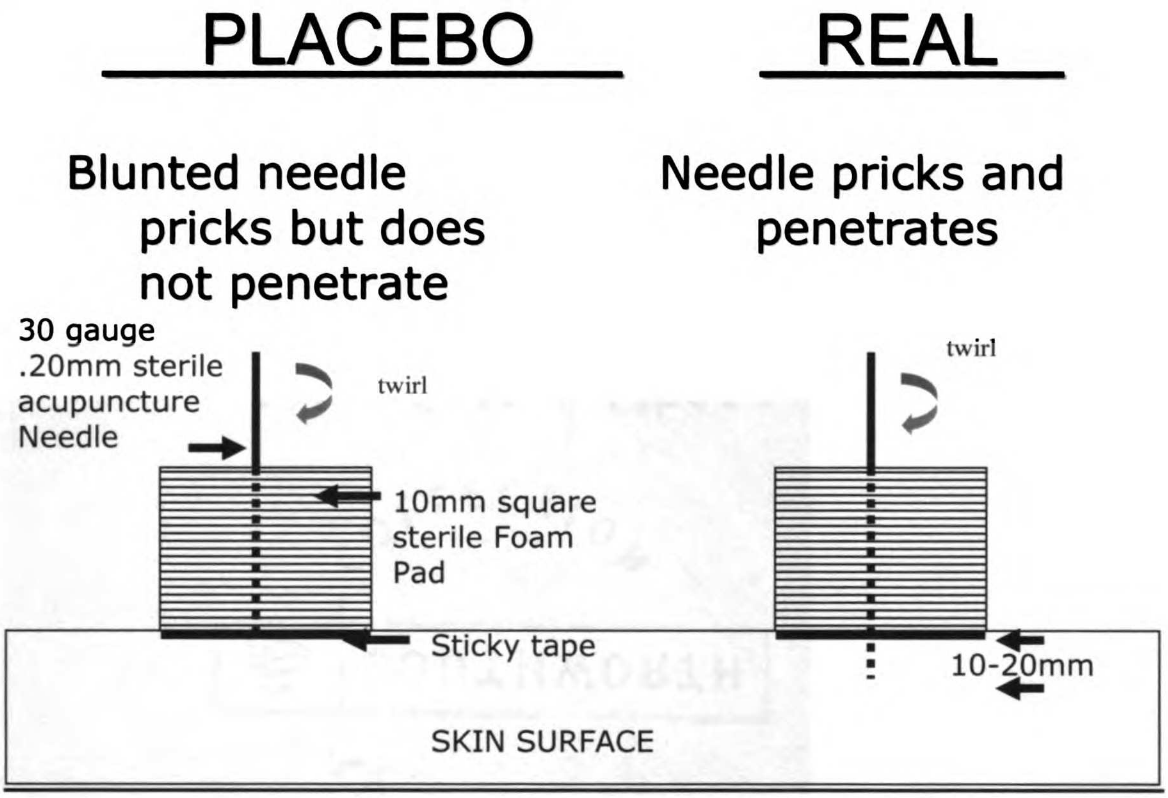
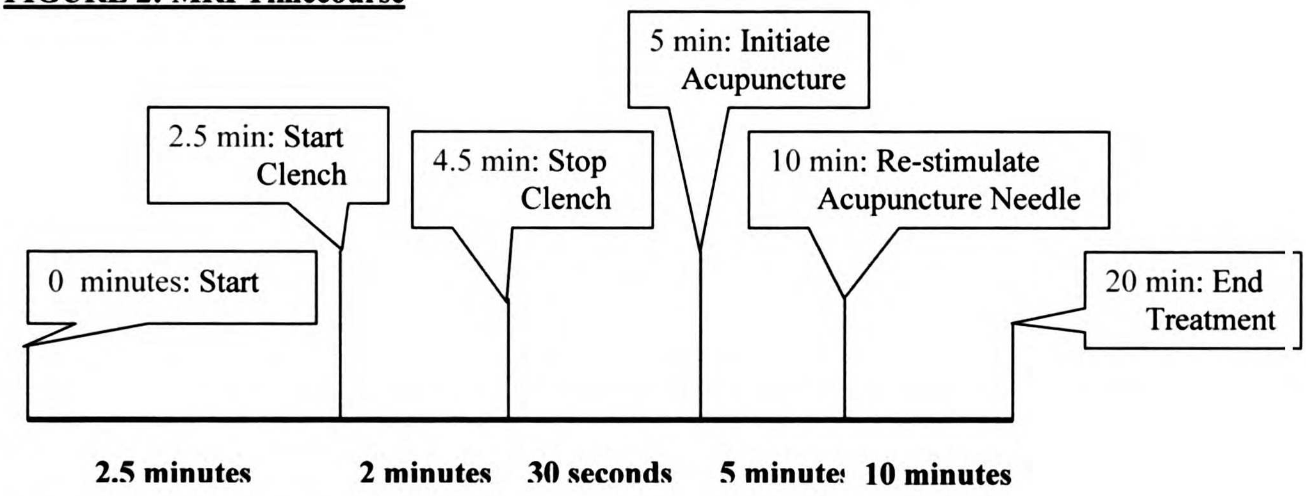


FIGURE 2: MRI Timecourse



*All subjects were submitted to this 20 minute long timecourse.

FIGURE 3: Brain Activations Prior to Clench

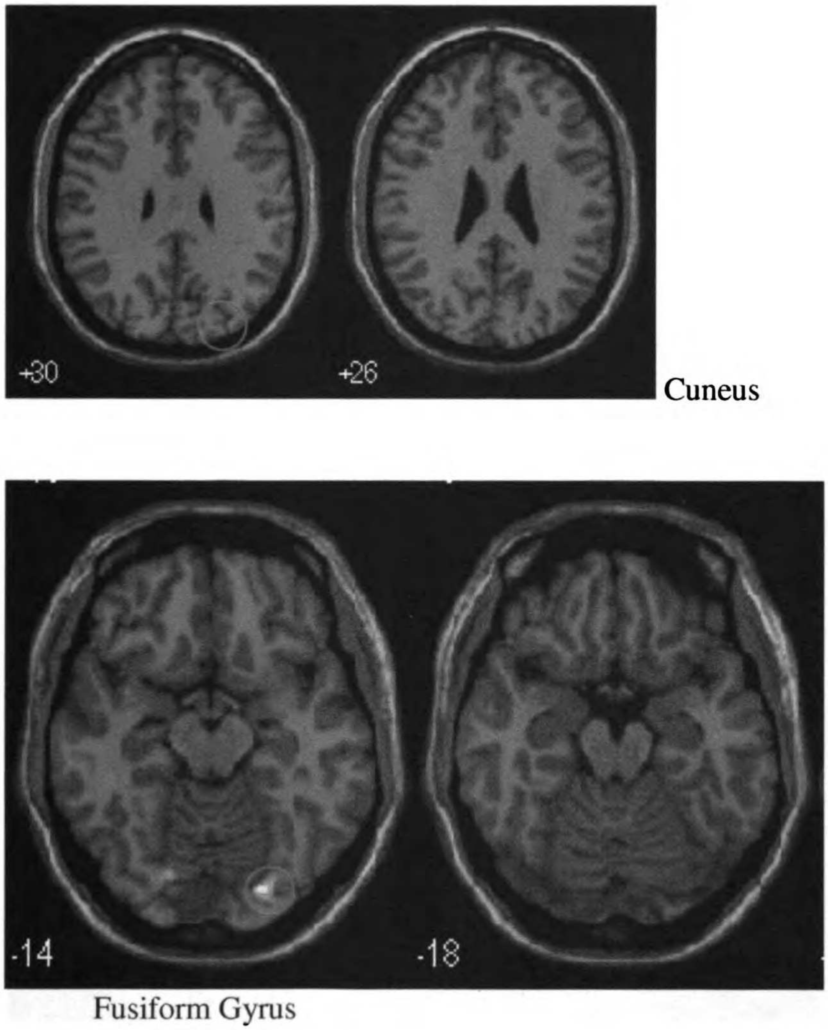
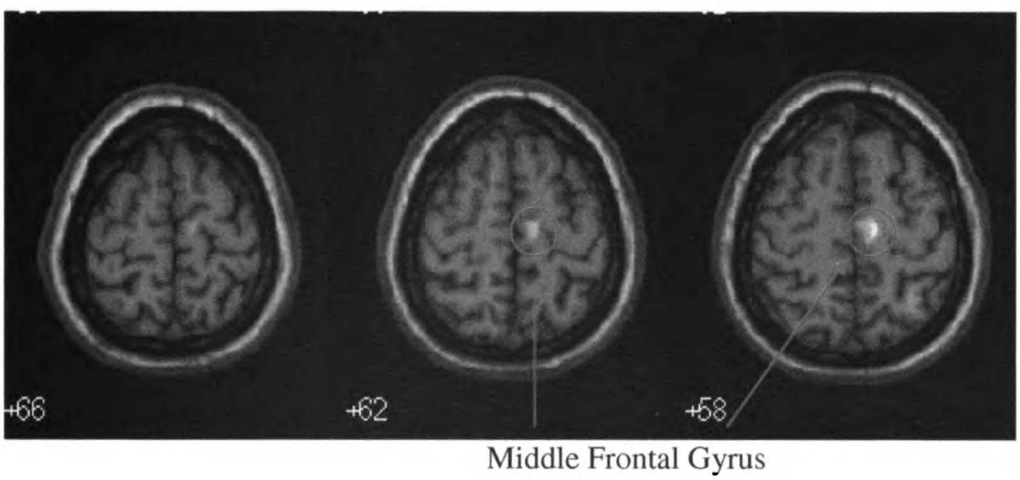
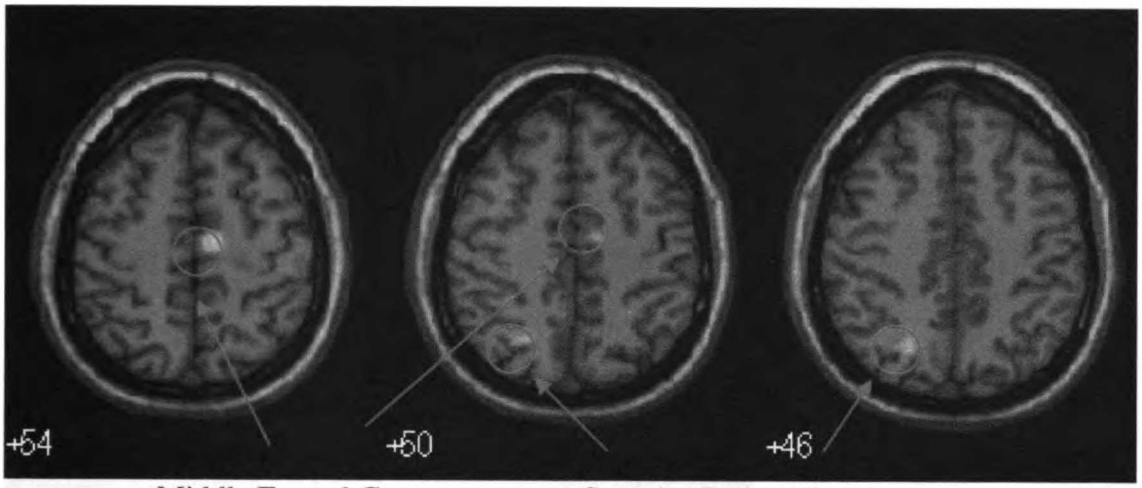
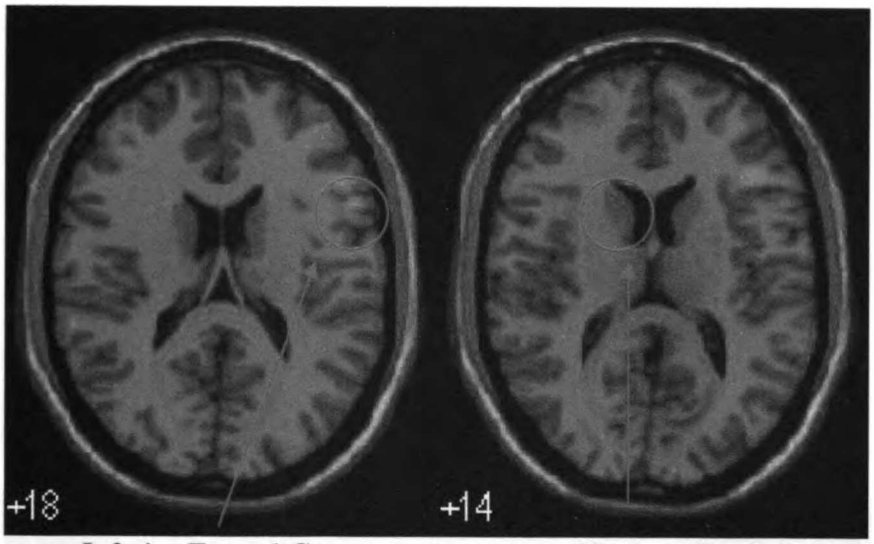


FIGURE 4: Brain Activations After Clench

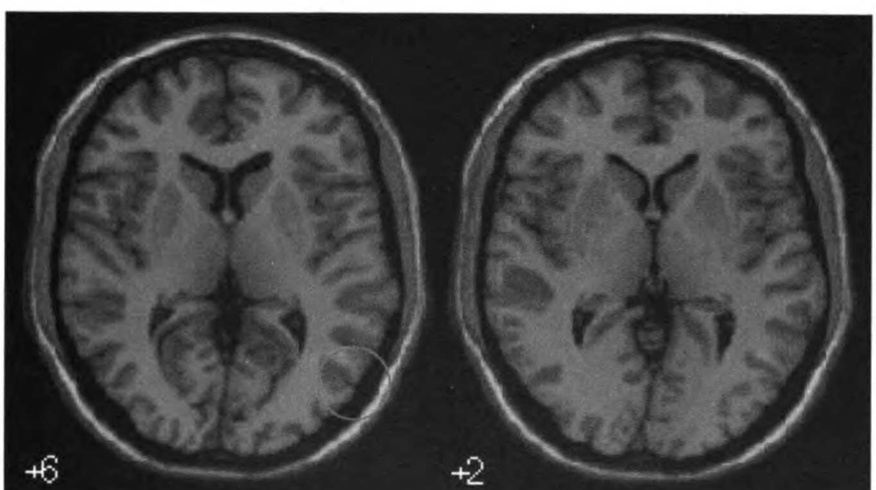




Middle Frontal Gyrus Superior Parietal Lobule

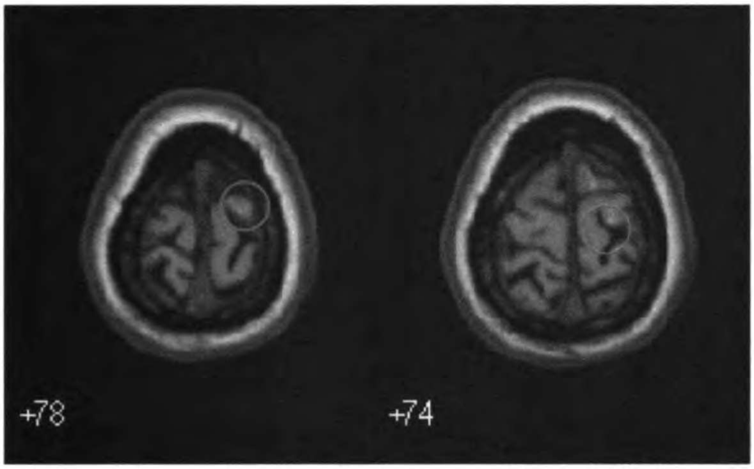


Inferior Frontal Gyrus Nucleus Caudalis

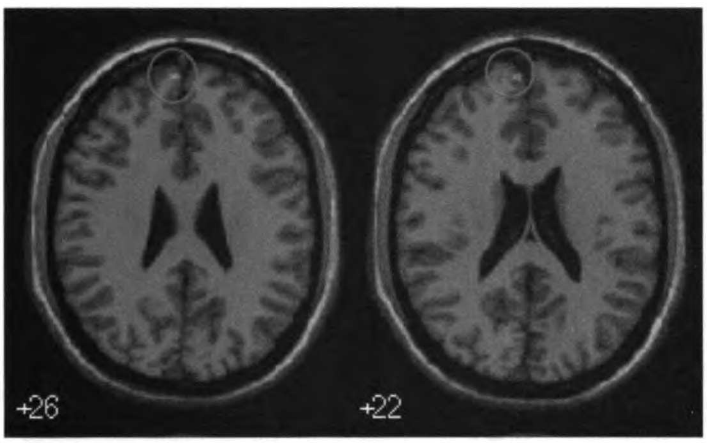


Middle Temporal Gyrus

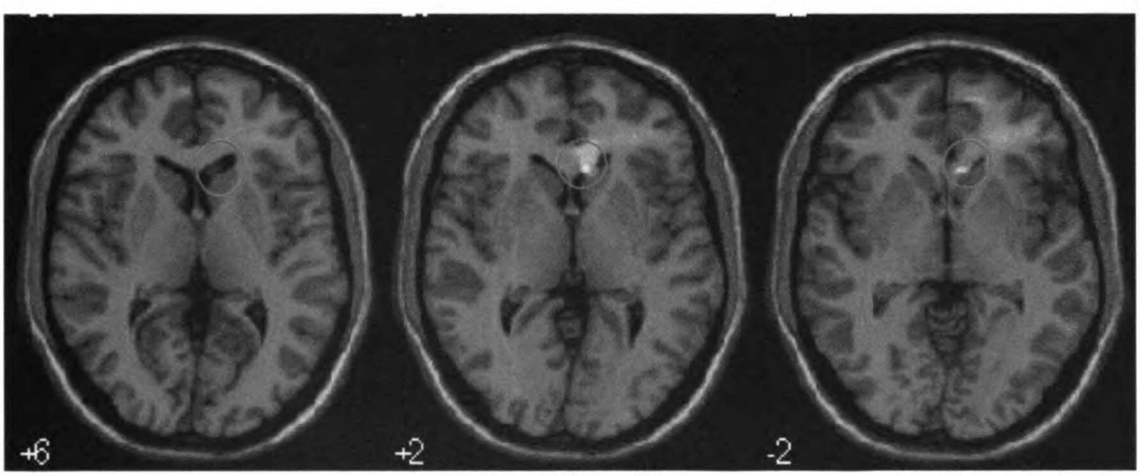
FIGURE 5: Brain Activations During Acupuncture



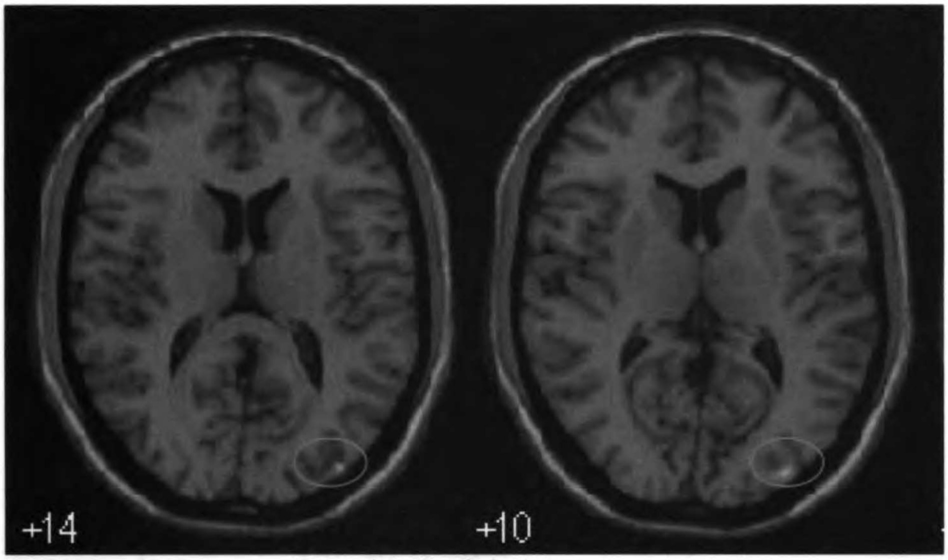
Precentral Gyrus



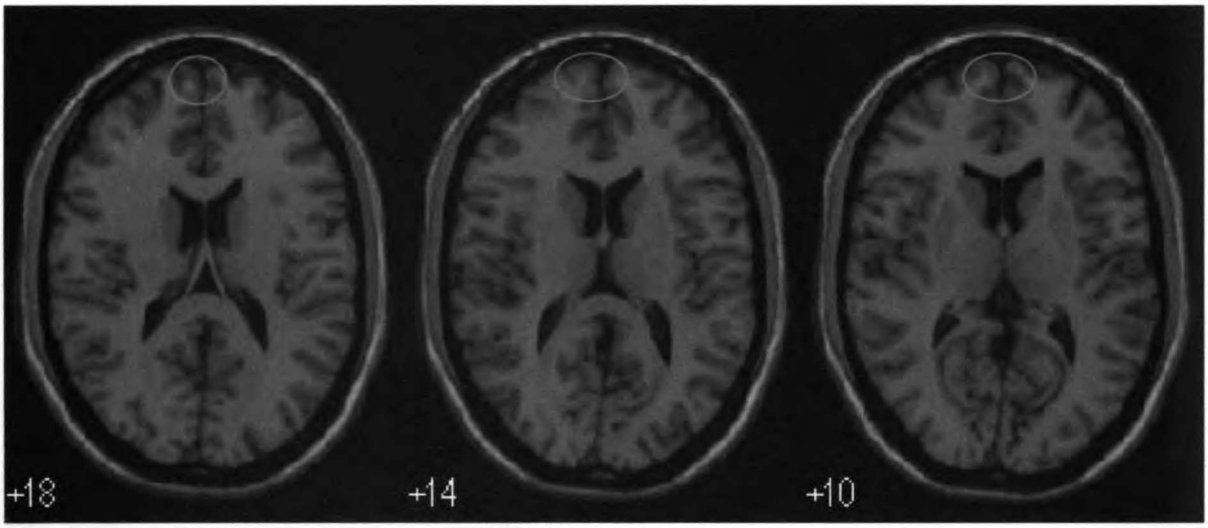
Superior Frontal Gyrus



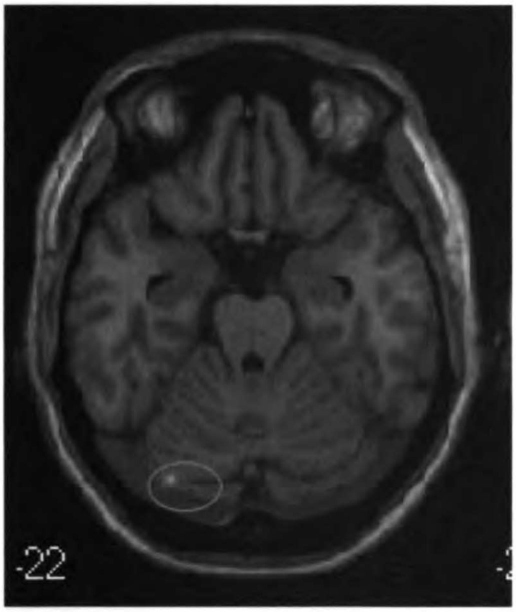
Lateral Ventricles



Superior Occipital Gyrus

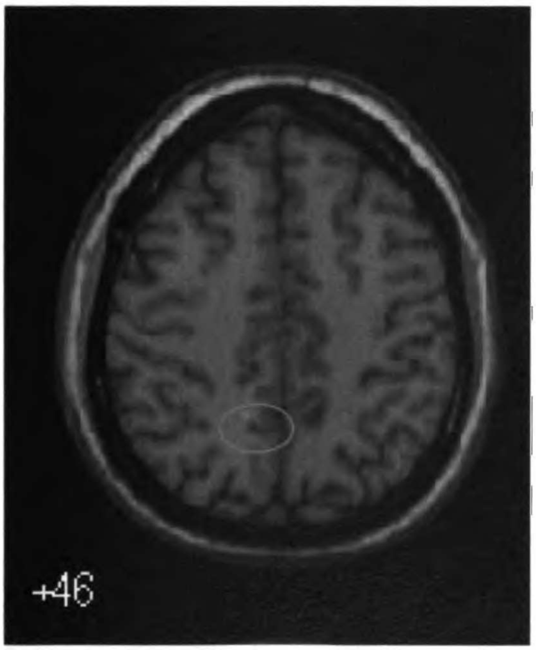


Middle Frontal Gyrus

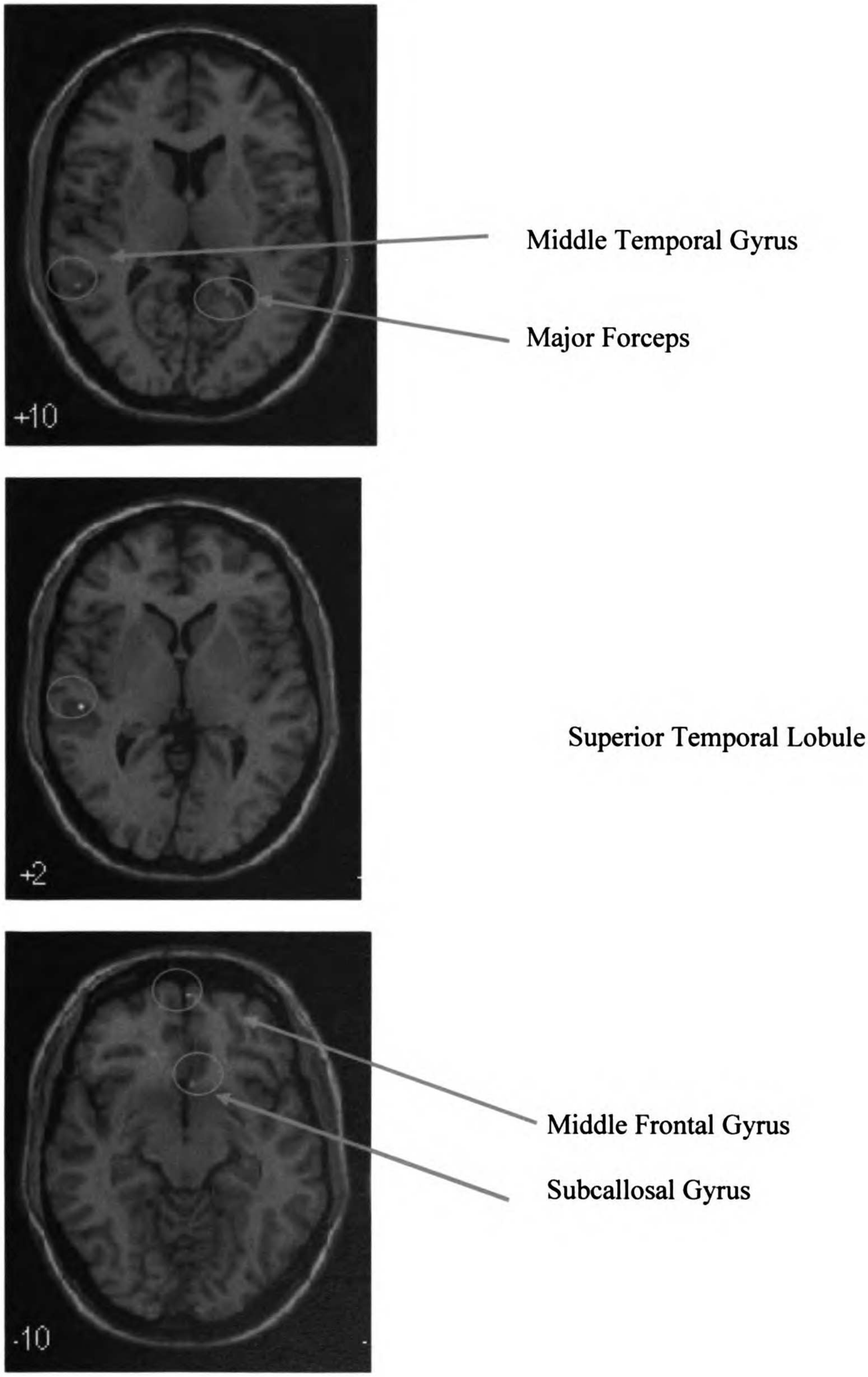


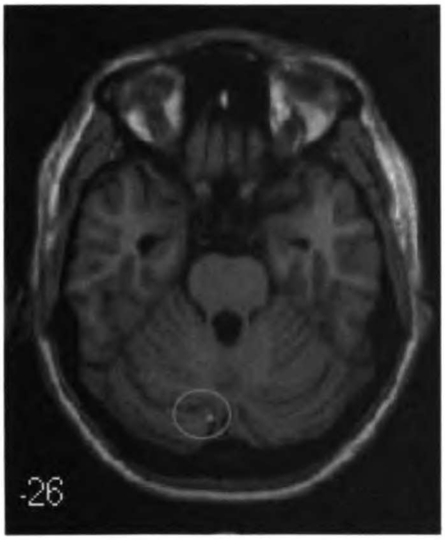
Fusiform Gyrus

FIGURE 6: Brain Deactivations During Acupuncture



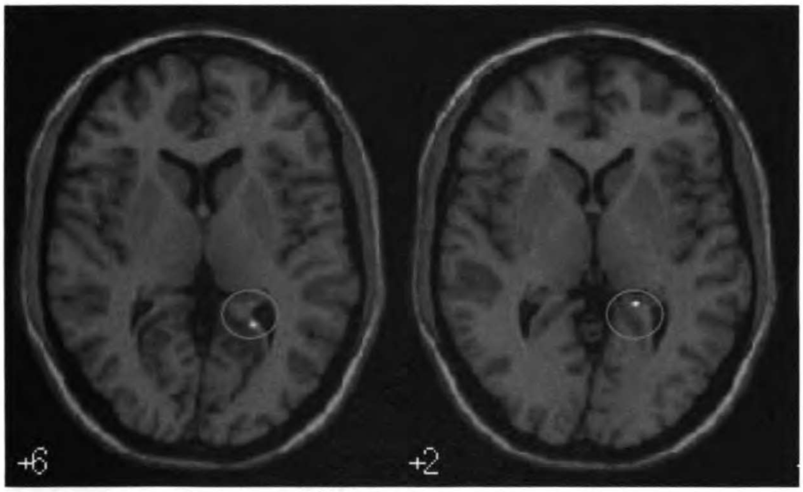
Precuneus


+10
Middle Temporal Gyrus
Major Forceps
+2
Superior Temporal Lobule
-10
Middle Frontal Gyrus
Subcallosal Gyrus

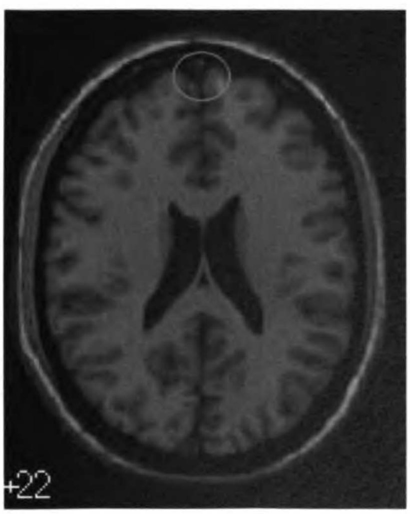


Fusiform Gyrus

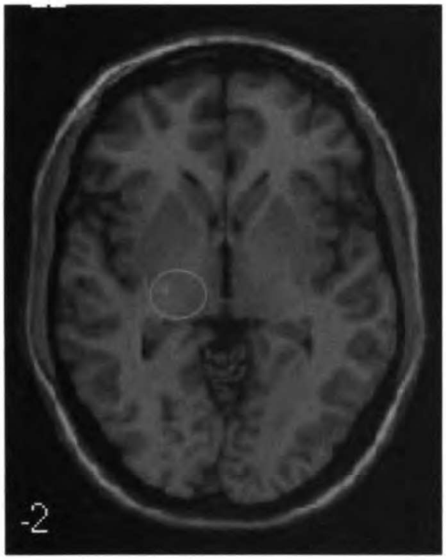
FIGURE 7: Brain Activations During Sham Acupuncture



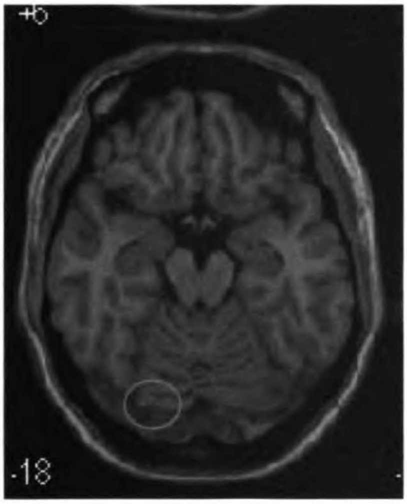
Cingulum



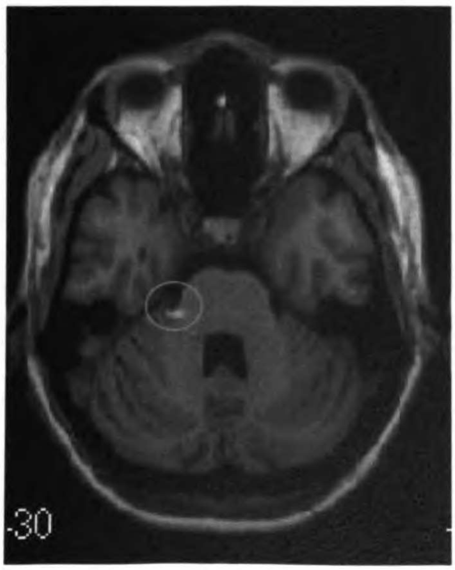
Middle Frontal Gyrus



Lateral Pallidus Globule

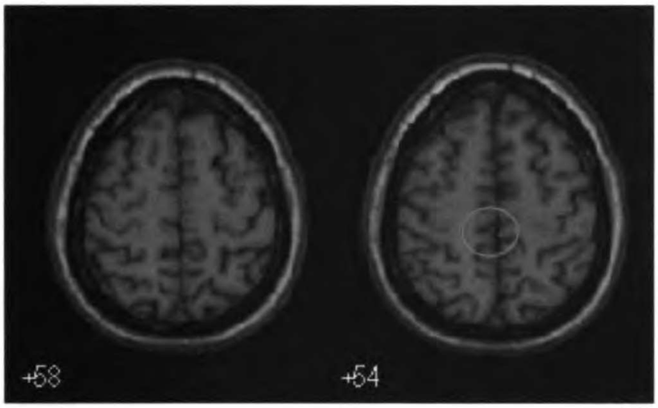


Fusiform Gyrus

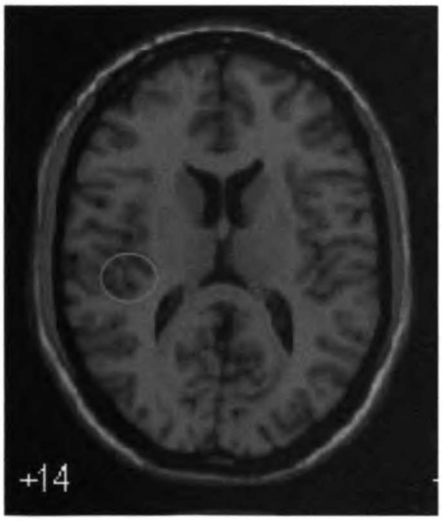


Parahippocampal Gyrus

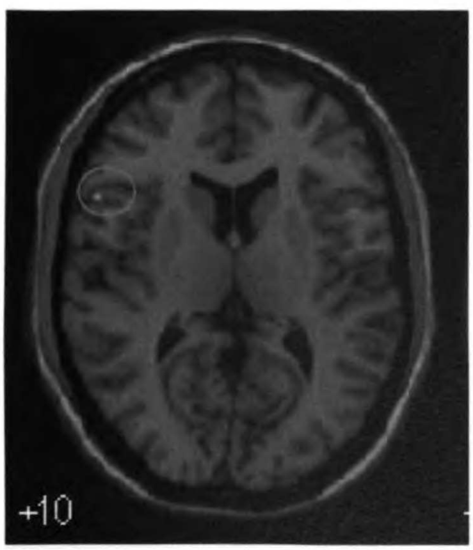
FIGURE 8: Brain Deactivations During Sham Acupuncture



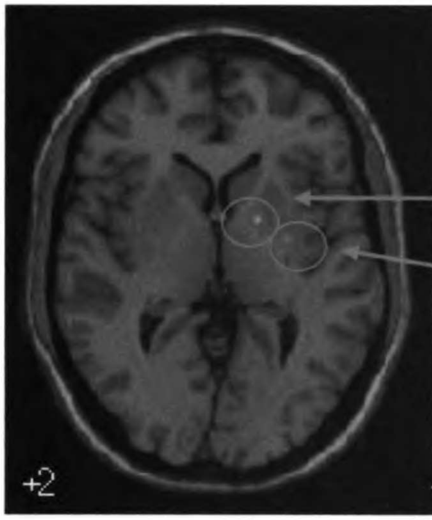
Paracentral Lobule



Transverse Temporal Gyrus

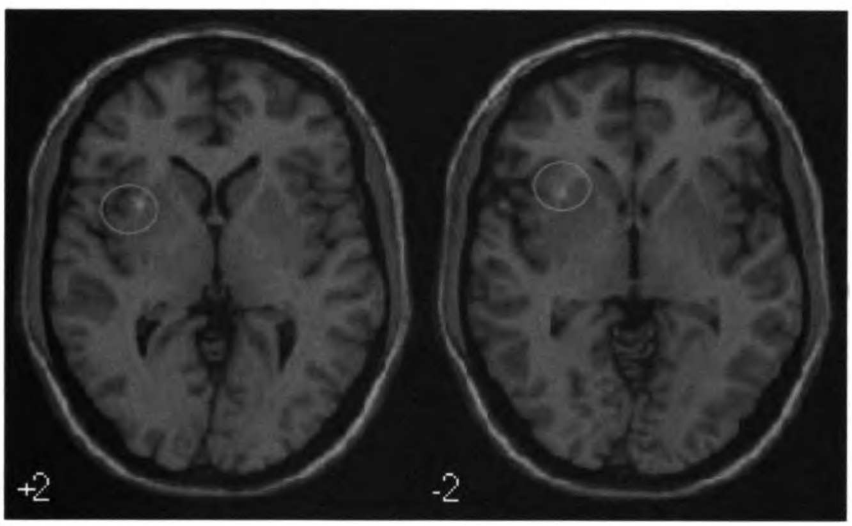


Precentral Gyrus

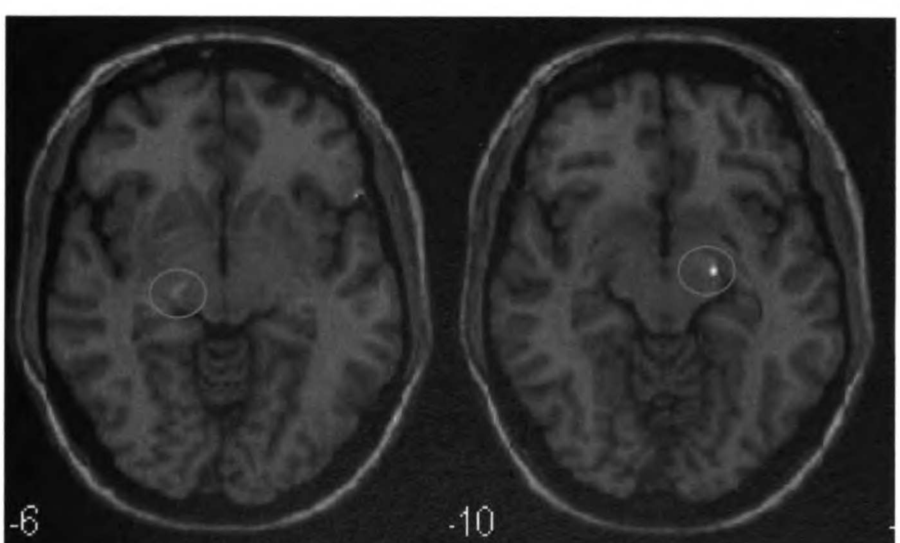


Lateral Pallidus Globulus

Putamen (right)

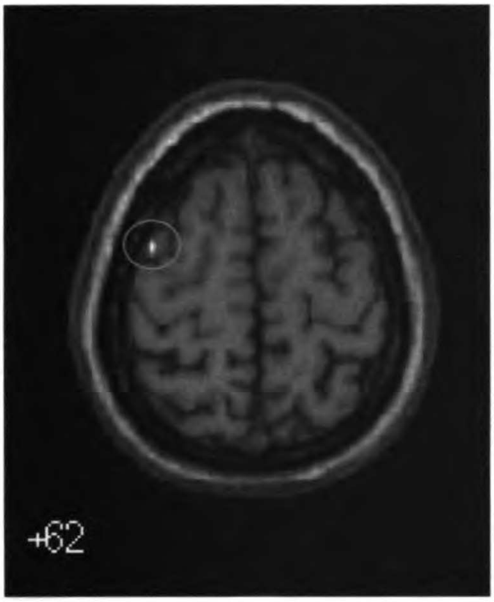


Insula



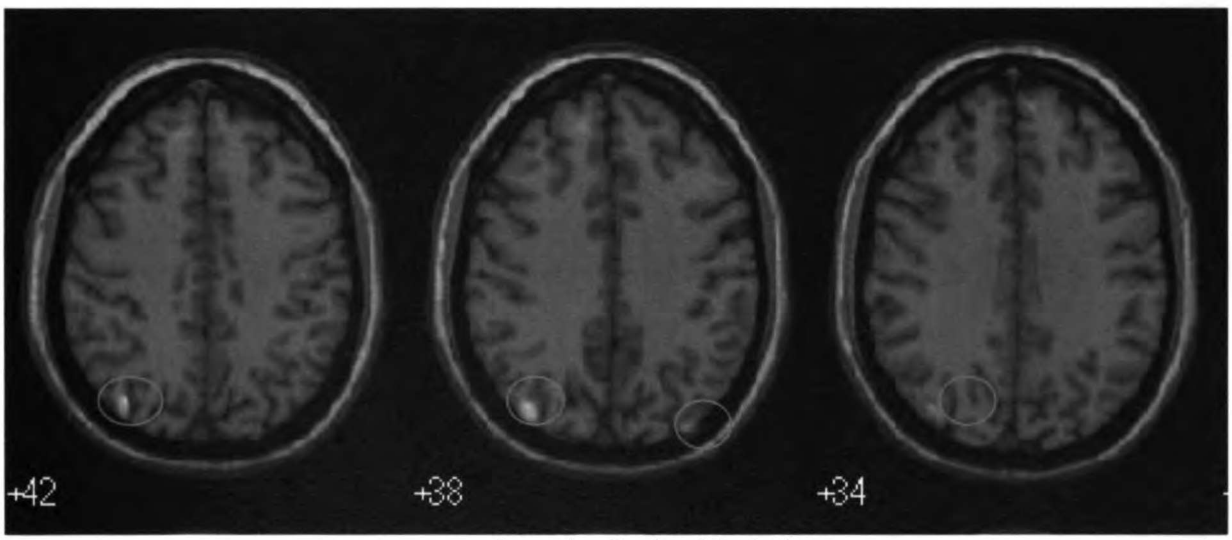
Optic Tract

FIGURE 9: Brain Activations in Subjects That Believed They Received Acupuncture

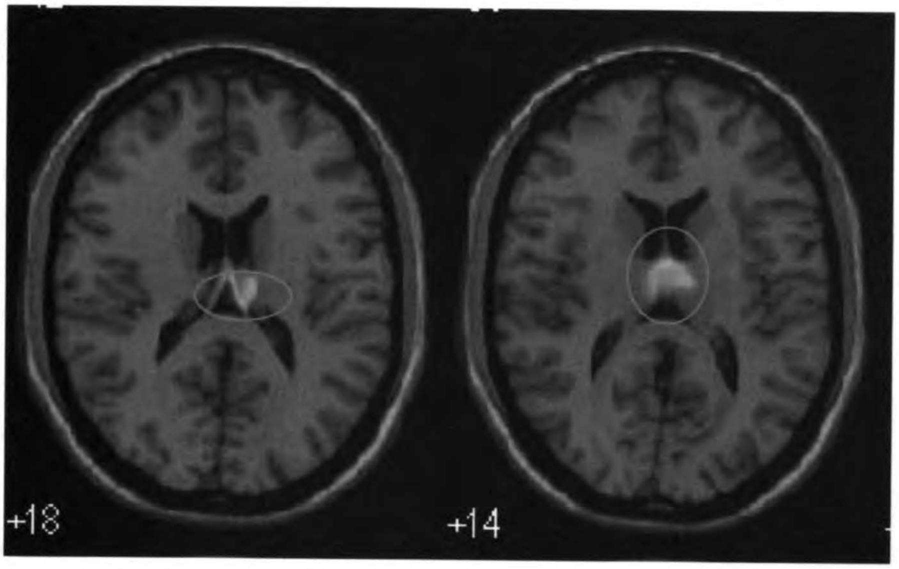


Middle Frontal Gyrus

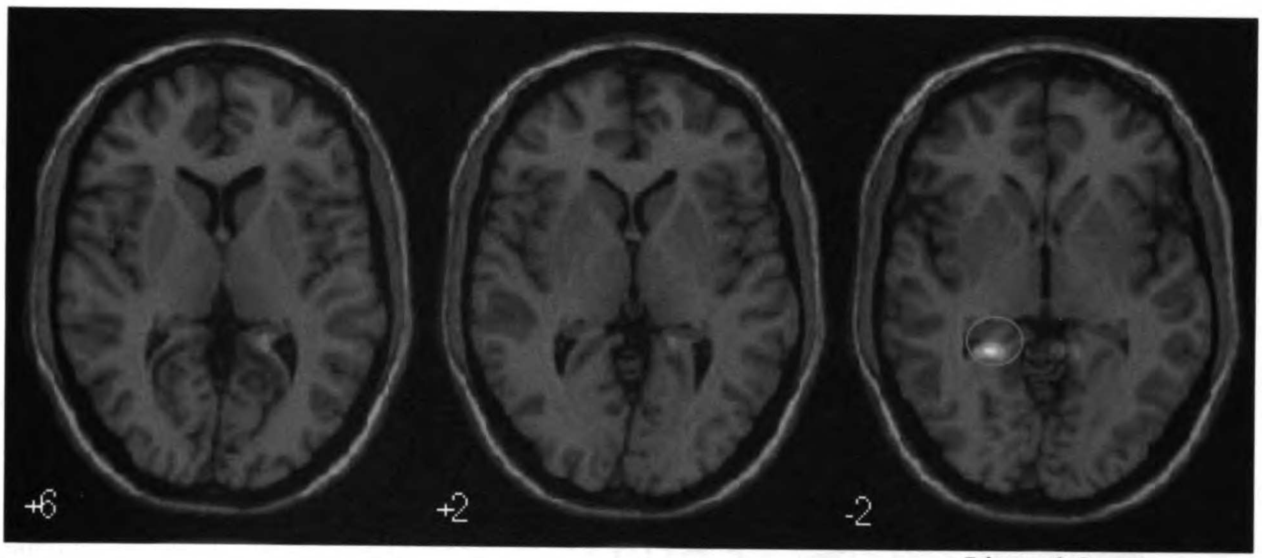
FIGURE 10: Brain Activations in Subjects That Believed They Received Sham Acupuncture



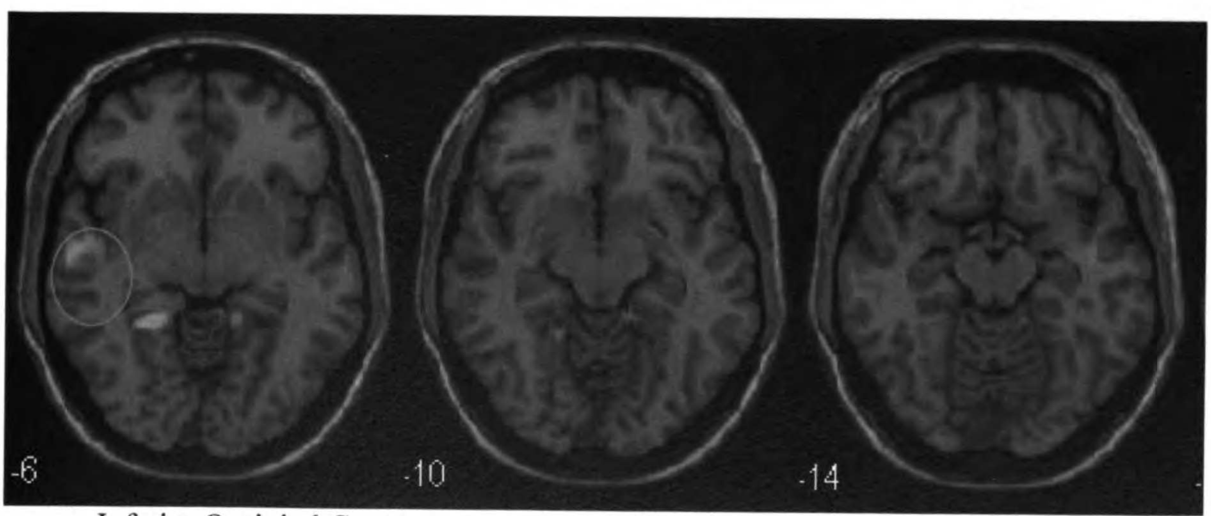
Superior Parietal Lobule



Fornix



Lingual Gyrus



Inferior Occipital Gyrus

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APPENDIX 1: Consent Form

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO BE A RESEARCH SUBJECT

fMRI shows specific brain areas activated with acupuncture (LI4) in patients with myofascial pain of the jaw muscles: A Pilot Study

A. PURPOSE AND BACKGROUND

Acupuncture has shown possible usefulness as an acceptable alternative treatment for myofascial pain of the head and neck.

Greg Goddard D.D.S. and his associates of the UCSF Center for Orofacial Pain in the Department of Oral and Maxillofacial Surgery are studying the outcome of using acupuncture techniques in the treatment of certain jaw joint disorders by looking at brain functions using magnetic resonance imaging (MRI).

I am being asked to participate in this study because I have a jaw joint disorder.

B. PROCEDURES

If I agree to be in this study, the following will happen:

1. I will agree to stop taking any analgesic medications (NSAIDS, acetaminophen) at least 1 day prior to the study.
2. I will be assigned to one of two groups that either receives placebo acupuncture or acupuncture. Acupuncture consists of inserting two fine needles through thin foam and the skin at special spots on the hand and face called "acupuncture points." Placebo acupuncture consists of inserting one fine needle through thin foam that doesn't penetrate the skin at the acupuncture points.
3. I will have a 50/50 chance of being placed in one of the two groups. Neither the doctor nor myself will make the choice so that bias in the study is reduced.
4. I will be placed in an MRI machine for 30 minutes. Three sets of MRIs will be done over the course of 30 minutes. I will be clenching for 2 minutes.
5. I will rate pain to a pressure gauge on my jaw muscles before and after receiving acupuncture treatment. I will also rate my current pain without the pressure gauge before and after acupuncture treatment.
6. Total time for the study will be a one time visit of one hour and a half at China Base Landing located at the UCSF Mission Bay Campus.

C. RISKS/DISCOMFORTS

1. Acupuncture involves penetration/pressure of the skin. Bruising and risk of infections are rare occurrence. Sterile needles are used. I may experience minor pain. Acupuncture treatment might not be effective and my current pain may not improve or worsen.

2. Clenching for 2 minutes may cause a range of discomfort to my jaw muscles. The discomfort may range from mild to severe and may last for a few minutes or longer.

3. The pressure gauge testing will cause a range of discomfort for a few seconds, similar to pressing a muscle with my finger. This discomfort may range from mild to severe and may last for a few minutes or longer.

4. Participation in this study may involve a loss of privacy, but information about myself will be handled as confidentially as possible within the law. My name will not be used in any publications or reports resulting from this study.

5. I will be assigned to a treatment program by chance. The treatment I receive may prove to be less effective or to have more side effects than other study treatment or than other available treatments. This will not be known until after the study is completed and the data has been analyzed.

6. MRI involves placing my whole body in a tube and being still in one position for 30 minutes. I may feel claustrophobia. There will be no radiation involved.

7. Acupuncture needles will be in close proximity to the MRI magnet. It is assured that the acupuncture needles will not create a magnetic hazard.

8. Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during my examination, which could in the process possibly harm me. Precautions have been taken to prevent such an event; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If I have a piece of metal in my body, such as a fragment in my eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, I will not be allowed into the MRI room and cannot have an MRI.

9. My participation may mean some added discomfort for me. In particular, I may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why I will be asked to wear ear plugs. At times during the test, I may be asked not to swallow for awhile, which can be uncomfortable.

10. Because the risks to a fetus from MRI are unknown, pregnant women must not participate in the study.

Treatment and Compensation for Injury:

If I am injured as a result of being in this study, treatment will be available. The costs of such treatment may be covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, I may call the office of the Committee on Human Research at (415) 476-1814.

D. BENEFITS

If I am placed in the group that receives acupuncture designed to treat my jaw muscle pain, and it proves to treat my condition with fewer side effects than the current standard therapy, I may benefit by participating in the study. This, however, cannot be guaranteed.

E. ALTERNATIVES

I have the right to drop out of the study at any time and seek standard treatment in the form of analgesic medications, physical therapy, or pain management.

F. COSTS

No costs will be charged to me for being in this study.

G. PAYMENT

I will be paid $100 upon completion of this study.

H. QUESTIONS

This study has been explained to me by Dr. Greg Goddard or the person who signed below and my questions were answered. If I have any other questions about the study, I may call Dr. Goddard at (415) 476-2522.

I. CONSENT

I have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

Participation in research is voluntary. I have the right to decline to participate or to withdraw at any point in this study without jeopardy to my medical care/employment/student status,

If I wish to participate, I should sign below.

Date	Subject's Signature
Date	Person Obtaining Consent

APPENDIX 2: Committee on Human Research Protocol

fMRI shows specific brain areas activated with acupuncture(LI4) in patients with myofascial pain of the jaw muscles: A Pilot Study.

1. AIM/PURPOSE

The purpose of this study is to determine if acupuncture activates specific areas of the anterior cingulate cortex and thalamus of the brain with pain inhibitory function using functional magnetic resonance imaging (fMRI). This study will also evaluate short-term pain reduction from acupuncture by using a visual analog scale (VAS) pain rating of mechanical pressure on the masseter muscle and a numerical analog scale (NAS) pain raiting of general face pain.

The hypothesis is that acupuncture at the large intestine point LI 4 reduces pain by acting on the CNS. The fMRI should show a more significant decrease of activity in the anterior cingulate cortex and thalamus of the brain with acupuncture treatment in comparison to the placebo acupuncture treatment. The acupuncture treatment should induce a greater decrease in the degree of VAS pain rating on the masseter muscle than the placebo acupuncture treatment.

2. BACKGROUND

Epidemiological data indicate that TMD is most prevalent in the fourth and fifth decades of life thus, TMD afflicts persons who are in their most productive years. In addition, recent work demonstrated that patients with TMD took sick leave significantly more often than individuals who did not have TMD (Kuttila et. al., 1997). In fact, it is estimated that 17,800,000 workdays are lost each year for every 100,000,000 full-time working adults in the United States due to TMD representing a significant cost to the economy (Dworkin et. al., 1993). Temporomandibular disorders (TMD) are more prevalent among women than among men (Winocur et al., 2003). Acupuncture has been used for the treatment of temporomandibular disorders, as well as for other musculoskeletal pains. The U.S. National Institutes of Health (NIH), in its consensus statement on acupuncture of November of 1997, states that promising results have been shown for postoperative dental pain (Acupuncture, 1997). The NIH stated that in other situations such as myofascial pain, acupuncture may be useful as an adjunct treatment or an acceptable alternative treatment. Many controlled acupuncture studies have yielded promising results in the areas of chronic pain. It was found that the effective rate of acupuncture treatment of 477 cases of myofascial pain dysfunction is 93.1% by sensitizing Hoku and Min Yin points (Wang et. al., 1998). How acupuncture-induced analgesia occurs is not well understood. In animal studies, it has been shown to be mediated by humoral factors via the cerebrospinal fluid (CSF). By having CSF from acupuncture-treated rabbits infused into recipient rabbits, the analgesic effects were observed in the recipient rabbits; thereby suggesting that acupuncture-induced analgesia may be mediated by substances released in the CSF (Shen, 2001). Further response to acupuncture was indicated by using fMRI to evaluate brain response (Yoshida et. al., 1995). Specifically, fMRI can demonstrate the CNS pathway for acupuncture stimulation when acupuncture at acupoints ST.36 (on the leg) and LI.4 (on the hand) activates structures of descending antinociceptive pathway and deactivates multiple limbic areas sub-serving pain association. This indicates the CNS mechanism of acupuncture analgesia the possibility of endogenous pain modulation circuits in the human brain (Wu et. al., 2002). Where pain modulation occurs in the brain was indicated when manual needle manipulation produced prominent decreases of fMRI signals in posterior cingulate, superior temporal gyrus, putamen/insula at LI4 Hoku acupoints (Kong et al., 2002). Another study found that the anterior cingulate cortex and thalamic areas were activated as a result of pain stimulation. Decreased activation in these areas was noted following both meridian acupuncture and sham acupuncture. This concluded that acupuncture appears to inactivate the brain regions involved in the transmission and perception of pain (Cho et al., 2002).

3. SIGNIFICANCE

TMD has been identified as the chief cause of pain, which is not of dental origin, in the orofacial area, and is defined as a subgroup in the category of musculoskeletal disorders. Myofascial pain is a subgroup of TMD. Myofascial pain of the jaw muscles is a significant medical problem that has high costs to society in terms of time lost off work and high medical costs. This pilot study is important because studies evaluating the efficacy of acupuncture as a treatment for myofascial pain are needed. Acupuncture treatment for chronic pain patients can be a cost effective therapy, either as a supplemental or alternative therapy to current drug therapy of pain medications. If acupuncture serves as an effective treatment for myofascial pain of the jaw muscles, it would be more cost effective and less invasive than many treatments now being employed such as rebuilding the teeth and surgery. The evidence that acupuncture has a specific effect in the CNS is mounting. Our hypothesis is that CNS activation by acupuncture as seen on fMRI in patients with chronic myofascial pain is different than with placebo acupuncture. The short-term pain on a VAS will decrease in the functional acupuncture group compared to the placebo group. Evidence that acupuncture has a direct effect on the CNS will advance our scientific understanding of how acupuncture works.

4. METHODS

A. General Study Design

15 patients with chronic myofascial pain who are currently being seen at the UCSF Temporomandibular Disorder Center will be invited to participate in the study. The 15 patients will be randomly distributed into 2 groups. Both groups will be subjected to a painful period of muscle pain by clenching their teeth for 2 minutes. One group will receive functional acupuncture while the other group will receive placebo acupuncture

for 15 minutes. All patients will be subjected to 15 minutes of acupuncture treatment (acupuncture or placebo treatment dependent on the particular group patient is randomly placed in) under fMRI image scanning. fMRI scans will be taken prior to acupuncture treatment.

Two methods of pain measurement, the Visual Analog Scale (VAS) rating system to a pressure algometer reading and a numerical analog scale (NAS) will be given pre and post- acupuncture treatment. All data obtained will be analyzed.

B. Methods of Data Analysis

Data analysis will be based on functional MRI (fMRI) analysis. Z.H. Cho from U.C. Irvine, who is blinded to the subjects grouping, will assist in analyzing the fMRI images. All areas of the brain will be analyzed, with emphasis on the anterior cingulate cortex and thalamic areas.

General steps of fMRI data processing are usually performed by SPM99 analysis package. To correct motion artifacts, a realignment algorithm is used. For normalization of the human brain size, we can employ a standard template image such as the Talairach space. The SPM99 offers its standard template images such as EPI (Echo Planar Imaging), PD (Proton density) imaging, and T1 imaging etc. for convenient display.

Statistical analysis of the data will be as follows:

FMRI data are usually collected in an axial form and reformatted to obtain both sagittal and coronal views, and the functional activation data are superimposed onto the EPI template images for visualization. To further visualize the dynamic or time-dependent physiological responses of cortical activation, all the data sets are reprocessed with the DRA technique (made in our group) with up to several discrete time-delayed correlation functions to extract the time-dependent data. In each image data, p-values are obtained and used as threshold for statistical significance. These data are compared with the data from conventional processing technique (SPM99).

Pain will be measured using the VAS (Visual Analog Scale) pain rating system to a pressure algometer reading. A pressure algometer gauge will be used at maximal tolerable pain to assess at which pressure the patient feels pain. Following the pressure assessment, the subject will rate their pain on the VAS form. On the VAS form, the subject will indicate approximately the intensity of the pain on a 100 cm long line. The researcher will then take a ruler and measure the distance in centimeters to rate the intensity of the pain the patient experienced. A numerical analog scale (NAS) is a brief questionnaire that assesses the level of pain, on a scale from 0-10 (10 being the most intense pain imaginable), the patient is currently experiencing around the head and neck area. Both pain rating methods will be used pre and post-acupuncture treatment. One modification is with the post acupuncture treatment measurement with the algometer pressure gauge. The algometer pressure gauge will be set at the same pressure that the patient had indicated pain prior to the acupuncture treatment. This way there is consistency in the assessment of pain the patient experiences since the patient can indicate whether there is greater or less pain at the same pressure.

All data obtained will be compared at the subject level and group level for both pre- and post-acupuncture treatment.

C. Subject Selection

1. Patients currently seeking treatment from the UCSF TMD Center will be recruited to participate in this study. 15 patients diagnosed with chronic myofascial pain who meet the following inclusion criteria will be invited to participate in this study. These particular patients will be asked because the acupuncture treatment targets the alleviation of chronic myofascial pain. Patients will be randomly placed in the group receiving acupuncture and in the group receiving placebo acupuncture.

<u>Inclusion Criteria</u>

a. Male or female over the age of 18
b. Have a diagnosed chronic myofascial pain of the masticatory muscles
c. Has had a chief complaint of frequent pain (at least 4 times/week) in the jaw muscles for at least twelve weeks
d. Has a pain of at least 4 on a 0-10 numerical scale lasting at least 1 hour per day
e. Has a pain of the jaw muscle origin, including a complaint of pain and associated pain with localized areas of tenderness to palpation of the muscle
f. Has pain in the jaw, temples, face, preauricular area, or in the ear at rest or during function
g. Has pain in response to the palpation of 3 or more of the following 20 muscles sites (right and left side count as separate sites for each muscle): posterior temporalis, middle temporalis, anterior temporalis, origin of masseter, body of masseter, insertion of masseter, posterior mandibular region, submandibular region, lateral pterygoid area (intraorally behind the upper second molars), and tendon of the temporalis (intraorally on the ascending ramus). At least 1 of the sites must be on the same side as the complaint of the pain.

<u>Exclusion criteria</u>

a. Claustrophobic individuals who cannot tolerate the MRI scan.
b. Pregnant women
c. Patient taking any narcotic medication
d. Patients taking NSAIDS and acetaminophen, unless they agree to stop at least 1 day prior to study
d. Patient with metabolic disease (e.g., diabetes, hyperthyroidism)
e. Patients with coagulopathies (e.g., hemophilia, anti-coagulants)
f. Patient with neurologic disorders (e.g., dyskinesia, trigeminal neuralgia)
g. Patient with vascular disease (e.g., migraine, hypertension)
h. Patient with neoplasia

D. Subject Recruitment

1. While the patients are being treated at the UCSF Center for Orofacial Pain by Dr. Goddard, Dr. Goddard will offer the patients the opportunity to participate in the study.

E. Consent Process and Documentation

After the study has been explained to the patient by Dr. Goddard and the patient agrees to participate in the study, the consent will then be obtained.

F. Procedures

15 patients, from the UCSF TMD Center, diagnosed with myofascial pain and meet the inclusion criteria will be invited to participate in this study. The subjects will be randomly placed in two groups; one group will receive functional acupuncture and the other group will receive placebo acupuncture.

5. Dr. Greg Goddard and/or his associates will explain the study to the subject.
2. The patient will be taken to the MRI imaging center at China Basin Landing.
3. The patient will be asked to sign the UCSF human research consent form.
4. The patient will be randomly placed in the group receiving acupuncture or the group receiving placebo acupuncture.
5. The patient will be given an NAS pain rating form to fill out and a mechanical pain stimulus with a pressure algometer reading at maximal tolerable pain 5 minutes prior to receiving acupuncture treatment. A baseline pressure algometer will be used to elicit pain from the masseter muscles. The subject will then rate their pain to the mechanical stimulus on a VAS.
6. fMRI imaging will be taken of the subject for a few minutes using gradient echo sequence of the brain before acupunctural stimulation to obtain a baseline reading of pain.
7. The patient will clench their teeth for 2 minutes.
8. A second fMRI imaging will be taken of the patient after the clenching.
9. In both groups, the skin will be cleansed with an alcohol wipe. The acupuncture group will have 1 sterile needle inserted through a sterile foam pad to a depth of 10-20mm at Hoku L.I.4 point. The placebo acupuncture group will have 1 sterile blunted acupuncture needle inserted through a sterile foam pad 10mm distal and 10 mm lateral to Hoku L.I. 4 point, until the needle pricks the skin, but does not penetrate the skin. A new foam and alcohol wipe will be used for each patient. Dr. Greg Goddard will carry out the acupuncture.
10. The patient will be left in the MRI machine for 15 minutes with the acupuncture needles in place. A third set of fMRI imagings will be taken.
11. The patient will be given an NAS pain rating form to fill out and a mechanical pain stimulus with algometer duplicating the same pre-acupuncture pain stimulus. The patient will then rate their pain to the mechanical stimulus on a

VAS.

12. Subjects will answer a questionnaire to guess whether they were given a placebo or real acupuncture.

Acupuncture treatment

Acupuncture treatment will be performed by a state board licensed acupuncturist using disposable stainless steel needles, inserted through a sterile foam pad into the skin to the depth of 10-20 mm, until the needle sensation (DeQi) is reached. Needles will be left in place for 15 minutes and stimulated for 15 seconds at 10 minutes.
Placebo acupuncture will be performed by the same acupuncturist placing the needles through a sterile foam pad until they prick the skin, but do not penetrate skin.
The acupuncture point for treatment is listed below.

Acupuncture point	Location	Tissues	Skin Innervation	Muscle Innervation
Li 4 Hoku	Middle point of the os metacarpale II, on the prominence of the 1st m. inter ossei dorsales slightly towards the side of the index.	m. interosseus dors. m. abduct. Pollicis, m. lumbricale I	n. radialis r. superficialis C 6, 7, 8	n. ulnaris C8, Th 1 n. medianus C 8, Th 1

The subject's participation in this study will take a one time 1 hour visit at the UCSF Center for Orofacial Pain and the UCSF MRI Imaging facility.

G. Risks and Discomforts

1. Acupuncture involves penetration/pressure of the skin. Bruising is a rare occurrence. Sterile needles are used. Some subjects experience minor pain. Acupuncture treatment might not be effective and the patient's current myofascial pain may not improve.

2. MRI involves placing your whole body in a tube and being still in one position for about 30 minutes. Some people feel claustrophobia.

H. Treatment and Compensation for Injury

If the patient is injured as a result of being in this study, treatment will be available. The University of California depending on a number of factors may cover the costs of such treatment. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, the patient may call the office of the Committee on Human Research at (415) 476-1814.

I. Alternatives

The patient has the right to drop out of the study at any time.

J. Costs to the Subject

The patient will not be charged for participating in the study.

K. Reinbursement of Subjects

The patient will be paid $100 for complete participation of the study.

L. Confidentiality of Records

Participation in this study may involve a loss of privacy, but information about the subject will be handled as confidentially as possible within the law. The subject's name will not be used in any publications or reports resulting from this study.

5. Qualifications of Investigator

Greg Goddard, D.D.S. is an associate clinical professor of the Department of Oral and Maxillofacial Surgery at UCSF. Ernesto Villafuerte, D.D.S. is a volunteer faculty at the UCSF TMD clinic. Yoshi Shen, B.S. is currently a 2nd year student at the UCSF School of Dentistry. Brian Steele, B.S. is currently a 2nd year student at the UCSF School of Dentistry.

6. Reference to Special Requirements & Attachments

Form A: Visual Analog Scale (VAS) form pre- acupuncture treatment.
Form B: Visual Analog Scale (VAS) form post- acupuncture treatment.
Form C: Numerical Analog Scale (NAS) form pre-acupuncture treatment.
Form D: Numerical Analog Scale (NAS) form post-acupuncture treatment.
Form E: Questionnaire about real or placebo acupuncture.

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