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CONFERENCE REPORT

Neurobiological Correlates of Acupuncture: November 17–18, 2005

VITALY NAPADOW, Ph.D., Lic.Ac.,[1] J. MEGAN WEBB,[2] NANCY PEARSON, Ph.D.,[3] and RICHARD HAMMERSCHLAG, Ph.D.[4]

ABSTRACT

The "Neurobiological Correlates of Acupuncture" Conference was convened November 17–18, 2005 in Bethesda, Maryland. The conference was sponsored by the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH), U.S. Department of Health and Human Services (DHHS). Its goals were to encourage exchange of ideas regarding the direction of neuroimaging in acupuncture research as well as to discuss some of the challenges in this field. The use of neuroimaging, a relatively recent advance in the study of acupuncture, holds the promise of localizing and characterizing brain activity associated with acupuncture interventions in real time and in a minimally invasive way. Among the main challenges to research into the biological mechanisms of acupuncture are the multiple treatment variables and the difficulties of selecting appropriate experimental controls. Despite these challenges, numerous findings from acupuncture neuroimaging experiments were presented and discussed at the conference on topics related to possible signaling networks, sham acupuncture controls, acupoint specificity, acupuncture analgesia, acupuncture-associated brain response, and the potential for using neuroimaging in conjunction with translational and clinical acupuncture research. Future directions in acupuncture neuroimaging research, as recommended by conference participants, should focus on (1) continuing exploration of acupuncture signaling networks; (2) establishing standards and recommendations for performing and reporting acupuncture neuroimaging results; (3) enabling data sharing in the acupuncture neuroimaging community; (4) gaining a better understanding of placebo and control groups in acupuncture neuroimaging experiments; and (5) developing biomarkers that relate to physiologically and/or clinically relevant acupuncture responses to neuroimaging results.

INTRODUCTION

On November 17–18, 2005, a conference entitled "Neurobiological Correlates of Acupuncture" was convened in Bethesda, Maryland. This international conference brought together leading researchers who employ neurobiological methods, particularly neuroimaging, to study acupuncture mechanisms. The aims of the conference were to review data from this emerging field, to help identify important questions for future research in acupuncture neuroimaging, and to foster closer ties among investigators active in this research area.

The conference was sponsored by the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH), U.S. Department of

[1]Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital, Boston, MA.
[2]Department of Psychiatry, Massachusetts General Hospital, Boston, MA.
[3]National Center for Complementary and Alternative Medicine, National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, MD.
[4]Oregon College of Oriental Medicine, Portland, OR.

Health and Human Services (DHHS) with additional support from two other NIH Institutes, the National Institute on Drug Abuse (NIDA) and the National Institute of Neurological Disorders and Stroke (NINDS). The conference was chaired by Bruce Rosen, M.D., Ph.D., Professor in Radiology, Harvard Medical School and Director, Martinos Center for Biomedical Imaging; co-chairs were Richard Hammerschlag, Ph.D., Research Director, Oregon College of Oriental Medicine, and Vitaly Napadow, Ph.D., Instructor in Radiology, Harvard Medical School and Martinos Center for Biomedical Imaging.

After welcoming remarks by Nancy Pearson, NCCAM Program Officer and Margaret Chesney, NCCAM Deputy Director, the conference was opened with overview presentations by Bruce Rosen and Richard Hammerschlag. This was followed by four sessions: 1) The Physiology of Acupuncture; 2) Acupuncture Neuroimaging: Placebo and Sham; 3) Acupuncture Neuroimaging: Basic Research; and 4) Acupuncture Neuroimaging: Translational/Clinical Research. In his opening remarks, Bruce Rosen identified several challenges in this research field, not the least of which is trying to understand *how* acupuncture works while at the same time assessing whether it *does* work in the clinical sense. Systematic reviews of clinical trials of acupuncture for various conditions have produced equivocal conclusions, in large part because real acupuncture has not always been shown to be more efficacious than a sham acupuncture control intervention. Another challenge, involving explorations of acupuncture mechanisms, is the need to link acupuncture-induced changes across scales from the molecular to the human behavioral level. Neuroimaging may provide that link. Techniques such as Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Functional MRI (fMRI), and Magneto and ElectroEncephalography (M/EEG), offer a window into changes in brain activity associated with acupuncture and provide variable degrees of temporal and spatial resolution.[1]

Next, Richard Hammerschlag continued with the theme of acupuncture as a challenge to the Western biomedical paradigm. He cautioned that much of the research claiming to explore mechanisms of acupuncture has produced only correlational data, e.g., changes in blood-borne or cerebrospinal fluid biomarkers, or altered neural activity, after acupuncture stimulation. In addition, he reviewed some of the rich history of research investigating potential signaling pathways that might transmit the acupuncture analgesic effects from the acupuncture site to the brain.

The remainder of this conference summary briefly highlights topics presented in the four sessions, ending with suggestions for future work in the field. Complete copies of abstracts and presentations are available on CD (NCCAM Clearinghouse, 2006). As might be expected from investigations of a system as complex as acupuncture, it was clear from the oral presentations, discussions, and poster sessions that this conference uncovered more questions than it answered. However, it also identified important areas where future work might be creatively and productively focused.

SESSION 1: PHYSIOLOGY OF ACUPUNCTURE

Speakers in this session presented research on acupuncture signaling networks and physiology. First, Ji-Sheng Han, M.D. from the Neuroscience Research Institute at Peking University reviewed his extensive work on acupuncture's effect on pain and drug addiction.[2] He postulated that acupuncture has a general modulatory effect and works to bring the body back to homeostasis. Dr. Han's research data emphasized the importance of searching for physiological differences between acupuncture responders and nonresponders and that acupuncture responses in healthy subjects may be different from those in ill patients. Finally, he introduced one of the important themes that ran through many of the subsequent presentations and discussions. That is, we must strive to correlate changes in neuroimaging results with *therapeutic effects* produced by acupuncture in order to fully understand how acupuncture works. Specifically, acupuncture may activate many brain areas, as revealed by brain neuroimaging, but not all of these may necessarily reflect important functional changes, i.e., changes related to the therapeutic effect of acupuncture on the condition being studied.

Historically, the investigation of acupuncture analgesia has dominated acupuncture research. However, exploration of the effects of acupuncture on other physiological systems offers important insights into the possible mechanisms underlying acupuncture's biological effects. John Longhurst, M.D., Ph.D., Director of the Samueli Center for Integrative Medicine at University of California Irvine, described the neuroscience behind acupuncture's cardiovascular effect.[3] He showed that both manual and electroacupuncture at cardiac-related acupoints produce a depressor effect in a hypertensive animal model. This effect appears to be mediated by specific brain regions. One proposed pathway leads from the arcuate nucleus of the hypothalamus to the ventrolateral periaqueductal gray (PAG) and ultimately to the rostral ventrolateral medulla (rVLM) where modulatory neurotransmitters such as endorphins, enkephalins, and nonopioids, such as nociceptin, may downregulate a sympatho-excitatory state. Dr. Longhurst's presentation focused on the value of animal models in acupuncture research, because they enable the sampling of neurotransmitters from specific brain areas. This approach may be viewed as complementary to human neuroimaging research.

The final presentation in this session focused on biological events at the acupuncture point itself. Helene Langevin, M.D., LAc, Department of Neurology, University of Vermont, presented her work on connective tissue changes in response to needle insertion and manipulation.[4] These

changes may induce the first signals that transmit acupuncture stimulation to sensory nerves and other tissue receptors, although the exact mechanisms are not known. In addition, modulation of inflammatory and other cell mediators at the site brought about by the acupuncture-induced tissue changes may explain some of the long-term effects of acupuncture, which are somewhat more difficult to explain exclusively by nerve conductance mechanisms.

SESSION II: ACUPUNCTURE NEUROIMAGING: PLACEBO AND SHAM

This session tackled one of the most vexing problems in both clinical and basic acupuncture research: selection of an appropriate sham acupuncture control. Multiple acupuncture placebo controls have been used, including needling at nonacupuncture points, using noninsertion retractable sham needles, needling at true acupuncture points that are inappropriate for the condition being treated, superficial acupuncture at true or nonacupuncture points, and sham electrical stimulation. The first speaker, Ted Kaptchuk, O.M.D., from the Harvard Medical School Osher Institute, defined the ideal placebo control as one that "mimics in all manners the verum treatment but without physiological effect on the condition." Choosing an ideal placebo for acupuncture neuroimaging experiments is made especially difficult by our uncertainty as to how acupuncture induces its physiological and neurological effects.[5] Furthermore, Dr. Kaptchuk pointed out that some of the proposed physiological mechanisms for acupuncture analgesia may overlap with mechanisms of placebo analgesia.

Next, Todd Parrish, Ph.D., from the Department of Radiology at Northwestern University, described ongoing experiments aimed at deriving acupoint-specific brain responses using fMRI.[6] His approach attempts to evaluate whether traditional indications for different acupoints (e.g., improved hearing or sight) correspond to acupuncture-induced modulation in specific primary sensory cortices (e.g., auditory, visual). Acupoint specificity is a hallmark of TCM-style acupuncture, although it remains to be seen whether brain response is as specific as the purported indications of different acupoints.

Finally, Peter White, Ph.D. from the School of Health Professions and Rehabilitation Sciences, University of Southampton, United Kingdom explored the neural correlates of how a patient's belief in acupuncture affects acupuncture's therapeutic effectiveness on pain modulation.[7] He also investigated the brain response to Streitberger retractable needle stimulation, a potential sham control. His results using PET suggest that expectation related to patients' belief does have a mediating effect on neurophysiologic response and that the Streitberger needle might be a good control, or at least a less effective treatment than "real" acupuncture. In fact, while subjects were blinded as to verum or sham acupuncture stimulation, verum acupuncture produced greater activity in specific brain areas (insular cortex) than either Streitberger-needle stimulation (sham acupuncture) or a more overt placebo.

No consensus emerged from the session as to what the best sham or placebo should be for specific experimental paradigms. It was suggested that the sham or placebo control should be chosen based on the specific aspect of acupuncture the investigator is trying to control. Neuroimaging may well have a role in defining the brain responses associated with different forms of sham acupuncture, and how these responses may differ from those related to verum acupuncture.

SESSION III: ACUPUNCTURE NEUROIMAGING: BASIC RESEARCH

In general, neuroimaging has been shown to be an efficient way to gather information about activity in specific brain regions while exploring changes in neuroanatomy and inter-regional communication. This session explored ways that various neuroimaging technologies may provide approaches to explore the underlying mechanisms of acupuncture.

Zang-Hee Cho, Ph.D., from the University of California at Irvine, the first speaker, proposed a hypothalamic–pituitary–adrenal axis model of acupuncture action.[8] This model posits that via the hypothalamus, acupuncture modulates the autonomic, neuro-immunological, and neurohormonal systems. In his view, acupuncture is stimulation intensity- and frequency-specific, rather than point-specific, and its effects are mediated by the peripheral and central nervous system rather than traditional meridian theory. His recent fMRI data suggest that experimental pain processing is downregulated in the anterior cingulate cortex and thalamus after acupuncture stimulation.

Kathleen K.S. Hui, M.D., from the Martinos Center for Biomedical Imaging at Massachusetts General Hospital, presented her data from several studies supporting acupuncture processing in the limbic system of the brain.[9] Her results demonstrate that acupuncture induces fMRI signal decrease in a coordinated network of limbic regions, including the amygdala, hippocampus, cingulate, and cerebellar vermis. This decreased activity was in contrast to fMRI signal increase in similar brain regions in response to acupuncture-induced sharp pain. Hence, acupuncture sensation, termed *deqi*, may be the arbiter of fMRI signal response. Dr. Hui hypothesized that acupuncture may affect brain processing through a diffuse dopaminergic network that includes the limbic regions noted above.

This session closed with a talk by John Farrar, M.D., from the University of Pennsylvania School of Medicine, who applied SPECT to study acupuncture effects on patients in chronic pain.[10] His preliminary results suggest that acupunc-

ture modulates activity in the thalamus, possibly reversing pain-associated asymmetries in thalamic blood flow. Future work will aim to replicate these findings in a larger cohort of patients.

Because variability exists in the results and conclusions of different neuroimaging studies, investigators at the conference reached consensus on the need to develop an infrastructure for acupuncture neuroimaging data sharing. This would allow for exploration of larger datasets and perhaps a better understanding of which variables associated with acupuncture neuroimaging experiments are most predictive of the derived brain response.

SESSION IV: ACUPUNCTURE NEUROIMAGING: TRANSLATIONAL/CLINICAL RESEARCH

Although many neuroimaging studies investigating the biological mechanisms of acupuncture have been performed on healthy adult volunteers, several recent studies have begun to explore acupuncture processing in the brain in conjunction with clinical models. This direction of research holds great promise because longer term effects of acupuncture can be explored and used to inform concurrent or future clinical trials related to acupuncture. This session focused on several approaches for incorporating neuroimaging into clinical studies designed to evaluate the efficacy of acupuncture for various conditions.

The first speaker in this session, Judith Schaechter, Ph.D., from the Martinos Center for Biomedical Imaging at Massachusetts General Hospital, evaluated somatosensory processing in the brain of chronic stroke patients treated with acupuncture.[11] This fMRI study revealed that after acupuncture intervention (verum or sham), patients exhibited changes in motor cortex activity associated with the stroke-affected hand that were positively correlated with changes in somatosensory–motor function of the affected upper limb. There was a trend toward greater increases in motor cortex activity in patients treated with verum acupuncture than with sham acupuncture.

Vitaly Napadow, Ph.D., from the Martinos Center for Biomedical Imaging at Massachusetts General Hospital, described the effects of acupuncture on cortical plasticity and somatotopy in carpal tunnel syndrome (CTS) patients, as measured with fMRI.[12] In CTS, central somatosensory reorganization manifested as primary sensorimotor cortical hyperactivation, while adjacent fingers had overlapping or blurred representations in the primary somatosensory homunculus. A series of acupuncture treatments was found to produce clinical improvement, partial release from hyperactivation, and a return toward normal somatotopically separated finger representations. In fact, adjacent finger separation was found to correlate with median nerve dysfunction, and the change in this separation after acupuncture treatment was found to correlate with the change in dysfunction.

Richard Harris, Ph.D., from the Chronic Pain and Fatigue Center at the University of Michigan, presented preliminary results from a study of fibromyalgia.[11] A reduction in the fMRI response to pain was observed in the thalamus and insula after treatment. Moreover, PET scanning demonstrated decreased baseline carfentanil binding in the amygdala, hypothalamus, and rostral anterior cingulate and insular cortices after treatment. Clinical pain improvement was correlated with reduced carfentanil binding in the medial thalamus.

In general, conference attendees agreed that incorporating findings from neuroimaging studies into clinical studies of acupuncture efficacy is an important goal because it will enable the mechanism and efficacy of acupuncture to be evaluated in parallel. Furthermore, correlating findings from neuroimaging studies with clinical efficacy can inform the design of future trials and may even help optimize clinical acupuncture practice. However, neuroimaging is an expensive endeavor, and its incorporation into clinical trials needs to be considered carefully with regard to attaining adequate power.

In summary, this conference brought together researchers interested in using neuroimaging to explore the mechanisms of acupuncture. The presentations and discussions at the meeting revealed the usefulness of this technology in revealing underlying mechanisms of acupuncture on brain activity and its potential to act as a "bridge" between molecular investigations and clinical/behavioral studies. Although the focus was on neuroimaging, it is important not to lose sight of the fact that we still need to understand pathway(s) by which acupuncture stimulation is transmitted to the brain in order to fully interpret brain images and changes in neurotransmitters. These pathways may not completely operate through the nervous system, and it will be important to determine, for example, whether intercellular mediators released locally at the acupuncture site may be a result of neural activity, connective tissue responses, or other mechanisms.

The difficult question of what is the best placebo or sham control was not answered at this conference, but it is clear that neuroimaging can play a role in documenting differences in response to various types of controls and verum acupuncture, an important first step in approaching this problem. In addition, several presentations emphasized the need to correlate acupuncture neuroimaging changes with therapeutic effects in order to truly understand the mechanisms of acupuncture. This suggests a need for more mechanistic studies using clinical populations rather than just healthy individuals.

Another issue discussed at this conference, although not officially on the agenda, was the common approach of separating acupuncture from the more holistic traditional Asian medicine practices in order to study its biological mechanism. In traditional practice, acupuncture is a part of the larger tradition of Chinese and other Asian medical practices involv-

ing the use of herbs and other treatment modalities in combination with acupuncture. Furthermore, traditional diagnoses explain the rationale for certain combinations of treatments in terms that are difficult to interpret from a Western biomedical perspective, such as energy stagnation or imbalance. Much of the current research on acupuncture (whether neuroimaging or otherwise) removes acupuncture as one aspect of this traditional healing system from its larger context in order to evaluate it using accepted Western research paradigms. This may be more similar to the way acupuncture therapy is practiced in the United States and thus not completely removed from medical practice paradigms. It should also be noted that in some studies, the efficacy or action of acupuncture has been evaluated by stimulating a single acupoint on a nonclinical population—a situation vastly different from both a traditional or more Westernized acupuncture treatment. It is unclear what implications these departures from traditional practice paradigms have on the meaningfulness of research results. Although this issue was beyond the scope of this conference, participants agreed that it was important to explore in future research.

The presentations and discussions at this conference suggest that future directions in acupuncture neuroimaging research should focus on (1) continuing research on acupuncture signaling networks, (2) establishing standards and recommendations for performing and reporting acupuncture neuroimaging results, (3) enabling data sharing in the acupuncture neuroimaging community, (4) gaining a better understanding of placebo and control groups in acupuncture neuroimaging experiments, and (5) developing biomarkers that relate physiologically or clinically relevant acupuncture responses to neuroimaging results.

REFERENCES

1. Dale AM, Halgren E. Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. Curr Opin Neurobiol 2001;11:202–208.
2. Han JS. Acupuncture: Neuropeptide release produced by electrical stimulation of different frequencies. Trends Neurosci 2003;26:17–22.
3. Zhou W, Fu LW, Tjen ALSC, et al. Afferent mechanisms underlying stimulation modality-related modulation of acupuncture-related cardiovascular responses. J Appl Physiol 2005;98: 872–880.
4. Langevin HM, Churchill DL, Wu J, et al. Evidence of connective tissue involvement in acupuncture. FASEB J 2002; 16:872–874.
5. Kaptchuk TJ. Acupuncture: Theory, efficacy, and practice. Ann Intern Med 2002;136:374–383.
6. Parrish TB, Schaeffer A, Catanese M, Rogel MJ. Functional magnetic resonance imaging of real and sham acupuncture. Noninvasively measuring cortical activation from acupuncture. IEEE Eng Med Biol Mag 2005;24:35–40.
7. Pariente J, White P, Frackowiak RS, Lewith G. Expectancy and belief modulate the neuronal substrates of pain treated by acupuncture. Neuroimage 2005;25:1161–1167.
8. Cho ZH, Hwang SC, Wong EK, et al. Neural substrates, experimental evidences and functional hypothesis of acupuncture mechanisms. Acta Neurol Scand 2006;113:370–377.
9. Hui KK, Liu J, Makris N, et al. Acupuncture modulates the limbic system and subcortical gray structures of the human brain: Evidence from fMRI studies in normal subjects. Hum Brain Mapp 2000;9:13–25.
10. Newberg AB, Lariccia PJ, Lee BY, et al. Cerebral blood flow effects of pain and acupuncture: A preliminary single-photon emission computed tomography imaging study. J Neuroimaging 2005;15:43–49.
11. NCCAM Clearinghouse, P.O. Box 7923, Gaithersburg, M.D. (1-888-644–6226): single copies of the CD are available.
12. Napadow V, Liu J, Li M, et al. Somatosensory cortical plasticity in carpal tunnel syndrome treated by acupuncture. Hum Brain Mapping 2006 (in press).

Address reprint requests to:
Vitaly Napadow, Ph.D., Lic.Ac.
Martinos Center for Biomedical Imaging
Department of Radiology
Massachusetts General Hospital
Building 149, 13th Street
Room 2301—NMR Center
Charlestown, MA 02129

E-mail: vitaly@nmr.mgh.harvard.edu