# Editorial:
# I Think, Therefore I'm Well: the Amazing Brain

**Lawrence R. Huntoon, M.D., Ph.D.**

Development of functional magnetic resonance imaging (fMRI) has opened a whole new window on the brain. Patients with severely impaired consciousness, who were previously thought to be incapable of cognitive or sensory function, have been found, with the use of fMRI, to have stimulus-activated cortical networks, despite lack of any consistent or reliable motor response.[1]

With the emergence of real-time fMRI, combined with special virtual reality goggles, it is now possible to see one's own brain function in real time.[2] Moreover, the feedback provided by real-time fMRI may provide a means for self-modulating pain, cancer, inflammation, and the immune system. Current studies and/or planned studies using fMRI feedback to treat attention deficit hyperactivity disorder, anxiety disorders, depression, post-traumatic stress disorder, and stroke are already in the works.

## Pain

Recent research has revealed that it is possible for subjects to selectively control neural activity in the rostral anterior cingulate cortex, an area known to be involved in the control and regulation of pain perception. Using real-time fMRI feedback, some chronic pain patients, who had inadequate pain control with traditional medication treatment, were able to reduce their pain significantly (44–64 percent, more than triple the pain reduction in the control group).[3]

Interestingly, there is also evidence linking the rostral anterior cingulate cortex to the so-called placebo analgesia effect[4] and even to the pain of social rejection.[5] The rostral anterior cingulate cortex is also known to have a dense population of opioid receptors, suggesting a possible mechanism to explain the placebo effect and the effect of self-regulation of pain.

Although it is still not known precisely how subjects are able to selectively modulate the activity in specific areas of the brain, the possibility of learning to control one's own chronic pain without use of drugs and drug-related side effects is very exciting.

## Stress, Cancer, and Inflammation

The ability to modify one's response to stress may have a significant impact on cancer, inflammation, the immune system, and the ability of the body to heal itself. The capacity to remain calm in the face of a life-threatening diagnosis may be critical to surviving the disease. The importance of reducing the effects of stress in cancer has become so crucial that some have referred to behavior as the sixth vital sign in cancer patients.[6]

Studies have shown that stress hormones like norepinephrine increase production of matrix metalloproteinases and vascular endothelial growth factor, which in turn promote the spread and growth of certain cancers (ovarian cancer,[7] nasopharyngeal carcinoma[8]). The possibility of modifying the activity in selective areas of the brain involved in the stress reaction, using fMRI feedback, may provide a means of controlling circulating stress hormones that complements other low-technology methods currently available (progressive muscle relaxation, stress-relaxation techniques, visualization, yoga).

The ability to self-modify inflammation and chronic inflammation could affect a variety of diseases, including sepsis, arthritis, coronary artery disease, type II diabetes mellitus, multiple sclerosis, Crohn's disease, periodontal disease, and a host of others. Stress has been shown to cause high levels of the cytokine interleukin-6, which in turn is linked to chronic inflammation and slow wound healing.[9]

Recent research has identified a cholinergic antiinflammatory pathway mediated by the vagus nerve, which inhibits the release of cytokines, thus protecting against cytokine-mediated injury and diseases.[10] Current evidence suggests that the vagus nerve both informs the brain about the state of peripheral inflammation and modulates inflammation, including inflammation related to atherosclerosis and coronary artery disease.[11] Some have suggested using electrical stimulation of the vagus nerve to control inflammation and to prevent damage caused by excessive inflammation and chronic inflammation.[12] The ability of some individuals to slow their own heart rate by increasing vagal activity suggests that there may be a less invasive way to accomplish self-regulation of inflammation. The possibility of further refining control over vagal activity with fMRI feedback training, so as to suppress hyperinflammatory responses or chronic inflammation, is an area worthy of further exploration.

## Immunomodulation

Another recent study, done at the University of California at Los Angeles Cousins Center for Psychoneuroimmunology, has provided evidence of the ability of individuals to regulate their own immune systems. This 25-week study showed that older individuals who perform Tai chi chih (a non-martial-arts form of Tai chi) are less susceptible to developing shingles than the control group.[13] The level of immunity in the Tai chi group was twice that found in the control group and was comparable to the level of immunity achieved by the *Varicella zoster* vaccine. The potential implications of this finding are enormous. The possibility of self-regulating one's immune system, so as to boost immunity against pneumonia, influenza, and other infections without vaccines or medications, is another intriguing area worthy of further study. There may even be some way to modify autoimmune diseases with behavioral intervention and/or fMRI feedback training.

## Neural Plasticity

Our understanding of neural plasticity in the mature central nervous system is another area that has undergone dramatic change since 1980. Prior to 1980, it was thought that the mature central nervous system had little or no capacity to reorganize and/or repair itself following insult or injury. This view was particularly evident in the area of stroke, where any improvement in motor function beyond six months or a year following stroke was considered highly unlikely if not impossible. However, studies on conditioned suppression of movement, known as learned nonuse (involving the paretic limb), led to the development of constraint-induced movement therapy (CI therapy).[14] Constraint-induced movement therapy has been highly successful in improving motor function involving a weak upper extremity following stroke. Given the success of fMRI feedback in self-modulating specific areas of the brain in initial studies in the area of pain management, the possibility of using fMRI feedback in conjunction with CI therapy, so as to facilitate central nervous system motor pathways, is yet another area worthy of further exploration.

## Conclusion

Development of fMRI real-time feedback, and the demonstrated ability of individuals to modify neural activity in specific areas of the brain with clinical benefit, represent major advancements in medicine. Although our knowledge concerning how fMRI feedback works or how to implement training most effectively for various diseases and conditions is in its infancy, the concept of beneficially affecting one's own health using one's own brain is a most extraordinary and healing thought.

**Lawrence R. Huntoon, M.D., Ph.D.**, is a practicing neurologist and editor-in-chief of the *Journal of American Physicians and Surgeons*. Contact editor@jpands.org.

**REFERENCES:**

[1] Schiff ND, Rodriguez-Moreno D, Kamal A, et al. MRI reveals large-scale network activation in minimally conscious patients. *Neurology* 2005;64:514-523.

[2] Omneuron Technology. Available at: www.omneuron.com/technology.html. Accessed Apr 17, 2007.

[3] DeCharms RC, Maeda F, Glover GH, et al. Control over brain activation and pain learned by using real-time functional MRI. *Proc Nat Acad Sci* 2005;102:18626-18631. Available at: http://www.pnas.org/cgi/content/abstract/0505210102v1. Accessed Apr 17, 2007.

[4] Seminowicz D. Believe in your placebo. *J Neurosci* 2006;26:4453-4454. Available at: www.jneurosci.org/cgi/content/full/ 26/17/4453. Accessed Apr 17, 2007.

[5] Anon. Brain imaging captures pain of social rejection. *Mind Body Connection* UCLA Winter 2007;1(1):2 Available at: http://www2.healthcare.ucla.edu. Accessed Apr 17, 2007.

[6] Anon. Behavior—a sixth vital sign in cancer patients. *Mind Body Connection* UCLA Winter 2007;1(1):3 Available at: www2.healthcare.ucla.edu. Accessed Apr 17, 2007.

[7] Holland E. Stress hormones may play new role in speeding up cancer growth. *Ohio State Univ Research,* Nov 1, 2006. Available at:researchnews.osu.edu/archive/epinorepi.htm. Accessed Apr 17, 2007.

[8] Yang E. Norepinephrine up-regulates the expression of vascular endothelial growth factor, matrix metalloproteinase (MMP)-2, and MMP-9 in nasopharyngeal carcinoma tumor cells. *Cancer Res* 2006;66:10357-10364.

[9] Holland E. Stress substantially slows human body's ability to heal. *Ohio State Univ Research News,* December 2005. Available at: http://researchnews.osu.edu/archive/wounheal.htm. Accessed Apr 17, 2007.

[10] Tracey K. Physiology and immunology of the cholinergic anti-inflammatory pathway. *J Clin Invest* 2007;117(2):289-296.

[11] Gidron Y. Vagus-brain communication in atherosclerosis-related inflammation: a neuroimmunomodulation perspective of CAD. *Atherosclerosis,* Nov 11, 2006. Available at: http://lib.bioinfo.pl/pmid:17101139. Accessed Apr 17, 2007.

[12] Pavlov V. Controlling inflammation: the cholinergic anti-inflammatory pathway. *Biochem Soc Trans* 2006;34(Pt6):1037-1040.

[13] Irwin M. Practicing Tai chi boosts immune system in older adults, UCLA Study Shows. *UCLA News,* Mar 22, 2007. Available at: www.newsroom.ucla.edu/ page.asp?relnum=7806. Accessed Apr 17, 2007.

[14] Taub E, Miller NE, Tovack TA, et al. Technique to improve chronic motor deficit after stroke. *Arch Phys Med Rehabil* 1993;74:347-354.