MACHINING PHYSIOLOGICAL INTELLIGENCE

By William J. Tyler

Humans have attempted to control brain function using state-of-the-art tools since Neolithic times. Trepanation, conducted by ancient people using rocks and stones, involved the punching of holes through the skulls of living people. It is believed to have been a ritualistic procedure used to liberate evil spirits producing diseases such as epilepsy. Still today, we drill through the skulls of awake patients using seemingly archaic methods to implant brain stimulating electrodes into the heads of diseased patients. This brief review provides an account of emerging concepts useful in the study and control of human brain function.

Learning and Memory: All About Timing

Scientists began the modern study of intelligence around the turn of the 20th century by systematically investigating the way animals learn, remember, and behave. The Russian physiologist Ivan Pavlov is credited for providing the first thorough description of "conditioned reflexes" or how animals can learn simple relationships among environmental cues. Most readers will be familiar with the classic experiments in which Pavlov taught dogs the ringing of a bell signaled food. The key finding from these early classical conditioning experiments was that the timing of events is crucial to an animal's ability to learn relationships between stimuli. Pavlov's dogs were conditioned over time to salivate or physiologically expect food only when the bell immediately preceded their meals. If Pavlov randomly rang the bell both before and after his dogs were fed then they could not "learn" the bell signaled food. These observations highlight the fact that we learn relationships among cues based, in part, on their temporal proximity.

In 1911, American psychologist Edward Thorndike described how cats learn to escape from puzzle boxes based on trial and error rather than rational problem solving. Based on his observations, Thorndike proposed the outcome of a particular behavioral response (reward or punishment) governed the likelihood of reproducing that response. He further posited that repetition and recency strengthened stimulus-response associations. These original conventions were later expanded by other prominent behavioral scientists such as John Watson, B.F. Skinner, and Donald Hebb.

In 1973, Tim Bliss and Terje Lømo described the discovery of a form of brain plasticity known as long-term potentiation (LTP). The discovery immediately generated excitement in neurosciences since it was made in a brain region known as the hippocampus. The medial temporal lobe, including the hippocampus, had been previously identified by William Scoville and Brenda Milner as being important for the formation of long-term memories as observed through their case studies of patient H.M. Today, hippocampal LTP is the mostly widely accepted cellular substrate of learning and memory. In its modern conventions, we have an intimate portrait of how the brain processes, integrates, stores, and recalls information.[1,2]

The basic concept of how a brain learns and remembers is rather simple. Synapses, junctions where two neurons communicate with one another, that are active simultaneously become stronger over time. Conversely, synapses not simultaneously active become weaker or disappear altogether. LTP is the process of persistent strengthening while the long-lasting weakening of synapses is known as long-term depression (LTD). Since many synapses can be either strengthened or weakened depending on the timing of their activity, LTP and LTD are often collectively described as spike-timing dependent plasticity (STDP).[3] Learning and memory are dependent on our brain's ability to change the strengths of its connections based on the temporal patterns of its activity. Over the past half-century, neuroscience has assembled a long list of ions, molecules, genes, proteins, and electrical activity patterns capable of modulating plasticity in one manner or another. Some of these neuromodulators enhance learning and memory while others impair it. By no means does neuroscience possess all the answers underlying human cognition, learning, and memory. However, we do possess enough prerequisite knowledge for further delving into human brain function with the aim of better understanding and controlling it.

Unraveling Neural Circuits

The brains of animals (including humans) possess the ability to differentially process, synthesize, and integrate information based on past experience (memory), levels of physiological arousal (stress or anxiety), and the contexts of sensory cues (associations), combined with the previous outcome of an action (reward or punishment). These abilities rely on complex brain circuits serving different functions. Just as we know the hippocampus is a brain region vital to learning and memory, we know other neural circuits are involved in regulating complex behaviors and emotions such as motor control, planning and execution, pleasure and pain, fear, aggression, eating, sleeping, and addiction. Collectively, these circuits work in unison to form the basis of physiological intelligence. Knowing what each circuit does and how it does it provides the base knowledge needed to manipulate brain function for a desired outcome.

Besides fMRI, which suffers from poor spatial resolution, numerous functional brain mapping methods are beginning to flourish due to recent gains in computational power. For example, the emerging field of connectomics employs optical microscopy, electron microscopy, and computer-assisted reconstructions to map all the synaptic connections of a brain. Similar molecular brain mapping studies, such as those being conducted by the Allen Brain Institute, will also provide useful information for continuing to unravel brain function and the physiological basis of human intelligence. It is important to recognize that a working knowledge of functional neuroanatomy fulfills the first criteria needed in order to tap into brains and predictably regulate them for various purposes. Modern neuroscience already possesses a wealth of functional brain anatomy knowledge, and neurotechnology is putting it to use.

Modifying Behaviors and Manipulating Brain Function Through Stimulation

In 1870, nearly a decade before Pavlov received his doctorate degree, Gustav Fritsch and Eduard Hitzig

> **"The *mind* is its own place and in itself, can make a Heaven of Hell, a Hell of Heaven."**
>
> — John Milton

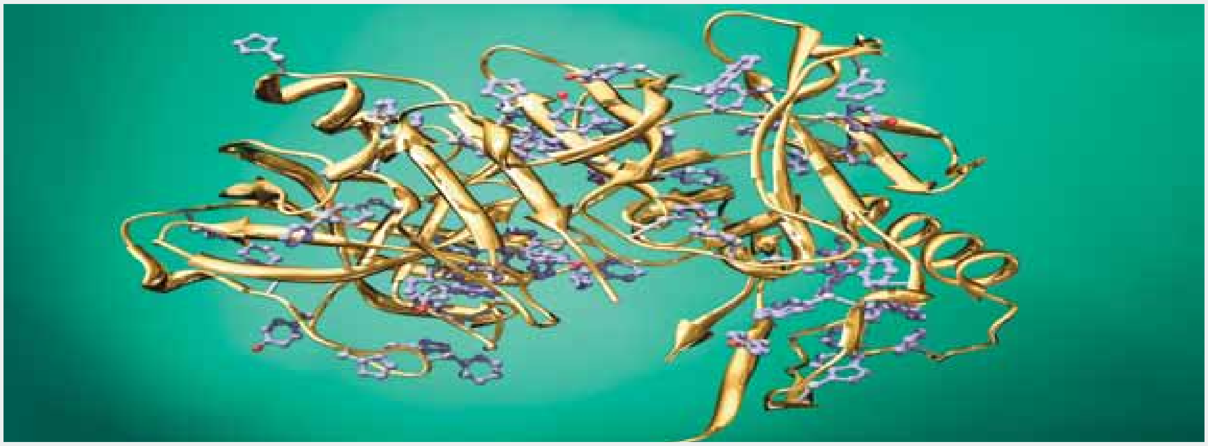
first demonstrated the electrical stimulation of a brain. They showed that electrical stimulations of a dog's cortex could be used to produce movement behaviors. Four years later, Roberts Bartholow similarly demonstrated the electrical stimulation of the human cortex for the first time.[4] Later in the 1920s, Walter Hess reported he could evoke behaviors such as aggression, feeding, and sleep/wake cycles depending on where he stimulated an animal's brain. Using similar functional brain mapping strategies in the 1940s and 50s, Wilder Penfield and Herbert Jasper began mapping the brains of patients suffering from epilepsy prior to the surgical removal of diseased tissue. At the same time these demonstrations of acute brain stimulation were proving useful during functional neurosurgery, Jose Delgado, a neuroscientist at Yale University who was motivated by the experiments of Hess, Penfield, and others, began pioneering implantable brain electrodes or "stimoceivers."[5]

Today, Delgado is recognized as a revolutionary individual partially responsible for developing modern electrical brain stimulation techniques using deep-brain stimulating (DBS) electrodes. Gaining popularity and acceptance, DBS electrodes are useful in the treatment of a variety of drug-resistant neurological diseases and psychiatric disorders including epilepsy, depression, Parkinson's disease, and others.[6-7] Delgado's ideas stemmed from observations that brain stimulation could pacify aggression and other maladaptive behaviors in animals including cats, monkeys, and humans. He is perhaps best known for his demonstration of remotely controlling a bull by stopping its raging charge towards him only using a brain implanted stimoceiver (See *Web Links of Interest*). However, Delgado's visions of using implantable brain stimulating electrodes to create a "psychocivilized society" was so controversial that he was ostracized by his scientific peers and left the United States in the early 1970s to return to his home in Spain.

Currently, neuromodulation is one of the fastest growing markets and is bearing witness to the rapid development of newer generations of brain implantable electrodes fabricated from a variety of biocompatible nanomaterials. These brain stimulation technologies serve as potential platforms for future brain-machine interfaces and may yet lead to more highly evolved societies as similarly envisioned by Delgado. By far, the major limitation of electrical stimulation is that no matter how small or how biocompatible an electrode can be made, it will always require some type of invasive procedure to be inserted into the brain. Electrodes also risk failure, in which case they must be removed and/or replaced.

The Brain Unplugged

In the early 1980s, a paradigm shift began when Anthony Barker showed that magnetic coils placed outside the head could noninvasively stimulate brain activity. This method pioneered by Barker is known as transcranial magnetic stimulation (TMS) and was recently approved by the FDA to treat drug-resistant depression. Other noninvasive brain stimulation techniques that do not necessitate surgery exist. These include transcranial direct current stimulation



(tDCS), electroconvulsive shock therapy (ECT), and cranial electrotherapy stimulation (CES). These methods, in particular TMS and tDCS, have been shown not only capable of treating some neurological disorders, but have also been demonstrated to modify neuronal plasticity in the cortex such as LTP and LTD leading to speculation that they can be used to manipulate learning and memory.[8-10] The utility of TMS and tDCS is somewhat limited, however, due to its poor spatial resolution of ≈ 1 cm and inability to reach deep-brain circuits.[8, 11] To circumvent these limitations, my laboratory at Arizona State University has recently developed novel brain stimulation methods employing pulsed ultrasound.

Ultrasound has a long history of safe use in medicine, mostly in its diagnostic imaging applications. Edmund Newton Harvey first showed in 1929 that ultrasound was capable of exciting the nerves and muscles in the legs and hearts of frogs and turtles. Since then, little attention has been given to the use of ultrasound as a brain stimulation modality compared to electromagnetic radiation. Using phased arrays, ultrasound can be focused through human skulls to deep-brain regions. Based on these and other observations, we began studying the potential of using ultrasound to stimulate brain activity. We recently reported that transcranial pulsed ultrasound can noninvasively stimulate movement behaviors in mice, as well as certain brain wave activity patterns in the hippocampus known to underlie certain cognitive processes, such as memory trace formation.[12] Further, we found that transcranial pulsed ultrasound has a spatial resolution approximately five times better than that reported for TMS or tDCS. Thus, the ability to stimulate intact deep brain circuits with pulsed ultrasound may permit the unplugging of minds from machines — to eliminate the need for surgically implanted brain stimulating electrodes while reaching deep brain regions with millimeter spatial resolutions.

Not only does this ultrasonic neuromodulation technology pose exciting possibilities for treating a broad spectrum of neurological and psychiatric diseases, it paves the way for forthcoming brain-computer interfaces due to its noninvasive nature. In these forward-looking applications, we envision the use of our technology in defense and national security industries, recreational applications such as video gaming, and future generations of social entertainment networks beyond the wildest imaginations of Apple, Facebook, and Google. We believe that brain stimulation is on the cusp of enabling the machining of physiological intelligence. Q

WEB LINKS OF INTEREST:

Video of Jose Delgado's taming of a raging bull using remote controlled brain stimulation
http://www.youtube.com/watch?v=6nGAr2OkVqE&NR=1

The Neurostimulation Technology Portal
http://www.biotele.com/

Dr. William J. Tyler *is an Assistant Professor of Neurobiology and Bioimaging at Arizona State University. He received his B.S. and Ph.D. from the University of Alabama at Birmingham before conducting his postdoctoral fellowship at Harvard University. Dr. Tyler utilizes cutting-edge technology to investigate a wide range of problems in modern neuroscience and has made leading contributions to our understanding of synaptic transmission and plasticity. Most recently, he developed novel methods for the noninvasive remote stimulation of brain circuits using transcranial pulsed ultrasound. This ultrasonic neuromodulation technology will have a major impact on emerging brain stimulation markets. To this end, Dr. Tyler co-founded SynSonix, Inc. and currently serves as its CSO while spearheading efforts to translate ultrasonic neuromodulation technology from bench-to-bedside. Dr. Tyler's research on ultrasonic neuromodulation is funded by the U.S. Army Research, Development and Engineering Command and a Defense Advanced Research Projects Agency (DARPA) Young Faculty Award.*

REFERENCES

[1] Bliss, T.V.P. and G.L. Collingridge, *A synaptic model of memory: long-term potentiation in the hippocampus*. Nature, 1993. **361**: p. 31-39

[2] Milner, B., L.R. Squire, and E.R. Kandel, *Cognitive neuroscience and the study of memory.* Neuron, 1998. **20**(3): p. 445-68

[3] Dan, Y. and M.M. Poo, *Spike timing-dependent plasticity: from synapse to perception.* Physiol Rev, 2006. **86**(3): p. 1033-48

[4] Harris, L.J. and J.B. Almerigi, *Probing the human brain with stimulating electrodes: The story of Roberts Bartholow's (1874) experiment on Mary Rafferty.* Brain and Cognition, 2009. **70**(1): p. 92-115

[5] Horgan, J., *The Forgotten Era of Brainchips. Scientific American*, 2005. **293**(October): p. 66-73

[6] Ressler, K.J. and H.S. Mayberg, *Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic.* Nat Neurosci, 2007. **10**(9): p. 1116-24

[7] Lozano, A.M. and B.J. Snyder, *Deep brain stimulation for Parkinsonian gait disorders.* J Neurol, 2008. 255 Suppl **4**: p. 30-1

[8] Wagner, T., A. Valero-Cabre, and A. Pascual-Leone, *Noninvasive Human Brain Stimulation.* Annu Rev Biomed Eng, 2007. **9**: p. 527-565

[9] Pascual-Leone, A., J. Valls-Sole, E.M. Wassermann, and M. Hallett, *Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex.* Brain, 1994. **117** (Pt 4): p. 847-58

[10] Huerta, P.T. and B.T. Volpe, *Transcranial magnetic stimulation, synaptic plasticity and network oscillations.* J Neuroeng Rehabil, 2009. **6**: p. 7

[11] Barker, A.T., *The history and basic principles of magnetic nerve stimulation.* Electroencephalogr Clin Neurophysiol Suppl, 1999. **51**: p. 3-21

[12] Tufail, Y., A. Matyushov, N. Baldwin, M.L. Tauchmann, J. Georges, A. Yoshihiro, S.I. Tillery, and W.J. Tyler, *Transcranial pulsed ultrasound stimulates intact brain circuits.* Neuron. **66**(5): p. 681-94