The Future of Brain Stimulation Treatments

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KEYWORDS

• tDCS • LIFUP • Focused ultrasound • tACS • Speed of onset • Durability • Circuit

KEY POINTS

- Over the past 80 years, several trends emerged in the field of brain stimulation that are likely to continue into the future, including being less invasive, more focal, better integrated with behavior, and using less energy.
- There are also several exciting new methods that may be disruptive in the field, including pulsed ultrasound stimulation and temporally interfering fields.
- The future growth of brain stimulation is promising. The focal nature of the stimulation produces minimal systemic side effects.
- Technology continues to advance to create even better stimulation methods. And we better understand the neuroplasticity methods by which to change the brain.

INTRODUCTION

Since Cerletti's first use of electroconvulsive therapy (ECT) in 1938, several themes have emerged in the field of brain stimulation. These include, with new technologies and even within existing technologies, gradual decreases in stimulation intensity, greater focality of treatment, increased specificity of brain stimulation targets, and greater public acceptance of therapeutic neuromodulation.

Remember that modern neuromodulation arose on a foundation of psychopharmacologic advancements in the 1920s and 1930s. Manfred Sankel and Ladislaus von Meduna recognized that overdoses of insulin and pentylenetetrazol (metrazol) that caused seizures improved schizophrenic symptoms.[1–3] Drawing on these clinical observations, Ugo Cerletti, an Italian epileptologist, developed ECT in 1938 as a means of producing seizures to remediate psychoses and, later, depression.[4] Cerletti's ECT 80 years ago was an epoch-shifting invention. For the first time, researchers and clinicians could reliably stimulate the human brain and the field of brain stimulation (or neuromodulation) was born. The next paradigm-shifting neuromodulation

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Psychiatr Clin N Am 41 (2018) 515–533
https://doi.org/10.1016/j.psc.2018.05.004
psych.theclinics.com
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invention, transcranial magnetic stimulation (TMS), grew out of creative thinking in response to a tricky problem and highlights how the field has historically moved toward using less invasive, lower energy stimulation. In 1980 at Queen Square in London, UK, Patrick Merton and Bert Morton found that transcranial electrical stimulation, applied at around 60 to 100 mA of electrical current through the scalp, could effectively cause muscle twitches and phosphenes (flashes of light) yet was too uncomfortable and even painful to tolerate.[5–7] Ingeniously reasoning that briefly pulsing electrical current through a loop of metal wire would create an electromagnetic field (Faraday's law), which in turn could cause neuronal discharge at the cortex without direct electrical stimulation through the skull, Tony Barker, working in Sheffield, UK, took aim at creating the first modern TMS device. Over several years and many failed machines (and some big explosions!), Barker was able to create a TMS machine and coil that could stimulate the cortex without significant pain. Now there was a method of focal and relatively pain-free brain stimulation of the superficial cortex in an awake and alert human! The subsequent neuroimaging revolution of the 1980s and 1990s was the key that unlocked the therapeutic potential of TMS and continues to be the background for evaluating and using neuromodulation. New neuroimaging methods, such as PET and MRI, allowed scientists to observe, for the first time, the structural and functional status of the brain, in health and pathology, and in real time (ie, before death). Armed with this information, neuroscientists now had maps of where potentially to apply transcranial brain stimulation in different diseases. In 1994, psychiatrists began to use TMS in medication-resistant depression (as defined by inadequate clinical response to $\geq$2 pharmacologic therapies).[8] Several multisite, double-blind controlled clinical trials, including the industry-independent OPT-TMS trial published in 2010,[9] firmly established its efficacy in acutely treating depression. In 2008, the US Food and Drug Administration (FDA) first cleared a TMS device, and now 6 TMS devices are FDA cleared for the acute treatment of depression. Herein, we highlight the key considerations and trends of neuromodulation and discuss and digest the use of several new preclinical and clinical brain stimulation technologies.

CONSIDERATION 1: NEUROMODULATION HAS BECOME LESS INVASIVE

A hallmark feature of neuromodulation over the past 80 years is the decreasing invasiveness of stimulation. By less invasive, we refer to the trend of subsequently developed forms of noninvasive brain stimulation using less strength of electrical or electromagnetic current over time (**Fig. 1**). To understand this, it is best to compare the amount of electricity that each brain stimulation method actually delivers. Many of us do not have a working knowledge of a milliamp, like we do an inch or a pound (or kilogram). We can, however, understand energy as how long it takes to power a light bulb (because this gets reflected in a utility bill we pay each month!). Using this scale ECT, which uses the greatest amount of energy in a single treatment session, only applies enough voltage and current to power a 60W light bulb for a mere 10 seconds. (Much to the surprise of even our laboratory's brilliant biomedical engineer, whose off-the-cuff guess was orders of magnitude longer). A single treatment session of the subsequent forms of neuromodulation would power the same light bulb for even less time: all less than 4 seconds!.

Another way to grasp this is to compare the summed amount of exogenous energy applied over a treatment session or treatment course to the amount of endogenous energy used by the brain in the same amount of time (**Fig. 2**). Because the human brain operates at 20 W, it produces enough energy constantly to power the 60 W light bulb one-third of the amount of time of the course of stimulation. For the 4 weeks a typical

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