A Brief History of Transcranial Magnetic Stimulation

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Ongoing advancements in neuromodulation, neuroscience, and health systems science promise to revolutionize psychiatry. The storied history of transcranial magnetic stimulation (TMS) shows how the insights of disparate fields can lead to translational breakthroughs. Understanding the maturation and ongoing refinement of TMS is instructive in predicting how the field itself may change in the future. Modern practitioners are likely to be most familiar with electroconvulsive therapy (ECT), a common, safe, and effective procedure that has gained popularity over time. Despite its therapeutic benefits, issues such as stigma stemming from media depictions, such as in the 1975 film "One Flew Over the Cuckoo's Nest" and the 2016 film "Suicide Squad," have hindered more widespread acceptance of this treatment modality. Moreover, the global neuronal activation resulting from an ECT-induced seizure does not allow researchers to determine which discrete anatomical sites require stimulation for treatment response (1). Further exploration of the origins of neuromodulation with electromagnetism in psychiatry can both contextualize current treatment modalities and provide inspiration for future developments.

Both before and after the development of ECT, researchers have strived to better understand the neural substrates underlying disease, and electricity has been frequently used as a tool to modulate brain activity. Such approaches with electricity were used as early as the late 18th and early 19th centuries and culminated in the works of Alessandro Volta (1745–1827), Luigi Galvani (1737–1798), and Giovanni Aldini (1762–1834). The works of Volta and Galvani were instrumental in developing modern understanding of electricity and electrophysiology, originally described as "animal electricity" or galvanism. In particular, Galvani's experiments on muscle contractions in frog legs in the 1790s elegantly supported the idea of intrinsic electrical activity within organisms and laid the groundwork for future research and treatment (2). Throughout the early years of the 1800s, Aldini used a voltaic pile, which is an early battery consisting of alternating discs of zinc and copper in an electrolyte solution, to stimulate the muscles of human cadavers as an extension of the galvanism hypothesis.

Before long, Aldini recognized the potential of electricity to treat living subjects with disease. He adapted his voltaic pile such that patients would place a hand at the bottom of the pile, and then the patients' parietal bone would be touched with a wire from the top of the pile (2). It had been noted, however, that the device made by Aldini was cumbersome to use and that it resulted in an unpleasant experience for subjects. Aldini experienced the stimulation from the device before using it on other subjects, and a transcript from his memoirs noted that he found the experience unpleasant: "First, the fluid took over a large part of my brain, which felt a strong shock, a sort of jolt against the inner surface of my skull. The effect increased further as I moved the electric arcs from one ear to the other. I felt a strong head stroke and I became insomniac for several days" (2). After personally verifying the safety of the device, Aldini went on to report that this treatment tool was used with a patient with melancholia in 1801, and he further reported successful treatment of parkinsonism with the device (2). Unfortunately, the therapeutic potential of these techniques was not exhaustively explored, because Aldini's research through the remainder of the mid-1800s focused on musculoskeletal demonstrations with human cadavers. However, modern techniques, such as transcranial direct-current stimulation (tDCS), are being evaluated for their ability to deliver nonpainful stimuli to discrete brain regions for the treatment of psychiatric disorders (3).

In subsequent decades, the field of neuromodulation therapy increasingly focused on ECT as a treatment tool, and other techniques remained largely confined to research. ECT was introduced as a treatment for psychiatric illness by Ugo Cerletti and Lucio Bini in 1938, continuing the use of electricity as a potential therapeutic agent. However, ECT was explicitly different from previous direct-current stimulation strategies in that the goal is global stimulation of brain activity to induce a seizure. Further refinements in ECT technique, such as use of anesthesia, paralytics, and modified waveforms of the electrical stimulus, improved the safety and tolerability of ECT over time (1). Despite these improvements, the procedure has several practical limitations, including the need for general anesthesia and postoperative recovery. Clinicians, researchers, and engineers have been challenged with the question of how to develop less invasive neuromodulatory techniques.

To solve this problem, we turn back to the work of Michael Faraday (1791–1867) and his contemporaries, such as James Clerk Maxwell (1831–1879), who experimentally and later quantitatively demonstrated the important interconnectivity of electricity and magnetism. An electrical current will generate a circular magnetic field around the current's axis. This axial magnetic field is even stronger if the coil through which current passes is helical, as is the case with a solenoid. The flux of the magnetic field itself can then induce an electromotive force in conductive material running perpendicular to it, such as neuronal axons.

Building upon this understanding, Anthony Barker and colleagues developed the first TMS device for research applications in 1985 (4). Barker was optimistic about the future of the technique and its research and therapeutic potential. In his original publication, he noted that "magnetic stimulation of the cortex is particularly effective [compared with electrical stimulation] because of the ability of the field to pass through high-resistance structures" (4). This insight has been further leveraged to modify the TMS coil so that the field can be optimized to target deeper structures, as is the case with the Hesed coil (H-coil), described by Roth and colleagues in 2007 (5). For many years, TMS was used as a tool to strategically and noninvasively target brain regions in research settings, but the next step to translational applications was close at hand.

In parallel to Barker's work, the "biological revolution" in psychiatry of the 1970s and 1980s led to a research drive to find physical substrates of mental illness. Although not without modern controversy, the metaphor of the mind as a complicated set of circuits whose perturbations can cause symptoms of mental illness has appealing research and treatment implications. Although research is ongoing to understand the discrete molecular underpinnings of mental illness, other technological breakthroughs, such as the computed tomography scan and functional magnetic resonance imaging, allowed researchers to learn about static and dynamic differences that were previously impossible to discern via gross pathology. In one such example, researchers correlated abnormal activity of the left dorsolateral prefrontal cortex to severity of depression (6). Therefore, the modern circuit-based understanding of mental phenomena provides exciting opportunities for targeted treatment of conditions such as depression (7).

It was subsequently theorized that modulation of the dorsolateral prefrontal cortex could be a specific treatment for depression, likely involving long-term potentiation in cortical neurons. Given a treatment target and selective means of modulating its activity, TMS made the leap from research tool to treatment modality in the early 2000s. A study by O'Reardon et al. (8) of 301 patients with depression was used as justification for U.S. Food and Drug Administration (FDA) approval in 2008. At that time, TMS was criticized as a cumbersome treatment, requiring 4–6 weeks of daily treatment for up to an hour, which limited access for patients as well as reimbursement opportunities (9).

Fortunately, TMS has continued to become more streamlined as research optimizes stimulation protocols. Stimulation-related variables, including stimulus intensity, frequency, time between stimulations, time of trains of stimulation, number of trains, and the total stimulus, have been modified to improve treatment response. One review article described theta-burst stimulation (TBS) as a powerful technique that could specifically induce long-term potentiation when given in an intermittent fashion (intermittent TBS) or long-term depression when given in a continuous fashion (continuous TBS) (10). The former is of extremely high interest in the treatment of depression. Recently, a group at Stanford developed the Stanford Neuromodulation Treatment protocol, which utilizes multiple intermittent TBS treatments throughout the day to condense the treatment duration from several weeks to 5 days (11). A recent article in the *American Journal of Psychiatry* showed superiority of this treatment over sham stimulation in patients with treatment-resistant depression (12).

Now, nearly 40 years after the development of the first TMS prototype, TMS is recognized as an effective treatment tool for a variety of illnesses, with FDA approval for the treatment of depression (2008), cortical mapping (2009), the treatment of migraine with aura (2013), the treatment of obsessive-compulsive disorder (2017), smoking cessation (2020), and the treatment of anxiety with comorbid major depressive disorder (2021), with varying devices and stimulation parameters (13, 14). TMS has been best studied for the treatment of depression; in one meta-analysis, the odds ratio of treatment response was 3.17 with left repetitive TMS, compared with sham stimulation (15). Although this odds ratio is less dramatic than the reported odds ratio for response to bilateral ECT in the same study (odds ratio=8.91), the paradigm of comparing new parameters of TMS with standard and sham treatments promises to improve the technique even further. The history of TMS demonstrates the importance of multidisciplinary collaboration and integration and of continually striving to improve existing treatments. As trainees, it is important that we understand this history of our field, advocate for our education in its implementation, and actively seek out ways to help our patients access neuromodulation treatments when indicated.

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