Preface
Neuromodulation

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INTRODUCTION

Psychiatric neuromodulation is defined as any intervention intended to alter nervous system function using energy fields such as electricity, magnetism, or both, with the goal to improve psychiatric symptoms or related conditions. This concept is not new: neuromodulation, in one form or another, has been used to treat physical maladies for over a thousand years,[1] although its use for psychiatric disorders became popular in the past century. Since the 1930s,[2] electroconvulsive therapy (ECT) has been recognized as an effective treatment for severe depression, catatonia, and other severe mental health disorders. Over the following decades, newer technologies emerged, including vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (rTMS), and deep brain stimulation (DBS); in the last decade, there has been renewed interest in other emerging technologies, including novel adaptations or approaches to rTMS (ie, those synchronized to brain rhythms; eg, Leuchter and colleagues[3]) or employing novel stimulation patterns (eg, Li and colleagues[4]), and low-intensity electrical stimulation.[5]

For a number of reasons, psychiatric neuromodulation has seen a recent surge of interest in clinical and research domains. Neuromodulation, at its core, targets electrical activity within brain networks, acting through different mechanisms than pharmacotherapy, offering the potential of treatment success, where medications have failed. Identifying and targeting specific neural circuitry or functional neural networks to reduce psychiatric symptoms may offer a level of mechanistic focality beyond that offered by ECT, pharmacotherapy, or most psychotherapies. Furthermore, despite decades of research, all currently available psychiatric pharmacology depends, in one form or another, on the manipulation of neurotransmitters related to the monoamine hypothesis.[6] While this approach was successful in bringing initial treatments to market, significant numbers of patients remain symptomatic despite the best evidence-based interventions.[7–9] Other systems, such as acetylcholine, seemed initially promising but ended in trial failure.[10,11] Furthermore, even the most

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promising new pharmacologic approach targeting the NMDA system with ketamine (eg, Murrough and colleagues[12]) has yet to translate into approved treatments, and early use indicates concern about safe long-term use.[13]

Another key driver in the application of clinical neuromodulation is its favorable side-effect profile. Clinicians, who are accustomed to managing and accepting a certain degree of side effects alongside clinical efficacy, may find the limited side effects of neuromodulation to be quite attractive. Neuromodulation is not associated with the risks of weight gain, diabetes, and sexual side effects shared by many pharmacologic interventions. Furthermore, outside of the risk of cognitive side effects of ECT, most adverse experiences with neuromodulation are constrained to treatment site discomfort and a very low risk of an isolated seizure event.[14]

DR PHILIP'S STORY

On a personal note, the story of how I started using neuromodulation was not straightforward. At the end of my psychiatry residency training, I worked under my mentor, Dr Linda Carpenter, on several different device-based clinical trials for depression at Butler Hospital. These included late-stage studies of VNS and DBS, and some of the early work in rTMS. This work continued into a neuromodulation fellowship, during which I more directly worked in rTMS while simultaneously managing an inpatient service at our local psychiatry hospital for about 3 years. During this time, I saw patients come and go, and despite my best efforts, many patients did not achieve meaningful improvement with my best-intentioned pharmacotherapy and psychotherapy. Yet, one observation was consistent: regardless of whether the medications worked, all my patients returned with a significant side-effect burden. A young man with first onset psychosis returned just as psychotic, and with diabetes and significant weight gain. A woman with severe depression returned with her depression, and now with no sexual drive and a feeling of emotional numbness. Another returned with crippling anxiety, now in addition to chronic gastrointestinal symptoms from their medication. Unfortunately, this is a partial list, and the memories go on. Some patients did quite well, but yet others did not, and not only did the medications not work, but also the patients were afflicted with side effects from my prescribing. As a physician, I took an oath to "do no harm," and I questioned whether I was doing the right thing. On the other hand, I was able to refer patients into this new area of neuromodulation, and particularly to our rTMS clinic. True, this didn't work for everyone, but when it didn't work, there were no crippling side effects with which to contend. After a few years, there was an opportunity for me to start my own neuromodulation service at the Providence VA, Rhode Island, and I took the opportunity as fast as I could. This is a field in its relative infancy, but the potential to reduce patients' symptoms is very real and reachable in the near term. While the greatest work to date remains in depression, I remain hopeful and optimistic that lessons learned from using neuromodulation in depression can be applied more broadly in the near term, to yield an entirely different way to care for patients suffering from these terrible diseases.

DR AARONSON'S STORY

I had never intended to become a "device guy." My career has been devoted to the recognition and treatment of severe, often treatment-refractory, mood disorders. After starting down a clinical/research path after residency, I grew frustrated with the limitations of clinical investigation and founded a large multidisciplinary outpatient practice with a focus on mood disorders, which, after 10 years, I further expanded to add a clinical trials component. This rekindled my research interests and led to my