Deep brain stimulation for major depression: A prototype of a personalized treatment in psychiatry

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Abstract

The introduction of deep brain stimulation for treatment-resistant disorders might very well lead to the most significant development in clinical psychiatry of the last 40 years possibly offering a rise in hope for patients to whom medicine had hitherto little to offer. Furthermore, translational research on neuromodulation will allow us to glean something about the underlying cause of patients' illnesses before figuring out a treatment that addresses the source of the problem. Major depression offers perhaps the best example of the rapid progress being made in understanding the biology of mental illness. We believe that focused, targeted treatment approaches that modulate specific networks in the brain will prove a more personalized, and thereby, effective approach to help treatment-resistant patients.

Keywords: PsychiatryDeep brain stimulation Depression Antidepressant Personalized treatment Neuronal network Treatment-resistant depression.

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Introduction

Major Depression is one of the most common and costly of all psychiatric disorders. While depression can be effectively treated in the majority of patients by either medication or some form of evidence-based psychotherapy, up to 20% of patients fail to respond to standard interventions [1]. For these patients, trial-and-error combinations of multiple medications and electroconvulsive therapy are often required. For patients who remain severely depressed despite these aggressive approaches, new strategies are needed.Converging clinical, biochemical, neuroimaging, and post-mortem data suggest depression is unlikely to be a disease of a single brain region or neurotransmitter system. Rather, it is now generally viewed as a systems-level disorder affecting integrated pathways linking select cortical, subcortical and limbic sites and their related neurotransmitter and molecular mediators. Treatments for depression can be viewed within a limbic-cortical system framework, where different modes of treatment modulate specific regional targets, resulting in a variety of complementary, adaptive chemical and molecular changes that re-establish a normal mood state [2]. Functional neuroimaging studies have played a critical role in characterizing these limbic-cortical pathways. Previous studies have demonstrated consistent involvement of the subgenual cingulate (Cg25) in both acute sadness and antidepressant treatment effects, suggesting a critical role for this region in modulating negative mood states [3].

Deep brain stimulation (DBS) is an invasive therapy in which implanted electrodes deliver high-frequency electrical stimulation to subcortical structures. While experiments in electrical brain stimulation have been ongoing almostsince the discovery of electricity, the modern era of DBS is usually traced back to successful reports in the early 1990s for movement disorders. Stereotactic lesions such as pallidotomy and thalamotomy were previously the state of the art in functional neurosurgery [4]. As DBS began to replace those lesions, forward-thinking psychiatrists recognized that lesions of the dorsal anterior cingulate cortex and anterior limb of the internal capsule were known to be effective for treatment-resistant major depressive disorder (MDD) and obsessive-compulsive disorder (OCD) DBS was soon studied for these disorders as well. Early open-label results in both OCD and MDD were promising This spurred a round of pivotal controlled clinical trials, with great hope that DBS would unlock a new era of psychiatric cures With those blinded, sham-controlled trials now ending, the future seems less bright. One major controlled trial in MDD failed futility analyses while another (Medtronic's

RECLAIM trial at the ventral internal capsule/entral striatum target) demonstrated negative results [5].

The NIMH-sponsored controlled trial for OCD closed in March 2015, and the first analyses may be available in late 2016. While it is now a standard of clinical care for Parkinson's disease, DBS in psychiatry remains mostly experimental. In this article, we will overview recent clinical trial results and early explorations of alternate anatomic targets. We will devote the majority of our discussion, however, to a discussion of what we can learn from these "failed" studies and how the field is moving forward. Our central thesis is that negative trial outcomes are not necessarily failures. Rather, they are an opportunity to begin understanding the mechanisms of DBS and its clinical effects [6]. That understanding can inform the ongoing development of new brain stimulation technologies. By linking the two, we can begin to design therapies that truly engage the biological underpinnings of mental illness and perhaps finally realize DBS' clinical promise [7].

DBS' mechanisms of action, we can also refine our anatomic targeting. Psychiatric DBS is implanted at coordinates defined by the line connecting the anterior/posterior commissures, not by specific fibers [8] [9]. The anatomy of Cg25 and VC/VS is heterogeneous among patients, and even experienced surgeons show variability in the ultimate electrode placement. Simulations of the subthalamic nucleus (STN) suggest that even 1 mm of error can dramatically change what tissues are activated . The Mayberg group has recently identified a set of white matter tracts directly behind the Cg25 target that may drive improvement in MDD. Preliminary data suggest that similar rules may apply for VC/VS. In the near future, we may be able to target DBS not to arbitrary coordinates but to defined white or gray matter structures that can be reliably localized for each patient. Other groups are developing "virtual patient simulation" tools to aid this. By simulating the tissue propagation of electrical and magnetic fields, it should become possible to place every DBS so to optimally capture the true functional target [10].

Conclusion

DBS for mood and obsessive-compulsive disorders has recently faced challenges, but we see reasons for optimism. The continued proliferation of targets and potential indications shows that the research community's enthusiasm and commitment have not diminished. The failure of trials based on simplistic targeting justifies a more rational, neuroscience-driven approach to DBS' development. Key to that will be studies where we ensure that every patient contributes something to our understanding of the underlying biology. That may include "serial n of 1" or other adaptive designs and will likely involve the use of devices that can record and report on the brain during therapy. Through that, the next decade should yield a much better knowledge of DBS' mechanisms of action, which should in turn translate to greater clinical efficacy. Just as importantly, it may allow us to define non-DBS approaches to modulating the same structures. That will expand the availability of novel neurotherapeutics to far more patients. There is a bright future ahead for specific and focal brain-based treatments in psychiatry, and with continued refinement, DBS will be a valuable part of that arsenal. Psychology has contributed significantly to theoretical understanding of certain mental processes studied in cognitive psychology and cognitive neuroscience. It also shows that neuroscientific research on motor imagery can benefit from increased collaboration with cognitive psychology. Overall, I conclude that the domain of offers cognitive researchers a rich and dynamic natural laboratory in which to study how the mind works.

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