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Brain stimulation in neuropsychiatry

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Evidence from neuropathological studies, as well as an emerging in vivo neuroimaging literature, has implicated abnormalities in neural circuitry in neuropsychiatric disorders, ranging from psychiatric and addictive disorders to neurodegenerative disorders. As such, neural circuits are being identified as a focus of therapeutic targets, as exemplified in the new classification framework for mental disorders (research domain criteria, RDoC) proposed by the National Institute of Mental Health (NIMH) of the National Institute of Health. Specifically, RDoC conceptualizes neuropsychiatric illnesses as ‘disorders of brain circuits’ (Insel et al., 2010). The observation that pharmacotherapies have limited benefit and serious side effects, in some cases, has stimulated interest in neural circuitry, as opposed to neurotransmitter systems, as a therapeutic target. Thus, there has been a renewed interest in brain stimulation methods to investigate, modulate, and treat abnormal neural circuitry in neuropsychiatric disorders.

Brain stimulation methods include techniques that modulate neurocircuitry through the application of electrical or magnetic stimuli to specific brain regions. In the past decade there has been an unprecedented development in technical and methodological aspects of brain stimulation, as well as therapeutic paradigms and applications. In addition to the well-established electroconvulsive therapy (ECT) treatment for mood disorders, another convulsive therapy is in development, magnetic seizure therapy (MST). The non-invasive brain stimulation techniques involve transcranial application of electrical or magnetic fields to the scalp at sub-convulsive levels, usually in an acute, repetitive manner. These methods include transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) that are being used to both define and treat abnormal neural circuitry. The convulsive therapies, particularly ECT, were the forerunner of these approaches, especially for the treatment of severe, chronic depression. Neurosurgical procedures include the implantation of devices to stimulate brain structures and associated neural circuits chronically. There are methods to stimulate brain circuits directly (such as deep brain stimulation (DBS)) or indirectly (such as vagus nerve stimulation (VNS)), which are being assessed for their therapeutic properties in a number of neuropsychiatric illnesses.

Studies of these brain stimulation methods have found a significant beneficial impact for the clinical management of the most treatment-refractory patients to a degree not observed with other anti-depressant strategies, including pharmacotherapy and psychotherapy. In addition to their great therapeutic potential, the integration of neurocognitive and neuroimaging assessments with brain stimulation methods provides a unique opportunity to understand the neurobiological consequences of modulating the function of neural circuits *in vivo*. Further, translational research in basic science models has elucidated some of the unique neurobiological effects of such therapies, including neurochemical effects and neurogenesis (Encinas et al., 2011; Stone et al., 2011) that support a potential benefit in patients for a variety of symptoms, including cognitive deficits, and can be evaluated in human studies using molecular imaging methods.

Initially, surgical brain stimulation approaches were applied to disorders in which the underlying neural circuitry was well established, including Parkinson's disease and dystonia. Multiple regions within the cortico-striato-pallido-thalamo-cortical (CSPTC) circuitry have been evaluated as sites for stimulation by the implantation of electrodes. More recently, neuropsychiatric disorders that are associated with dysfunction of cortical networks have been the focus of study. Some examples include investigations of using DBS to treat major depressive disorder (MDD) (Mayberg et al., 2005), obsessive-compulsive disorder (Greenberg et al., 2006), and Alzheimer's disease (Laxton et al., 2010). In these disorders, the site of electrode implantation was largely informed by neuroimaging data. There are emerging indications of brain stimulation therapies, particularly DBS, in some of the most difficult to treat symptoms in neuropsychiatry (e.g. levodopa-induced dyskinesia (Sankar & Lozano, 2011)).

The papers in this special issue of the *International Review of Psychiatry* focus on the application of non-invasive and surgical brain stimulation techniques to understand and treat neuropsychiatric disorders across the lifespan. A major emphasis of the issue, which reflects the activity in the field, is on brain stimulation in mood disorders. Allan and Ebmeier review the use of ECT and MST in the treatment of MDD, focusing on the development and efficacy of those convulsive therapies. McClintock and colleagues review the issue of neurocognitive effects of brain stimulation, specifically MST. Based on the available evidence, the authors make the important observation that MST is not associated with neurocognitive deficits. Regarding neurosurgical therapeutic approaches for MDD, Rizvi and colleagues review VNS and DBS, and present a comprehensive review of surgical targets, as well as preclinical and clinical mechanistic studies. Importantly, the authors review the extremely promising, long-term follow-up results of the initial cohort of patients with treatment refractory MDD studied by Mayberg et al. (2005) that show sustained benefit of sub-genual cingulate DBS over a 3- to 5-year follow-up interval. Jorge and Robinson review the use of brain stimulation in late life depression, particularly vascular depression. Depression in late life has received an increasing amount of attention due to its association with cognitive decline and increased mortality (Smith et al., 2007). Thus, there is an urgent need to develop effective and safe therapeutic strategies for patients who do not respond well to pharmacotherapy, and to target frontostriatal neural circuitry that has been implicated in late life depression. Finally, Croarkin and colleagues discuss the emerging data on the use of brain stimulation to treat childhood neuropsychiatric disorders including MDD, as well as

attention deficit hyperactive disorder (ADHD) and autism. The authors also discuss ethical considerations for the use of brain stimulation in this population.

Several papers focus on promising applications of brain stimulation to other neuropsychiatric disorders. The paper on movement disorders is written by Obeso and colleagues, who are a group that has led the field in integrating brain stimulation with neuroimaging (of both neural circuitry and neuro-chemical systems) to elucidate the neuropsychiatric symptoms of Parkinson's disease. They provide a comprehensive review of the integration of brain stimulation (DBS and TMS) with neuroimaging methods to understand the neurobiology of motor, cognitive and behavioural symptoms in Parkinson's disease. Barr and colleagues, who have made major contributions to both therapeutic and mechanistic studies of TMS in neuropsychiatric disorders, review the emerging field of brain stimulation to treat addictions. They provide a critical review of the studies to treat drug and alcohol abuse, in addition to a discussion of future directions for research.

Given the promising results of brain stimulation therapies and their increased use, ethical considerations have been an increasing area of focus (Rabins et al., 2009). Two papers are included in this special issue that highlight the ethical considerations of brain stimulations techniques by discussing their effects on personal identity. The paper by Jotterand and Giordano discusses the effect of these advanced brain stimulation techniques, particularly TMS and DBS, and they provide an ethical decision-making framework for clinicians and researchers. Mathews discusses the important issue of the use of implantable brain interfacing devices (IBIDs), specifically DBS, to modify personal identity and sense of self, and provides a discussion regarding informed consent and public policy.

We hope that the papers in this issue convey the excitement and the great potential for brain stimulation approaches, and will encourage the interdisciplinary, translational research that is needed to optimize therapeutic paradigms, to identify new and more effective treatment targets, and to understand the neurobiological effects of stimulating specific neural circuits. Neurocognitive and neuroimaging methods can be applied further to refine the neuroanatomic target and stimulation parameters for treatment, to understand the mechanisms underlying treatment response, as well as side effects, and to identify the best candidates for treatment. As the efficacy, safety, and ethical guidelines of brain stimulation therapies are further established, we look forward to new applications of these neural circuitry-based treatments to the clinical management of patients with the most treatment-refractory neuropsychiatric illnesses.

Editing this issue has been a remarkable experience to work with an outstanding group of colleagues. We are grateful to the authors and reviewers for their excellent contributions, and to the editors and editorial staff for giving us the opportunity to develop an issue on such an important topic.

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