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Research paper

Treating refractory mental illness with closed-loop brain stimulation: Progress towards a patient-specific transdiagnostic approach

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ABSTRACT

Mental disorders are a leading cause of disability, morbidity, and mortality among civilian and military populations. Most available treatments have limited efficacy, particularly in disorders where symptoms vary over relatively short time scales. Targeted modulation of neural circuits, particularly through open-loop deep brain stimulation (DBS), showed initial promise but has failed in blinded clinical trials. We propose a new approach, based on targeting neural circuits linked to functional domains that cut across diagnoses. Through that framework, which includes measurement of patients using six psychophysical tasks, we seek to develop a closed-loop DBS system that corrects dysfunctional activity in brain circuits underlying those domains. We present convergent preliminary evidence from functional neuroimaging, invasive human electrophysiology, and human brain stimulation experiments suggesting that this approach is feasible. Using the Emotional Conflict Resolution (ECR) task as an example, we show that emotion-related networks can be identified and modulated in individual patients. Invasive and non-invasive methodologies both identify a network between prefrontal cortex, cingulate cortex, insula, and amygdala. Further, stimulation in cingulate and amygdala changes patients' performance in ways that are linked to the task's emotional content. We present preliminary statistical models that predict this change and allow us to track it at a single-trial level. As these diagnostic and modeling strategies are refined and embodied in an implantable device, they offer the prospect of a new approach to psychiatric treatment and its accompanying neuroscience.

1. Introduction

Mental disorders are the single largest cause of disability worldwide (Whiteford et al., 2013). In the wake of recent military conflicts, they have become a major source of morbidity and mortality among warfighters and Veterans (Kessler et al., 2014; Reger et al., 2015). Disorders of concern in this population include post-traumatic stress disorder (PTSD), major depressive disorder (MDD), generalized anxiety disorder (GAD), substance use (SUD), and traumatic brain injury (TBI). Within those disorders, as with many other psychiatric diagnoses, there has been no change for decades in the overall mortality despite extensive research (Insel, 2008, 2009). Psychotropic medications adjust neurotransmitter levels globally across the brain. This fails to address the mechanisms of mental illness. If depression were a monoamine deficit, or schizophrenia a syndrome of excess dopamine, antidepressants and antipsychotics would exceed their roughly 30–40% efficacy (Lieberman et al., 2005; Warden et al., 2007; Gaynes et al., 2009; Lieberman and Stroup, 2011). The situation is worse for anxiety disorders, particularly PTSD and GAD (Thomas et al., 2010; Hoge et al., 2014). Serotonin reuptake inhibitors (SRIs), the mainstay of evidence-based pharmacology for anxiety, have modest efficacy at best (Jonas et al., 2013). Benzodiazepines (BZDs) are much stronger anxiolytics, bringing immediate short-term relief. Unfortunately, that relief can become an avoidance behavior that reinforces and worsens maladaptive responses to anxiety. BZDs also have direct addictive potential and can be rapidly fatal in overdose. Psychotherapy, particularly exposure-

Abbreviations: DBS, deep brain stimulation; ECR, Emotional Conflict Resolution; GAD, generalized anxiety disorder; gMVR, generalized multivariate autoregressive; MDD, major depressive disorder; MVAR, multivariate auto-regressive modeling; PPI, psychophysical interaction analysis; PTSD, post-traumatic stress disorder; SUD, substance use disorder.

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based therapy, has substantially greater efficacy and is often considered the true first-line treatment (Powers et al., 2010; van den Berg et al., 2015). Unfortunately, well-trained therapists are expensive and difficult for most patients to access.

More recently, a new tool has emerged: targeted electro-magnetic brain stimulation. As mental illness became understood as a dysfunction of brain circuits, investigators have sought to re-regulate those circuits (Insel, 2010; Insel and Wang, 2010). We have known for decades that targeted stereotactic lesions can be remarkably effective even in refractory cases of depression and obsessive-compulsive disorder (Kelly et al., 1973; Bingley et al., 1977; Ballantine et al., 1987; Rauch et al., 2001; Dougherty et al., 2002; Greenberg et al., 2010a; Yang et al., 2013). Stimulation may replicate the benefits of those lesions while also being reversible. Vagus nerve stimulation (VNS) and transcranial magnetic stimulation (TMS) are both approved for MDD (George et al., 2005; Aaronson et al., 2013; George et al., 2010; Johnson et al., 2013). The most promising approach, however, remains deep brain stimulation (DBS). Early open-label reports of DBS for MDD and OCD were encouraging, with high response rates even in treatment-resistant cases (Mayberg, 2009; Malone et al., 2009; Greenberg et al., 2010b). In randomized controlled trials, however, DBS for MDD failed to meet endpoints (Morishita et al., 2014; Dougherty et al., 2015). DBS for OCD is only available under a Humanitarian Device Exemption (HDE), because very few patients will ever qualify for surgery (Garnaat et al., 2014).

We attribute those failures to the neglect of a key fact: mental disorders are not static. Symptoms wax and wane across days or hours. In PTSD and anxiety disorders, they can flare and remit on the order of minutes. Standard DBS is *open loop*: it delivers a constant level of treatment, regardless of sleep-wake cycles, current symptom levels, or side effects. Adjustments occur only at clinical visits, weeks to months apart. This is a mis-match between the time course of the disease and the timing of clinical adjustments. One solution is *closed loop* stimulation, in which the device itself adjusts stimulation by inferring the patient's immediate clinical need from the brain's electrical activity (Ward and Irazoqui, 2010; Widge et al., 2014). Such approaches are clinically approved in epilepsy (Morrell, 2011), and have shown promise in Parkinson's disease (Rosin et al., 2011; Little et al., 2013). The challenge for psychiatric DBS is identifying the biomarkers – the neural signatures of mental illness and its fluctuating symptoms. Many investigators have sought these, often through neuro-imaging and electroencephalography (EEG). Despite decades of work, there is no known electrical signature of the symptoms of any mental illness. Many putative signatures do not replicate on subsequent testing (Whelan and Garavan, 2013; Widge et al., 2013; McLoughlin et al., 2014).

In response to those challenges, we describe a new approach to psychiatric DBS, funded by the Defense Advanced Research Projects Agency (DARPA) as part of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. The essence of the TRANSFORM DBS (Transdiagnostic Restoration of Affective Networks by Systematic, Function-Oriented Real-time Modeling and Deep Brain Stimulation) project is a *transdiagnostic framework*. We consider psychiatric disorders as embedded in a multi-axial space of "functional domains", similar to the National Institute of Mental Health's Research Domain Criteria (RDoC) framework (Cuthbert and Insel, 2013). We believe that these domains, being grounded in objectively measurable behavior, will have stronger and more replicable neural correlates compared to clinical psychiatric diagnoses (Widge et al., 2015). We first overview the rationale for this domain-oriented framework, identify an initial set of functional domains, and link them to disorders of national military significance. We then present a series of preliminary experiments demonstrating that these domains can be measured both non-invasively and invasively in the awake, behaving human, that the electrical and behavioral measurements are amenable to mathematical modeling, and that those models may be used to develop brain stimulation that changes psychiatrically relevant behaviors. We conclude with discussion of the next steps to turn these concepts into a clinical device. All experiments described herein were approved by the Massachusetts General Hospital Institutional Review Board and were subject to second-level review by the Army's Human Subjects Research Protection Office (HRPO).

2. Rationale and coverage for the transdiagnostic framework

Progress in the basic and clinical neurosciences has advanced our understanding of psychopathology. This has placed an increasing emphasis on dysfunction that cuts across domains of functioning (e.g., Negative Valence, Positive Valence, Cognitive Processes, Social Processes), as embodied in RDoC. That suggests the possibility of classifying an individual patient's mental illness based upon his/her specific patterns of dysfunction, rather than relying upon symptom clusters that show poor reliability (Regier et al., 2013). A domain-oriented approach may address the high rates of comorbidity and heterogeneity found under the checklist-based system of the Diagnostic & Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013). For TRANSFORM, we have adopted six initial domains: Fear Extinction, Reward Motivation, Emotion Regulation, Decision Making/Impulsivity, Cognitive Flexibility, and Learning/Memory. These overlap with RDoC constructs, but are more specifically tailored to the clinical disorders we hope to address. Each is impaired across disorders of military interest (Table 1), each has well-established and validated metrics, and each has been linked to specific brain areas and circuits.

The domain-oriented approach resolves two related problems: diagnostic overlap and heterogeneity within single diagnoses (Fig. 1). First, patients with ostensibly different disorders may share strong common phenotypes. For example, PTSD patients frequently have deficits in Emotion Regulation, which is linked to brain connectivity between frontal regions and the amygdala (Milad et al., 2009; Rougemont-Bücking et al., 2011; Etkin et al., 2011). That dysregulation is also commonly seen in MDD (Rive et al., 2013; Heller et al., 2013), and the two disorders are often comorbid (Regier et al., 2013; Bleich et al., 1997; Campbell et al., 2007). PTSD and MDD also have a common deficit in Cognitive Flexibility: PTSD often involves perseveration on what a patient could/should have done in the moment, whereas MDD frequently has "stuck", ruminative thinking. The strong role of the prefrontal cortex (PFC) in mental flexibility (Miller and Cohen, 2001; Buschman et al., 2012; Siegel et al., 2015; Kehagia et al., 2010) links MDD and PTSD to TBI (Fig. 1A), which also shows perseverative behavior and often involves frontal injury. Thus, a DBS intervention that targeted Cognitive Flexibility could be applicable to multiple patient groups who, from a categorical perspective do not have the "same disease".

The other limitation of categorical diagnosis is heterogeneity. MDD is a prime example: with 9 diagnostic criteria, 5 of which must be present to confirm the diagnosis, there are 126 different clinical phenotypes, many of which have almost no symptoms in common. Individual patients with MDD may be profoundly emotionally labile (Emotion Regulation), flattened and anhedonic (Reward Motivation), or stuck in rigid, self-flagellating guilt (Cognitive Flexibility). DBS in any given brain circuit can likely only address one of those domains (Fig. 1B), suggesting that applying it to the heterogeneous construct of "depression" is predestined to find only weak clinical signals. We believe this was the key weakness in recent DBS trials in MDD, and that our domain-focused approach can overcome it (Widge et al., 2015). Put another way, patients with the same categorical diagnosis may have completely non-overlapping clinical or neurological phenotypes. The next two sections will give an example of such a situation and the ways in which the TRANSFORM approach can resolve it.

(B), three patients with MDD (notionally the "same") may differ on the domains of cognitive flexibility, approach and avoidance to stimuli, and emotional lability.

Table 1: TRANSFORM working map between domains, assessment instruments (self-report and psychophysical), DSM-5 disorders, and implicated brain regions. Questionnaires: ASI = Anxiety Sensitivity Index, ATQ = Adult Temperament Questionnaire, STAI = State-Trait

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