



# The frontiers in brain imaging and neuromodulation: a new challenge

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More than ever before, it is imperative to find effective treatments for most of our psychiatric disorders. Imagine that in 2020, and despite a widespread use of antidepressant treatments, the World Health Organization projects the burden of depression to become second only to ischemic heart disease (Hirschfeld, 1998; Greden, 2001). In fact, of the top ten causes for years lived in disability, three are psychiatric illnesses. Depression is second, but alcoholism and dementia are prominently featured too. Both bipolar disorder and schizophrenia will also continue to cause significant suffering. These psychiatric conditions are chronic and not fully responsive to treatments. Patients often relapse. The reasons for these dire projections lie primarily in the phenomenological approach of our diagnostic approach, our incomplete understanding of the heterogeneous pathophysiology of psychiatric illnesses and the limited efficacy of our therapeutic arsenals.

Modern scientific conceptualization of brain functions and localizations began to emerge from animal experiments, cadaver dissections, and clinical observations conducted by Broca (1865), Jackson (1873), and others in the mid 19th century. Ideas of regional brain functional localization and electrochemical neuronal transmission would later evolve into the contemporary neuronal network models that guide and inform much of the current applications of somatic treatments in neuropsychiatry. Over the past two decades, the rate of evolution of imaging technology and of study design has been breathtaking. Such investigations have shifted the debate from a reductionist “phrenology-like” attributions of mental phenomena, including psychiatric symptoms, to a broader dynamic interplay amongst various brain regions. Their utility in defining causation or providing tangible diagnostic tools for clinicians remain however very limited (Bullmore

and Fletcher, 2003). This may be due in large part to restrictive sampling, study designs, and analytic methods. As the field matures, it has become apparent that the next challenges will have to integrate multimodal imaging techniques (Fox et al., 2009), cross-validations with genetic studies (Frodl et al., 2008) and a departure from cross-sectional studies, in addition to data pooling to achieve representative sample sizes. The combination of transcranial magnetic stimulation (TMS) and other brain stimulation tools, also offers unique opportunities to move away from the correlative nature of imaging results (Bohning et al., 1998).

The use of somatic interventions to control or treat mental symptoms dates back to ancient times (Tourney, 1967; Clower and Finger, 2002). Evidence for burr holes drilled into the skull to “cure the demons” goes back to the Neolithic age. The notions that convulsions and fever may help mental disorders have been known since Hippocrates, while in medieval times, make-believe surgeries were performed to extract the “stone of madness.” The current status of non-pharmacological brain stimulation therapies to treat psychiatric conditions is also rapidly evolving. Research applications range from the benign (transcranial direct current stimulation, tDCS) (Been et al., 2007) to the invasive (deep brain stimulation, DBS) (Benabid et al., 2003) and cover a wide spectrum of disorders. Convulsive and sub-convulsive targeted brain stimulation treatments are inherently different from pharmacological interventions. An electrically stimulated cell will primarily produce a restricted range of responses inherent to its functionality (Ranck, 1975; Nahas et al., 2003a). Brain stimulation modulates the system’s endogenous responsiveness and presumably, when delivered appropriately, allows it to recruit adaptive strategies. Random or deterministic influences (e.g., electrical stimuli, object presentation, or emotional deprivation)

on biological systems have been shown to produce variable results depending on the type, intensity, frequency, and threshold of the stimulus. Long term potentiation (LTP) or long term depression (LTD) can alter synaptic plasticity and learning (Iadorola et al., 1986; Buzsaki et al., 1987; Huang et al., 2005). An optimal amount of added energy, whether it is electrical stimulation or “simulated noise,” can enhance the detection of a weak signal, a phenomena known as stochastic resonance (Huber et al., 2003). As it stands electroconvulsive therapy (ECT) remains the most widely adopted clinical brain stimulation therapy. And while efficacious, the relapse rates associated with it are very high. Both TMS and vagus nerve stimulation (VNS) are US FDA approved for depression and DBS is approved for obsessive compulsive disorder (OCD) under a humanitarian device exemption. But TMS is an acute treatment for mild to moderate TRD (Oreardon et al., 2007), but not in TR-BD (Nahas et al., 2003b; George et al., 2009) and little is known about its role in maintenance therapy (Janicak et al., 2007). VNS on the other hand is a surgical procedure that delivers chronic treatment, is associated with relatively low relapse rates (Nahas et al., 2005) but is not supported by *Class 1* evidence (Nahas et al., 2003b). The open reports of continuous high frequency DBS in depression and Tourette’s syndrome and epidural cortical stimulation in depression are encouraging but preliminary.

One of the recurring themes within each of the techniques is the currently inadequate understanding of the translational neurobiological effects of the “use parameters.” The future of this promising field will undoubtedly involve better translating the knowledge gained from preclinical cellular and non-human animal studies into clinical brain stimulation therapeutic uses. The challenge we face in developing these new treatments would be to maintain a kaleidoscopic perspective between the global

and the discrete. Neurodynamics and the study of changes in neuronal organization and behavior over time can render a larger perspective (Freeman, 2003), however discrete electrochemical neuronal networks are responsible of various experiential phenomena. Ultimately, the response of the cell and its capacity to buffer stress will dictate the adaptability of the system and the way it achieves homeostasis:

Neural connectivity and neuromodulation have become integral frameworks by which the field conceptualizes neuropsychiatric diseases and treatment interventions. But a fundamental challenge remains: how do we relate the dynamic interplay among brain regions to understand cognitive, emotional, or behavioral regulation to effectively treat our patients and improve their quality of life. I dare to think that the future is promising.

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