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GUEST EDITORIAL

Advancing psychiatric care through neuromodulation: From translational research to clinical practice

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Neuromodulation has been one of the most rapidly growing areas of interest in psychiatry over the past decades. In some sense, one might argue that "all psychiatry is neuromodulation." After all, psychiatric treatments alter brain function, even when the brain is not their direct target (1). For example, changes in stimulus-response associations induced by behavioral therapy are almost certainly mediated by the remodeling of neural circuits. However, when referring to neuromodulation in a narrower sense, we generally mean interventions that directly and purposefully target the brain or specific brain regions. These approaches may have a global scope, such as treatments affecting the whole brain (e.g., most psychopharmacological interventions), or they may target a specific cortical region, such as the prefrontal cortex (transcranial magnetic stimulation or transcranial electrical stimulation), or even a discrete nucleus within the basal ganglia, such as the subthalamic nucleus (deep brain stimulation [DBS]). These brain stimulation techniques, whether noninvasive or invasive, can be classified as "exogenous." In contrast, neural activity can also be modulated endogenously through neurofeedback, whereby individuals receive real-time information about specific patterns of brain activity and learn to modify them toward a predefined target (2). Neurofeedback may rely on noninvasive signals (e.g., functional magnetic resonance imaging [fMRI] and electroencephalography [EEG]) or invasive recordings (e.g., local field potentials [LFPs]).

Deep brain stimulation is of particular interest in (neuro)psychiatry due to its spatial precision and capacity to modulate specific anatomical targets and circuits. To date, most studies have focused on depression, obsessive-compulsive disorder (OCD), and Tourette syndrome (TS). In depression, primary targets include the subgenual cingulate cortex (SCC), the ventral capsule/ventral striatum (VC/VS), and the medial forebrain bundle (MFB) at its origin in the ventral tegmental area. Reports across these targets describe substantial clinical improvement, although results from placebo-controlled trials have been mixed (3). In TS, studies have demonstrated up to a 50% reduction in tic severity (4). In OCD, the literature reports improvements of approximately 40% in both obsessions and compulsions, as well as significant differences between real and sham stimulation (5, 6). It is important to remember that for all psychiatric indications, symptoms need to be refractory to standard treatments, and a careful multidisciplinary screening process must be applied. There are also strict regulations (which vary across jurisdictions) regarding the certification of medical devices and oversight, of which psychiatrists need to be aware. Moreover, because this is still a relatively new field and the available evidence from randomized controlled trials is based on small patient samples, psychiatric DBS programs should be accompanied by data collection for research and auditing purposes.

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Another area of neuromodulation that can potentially achieve high neuroanatomical precision is neurofeedback training. During neurofeedback, information about brain activity is provided in (almost) real time to the patient, who can then attempt to modify the brain activity parameter that is being fed back (7). For example, in EEG neurofeedback, the target signal might be the ratio between alpha and theta rhythms measured at a particular electrode. In fMRI-based neurofeedback, the target signal might be the average activation of the left amygdala or the functional connectivity between different cortical areas. Examples of clinical applications—still at the investigational stage—include depression (8, 9), Parkinson's disease, (10) and phobia (11).

Although conceptually very promising, fMRI neurofeedback has not yet been established as a routine treatment technique. Challenges include the standardization of protocols (12) and target signals, as well as reliance on high-end magnetic resonance imaging (MRI) systems. Translation into ambulatory neurofeedback systems, such as EEG fingerprinting of fMRI signals, (13) holds considerable potential. Another limitation, common to all neuromodulation techniques in psychiatry, is the limited understanding of underlying disease mechanisms. Without clear neurophysiological markers of pathology, it is difficult to determine what exactly should be "corrected" through psychiatric neuromodulation. A better understanding of the neural substrates of psychopathology, for example, through symptom provocation techniques (within ethical and safety limits, of course), may provide one avenue for identifying more refined (and personalized) treatment targets. Another approach would be to learn from the neural effects of treatments that are already effective and attempt to replicate them using neuromodulation, ideally with less invasive and/or better tolerated interventions. One example is the ongoing effort to develop neurofeedback protocols inspired by the network effects of deep brain stimulation (14).

Along similar lines, there is considerable interest in identifying biomarkers that can track the therapeutic effects of DBS and guide adjustments in stimulation delivery. Such "closed-loop" adaptive DBS is currently available only for Parkinson's disease, (14) although proof of concept has also been demonstrated for Tourette syndrome (15). For other neuropsychiatric conditions, particularly those in which symptoms and their improvement evolve over longer time scales (hours to days), identifying suitable electrophysiological DBS targets may be even more challenging. The continued refinement of neuromodulation techniques, whether invasive or non-invasive, therefore requires close collaboration between clinicians, neuroscientists, and engineers, as well as careful attention to the perspectives and needs of patients (16) (https://www.diepresearchproject.com/).

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