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Review

Neurosurgical neuromodulation therapy for psychiatric disorders

Manish Ranjan [a,*], James J. Mahoney III [b,c], Ali R. Rezai [a,c]

[a] Department of Neurosurgery, WVU Rockefeller Neuroscience Institute, Morgantown, WV, USA
[b] Department of Behavioral Medicine and Psychiatry, WVU Rockefeller Neuroscience Institute, Morgantown, WV, USA
[c] Department of Neuroscience, WVU Rockefeller Neuroscience Institute, Morgantown, WV, USA

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ABSTRACT

Psychiatric disorders are among the leading contributors to global disease burden and disability. A significant portion of patients with psychiatric disorders remain treatment-refractory to best available therapy. With insights from the neurocircuitry of psychiatric disorders and extensive experience of neuromodulation with deep brain stimulation (DBS) in movement disorders, DBS is increasingly being considered to modulate the neural network in psychiatric disorders. Currently, obsessive-compulsive disorder (OCD) is the only U.S. FDA (United States Food and Drug Administration) approved DBS indication for psychiatric disorders. Medically refractory depression, addiction, and other psychiatric disorders are being explored for DBS neuromodulation. Studies evaluating DBS for psychiatric disorders are promising but lack larger, controlled studies. This paper presents a brief review and the current state of DBS and other neurosurgical neuromodulation therapies for OCD and other psychiatric disorders. We also present a brief review of MR-guided Focused Ultrasound (MRgFUS), a novel form of neurosurgical neuromodulation, which can target deep subcortical structures similar to DBS, but in a noninvasive fashion. Early experiences of neurosurgical neuromodulation therapies, including MRgFUS neuromodulation are encouraging in psychiatric disorders; however, they remain investigational. Currently, DBS and VNS are the only FDA approved neurosurgical neuromodulation options in properly selected cases of OCD and depression, respectively.

Introduction

Psychiatric disorders are widely recognized as one of the leading causes of disease burden [1]. While current behavioral and/or pharmacological interventions are effective in controlling psychiatric symptoms, a subset of individuals remain treatment-refractory to these standard approaches. Long-term use of psychotropic medications is also associated with a range of adverse effects, including the development of additional psychiatric symptoms [2]. In recent years, neuromodulation has emerged as a potential adjunctive treatment for treatment refractory cases [3–6]. Deep Brain Stimulation (DBS) has evolved as an effective and cost-effective neuromodulation treatment for properly selected patients with movement disorders. Specifically, it is the standard of care for Parkinson's disease (PD), essential tremor (ET) and dystonia and was also recently approved for a non-movement disorder indication, drug-resistant epilepsy. With increasing understanding of dysfunction within neural networks and circuitry found in neuro-psychiatric disorders, DBS has been considered for individuals with psychiatric diseases who are refractory to standard of care treatments. At the current time, obsessive-compulsive disorder (OCD) is the only FDA approved indication [under humanitarian device exemption (HDE)] for DBS among psychiatric disorders. However, there are several additional indications being investigated including mood disorders, substance use disorder (SUD), and other psychiatric disorders. Among other neurosurgical neuromodulation therapy, vagus nerve stimulation (VNS) is the only approved therapy by the U.S. FDA (the United States Food and Drug Administration) for treatment-refractory depression. Recently, MR-guided Focused Ultrasound (MRgFUS) is emerging as a novel non-invasive neurosurgical neuromodulation therapy. Early experiences of MRgFUS neuromodulation are encouraging in psychiatric disorders; however, MRgFUS still remains investigational. In this paper, we will review the pertinent literature, background, and findings of neurosurgical neuromodulation therapy such as DBS, VNS and MRgFUS in OCD, depression, addiction, and other psychiatric disorders.

Obsessive-Compulsive Disorder (OCD)

Obsessive-compulsive disorder (OCD) is among the top ten leading causes of disability worldwide, affecting 2–3% of the population [7–9]. OCD is characterized by the presence of obsessions and/or compulsions,

* Corresponding author.
E-mail address: manish.ranjan@hsc.wvu.edu (M. Ranjan).

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which are commonly associated with anxiety and impaired functioning, disability and adversely affecting quality of life (QoL). The pathophysiology and the etiology remains elusive; however, abnormalities are noted in the various cortical and subcortical brain activities, especially the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex (DLPC), the head of the caudate nucleus and the thalamus [10]. The emerging neuroimaging evidence suggests cortico–striato–thalamo–cortical (CSTC) circuits that are involved in sensorimotor, cognitive, affective and motivational processes in OCD [9]. Alterations in other circuits (fronto-limbic, fronto-parietal, cerebellar) also play a role in OCD and abnormalities in these different neurocircuits likely interact with each other to generate the complex OCD phenotype [9,11]. Several effective treatments for OCD evolved overtime targeting dysfunctional neurocircuit, which included first line therapy with cognitive–behavioral therapy (CBT) and pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs).

Despite available effective therapy, approximately 25% of patients remain refractory to the best available therapy, leading to significant morbidity and higher mortality [12–14]. Neurosurgery is considered in such refractory and severe cases. Historically, capsulotomy (ablation of the anterior limb of the anterior capsule) targeting dysfunctional basal ganglia−thalamocortical loop has demonstrated a good therapeutic response [15]. With the emergence of deep brain stimulation (DBS) as a reversible and non-destructive neuromodulation therapy in movement disorders, there was a significant interest in exploring DBS as a therapeutic option in OCD and other psychiatric disorders [16]. Given prior experience and promising results of capsulotomy, anterior limb of internal capsule (ALIC) DBS was considered for DBS target for OCD. The upcoming paragraph will be discussing ALIC DBS and other DBS targets [ventral capsule/ventral striatum, nucleus accumbens (NAc), nucleus of the stria terminalis (BNST), subthalamic nucleus (STN), inferior thalamic peduncle (ITP) and globus pallidus interna (Gpi)] studied for OCD.

Anterior limb of internal capsule (ALIC) DBS was proposed as a potential alternative to capsulotomy following favorable results in three out of four patients for treatment refractory OCD [17]. Subsequently, significant improvement in the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) score and Global Assessment of Functioning (GAF) scale were reported in six patients with medically refractory OCD following bilateral ALIC DBS [18]. Different parts of the CSTC, including the ventral striatum, ventral capsule, and nucleus accumbens (NAc), have been targeted for stimulation and often overlap. It has been increasingly recognized that targets are nominally different but comprise similar regions and potentially similar networks [19,20]. ALIC target was gradually modified to the ventral capsule/ventral striatum (VC/VS) and nucleus accumbens (NAc) target [21]. A metacentric study of ALIC-VC/VS DBS in 26 patients with refractory OCD reported a responder rate of 62% with an average 13.1-point reduction in the Y-BOCS post-DBS [22] leading to FDA approval for severe treatment-resistant OCD. Further supporting the potential of DBS for OCD, in a large cohort of 50 patients of treatment refractory OCD who received ALIC DBS, OCD symptoms were reduced by 39% and half of the patients were deemed responders (≥35% reduction in Y-BOCS) with a minimum follow-up of 3 years [23]. In a double-blind crossover NAc DBS study of 16 patients with treatment refractory OCD, nine patients were responder with a 72% reduction in Y-BOCS score in open phase [24]. Upon further evaluation of ALIC-VC/VS DBS in patients with OCD, greater therapeutic improvement was noted in more posterior sites [22]. This led to implantation of the DBS electrode posteriorly, targeting the bed nucleus of the stria terminalis (BNST). The BNST is located posterior to the anterior commissure and lateral to the fornix and receives major input from the amygdala. BNST serves as an important processing hub for limbic information, threat monitoring, and anxiety regulation. Studies of BNST DBS in OCD reported a favorable result, however, experience is still limited [25–27].

Observation from STN (subthalamic nucleus) DBS in PD showed significant improvement in comorbid OCD symptoms [28,29] led to exploration of STN as a therapeutic target for OCD. A randomized, double-blind, crossover, multicenter study investigated efficacy of bilateral STN-DBS in 16 patients with severe refractory OCD and reported a significant reduction of OCD symptoms [30]. To further investigate the relative effect of DBS in NAc/VC and STN for OCD, electrode contacts covering NAc and VC (Medtronic model 3387) and electrodes in anteromedial STN (amSTN – Medtronic model 3389) were placed in same six patients and assessed in a double blinded fashion [31]. There was a significant but equivalent reduction in OCD symptoms with DBS irrespective of the DBS target, with only mild additive improvement with combined stimulation of both the targets.

Evidence from neurocircuitry suggestive of dysfunctional thalamic-orbitofrontal circuitry, inferior thalamic peduncle (ITP) was explored as a DBS target in OCD, which is a white matter tract that transmits bidirectional information from the OFC to the thalamus. DBS of the ITP was reported as a favorable outcome in treatment refractory OCD [32,33]. Specifically, findings in six patients with medically refractory OCD revealed a 100% responder rate with a 51% improvement in Y-BOCS scores at one-year [34]. In a separate independent investigator driven open-label study in five patients with treatment refractory OCD, all patients were responder at one year with 52% improvement in the Y-BOCS score [33]; however, DBS was explanted in one patient after one year due to the device becoming the object of patient's obsession. Results of ITP DBS appear encouraging, although there are limited reports of the potential utility of ITP DBS in OCD.

Globus pallidus internus (GPi) emerged as another potential target for OCD. GPi DBS in 4 patients with Tourette syndrome with comorbid OCD resulted in significant improvement in OCD symptoms [35]. In addition, another report indicated a 48.5% reduction in OCD symptoms following amGPi (anteromedial GPi) DBS suggesting GPi as one of the viable targets for OCD [36]. As with ITP DBS, GPi DBS experience in OCD is very limited but encouraging.

Overall, DBS therapy appears effective in symptom reduction in medically refractory OCD, irrespective of the target studied or study design [21,24,28,32,37–39]. Various targets have been investigated for DBS in patients with OCD with comparable results; however, there appears to be heterogeneity in targeting 'nomenclature,' especially the striatal targets, as targets are anatomically overlapping. It appears that multiple targets are stimulated based on the volume of tissue activated. Interestingly, connectomic analysis of DBS OCD across 4 centers targeting the ALIC, the STN, and the NAc revealed a common fiber bundle was associated with optimal clinical response [20].

Results from a meta-analysis, which included 352 cases from 9 RCT and 25 non-RCT studies, indicated 66% of individuals who received DBS were full responders [40]. Furthermore, they reported a 47% reduction (14.3 points) in Y-BOCS scores with comparable findings between RCTs and non-RCTs. These findings are consistent with an earlier meta-analysis of 31 studies that included 116 patients which reported similar response rate (60%) and reduction in OCD symptoms (45.1%) [41]. Importantly, the clinical response to DBS is sustained and possibly improves over a longer duration of use. When comparing the short-term response (<36 months) and long-term response (>36 months), while the reduction in the Y-BOCS was similar (47.4% vs 47.2%, respectively), more patients were considered responders (defined as reduction in Y-BOCS scores >35%) in the long-term compared to the short-term (70.7% vs 60.6%, respectively) [42]. Moreover, DBS not only reduced OCD symptoms, but also improved other social dynamics. For example, patients with DBS for OCD were able to secure employment after DBS at a higher rate relative to prior to DBS. In some cases, patients have had post-DBS improvements to the extent that they were able to reduce or discontinue their psychotropic medication [23].

DBS is a safe and effective treatment option in carefully selected patients with severe, treatment refractory OCD cases and is likely an underutilized treatment option. Although DBS for OCD is an FDA-approved indication, this treatment option should be done by a multidisciplinary team with expertise in DBS for psychiatric disorders, given the complexity of OCD, and the intricacies of dynamic mental health

needs in these patients. The most investigated and greatest evidence for DBS in OCD involves targeting the VC/VS; however, other DBS targets have been explored with positive results. Currently, there is no clear consensus about the best or optimum DBS target for OCD and is likely governed by the treating groups experience, and practice, but there appears a common neural pathway engagement.

Depression

Depression is a leading cause of psychiatric related disease burden globally, affecting not only the quality of life and daily functioning of the individual but is also associated with reduced life expectancy and suicide [1,43,44]. Relatively little is known about its pathogenesis, despite extensive research. Genetic predisposition that underlie disease vulnerability with the complex multifactorial interplay of the interaction of genes, early-life adversity, the epigenome in influencing gene expression and environmental factors play a role in depression [45].

The circuit-level mechanisms underlying depression pathophysiology are also not well known but have had significant advancement in recent years. Meta-analyses of neuroimaging studies have identified a network of brain regions that are consistently altered at the group level in depressed patients, including the dorsolateral PFC, orbitofrontal cortex, anterior cingulate cortex, anterior insula, amygdala, hippocampus, basal ganglia, thalamus, and cerebellum [46].

Unlike other serious mental disorders, there are a multitude of evidence-based effective treatments for depression [45]. However, despite advances in behavioral and pharmacological treatments, as many as 30% of patients diagnosed with depression remain refractory to treatment [47,48]. The unmet needs in the treatment of depression have led to the exploration of novel treatments. Based on the framework involving DBS in movement disorders, advancement in functional imaging and the emerging understanding of neural network in depression have led to exploring DBS in treatment-refractory depression (TRD) [49–54].

Subgenual cingulate cortex (SCC) was the first potential DBS target for depression based on functional imaging [55]. Hypermetabolism in subcallosal cingulate area could be activated by the induction of sadness in depression leading to exploration of SCC as a DBS target for depression [50,53]. Chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with a sustained remission of depression in four of six patients [53]. Antidepressant effect was associated with a marked reduction in local cerebral blood flow, as well as changes in downstream limbic and cortical sites. At 3–6 years follow-up, SCC DBS was associated with treatment response rates of approximately 60–70% [56]. While the SCC DBS was being studied as a therapeutic DBS target for depression, observation of improvement in comorbid depressive symptoms in individuals receiving VC/VS DBS for OCD [21] led to exploration of VC/VS as a DBS target for the treatment of refractory depression. Significant improvements in depression were observed with DBS, with a responder rate of 40% at 6 months (53.3% at last follow-up) and a remission rate of 20% at 6 months (40% at last follow-up) [57]. However, these results could not be reproduced in controlled studies. Two industry-sponsored multicenter randomized sham-controlled trials of either SCC or VC/VS DBS in depression failed to reach expected improvement in the primary outcome measure at trial endpoint [58,59].

Successful DBS outcome in open label study but not in the blinded study led to exploration of appropriate patient selection and individualizing the treatment/targeting. Brain imaging, especially diffusion tensor imaging (DTI), allows for personalized charting of the tract and personalized DBS targeting. Following the observation that a PD patient treated with STN-DBS developed hypomania when the stimulation extended more medially than intended (into the superolateral medial forebrain bundle (slMFB) [60], the slMFB was explored as a tractographically defined DBS target for depression [61]. In an open-label, proof-of-concept study, rapid antidepressant effects were seen in six of seven patients with treatment-refractory depression (TRD) with MFB DBS and the benefits were maintained for at least 12–33 weeks [62]. The results of slMFB DBS appear promising, as long-term data in over 30 patients from two centers reported a response rate of 70% [61]. Similar to tractographically defined slMFB target, white matter tract blueprint as a convergence of four tract pathways – the forceps minor, cingulum, uncinate fasciculus, and frontal-striatal fibers emerged when comparing non-responders to responders in SCC DBS [63]. Active electrodes at the convergence of these four white matter tracts in depression resulted in an 82% response rate. While this was an open-label study, the finding provided evidence for the potential individualized DBS targeting. Other targets considered for DBS in TRD include inferior thalamic peduncle (ITP) [64], the lateral habenular complex [65], and the ventral caudate [66] with promising results which require validation in larger controlled studies.

A review of 32 studies which included 291 patients receiving DBS targeting different brain structures including the SCC/sgACC (subgenual anterior cingulate cortex), VC/VS, and NAc revealed that 1/3 of patients achieved complete remission, 1/3 of patients demonstrated symptom improvement, however, 1/3 of patients did not achieve appreciable benefit [67]. Furthermore, a systematic review and meta-analysis of 10 papers from 9 studies, 7 of which were double-blind RCTs, revealed that active DBS was associated with a higher response than patients receiving sham treatment [68]. Open label studies in depression were promising but the controlled studies did not demonstrate the expected improvement.

DBS does appear to be effective in subset of patients with depression, however, that needs further characterized. Depression is remarkably heterogeneous disorder consisting of multiple subtypes, variable presentations, and varying neurobiological differences [69]. Different DBS targets addressed specific symptoms better than others suggesting possible different mechanisms of action as well. It is also possible that the futility of two industry-sponsored RCTs is attributed to the premature evaluation of the primary endpoint, thereby hindering the ability to distinguish between the therapeutic effects of DBS and those attributed to a placebo [70]. While the SCC DBS trial was discontinued after futility analysis because there was no difference in response rates between the active and sham stimulation arms after 6 months, approximately one-half of the patients were deemed to be treatment responders after 18 months to 2 years of open-label stimulation [58]. This again reflects the complexity and heterogeneity of psychiatric disorders and possibly longer duration of modulation of brain network. DBS for depression is a complex and evolving process. Lessons from the failures and sub-group analysis with individualized neurocircuitry based DBS interventions could be promising for future studies to investigate and validate the role of DBS in depression.

Addiction

Addiction is a major health care crisis, and the number of deaths form alcohol, smoking, and illicit drug use surpassed the number of deaths from all cancers combined [71]. Moreover, opioid overdose alone is the leading cause of non-accidental death [72]. Current treatment for substance use disorder (SUD) is far from ideal. Approximately 50–85% of individuals with SUD are known to relapse within 1-year of treatment initiation [73,74] As such, novel treatments for SUD are critically needed. As we understand more about the neurocircuitry of the various neurological and psychiatric disorders, including SUD, modulating such pathways appears to be a promising approach [54,75].

DBS has been explored as an adjunctive treatment for refractory SUD and has shown potential in reducing substance craving and use. The nucleus accumbens (NAc) has emerged as a key nodal center of the reward circuit and is crucial for mediating motivated behavior via the corticobasal ganglia-thalamic loop [19,75–77]. NAc activation was seen with drug expectancy, euphoria, and craving on functional brain imaging [78] and plays a key role, together with the ventral tegmental area, in the binge/intoxication [79]. Neuroanatomically, NAc incorporates the convergence of fiber bundles from the anterior cingulate, the amygdala,

hippocampus, hypothalamus and the brainstem – structures which are critical to the reward circuitry and addiction processes. Various animal studies have explored targeting neural regions to modulate the network in addiction. The NAc was the most studied and promising target though other targets were also explored which included subthalamic nucleus (STN), dorsal striatum, lateral habenula, medial prefrontal cortex (mPFC), and lateral hypothalamus [80,81]. The majority of studies have targeted either the NAc core or shell and demonstrate that NAc DBS could be an effective and promising target to modulate the addiction network [80–84].

Clinical insight of DBS for SUD emerged when NAc DBS was performed on a patient with refractory OCD and resulted in an unintended alleviation of the patient's comorbid alcohol use disorder [85]. Importantly, this was independent from, and was not associated with, any improvement in the patient's OCD symptoms. Subsequently, 10 patients were reviewed who received NAc DBS for various psychiatric indications, including Tourette's syndrome (TS), obsessive-compulsive disorders (OCD), or anxiety disorders. Among these patients, three patients achieved unintended cessation of cigarette smoking [86]. Given these findings, bilateral NAc DBS was performed in three patients with chronic resistant alcohol use disorder (AUD), two of whom achieved abstinence while one patient demonstrated a remarkable reduction of alcohol use [87]. Subsequently, the authors reported long-term outcomes of DBS for AUD in five patients. Two patients remained abstinent for many years, while three patients showed a marked reduction of alcohol consumption at follow-up, extending up to eight years [88]. In another open label study, eight patients with heroin addiction underwent custom made DBS electrodes implantation, traversing through the ALIC into the NAc, and were followed for at least 24 months [89]. Five patients achieved alcohol abstinence for more than three years, two relapsed after achieving six months of abstinence, and one patient was lost to follow-up at three months. Abstinence was also associated with reduced alcohol craving. Furthermore, DBS of the NAc and ALIC not only improved the quality of life and alleviated psychiatric symptoms in this cohort but was also associated with objective change in neuroimaging. Brain regions associated with SUD demonstrated increased glucose metabolism. Various case reports and series' have been encouraging and reported decreases in drug use [90–94].

Encouraging results were also reported on six patients with severe, refractory AUD who underwent NAc DBS [95]. All patients experienced a reduction in alcohol craving with significant reduction in alcohol consumption, alcohol-related compulsivity, and anxiety 12 months post-DBS. Improvements in compulsive drinking behavior were associated with reduced NAc metabolism on FDG-PET. NAc DBS has also been investigated for cocaine use disorder (CUD) in a double-blinded clinical trial where one patient received bilateral NAc DBS [96]. The clinical trial was structured to titrate and assess the effects of DBS in different phases (single blinded/double blinded/contentious stimulation). While there was an objective reduction in cocaine craving, there were no major differences between the “off” and “on" stimulation conditions during the blinded phase.

Recently, we reported the outcomes of open-label, safety and feasibility clinical trial of DBS for treatment refractory opioid use disorder (OUD) [97]. Four patients with refractory OUD with other co-occurring non-opioid SUDs underwent NAc/VC DBS. Two participants sustained complete substance abstinence (>1150 and >520 days), and one participant experienced relapse but at a considerably diminished frequency and severity [97]. Both the patients who achieved abstinence remain free from drug relapse to date. The DBS system was explanted in one participant due to noncompliance with treatment requirements and study protocol. Successful abstinence was associated with increased glucose metabolism in the frontal regions on FDG-PET neuroimaging, suggesting a biological effect of DBS and modulation of the neural network.

The results of DBS have been encouraging, but a long term-controlled study on a larger patient population is needed. While larger controlled studies are necessary, it is also paramount that the psychosocial status and challenges of this unique patient population need to be considered in future studies.

Eating Disorder

Eating disorder diagnoses involve a broad range of abnormal eating patterns that negatively impact health or psychosocial functioning, including anorexia nervosa, bulimia nervosa, and binge eating disorder. The treatment of eating disorders tends to involve multidisciplinary approaches; however, in spite of the best available therapies, outcomes remain suboptimal. Anorexia nervosa is among the psychiatric diseases with one of the highest mortalities. DBS was explored to modulate the limbic circuit in anorexia nervosa. In a phase 1 clinical trial, six patients with chronic, severe, and treatment-refractory anorexia nervosa underwent SCC DBS [98]. BMI improved in 3 patients from their historical baseline. There was also an improvement in mood, anxiety, affective regulation, and anorexia nervosa-related obsessions and compulsions in four patients. The clinical benefits were accompanied by changes in cerebral glucose metabolism in brain areas, specifically the anterior cingulate, insula and parietal lobe. Subsequently, the authors reported long-term experience in a larger patient population with encouraging results. In a cohort of 16 patients with treatment-refractory anorexia nervosa who underwent SCC DBS, there was improvement in the BMI as well as improvement in depression, anxiety, affective regulation, and emotional regulation [99]. There were also significant changes in cerebral glucose metabolism in key anorexia nervosa-related structures with DBS therapy. In a further follow-up of this cohort, investigators reported long-term outcomes for 15 out of 22 patients with SCC DBS who had received stimulation for three or more years [100]. Interestingly, patients continued to maintain improved BMI, and 3 patients (20%) restored normal BMI, but psychometric improvement seen on 1 year follow up were not sustained in the longer follow up.

Other investigators also explored DBS for anorexia nervosa with different targets. In a cohort of 28 female patients with NAc DBS, there were significant increases in BMI along with improvement in psychiatric scales, which were maintained over a 2-year period [101]. Other DBS targets including VC/VS, ALIC have also been explored with positive results in primary anorexia nervosa or comorbid anorexia nervosa [102,103]. Although DBS has been effective in improving BMI and other psychometric parameters, it has been associated with complications given the medical fragility of these patient population [100,102]. Therefore, DBS should be explored only with a multidisciplinary team managing behavioral eating disorders.

DBS for Other Psychiatric Disorders

Given the growing experiences with DBS in movement disorders and neuropsychiatric disorders, DBS for other psychiatric indications is re-emerging. NAc DBS was explored in schizophrenia with positive results in a single patient [104]. Prior to that, a patient with OCD having residual schizophrenia responded with NAc DBS [105]. Recently SNr (substantia nigra pars reticulata) DBS and Habenula DBS were reported with a positive response in schizophrenia [104,106]. Most of the experience with DBS in schizophrenia is case reports. NAc and subgenual anterior cingulate cortex (SgACC) DBS reported with positive results in a small case series [104,107]. Experience of DBS in schizophrenia is very limited. A larger controlled study is needed to explore role of DBS in schizophrenia.

One of widely prevalent and disabling psychiatric condition is post-traumatic stress disorder (PTSD). A significant portion of patients remain refractory to current available therapy. DBS of basolateral amygdala was found to be effective in reducing PTSD symptoms [108]. With the increasing awareness of neuropsychiatric circuits coupled with advancements in neuroimaging technology, investigators have reported tractographically defined placement of DBS electrodes within subgenual cingulum to maximize contact with the uncinate fasciculus, as well as

with the other white matter tracts of forceps minor and cingulum bundle [109]. DBS of the medial frontal cortex and uncinate fascicle resulted in compete resolution of PTSD on the Clinician-Administered PTSD Scale, along with improvements in depression, functioning, and quality of life (QoL) at 6 months. This was the only patient of this non-blinded, non--randomized, pilot clinical trial reported. While this trend is encouraging, a larger controlled study of longer duration is needed.

Other Neurosurgical Neuromodulation Therapy for Psychiatric Disorders

DBS is the leading neurosurgical neuromodulation intervention in the neurological and psychiatric disorders, however, vagus nerve stimulation (VNS) and newer emerging technology of focused ultrasound (FUS) or MR-guided focused ultrasound (MRgFUS) are other neurosurgical neuromodulation intervention for the psychiatric disorders studied. This section presents the brief review of the VNS and FUS neuromodulation in psychiatric disorders.

Vagus Nerve Stimulation (VNS) for Psychiatric Disorders

VNS is an FDA approved neurosurgical neuromodulation treatment for medically refractory epilepsy. VNS is standard of care for medically refractory epilepsy in appropriately selected patients with extensive experience worldwide with a 50–100 % seizure frequency reduction in 45–65 % of the patients [110]. Vagus nerve is the main output of parasympathetic nervous system and has extensive neural connection in the brain affecting the autonomic nervous system. Experience of VNS in epilepsy suggested concomitant improvement of comorbid mood disorder in patients with epilepsy [110]. The first prospective trial comparing the mood effects with VNS demonstrated significant improvement in mood compared to patients receiving AEDs alone [111]. In an open pilot study of VNS in 60 patients with treatment-refractory depression, the response rate was 30.5% for the primary 28-item Hamilton Rating Scale for Depression [HRSD [28]] measure, 34.0% for the Montgomery-Asberg Depression Rating Scale (MADRAS) [112]. In a randomized clinical trial (RCT), a total of 235 patients with nonpsychotic major depressive disorder or nonpsychotic, depressed phase, bipolar disorder was evaluated at ten weeks of masked adjunct VNS therapy to sham treatment. The VNS was shown to be safe and well tolerated. Although there was reduction in depression, but VNS did not demonstrate significant benefit at short-term follow up in treatment-refractory depression [113]. It is important to note that VNS stimulation dosing in this trial was limited to 1 mA. The study possibly also suggested that longer VNS treatment (greater than three months) may be needed to measure an antidepressant response. Later in the follow-up study, the same treatment-refractory depression patients with VNS were analyzed over the year following the acute phase of treatment. The study showed a pattern of growing response and remission rates at 3-, 6-, 9-, and 12-months following initiation of VNS treatment (HDRS mean of 28.0 $\pm$ 5.7 at baseline, 19.6 $\pm$ 9.7 at 12 months, $p < 0.001$) [114]. The FDA approved VNS for the treatment of chronic or recurring depression in 2005. In a prospective, open-label, nonrandomized, observational five-year study that included 795 patients with a major depressive episode reported a significantly higher five-year cumulative response rate (67.6% compared with 40.9%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%) [115]. A large prospective, multi-center, randomized controlled blinded (RECOVER) trial (ClinicalTrials.gov Identifier NCT03887715) is being conducted to assess VNS as an adjunctive therapy in patients with treatment-refractory depression. VNS is also explored in other psychiatric conditions such as schizophrenia, Alzheimer's disease, OCD, PD, PTSD, and fibromyalgia with either no effects or preliminary data on efficacy and is currently investigational [116].

Focused Ultrasound Neuromodulation for Psychiatric Disorders

Despite the effectiveness of DBS in appropriately selected patients with psychiatric disorders, DBS therapy is probably not best utilized in otherwise eligible patients [117,118]. One of the major deterrents for the utilization of DBS as a neuromodulation treatment for psychiatric disorders is the invasiveness of the procedure, implantable hardware, and the need to maintain the device/hardware over the long term. Recently, with the evolution of technology, MR-guided focused ultrasound (MRgFUS) has emerged as an FDA approved thermal ablative treatment for patients with essential tremor (ET) and PD, who are otherwise candidates for DBS and/or surgical treatment [119–123]. MRgFUS is a non-invasive method, which involves real-time MRI guidance and application of transcranial focused ultrasound and patient monitoring without a surgical incision or surgical hardware [119,120]. Given the wider acceptance and positive results of high-intensity MRgFUS ablative treatment in movement disorders [124–126], MRgFUS ablative treatment explored for psychiatric disorders. Similar to the ablative capsulotomy results, MRgFUS capsulotomy reported promising early and long-term response in OCD. In an initial cohort of 4 patients who underwent MRgFUS capsulotomy, there was gradual improvements in Y-BOCS scores (mean 33%) over 6-months. Additionally, all patients had immediate and sustained improvements in depression [127]. Subsequently, authors reported long-term follow up of 2-years in 11 patients with MRgFUS capsulotomy [128]. Patients continued to have sustained and significant improvement in Y-BOCS score as well as improvement in HAM-D and HAM-A scores. No significant and long-term adverse effects were noted and there was improvement in the memory and function as well. Separate independent investigators also reported encouraging results with MRgFUS capsulotomy in OCD and depression patients [129]. In their cohort of 6 patients of OCD and 6 patients of depression, 4 patients of OCD and 2 patients of depression were responders. The results of MRgFUS capsulotomy are promising but is ablative. Currently, the only FDA approved MRgFUS system designed for human application is the Insightec hemispheric transcranial multi-transducer system which is for high-intensity ablative treatment, however, non-ablative neuromodulatory interventions are being increasingly investigated including for psychiatric disorders. Unlike high-intensity focused ultrasound, non-ablative focused ultrasound treatment utilizes a non-thermal low frequency application of low-intensity focused ultrasound (LIFU). One of the non-ablative treatment options utilizing LIFU involves opening of the blood-brain barrier (BBB) in Alzheimer's disease and other neurological disorders with low-intensity focused ultrasound with concurrent IV microbubble [130–133]. There are also ongoing investigations of low-intensity focused ultrasound (LIFU) neuromodulation for various psychiatric disorders which may provide a preferable alternative to DBS and other neuromodulation therapies given that focused ultrasound eliminates many of the limitations of DBS. Specifically, LIFU offers non-invasive, non-ablative, real-time MRI guidance with precise spatio-temporal resolution for targeting cortical and subcortical deep brain structures and has demonstrated the ability to modulate neural networks [134–138]. Although there is limited experience of LIFU neuromodulation in psychiatric disorders, there have been promising results using another experimental MR-guided low-intensity focused ultrasound system (Brainsonix) in neurological diseases such as epilepsy, disorder of consciousness, and traumatic brain injury (TBI) [138–140]. Similarly, promising results were reported with navigation guided FUS neuromodulation (NaviFUS) in epilepsy [141].

The clinical study of LIFU neuromodulation for psychiatric disorders, was not available until recently. As a proof-of-concept study, we evaluated the safety and feasibility of transcranial MR-guided LIFU in patients with substance use disorders (SUD). LIFU neuromodulation of the NAc (applied unilaterally to the left then right NAc) at two different doses (60W and 90W). LIFU neuromodulation was safe and well-tolerated. Patients receiving the enhanced dose (90W) demonstrated a

therapeutic effect with an acute reduction in drug craving, which persisted through the 90-day follow-up [142]. Subsequently, we demonstrated that LIFU neuromodulation of the NAc (applied bilaterally and simultaneously) was safe, feasible and again showed substantial decreases in craving for multiple substances both acutely and over a 90-day period in a participant with OUD and several co-occurring SUDs [143].

MR guided LIFU shows promise as a method of neuromodulation in patients with neuropsychiatric indications. We have also initiated a clinical study to evaluate LIFU neuromodulation in Alzheimer's disease (ClinicalTrials.gov Identifier: NCT05997030). While the initial results and experiences in patients with SUD are positive, further evaluation through a larger controlled study is needed to validate therapeutic neuromodulation in otherwise treatment refractory SUDs and other psychiatric disorders. Studying the underlying mechanisms of neuromodulation, patient identification, and refining targeting are important steps in establishing MR-guided LIFU as a neuromodulation treatment in SUD and other psychiatric disorders.

Neurosurgical Neuromodulation: Current Status and Road Ahead

Despite advancements in the medical and behavioral therapy, a significant number of patients with psychiatric disorders remain treatment refractory. Psychiatric disorders, especially those which are treatment refractory, are a major cause of disability and carries increased risk of suicide and death. Neurosurgical treatment of psychiatric disorders should be carefully considered with multidisciplinary evaluation and ethical consideration. Neuromodulation with DBS is favored, as this is non-ablative, reversible, adjustable as parameter modifications can be made. DBS is currently approved for severe treatment refractory OCD under HDE, while DBS for depression, addiction and other diseases are actively being explored. DBS for psychiatric disorders is promising but is also challenging. Unlike movement disorders such as Parkinson's disease and essential tremor where there is a defined phenotypic form, psychiatric diseases are heterogeneous with little to no immediate feedback with DBS stimulation. A better understanding of phenotypic forms of psychiatric diseases and individualized targeting may boost the utility as well as the acceptability of DBS therapy. Transcranial MR-guided LIFU is an emerging non-invasive neuromodulation therapy with promising preliminary results in substance use disorders (SUD). Larger controlled studies are needed to evaluate and validate the use of DBS and other emerging therapies such as focused ultrasound in psychiatric disorders.

Author's Contribution

Conception and design: Ranjan, Mahoney, Rezai.

Acquisition, and interpretation of review data: Ranjan, Mahoney, Rezai.

Drafting the article: Ranjan, Mahoney.

Critically revising the article: all authors.

Reviewed submitted version of manuscript: all authors.

Approved the final version of the manuscript on behalf of all authors: Ranjan.

Administrative/technical/material support: Rezai, Mahoney, Ranjan.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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