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Neuromodulation In Psychiatric Disorders – An Overview

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Introduction

The history of psychosurgery has been tumultuous and chequered. Perhaps no branch of neurosurgery has received so much attention, risen to great heights and plumbed depths in a short span of time. From a Nobel prize for psychosurgery to being banned and gradually rising like a phoenix, it has been a roller coaster ride. In this article we give an overview of intervention in psychiatric disorders and review the recent literature on the upcoming and promising field of neuromodulation in Psychiatric disorders.

History

The earliest record on trephining for relief of pain, melancholia dates back to 1500 BC. Roger of Salerno in 1180 explained the process of opening the skull in mania or melancholy to permit the noxious material to be exhaled. There have been innumerable paintings from the Middle Ages which depict trepanations for psychiatric disorders. Goltz (1881) proposed after experiments on dogs that neocortical resection induced rage and temporal lobe resection resulted in calmer animals, while Gottlieb Burckhardt, considered by some to be the father of modern psychosurgery, was the first to perform surgery on the brain for psychiatric disorders - first topectomy on a patient with psychiatric illness in 1888. The next procedures were carried out by Lodovicus Puusepp in 1910 when he sectioned the cortex between frontal and parietal lobes in 3 patients for manic depressive disorders. [1] Prominent among others include Maurice Ducoste, the inventor of lobotomy for psychiatric disorders. [2] However, the most famous of all was Egaz Moniz, who along with Almeida Lima performed the first prefrontal leukotomy on a woman with melancholy and paranoid delusions. This was based on the presentations of Fulton and Jacobsen in 1935, at the Second World Congress of Neurology in London, where they described the calming effect of frontal lobe surgery in Chimpanzees. [1]

Moniz presented the results of his first 20 leukotomies to the Academy of Medicine in Paris. In 1937, Moniz had coined the term *psychosurgery.* despite the lack of efficacy, his results were welcomed and eventually he was awarded the Nobel prize for his work on prefrontal leukotomy. Walter Freeman (neuropsychiatry) and James Watts (neurosurgeon) gradually refined the procedure and reported the results of the first 200 lobotomy cases in 1942 with 63% improvement. While there were significant complications, Freeman went on to develop the transorbital lobotomy which took 15-20 minutes without the use of anesthesia. This procedure almost developed into a crusade for Freeman who would go around the country in so called 'Lobotomobiles' to perform the procedure. He used the media to sensationalize and popularise the procedure despite significant misgivings of his colleagues. This led to an explosion of the procedure and quickly degenerated into misuse. Newton analysed 10000 cases of frontal lobotomies and though they reported 70% improvement, the complications were high and soon lead to calls of restraint by prominent figures. This led to introduction of multiple procedures including the open bilateral inferior leukotomy , open cingulotomy, bimedial leukotomy, and orbital undercut. [3,4,5] Despite the calls o restraint the procedures were being performed till the introduction of Chlorpromazine in 1954, followed by other drugs which demonstrated better efficacy and outcomes. Gradually Psychosurgery died out and only stereotactic lesioning were being performed which also were discontinued or banned. Over the past 20 years, with the introduction of neuromodulation in form of Deep brain stimulation and the realisation of limitations of medical and cognitive therapy, psychosurgery is slowly making a comeback, albeit with stricter regulations.

In India Dr. MV Govindaswamy and Dr Balakrishna Rao were the first to conduct psychosurgery in India. They Performed leucotomies at the Mysore Government Mental Hospital MGMH (Now NIMHANS) in 1942 and published their study in the Lancet, 1944 on the "Bilateral Prefrontal Leucotomy in Indian Patients. Dr Ramamurthi, Dr V Balasubramaniam and Dr Kanaka at the Institute of Neurosciences – Chennai in the 1960's and 70's performed multiple stereotactic procedures for psychiatric disorders including Stereotactic Hypothalamotomy/Amygdalotomy for Hyperkinetic behaviour disorders, Stereotactic mesencephalic reticulotomy, Stereotactic thalamo-laminectomyand Pulvinotomy.

Overview of neuromodulation for various psychiatric disorders

Obsessive-compulsive disorder

Obsessive-compulsive disorder is characterized by the presence of repeated intrusive thoughts (called obsessions) associated with repeated mental and physical acts (compulsions) that the individual feels driven to perform in response to the obsessions. It has a lifetime prevalence of 1-3% [6]. It has onset often in adolescence and early adulthood and runs a chronic course when untreated. It is often a disabling condition and markedly impairs the quality of life [7]. The first line of treatment includes high-dose selective serotonin reuptake inhibitors (SSRI) and cognitive-behavior therapy (CBT) [8]. Augmentation with dopamine agonists, 5HT3 antagonists, glutamate modulators is helpful in partial/non-responders [9]. However, around 10-20% of patients with OCD suffer from chronic, severe and treatment-refractory OCD. DBS is a treatment option for these patients [10].

DBS targets for OCD

Neuroimaging studies have found evidence for the involvement of the multiple cortico-striato-thalamo-cortical circuit emanating from the frontal regions in OCD. These parallel yet partially segregated circuits are involved in the regulation of cognition, motivation and emotions [11,12]. Supporting this hypothesis, evidence collected over the decades suggest significant efficacy with ablative surgeries which create lesion to disrupt in this circuit [13,14]. The procedures commonly employed for OCD include anterior capsulotomy (lesions in the anterior limb of internal capsule, followed by cingulotomy (lesions around the anterior cingulate cortex in the cingulum bundle) [15]. The former procedure has been more widely employed in the treatment of OCD.

Bart Nuttin and colleagues in were the first to simulate anterior capsulotomy through high-frequency DBS over the anterior limb of internal capsule (ALIC) [16,17]. Encouraging results from this procedure stimulated interest in reversible neuromodulation for OCD. Multiple groups across the globe evaluated DBS of this target with encouraging results. The distal contact is inserted in the nucleus accumbens (NAc), which is involved in the reward pathway. This trajectory, known as the ventral capsule/ventral striatum (VC/VS), stimulates the ALIC and/or the adjoining NAc [18,19]. With experience, the target has been refined to stimulate a more posterior region in ALIC, just anterior to the anterior commissure [20]. It has been observed that the distal contacts in the posterior targets may stimulate the bed nucleus of stria terminalis (BNST), which has been found to be associated with improved response [21]. Thus, there are some minor variations in this target, stimulating the ALIC or the NAc or the BNST.

A consortium of DBS researchers in France evaluated a different target i.e., the anteromedial subthalamic nucleus (amSTN), based on early evidence in patients with comorbid Parkinson's disease [22]. This region of the STN is involved in the regulation of the cognitive and emotional functions. STN is involved in response inhibition and decision making, which are cognitive functions that have been found to be impaired in OCD [23-25]. A randomized controlled trial (RCT) conducted by this group showed that active DBS over this target is superior to sham stimulation [22]. An ongoing Indian study is evaluating biomarkers to predict response to DBS in this target [26].

The supralateral branch of the medial forebrain bundle (slMFB), which is hypothesized to be involved in reward functioning, has shown preliminary encouraging evidence [27]. There is some controversy with regards to the nomenclature of this white matter tract that connects the ventral tegmental area (VTA) to the orbitofrontal cortex (OFC) [28]. This white matter bundle is targeted based on patient-specific tractography.

Evidence

A major challenge in conducting double-blinded RCTs in OCD and other psychiatric disorders is the response latency, which may take up to months. The programming is conducted over a prolonged period, leading to methodological difficulties. Nevertheless, evidence from small RCTs which optimized stimulation followed by blinded "ON" vs "OFF" stimulation for a period of up to 3 months has shown statistically significant difference in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score between the active vs sham stimulation for amSTN, NAc and BNST [18,21,22]. An evidence guideline recommended amSTN DBS with level 1 evidence and NAC/BNST DBS with level 2

evidence [29]. A UK-based study comparing DBS of VC/VS and amSTN showed that stimulation of both targets had similar efficacy in reduction of OCD symptoms. There were some differences in the secondary outcome though, with the VC/VS DBS showing better improvement in mood and the amSTN DBS showing better improvement in cognitive functioning (cognitive flexibility) [30]. The US FDA approved ALIC DBS for OCD (via humanitarian exemption) in 2003. A recent meta-analysis found that 67% of patients who underwent DBS for OCD were responders at last follow-up [31].

Future directions

OCD in its severe form can be highly disabling. DBS has shown promising and consistent results in patients with severe OCD who are refractory to medications and CBT. Despite this, there is still a dearth of acceptance and utilization of the treatment, possibly due to the stigma of psychiatric disorders and psychosurgery [32,33]. There is a need for widespread education regarding the procedure and its efficacy. Neuroimaging studies based on normative connectome data have shown that the most effective DBS targets stimulate the same white matter pathway connecting the anterior cingulate cortex/ventrolateral prefrontal cortex with the subthalamic nucleus [34]. Thus the seemingly disparate targets may actually be stimulating the same region. This paves way to further research on connectome-based DBS. Another exciting development is the evaluation of electrophysiological markers from the target regions that are associated with symptoms and treatment response [35,36] a potential strategy for improving efficacy of DBS for neurological and psychiatric disorders. This approach requires identifying neural biomarkers of relevant behavioral states, a task best performed in ecologically valid environments. Here, in human participants with obsessive-compulsive disorder (OCD. This can pave the way for closed-loop stimulation, which may markedly improve the battery life. Evaluation of these biomarkers may also assist in programming which is often protracted due to the delay in treatment response.

Neuromodulation for Alzheimer's disease

Alzheimer's disease

Alzheimer's Disease (AD) is the most common cause of dementia. [37] Despite the advancement in therapeutics, there is no definitive therapy for AD, and it carries considerable economic, societal, and healthcare burden. Novel non-pharmacological treatments are much needed. Positive experience and long history of the neuromodulation in neurodegenerative disease such as Parkinson's disease (PD), deep brain stimulation (DBS) and other functional neurosurgical interventions are being explored in AD therapeutics. We will outline the current landscape of neurosurgical neuromodulatory intervention in Alzheimer's disease.

Neuromodulation involves altering neuronal activities through the delivery of a stimulus, which may not be limited to electrical or magnetic stimulation to a defined target. Although transcranial magnetic stimulation (TMS) is an FDA approved indications for treatment refractory depression and obsessive-compulsive disorder (OCD), however, TMS still is investigational in AD. There has been encouraging trend with the clinical studies of TMS in AD targeting dlPFC, precuneus, inferior frontal gyrus, parietal cortex, temporal cortex, Broca's area, and Wernicke's area. [38,39] As such, TMS is an attractive option given its non-invasiveness and potentially neuromodulatory effects as well as relative availability of expertise and infrastructure given clinically approved indications and practice. Further larger and controlled studies are needed to explore and validate use of TMS in AD.

Deep brain stimulation (DBS) in Alzheimer's disease

There is a rich experience of neuromodulation with deep brain stimulation (DBS) in neurodegenerative disorder such as PD. DBS is standard of care in patients with Parkinson's disease, dystonia, essential tremor, and epilepsy. Among psychiatric conditions, OCD is the only FDA approved indication under Humanitarian Device Exemption (HDE) and investigated for other neuropsychiatric disorders including Alzheimer's disease, treatment refractory depression, anorexia nervosa, PTSD, and addiction. [40,41]

DBS targets for Alzheimer's disease

DBS of the fornix (DBS-f)

DBS for AD conceptualized after a case report which reported acute stimulation induced recall of autobiographical memories and improved performance on tests of memory

and spatial associative learning on chronic stimulation of fornix in a case of bilateral hypothalamic DBS for obesity. [42] This observation led to a phase 1 clinical trial of DBS in patients with mild AD. [43] Six patients with early AD underwent bilateral fornix DBS. Procedure was well tolerated and there were no serious adverse effect. There was some evidence slowing in the rate of cognitive decline at 6 and 12 months in few of the patients. FDG PET scans showed early reversal of the impaired glucose utilization in the temporal and parietal lobes, which was maintained after 12 months of continuous stimulation. This led to Advance DBS-f phase 2 double-blind randomized controlled trial of forniceal DBS in 42 patients with mild AD. [44] Study did not show significant difference between forniceal DBS and no stimulation, however, patients receiving stimulation showed increased metabolism at 6 months but that was not significant at 12 months. A subgroup analysis revealed that patients older than 65 years of age had less decline than patients who received sham stimulation, whereas patients younger than 65 years of age had significantly worsening cognitive measure. Further larger study needed to evaluate the effects of forniceal DBS in patients with AD.

Nucleus basalis of Meynert (NBM) DBS

One of the early events in AD is neurodegeneration affecting cholinergic nuclei. Nucleus basalis of Meynert (NBM) is one of the principal sources of cholinergic innervation of the cerebral cortex and cholinergic neurotransmission considered critical in the memory leading to NBM as potential target for neuromodulation in AD. A single case report of NBM DBS was reported at early as 1985 but there was no significant clinical benefit, however, PET scan showed preserved cortical glucose metabolic activity in the ipsilateral temporal and parietal lobes while it declined elsewhere in the cortex. [45] Phase I trial NBM DBS in six AD patients with subsequent additional four patients did show some but nonsignificant effect on cognitive or functional impairment [46-48]. Chronic NBM stimulation appeared to prevent the expected decline in glucose metabolism in frontal, temporal and parietal cortices on FDG-PET. [46]

VC/VS DBS

Another area for neuromodulation was explored targeting ventral capsule/ventral striatum (VC/VS) region to modulate frontal lobe behavioral and cognitive networks. In three patients with VC/VS DBS, there was less decline in the behavioral and cognitive functioning when compared with matched groups from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. [49] There was minimal changes or increased metabolism on FDG-PET in frontal cortical regions with chronic VC/VS DBS. This study, however, was targeting primarily to modulate frontal network to improve executive and behavioral deficits.

Evidence

The observational and exploratory studies suggest positive response of DBS in AD, however, randomized controlled study failed to demonstrate significant benefit of DBS in AD. Even with failed studies, there appears to be a subset of patient that could be helped with the DBS therapy.

Current status and future direction

DBS for AD is currently investigational with some early promising but equivocal result that needs further larger controlled study to evaluate the effectiveness and/or possibly exploring novel target to modulate brain network to improve memory or at least to prevent the cognitive decline. This is particularly challenging given different variant of AD and the fragility of the patient population. With further studies potential biomarker and specific clinical subtype may guide the proper patient selection to benefit patients with DBS in AD.

Major depressive disorder

Major depressive disorder (MDD) is a heterogenous condition characterized by persistent low mood and/or anhedonia, associated with somatic (disturbed sleep, appetite) , cognitive (feelings of hopelessness, worthlessness, suicidal thoughts) and behavioral (psychomotor agitation or retardation) symptoms [50]. Different combinations of the above symptoms may be seen in patients with varied course and treatment response. It has a highly prevalent condition with a lifetime prevalence of around 5.5% in India [51] and is a leading contributor to global burden of disease [52] life expectancy increases,

and populations age, non-fatal outcomes of diseases and injuries are becoming a larger component of the global burden of disease. The Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (GBD 2016. Although MDD is known to occur across age groups, it is more common in young adulthood [50]. The course is varied, but recurrence is common. Etiology is often multifactorial with psychosocial, genetic, neurobiological and systemic contributions, which further attests to the heterogeneity of the condition [53,54] motivating a renewed interest in rethinking our approach to diagnosing depression for research purposes and new efforts to discover subtypes of depression anchored in biology. Here, we review the major causes of diagnostic heterogeneity in depression, with consideration of both clinical symptoms and behaviors (symptomatology and trajectory of depressive episodes. The first line treatments include antidepressant medications and/or psychotherapy. Electroconvulsive therapy (ECT) is helpful in treatment resistant patients and those with acute suicidality. Non-invasive neuromodulatory interventions such as repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC) is also helpful [55]. Nevertheless, a substantial minority of patients have severe chronic and treatment refractory depression (TRD), for whom surgical interventions including DBS are attempted.

DBS targets for MDD

TRD has been treated with ablative procedures including cingulotomy and sometimes capsulotomy [56]. The impetus for DBS for MDD arose from the observation of mood improvement mood in OCD patients undergoing VC/VS DBS [57]. Thus VC/VS was the first target evaluated for DBS in MDD [58]. Helen Mayberg *et al* employed a more neurobiologically informed target i.e. the subcallosal cingulate cortex (SCC) [59]. This was based on functional imaging studies that demonstrated hyperactivity in this region, both in patients with chronic depression and during transient sadness in healthy volunteers [60]. Further, the connectivity of SCC predicts response to treatment for MDD [61]. The so-called slMFB is hypothesized to be involved in the reward pathway and hence stimulated for treatment resistant depression [62]. As discussed earlier, there is some controversy of the nomenclature of this target]. The inferior thalamic peduncle, a white matter bundle connecting the non-specific thalamic bundle and orbitofrontal cortex, has been targeted for DBS in MDD, based on animal models and neurobiological evidence [63]. The habenula, a component of the brain's anti-reward pathway, has also shown been evaluated as a potential DBS target for MDD [64-66].

Evidence

As of date, there are relatively more studies on VC/VS and the SCC compared to the other targets. Early open-labelled studies showed promising results with a response rate of around 40% for VC/VS DBS and up to 67% with SCC DBS [67-69]. As in OCD, there is a latency of treatment response of around 6 months to 1 year. This prompted two industry sponsored multicenter RCTs, the RECLAIM trial targeting the VC/VS [65] and the BROADEN trial on SCC DBS [66]. Both the trials had similar methodology of double blinded true vs sham stimulation before optimization of stimulation parameters. Both the trials did not show encouraging results during interim analyses and were stopped by the sponsors despite not meeting the criteria for futility. On the other hand, other small RCTs found significant difference between the true vs sham group when the randomization was done after a period of initial stimulation optimization [67,68]. The slMFB has shown striking early improvement with both active and sham stimulation, raising the issues of microlesion and placebo [67,69,70]. There is preliminary evidence for ITP [63] and lateral habenular DBS [64] for MDD.

Future directions

It is speculated that the suboptimal performance of the VC/VS and SCC DBS in the multisite RCTs could be due to methodological issues [71]and there is a great need for new treatments. In the last decade, investigators piloted novel deep brain stimulation (DBS. The initial optimization of stimulation parameters is of paramount importance for DBS in psychiatric disorders, due to the delay in onset of response. Hence, future studies should emulate the methodology employed in OCD and by Bergfield *et al* [67] for MDD, with blinded "ON" vs "OFF" stimulation following an initial optimization of parameters. Further, recent evidence suggests that targeting the SCC based on white matter tractography may lead to more promising results [72]. It has been hypothesized that the SCC DBS targets the negative valence system, while the VC/VS and slMFB

DBS target the negative valence system. It is postulated that they may act on different symptoms (improvement in low mood vs increased energy/initiative) [57,73]. There is need for further study whether this can lead to personalized DBS based on symptom profile. Similar to OCD, electrophysiological biomarkers are also being studied in MDD, which can pave way for personalized and close-loop stimulation [74]. Thus, there is still a lot of ongoing exciting work in this area and the setbacks from the initial studies have helped improve the methodology and surgical techniques of DBS studies.

Anorexia Nervosa

Anorexia nervosa (AN) is a severe and chronic psychiatric disorder, often affecting young females. It is characterized by reduced energy intake, due to fear of gaining weight and placing undue importance on weight. This leads to a markedly reduced body weight, often leading to endocrinological and metabolic complications. In addition to restricted food intake, the individual may involve in other repetitive behaviors like excessive exercise, purging, use of laxatives etc. [50] Due to the metabolic complications and comorbidities, AN is the most lethal psychiatric disorder [75]. The treatment consists of enhanced cognitive behavior therapy (E-CBT), nutritional interventions and family therapy. There is preliminary evidence for use antipsychotics as adjunctive treatment [76]. A substantial proportion of patients have a chronic protracted course with severe psychological and physiological dysfunction.

DBS target for AN

DBS has been evaluated as a treatment in such patients with severe chronic treatment-refractory AN. Based on neuroimaging studies and phenomenology, AN is hypothesized to be associated with dysfunctional of the mesolimbic reward pathway [77,78]. Similar dysfunction has been implicated in OCD and MDD. Further, both OCD and MDD are commonly comorbid with AN. Thus, AN has been treated with the same DBS targets evaluated in OCD and MDD [79,80]which may be life threatening if not treated and often coincide with psychiatric disorders. We sought to investigate whether deep brain stimulation (DBS. The evaluated targets include SCC, NAc, BNST and ALIC.

Evidence, current status and future direction

The evidence consists of small open-labelled trials. All these targets have shown promising results with improvement in BMI and symptom severity. A recent network meta-analysis found SCC to be the most promising target followed by BNST, NAc and ALIC [80]. However, it should be remembered that the evidence is preliminary. Given the relatively low prevalence of the condition in treatment settings, multicenter trials may be required for conducting double-blinded RCTs with sufficient power.

Addiction

Addiction is a major health care crisis, and the number of deaths form alcohol, smoking, and illicit drug are alarming. Even with best available therapy, which includes medically assisted treatment (MAT), and psychosocial interventions relapse rate is as high as 50-70% [81,82,83]. Novel therapy is much needed to help curb this modern epidemic of addiction.

Over the years, neuromodulation has emerged as an area of interest for the potential treatment of SUD and has shown promise in reducing craving and use for several substances. [84] Most of the studies are focused on the rTMS to the dorsolateral prefrontal cortex (DLPFC) in an effort to decrease craving and use [85] and has shown positive results for a number of different substances [86,87]. While there have been inconsistent findings related to the efficacy of tDCS [88] and there also have been challenges to target the deep brain structures, especially the brain area/network engaged in reward circuit. Long term maintenance of rTMS therapy in the chronic course of addiction further limits the therapeutic utility in addiction.

Unlike TMS and other non-invasive forms of neuromodulation, DBS can precisely target subcortical structures with greater precision and accuracy, most importantly the NAc, which is considered the center of the reward circuitry and heavily implicated in addiction [89-93]. The DBS also has the added advantage of chronic long-term therapy maintenance. While the clinical results and FDA approval of DBS for OCD led to impetus of exploring and observing behavioural changes in psychiatric set up but the potential beneficial effect of DBS in addiction was observed from the STN DBS for PD and control

of associated dopamine dysregulation syndrome (DDS). [94] DDS is characterized by neuropsychiatric disturbances such as a condition characterized by neuropsychiatric disturbances such as psychosis, pathological gambling, hypersexuality, mood swings, and compulsive dopamine replacement–seeking behavior. [95] Role of dopaminergic pathway and modulation with STN as well the understanding of the neural circuitry led to interest in exploring DBS in addiction.

DBS target for addiction

Among the potential targets, NAc appears to be the most studied and promising clinical DBS target in addiction [96-100]. This was further supported by the observation that NAc DBS performed for OCD in a patient resulted in unintended but unaided alleviation of the patient's comorbid alcohol dependence, which was independent and not associated with any improvement in the patient's primary condition [101]. Subsequently authors reviewed 10 patients who underwent NAc DBS for psychiatric indication, such as Tourette's syndrome (TS), obsessive-compulsive disorders (OCD) or anxiety disorders (AD), and three patients could achieve cessation of cigarette smoking [102]. Muller *et al* reported bilateral NAc DBS targeting specifically treating addiction in three patients with chronic resistant alcoholism in an open label study [103]. Two patients could achieve abstinence while substantial reduction was seen in one patient. They subsequently reported a long-term outcome of DBS in alcohol addiction in five patients. Two patients achieved abstinent for many years while marked reduction of alcohol consumption was seen in other three patients at a follow up extending up to 8 years [104]. These encouraging results led to exploring NAc DBS in more rigorous way. A double-blinded trial of NAc DBS for cocaine addiction was initiated, where one patient received bilateral NAc DBS [105]. The study was designed to assess the NAc DBS in different phases (single blinded/double blinded/contentious stimulation). Although there was an objective decline in the cocaine craving but there were no major differences between the "off" and "on '' stimulation state at 2.5-years. In one of the studies with customed DBS lead implanted through anterior limb of internal capsule (ALIC) into NAc in eight patients with a minimum follow up of 2 years [106], investigators reported that five patients could achieve abstinence for more than three years. Two patients relapsed after six months of abstinence and one patient lost to follow-up at three months. Degree of cravings for drug use after DBS therapy was also reduced, if the patients continued to remain abstinent. Additionally, NAc/ ALIC DBS not only improved craving, quality of life and alleviated psychiatric symptoms but was also associated with the objective changes in the neuroimaging. Brain regions associated with addiction had increased glucose metabolism. [106] Not only there are clinical evidence of the positive outcome and imaging correlative finding of DBS NAc in addiction but also there are some electrophysiological changes with active DBS in addiction. Concurrent EEG changes were reported in a abstinent patient of chronic heroin addiction with effective DBS contact stimulation. [107] Various small series and case reports have been encouraging and were reported decrease in drug use [108-111].

In a phase I study, six patients underwent bilateral NAc DBS for severe, refractory alcohol use disorder (AUD). [112] All patients had reduction in craving with a significant reduction in alcohol consumption, alcohol-related compulsivity, and anxiety at 12 months. Reduced NAc metabolism by 6 months was noted on FDG-PET, which correlated with improvements in compulsive drinking behaviors. Recently, investigators at WVU Rockefeller Neuroscience Institute reported the outcomes of National Institute of Drug Abuse (NIDA) sponsored open-label, safety and feasibility clinical trial of DBS for treatment refractory opioid use disorder (OUD) [113]. Four patients with refractory OUD with other co-occurring non-opioid SUDs underwent NAc/VC DBS. Two participants had sustained complete substance abstinence while one participant experienced relapse a bit at a diminished frequency and severity [113]. The DBS system, however, was explanted in one participant due to noncompliance. Participants with successful abstinence demonstrated increased glucose metabolism in the frontal regions on FDG-PET neuroimaging, which again supports the biological effect of DBS and modulation of the neural network.

Evidence

Open label observational studies and some limited controlled studies suggest promising role of DBS in addiction, however, rigorous long-term larger studies are lacking.

Current status and future direction

The results of DBS in addiction are encouraging, but a long term-controlled study on a larger patient population is needed. Currently DBS for addiction is investigational and should only be done under research study. It is also paramount important that the psychosocial status and challenges of this unique patient population need to be considered in future studies. Identifying ideal candidate and individualized targeting could help this patient population but need further study.

Other Indications

AUTISM

Sturm *et al*., 2012 Was the first to apply DBS to a patient with Kanner's autism and life-threatening self-injurious behavior (SIB). [114] The target chosen was the basolateral nucleus of the amygdale (BLn) of a 13-year-old boy. The amygdala was chosen -because of its established role in rage, social processing, and fear (mental abilities that are thought to be impaired in autism). After 24 months, SIB and core symptoms of autism spectrum in emotional, social, and cognitive domains improved, (although the scores relied on subjective day-to-day reports by the boy's parents).

Segar *et al* (2015) Mentioned the beneficial effects of BLn DBS for a 24-year-old patient with severe autism and Kleefstra syndrome, a rare genetic condition with TS and OCD- like symptoms. At three years follow up - sustained improvement was noticed in coprolalia and also her TS and OCD-like symptoms. [115] Stocco and Baizabal-Carvallo (2014) operated upon two patients two patients with severe stereotypies. A 19-year-old woman who underwent DBS at the GPi. At 13 months post-DBS, her score on the Hopkins motor stereotypy rating scale (JHMRS) decreased by 91.3% (from 46 to 4). Another patient was a 18-year old who underwent DBS of both the ALIC and GPi; however, at 6 months post-surgery, no significant response was noticed. [116]

Summary: Marini *et al* in 2023 in their metanalysis of 16 patients said that while at present it is too early to draw conclusion with the limited data, some patients with ASD (autism spectrum disorder) may benefit mainly to treat the comorbid conditions. [117] While DBS of the amygdala may be more effective for ASD patients with predominantly social dysfunctioning while ASD patients with compulsive behaviors or stereotypies might benefit more from stimulation of striatal areas.

SCHIZOPHRENIA

In animal models, DBS of the NAc or mPFC improved schizophrenia-like deficits in rats, such as impaired sensorimotor gating and attentional selectivity (Bikovsky *et al*., 2016). [118] The first medical application of DBS in an experimental setting was in a patient with schizophrenia (Heath *et al*., 1955). For over 50 years, no further research was conducted. With increasing knowledge of heterogeneous dysfunctions in brain networks attributed to schizophrenia, DBS targeted at these networks is reappearing as a treatment option. High-frequency DBS in the NAc is thought to stabilize dopamine transmission in the midbrain, which may control symptoms of schizophrenia.

While very few patients have been operated Worldwide, Corripio *et al* performed a clinical trial on treatment resistant schizophrenia in 8 patients. They targeted the NAcc and Subgenual ACC as the targets. They found that 4/7 patients met the symptomatic improvement criteria and they concluded that DBS may have therapeutic effects in a carefully selected cohort of patients. [119]

Anxiety disorders and Post traumatic stress disorders (PTSD)

In animal studies, DBS of the dorsomedial VS (VC/VS homologue of rats) enhanced fear extinction recall relative to sham stimulation. There have been a few studies which have reported reduction of anxiety in most patients treated with DBS for OCD. While in PTSD, over-activity in the amygdala- hippocampus axis, may explain excessive autonomic fear responses (Taghva *et al*., 2013). [120] Ventro-medial PFC (vmPFC), responsible for inhibiting the amygdala, is generally under-active in PTSD DBS of the basolateral nucleus of the amygdala (BLn), the site of the amygdala that mediates extinction learning, may reduce the functional output of the amygdala and thereby compensate for ineffective vmPFC control. Langevin *et al* (2015) reported a case who underwent BLn (basolateral nucleus of amygdala) DBS in treatment- refractory PTSD. [121] At 8

months of treatment there was a 37,8% reduction on the Clinician-Administered PTSD Scale (CAPS Currently there is very little evidence for the use of DBS in the treatment of anxiety disorders. [122] "Recently, 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 in a single patient. [123]

Summary and Conclusions

As has been described above the advent of DBS has stimulated a keen interest in surgery for functional disorders. While still in its infancy, the future is promising and more trials are underway in various centers for various pathologies. However, a word of caution is necessary to avoid the excesses of the past and take the best steps to provide relief to the suffering. It is also of paramount importance to have rigorous ethical oversight of clinical research in exploring innovative treatments in these vulnerable patient population.

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Conflicts of interest
There are no conflicts of interest.

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