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Deep brain stimulation for psychiatric disorders: A review

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ABSTRACT

Deep Brain Stimulation (DBS) is a neurosurgical procedure via the placement of neurostimulator, which is a medical device also known as brain pacemaker. The electrical impulses, which are sent to s pecific targets of brain through implanted electrodes, used in the treatment of some neurological and psychiatric disorders. While the mechanisms of action of DBS on the physiology on brain cells and neurotransmitters are controversial, it is well known that high-frequency electrical impulses into specific brain areas can diminish certain symptoms of some neurological and psychiatric disorders. DBS is already approved as a treatment for several neurological disorders by the Food and Drug Administration (FDA). It is approved as a treatment for essential tremor in 1997 and Parkinson's disease since 2002, for dystonia in 2003 and for epilepsy in 2018. There are also variety uses of DBS in psychiatric disorders with resistance to treatment, such as obsessive compulsive disorder, Tourette's syndrome, major depressive disorder, post-traumatic stress disorder, appetite disorders, alcohol and substance use disorders and also schizophrenia. This article outlines using of deep brain stimulation as a treatment method for psychiatric disorders which are resistant to medical treatments and psychotherapies, as well as the appropriate anatomical targets and the possible mechanism of actions.

Key words: Deep brain stimulation (DBS), psychiatric disorders, resistant, treatment.

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Introduction

The development of modern deep brain stimulation (DBS) begins with the investigations of the treatment choices for Parkinson's disease, in late 1980s [1]The discovery of the beneficial effects of electrical stimulation to basal nuclei on the improvement of the Parkinson's disease symptoms can be accepted as landmark for DBS application areas. Subsequently, some other neurological diseases including dystonia, essential tremor, and epilepsy were begun to treat via DBS. In the course of time, DBS has also been begun to treat psychiatric disorders with resistance to psychopharmacology and psychotherapy. Obsessive and compulsive disorder is the first psychiatric indication for DBS, approved by FDA. Clinical outcomes of psychiatric improvement following DBS in obsessive-compulsive disorder (OCD) and the developments in neuroimaging studies opened up new frontiers for other resistant psychiatric diseases. In the length of time, uses of DBS have begun to include other psychiatric disorders, such as Tourette's syndrome, major depressive disorder, post-traumatic stress disorder, appetite disorders, alcohol and substance use disorders and schizophrenia.

While the exact mechanism of action of DBS is not well known yet, there are some hypotheses

which try to explain the mechanisms [2,3,4,5]. One of the most considered hypotheses is the blockade of the depolarization and consequently blockage of neuronal output by direct effect of electrical currents. The other hypothesis is the synaptic inhibition of the neurons which are near the stimulating neurons, via the activation of inhibitory axon terminals with synaptic connections to neurons near the stimulating electrode. There is another hypothesis about desynchronization of abnormal oscillations of neurons near to the electrodes. Antidromic activation of the neurons near the electrodes is also a considered hypothesis.

DBS is a non-destructive procedure and this provides significant benefits such as being adjustable and largely reversible [6]. However, since it is a neurosurgical procedure, it may lead to some postoperative complications. Intracerebral hemorrhage is one of the most significant early postoperative complications and the risk is approximately 1%-%3 per lead [7]. Central nervous system infection is another significant early postoperative complication and the risk is around 1%-9% [8].

Ischemic stroke (1%), seizure (0-3%), and postoperative confusion (21%) are other possible complications [9]. Since DBS is an invasive surgical procedure and it can lead to such complications, it must be thought in psychiatric diseases for only resistant conditions. Therefore, DBS is thought as a treatment choice in psychiatry only when obsessive-compulsive disorder, Tourette's syndrome, major depressive disorder, post-traumatic stress disorder, appetite disorders, alcohol and substance use disorders and schizophrenia are severe, intractable and resistant to maximal psychotherapy and several psychotherapies.

Obsessive-Compulsive Disorder

Obsessive-Compulsive Disorder (OCD) is one of the most common psychiatric illnesses, affecting approximately 2–3% of the general population [10]. About 10% of the patients are accepted as treatment-refractory, since they have still intractable symptoms despite of proper pharmacological and psychotherapeutic treatments. [11] For some of these patients, deep brain stimulation offers an appropriate treatment choice and OCD is the first psychiatric indication for applying of DBS, approved by FDA in 2009 [12]. Therefore there are several case reports and trials about using of DBS to treat OCD. Clinical outcomes of psychiatric improvement following DBS in Obsessive-Compulsive Disorder (OCD) has opened up new frontiers for other treatment-resistant psychiatric diseases.

Since OCD is associated with the abnormalities of corticobasal nuclei networks, there are several targets of DBS for OCD [13]. Some targets are more effective since they have ability to capture prefrontal, anterior cingulate and basal nuclei connections of limbic system, including anterior limb of internal capsule (ALIC) which modulates anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) connections, medial subthalamic nucleus which modulates the OFC/ACC hyperdirect pathway and the subthalamic nucleus–ventral pallidal loop, ventral striatum which modulates reward system, and midbrain target which modulates the ascending ventral tegmental area fibers[13]. The studies demonstrated that there had been no significant difference in clinical outcomes between these targets [13,14].

In a meta-analysis study which was performed in 2015, thirty-one studies containing 116 subjects were addressed. For 83 subjects, DBS was applied to striatal areas, including anterior limb of the internal capsule, ventral capsule and

ventral striatum, nucleus accumbens and ventral caudate. For 27 subjects, DBS was applied to subthalamic nucleus. And for 6 subjects, DBS was applied to inferior thalamic peduncle. The findings of the study expressed that the reduction in global percentage of Yale-Brown Obsessive Compulsive Scale had been estimated at 45.1% and global percentage of responders at 60.0% [1].

In another prospective observational study, DBS was applied to bed nucleus of the stria terminalis/anterior limb of the internal capsule of six patients suffering from severe to extreme treatment resistant OCD. They were followed for four to eight years and the results demonstrated that four of six patients with treatment resistant OCD had shown a permanent improvement after DBS to ALIC [15].

Treatment Resistant Depression (TRD)

Despite of maximal medical and psychiatric therapy for long years, approximately 20% of depression patients continue to present symptoms [7]. For these group of patients, especially who still have had multiple episodes of major depression for long years with Hamilton Depression Rating Scale between 25-40 despite they were applied all other treatment choices including maximal pharmacotherapy and cognitive-behavioral therapy, DBS seems to be an effective choice [7] .There has been two beneficial guides to select the targets for DBS in Treatment Resistant Depression. One is clinical outcomes of psychiatric improvement following DBS in Obsessive-Compulsive Disorder, and the other one is neuroimaging studies [16,17]. The neuroimaging studies and both open-label and randomized controlled trials to date demonstrate that Subcallosaal Cingulate Cortex, Nucleus accumbens, Ventral Capsule and Ventral Stiratum and Medial Forebrain Bundle seemed to be main targets for DBS in treatment resistant depression. The most common investigations have been focused on Subcallosal Cingulate Cortex (SCC), also referred to as Brodmann area 25 (BA25) or subgenual cingulate (Cg25). It has multiple connections including nucleus accumbens, hypothalamus and brain stem. Activity increase in SCC has been thought to lead to depressive symptoms, and a decline in increased activity of this region has been linked to normalization of the activates of other brain regions which are connected to SCC, including nucleus accumbens, hypothalamus and brain stem. These connections of SCC allows for clinical response to DBS, including normalization of lack of interest, anhedonia, appetite problems, circadian and sleep disturbances, and abnormal stress responds and cortisol metabolism [18].One of the open label and single blind trials, which was performed by Holtzheimer et al. in 2012 with 17 participants, were reported with 65% response and 41% remission [7]. Another studied region of brain for DBS in TRD is nucleus accumbens, which has been demonstrated as smaller size and decreased activation to reward in severe anhedonia [19]. There are 11 open label case series, which was reported by Bewernick et al in 2012. They conducted 45% response and 9% remission one to two year follow up after DBS procedure [20]. Ventral Capsule/Ventral Striatum (VC/VS) is also an investigated area for DBS in TRD. Activity increase in VC/VS and its connections found positively correlated to higher depression scores in the CES-D score [21]. A randomized, double blind, sham-controlled, multisite study with 30 participants was published by Dougherty et al in 2014, with the result of 23% response and no significant difference between sham & control arms [22]. Another target for DBS in TRD is Medial Forebrain Bundle,

which plays a crucial role in the reward pathway. It has been pre-operatively showed that there was a strong linkage between the active electrode contact and the medial PreFrontal Cortex, by using individual Deterministic Diffusion Tensor Imaging [17]. In 2013, Schlaepfer et al published 7 case series. The results were 86% response and %57 remission rate on the background of 12 to 33 week follow up [23]. Another study about DBS in TRD was published by Fenoy et al. in 2016. The result of the study, which was an opel label trial with 4 participants, was 66% response on the background of 26 weeks [24]

Tourette syndrome (TS)

While there are more than 7 different targets for DBS as a treatment method for Tourette's syndrome (TS), it can be claimed that main targets which have essential roles for treatment of TS by DBS are the centromedian-parafascicular thalamic complex (CM-PF) and the Globus pallidus interna. There are plenty of studies which have been reported about successful treatment of TS with stimulation in the CM-PF and ventral tier of the thalamus [25]. About DBS of Globus pallidus interna to treat severe Tourette's syndrome, largest series reporting a mean decrease in Yale Global Tic Severity Score of 50% were published in 2012[26]. In a recent study which was performed with eight adult patients who were resistant to Tourette's syndrome medically, bilateral electrodes were implanted in the centromedian-parafascicular thalamic complex and the nucleus ventro-oralis internus. On the course of one following year after DBS to these areas of thalamus, it has been reported that tic severity symptoms and comorbidities were diminished and the quality of life improved [27].

Treatment Resistant Schizophrenia

Up to 30 % of Schizophrenia patients are thought to be the resistant to antipsychotic drug treatment, and 60% of these includes resistance to Clozapine [28]. Researchers investigated targeting the nucleus accumbens (NAc), hippocampus, globus pallidum internal segment, mediodorsal thalamus (MD), and medial septal nucleus (MSN) to be able to have a decline in the positive symptoms and improve the negative symptoms of schizophrenia patients with anti-psychotic resistance including Clozapine [29]. The most effective results seemed to be obtained in the studies which targets NAc by DBS. One of the cases is conducted by Corripio et al. NAc of schizophrenia patient was targeted by DBS and it was observed a 62% reduction in positive symptoms and 33% improvement in negative symptoms, following 4 weeks of unilateral left side stimulation[30]. There is also a pilot randomized cross-over clinical trial which investigated the effectiveness of DBS on eight schizophrenia patients with the resistance to anti-psychotic treatment including clozapine. Nucleus accumbens and subgenual anterior cingulate cortex regions of their brains were targeted by DBS. This tiral demonstrated that the placement of the electrodes in nucleus accumbens had more effective results than that in the subgenual anterior cingulate gyrus. Moreover, according to this trial, targeting of nucleus accumbens by DBS seemed to be beneficial on hallucinations and delusions [28].

Post-Traumatic Stress Disorder (PTSD)

The use of DBS to treat PTSD mainly aims to change the activity of the regions distant from the target, via the activation of the neuronal projections [31]. Glutamatergic projections from infralimbic neurons of ventromedial prefrontal cortex to intercalated cells of

amygdala play an essential role in the ceasing Central Amygdala cell activation, consequently leading to fear extinction [32]. Animal models showed that high frequency stimulation of the infralimbic neurons of ventromedial prefrontal cortex caused a decline on firing frequency of BasoLateral Amygdala principal cells, which is thought to be secondary to an increase in intercalated cell stimulation and inhibition of Central Amygdala cell activation [31,32]. A group of mice with poor fear extinction, which were closely similar to a clinical PTSD in humans, were used by .Reznikov et al. and study showed that high frequency stimulation had led to a decrease in fear responses and anxiety behavior, as well as prevented return of PTSD-like symptom [31,33]. There are also some human cases about the using of DBS for the treatment of PTSD. One of these cases is a 48-year old-man with a combat-related PTSD which is resistant to treatment. After his bilateral BasoLateral Amygdala had been applied DBS, he was observed for 8 months and it was reported that his symptoms had diminished 35% without a major adverse event [34].

Appetite Disorders

DBS seems to be an alternative treatment option for Refractory Obesity and Anorexia Nervosa (AN). Studies have demonstrated that central nervous system had had plenty of potential DBS targets for both disorders. The Lateral Hypothalamus, Ventro Medial Hypothalamus and Nucleus accumbens have all been shown to have elements of success as DBS targets in animal models of refractory obesity [35]. DBS targeting bilateral Lateral Hypothalamus was performed by Whiting et al, in order to treat refractory morbid obesity. There was no serious adverse effects; trend toward weight loss in 2/3 patients was found [36]. One of the largest trials about DBS treatment of AN was demonstrated by Lipsman et al. in 2017. DBS of the subcallosal cingulate gyri of 16 patients who had AN disease was performed and the trial showed that the patients had a significant improvement in BMI as well as other psychological result [37].

Alcohol and Substance Use Disorders

While the exact mechanisms of DBS on its clinical effects are unclear, DBS is thought to be able to modulate and manipulate neural circuits in reward pathways, consequently enable to change addictive behaviors [38]. Three alcohol use disorder cases were investigated for the effect of nucleus accumbens stimulation by DBS, and found a decrease in alcohol consumption as well as craving levels. After DBS stimulation, two of three participants remained abstinent, while the third reduced his alcohol consumption considerably, at 1 year follow-up [39]. There are also two studies investigating the use of DBS on cigarette smoking and nicotine-dependence targeting the nucleus accumbens. One is conducted by Kuhn et al, which demonstrated 3/10 patients cessated smoking on the first attempt after surgery, without a relapse for a mean of 28 months conducted a study in nicotine craving and cigarette consumption. Moreover, the remaining seven participants had a significant decrease in cravings and consumption [40]. The other study, which was conducted by Mantione et al, demonstrated that nicotine craving and cigarette consumption had significantly decreased in a participant, who originally treated by DBS for refractory Obsessive-Compulsive Disorder[41].. A longitudinal, crossover case study with a 36-year-old cocaine-dependent male participant showed that craving and consumption of cocaine had

been decreased by active DBS targeting to nucleus accumbens [42]. There are also some case reports which demonstrated that DBS might be a treatment option for Methamphetamine addiction patients [43]. It can be claimed that there are more conducted studies about the effect of active DBS on heroin consumption or craving in heroin-dependent participants, than the other substance use disorder studies. Common results of these studies showed that targeting the nucleus accumbens had demonstrated a significant decrease in cravings and consumption, as well as increase in abstinent participants [44].

Conclusion

Psychiatric disorders can resist despite of psychopharmacology and psychotherapy and therefore seem to be one of the major sources of disability in the world. For the psychiatric disorders which are resistant to non-surgical treatment methods, DBS appears a promising treatment model. Up to date, the most common case reports and trials performing uses of DBS in psychiatric disorders have been conducted about refractory OCD, since it had been the first FDA approved disorder in psychiatry for DBS treatment. It can be accepted as the landmark of using DBS in psychiatry, because several outcomes have been provided from these and they have opened up new frontiers for other treatment-resistant psychiatric diseases. Developments in neuroimaging studies have also helped for using areas of DBS in psychiatry. Intracranial targets detected via the help of the developments in neuroimaging and specific circuits which were crucial for psychiatric conditions could be modulated. While the exact mechanisms of DBS on its clinical effects and its most available anatomical targets for the certain psychiatric diseases are still unclear, there have been plenty of case reports and trials which demonstrate the beneficial effects of DBS in neuropsychiatric disorders. However, it can be still claimed that DBS was a new modality, especially compared to Parkinson disease, essential tremor, dystonia, epilepsy and psychiatric conditions other than OCD. Treatment resistant depressive disorder and Tourette's syndrome can be claimed as relatively more performed psychiatric conditions, although they are behind OCD. What DBS for schizophrenia, PTSD, alcohol and substance use disorders, appetite disorders and other potentially suitable psychiatric conditions need are more trials and more outcomes as well as new developments in neuroimaging which will be able to show the topography of brain and facilitate the placement of electrodes at effective stimulation sites.

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