Investigating Deep Brain Stimulation of the Habenula: A Review of Clinical Studies

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ABSTRACT

Objectives: The aim of this study was to examine the current scientific literature on deep brain stimulation (DBS) targeting the habenula for the treatment of neuropsychiatric disorders including schizophrenia, major depressive disorder, and obsessive-compulsive disorder (OCD).

Materials and Methods: Two authors performed independent data base searches using the PubMed, Cochrane, PsycINFO, and Web of Science search engines. The data bases were searched for the query (“deep brain stimulation” and “habenula”). The inclusion criteria involved screening for human clinical trials written in English and published from 2007 to 2020. From the eligible studies, data were collected on the mean age, sex, number of patients included, and disorder treated. Patient outcomes of each study were summarized.

Results: The search yielded six studies, which included 11 patients in the final analysis. Treated conditions included refractory depression, bipolar disorder, OCD, schizophrenia, and major depressive disorder. Patients with bipolar disorder unmedicated for at least two months had smaller habenula volumes than healthy controls. High-frequency stimulation of the lateral habenula attenuated the rise of serotonin in the dorsal raphe nucleus for treating depression. Bilateral habenula DBS and patient OCD symptoms were reduced and maintained at one-year follow up. Low- and high-frequency stimulation DBS can simulate input paths to the lateral habenula to treat addiction, including cocaine addiction. More data are needed to draw conclusions as to the impact of DBS for schizophrenia and obesity.

Conclusions: The habenula is a novel target that could aid in reducing neuropsychiatric symptoms and should be considered in circuit-specific investigation of neuromodulation for psychiatric disorders. More information needs to be gathered and assessed before this treatment is fully approved for treatment of neuropsychiatric conditions.

Keywords: DBS, habenula, major depressive disorder, obsessive-compulsive disorder, schizophrenia

Conflict of Interest: The authors reported no conflicts of interest.
INTRODUCTION

Deep brain stimulation (DBS) is a neuromodulatory therapy that has demonstrated significant clinical benefits and is currently most often used in the treatment of essential tremor and Parkinson disease.\(^1\) DBS has been studied for a wide variety of neurological and neuropsychiatric diseases, including Alzheimer disease, Tourette syndrome, and obsessive-compulsive disorder (OCD), among many others.\(^2\)-\(^4\) Most recently, concepts behind targeted, circuit-specific neuromodulation to treat psychiatric illness personalized to each patient with multisite stimulation-response mapping have been put forth in an effort to improve and individualize anatomical targeting,\(^1,6\) and we posit that the habenula may play an important role within this investigational paradigm.

The habenula, once considered a component of the “epithalamus,” is defined as a region located in the rostrocaudal segment of the dorsomedial corner of the thalamus.\(^7\) Upon being stained, the habenula can be divided into a medial nucleus that forms a section of the lateral wall of the dorsal recess of the third ventricle and a lateral nucleus that is ventral to the stria medullaris (Fig. 1). The medial habenula provides efferent outputs to the central part of the interpeduncular nucleus and receives afferent inputs from the triangular septum and bed nucleus of the anterior commissure. The lateral habenula (LHb) engages with afferent inputs from the lateral hypothalamus, basal forebrain, and preoptic area. The LHb also has efferents to the rostromedial tegmental nucleus (Fig. 2).\(^8\)

Over the years, several publications have reported that habenular stimulation 1) induces increased serotonin levels in the striatum mediated through the dorsal raphe nucleus (DRN), 2) increases noradrenaline in the hippocampus, medial frontal cortex, and nucleus accumbens, and 3) inhibits dopaminergic neurons in the substantia nigra.\(^9\)-\(^12\) The myriad potential effects associated with stimulation of the habenula prompted investigation into the treatment of a variety of conditions, including bipolar disorder (BD), obesity, depression, schizophrenia, OCD, and addiction.

In this review, the authors provide a comprehensive overview of studies investigating the role of DBS of the habenula. The current analysis aims to synthesize the results of clinical studies and of ongoing trials and to identify areas of research for future focus.

MATERIALS AND METHODS

Literature Search Protocol

The Preferred Reporting Items for Systematic Review Meta-Analyses (PRISMA) guidelines were used to conduct this systematic review. Two authors independently performed data base searches using the PubMed, Cochrane, PsycINFO, and Web of Science search engines. Within each data base search, the query (“deep brain stimulation” and “habenula”) was retrieved. The inclusion criteria involved screening for human clinical trials written in English and published from 2007 to 2020. Of those studies identified by these search criteria, clinical trials were excluded from the analysis if they were suspended, terminated, withdrawn, or had unknown status.

Data Extraction

From the eligible studies, country of clinical trial site, mean age, sex, number of patients included, and disorder treated were collected. General patient outcomes of each study were summarized, including symptom improvement and DBS programming parameters, when available.

Quality Assessment

The quality of available studies was assessed using the Risk Of Bias In Non-randomised Studies - of Interventions assessment for nonrandomized studies and interventions.\(^13\)

RESULTS

A total of 130 studies were identified through searching PubMed, Cochrane, PsycINFO, and Web of Science. Upon duplicate removal, title screening, and abstract screening, the study yielded nine studies for full-text screening. Of these nine, three were discarded after full-text review because of lack of inclusion of patients who underwent DBS specific to the habenula. Finally, six human studies that included 11 patients overall with various disorders who...
Table 1. Characteristics and Findings of Preclinical Studies.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Category</th>
<th>Subject type</th>
<th>Study description</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lax et al, 2013</td>
<td>Imaging</td>
<td>Sprague-Dawley rats</td>
<td>Rats were administered cocaine with jugular vein catheterization, and DBS implants were placed in a subset of rats. Some received DBS; some received sham. Rats self-administering cocaine also were measured with DTI. FG uptake also was measured in rats that underwent cocaine administration.</td>
<td>Reverse correlation was found when measuring FG-labeled LHb neurons with cocaine consumption. DBS reduced drug-seeking behavior for lower-cocaine-administered rats, but not high. Alternating current found reductions in drug-seeking behavior. High cocaine administration showed an increase in FA of the habenula when compared with saline.</td>
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<td>Yang et al, 2008</td>
<td>Immunohistochemistry</td>
<td>Sprague-Dawley rats</td>
<td>Rats with inescapable and unpredictable shocks conjugated cholera toxin with retrograde tracer when injected into the VTA, and 2 to 3 d later, brain slices were prepared, and they were searched for fluorescent cell bodies.</td>
<td>Presynaptic action onto the LHb contributes to learned helplessness model of depression. There was an increase in fluorescence.</td>
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<tr>
<td>Sartorius et al, 2010</td>
<td>Male Wistar rats</td>
<td></td>
<td>Rats with TCA resistance underwent high-frequency DBS (130 Hz; 200 μA; 90 μs).</td>
<td>Phosphorylation status of CaMKIIα/β, GSK3α/β, and AMPK in the IL to be negatively correlated with anti-depressant actions of DBS. CaMKIIα/β, GSK3α/β, and AMPK in the IL also are downregulating.</td>
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<tr>
<td>Schlaepfer and Bewernick, 2013</td>
<td>Sprague-Dawley rats</td>
<td></td>
<td>Rats were administered DBS or sham and brain slices were later analyzed.</td>
<td>In rats with high-frequency stimulation, c-Fos-ir was elevated when compared with sham of the LHb but not medial habenula. Both c-Fos protein expression and the frequency of spontaneous action potential firings, and spontaneous excitatory postsynaptic currents were high in the LHb neurons of ethanol-withdrawn rats. Stimulation reduced long-term intake of ethanol. Low frequency did not alter drinking behavior.</td>
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<tr>
<td>Schneider et al, 2013</td>
<td>Sprague Dawley rats</td>
<td>c-Fos immunohistochemistry and electrophysiological approaches were used to examine the LHb activity in rats that were addicted to ethanol. High-frequency stimulation was used and implanted in the LHb.</td>
<td>Stimulation reduced depression-like behaviors, and mTOR phosphorylation significantly increased excitatory postsynaptic potentials increased in the hippocampus. Frequency and width of spontaneous spikes generated by CA1 pyramidal neurons that contributed to calcium influx through the L-type voltage-dependent calcium channels increased.</td>
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<tr>
<td>Skandalakis et al, 2018</td>
<td>Sprague Dawley rats</td>
<td>DBS to the LHb was applied in a rat model of learned helplessness, and mammalian target of rapamycin phosphorylation was analyzed.</td>
<td>Habenula did not show changes in the medial forebrain bundle in Arc proteins. Mild increases in c-Fos were found in the habenula.</td>
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<tr>
<td>Senova et al, 2019</td>
<td>Wistar rats</td>
<td>Medial forebrain bundle was stimulated in rats, and Arc protein measurements were assessed with immunohistochemistry.</td>
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<tr>
<td>Zhang et al, 2020</td>
<td>Wistar rats</td>
<td>The dorsolateral periaqueductal gray matter was stimulated, and the effect on activation of different brain regions was measured by c-Fos immunohistochemistry on brain slices.</td>
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<tr>
<td>Friedman et al, 2010</td>
<td>Stimulation</td>
<td>Sprague Dawley rats</td>
<td>Electrodes were implanted into the LHb in rats that were trained to self-administer sucrose.</td>
<td>Stimulation reduced sucrose self-administrations. Lesion of the habenula increased sucrose-seeking behavior.</td>
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<thead>
<tr>
<th>Author, year</th>
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<th>Study description</th>
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<tbody>
<tr>
<td>Kaufling et al, 2009</td>
<td>2009 Sprague Dawley rats</td>
<td>LHb neurons were stimulated in anesthetized rats.</td>
<td>HFS of the STN modulated the firing of the LHb neurons. The data identify that the STN impacts on the LHb-DRN pathway. Moreover, this pathway may be part of the circuitry mediating the psychiatric effects of STN stimulation experienced by patients with Parkinson disease.</td>
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<tr>
<td>Tastevin et al, 2019</td>
<td>2019 Wistar rats</td>
<td>Rats were implanted with bilateral LHb DBS electrodes and were assigned to 100 Hz, 5 Hz, or sham (n = 8 per group).</td>
<td>100-Hz frequency stimulation was associated with increased exploratory behavior in the maze. In the swim test, 5-Hz stimulation was associated with decreased latency to and increased duration of immobility, and 100-mHz stimulation increased latency to immobility. Theta band stimulation of the LHb was associated with depressive-like behavior in Wistar rats.</td>
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<td>Meng et al, 2011</td>
<td>2011 Rat</td>
<td>Chronic DBS of the LHb in a rat model of depression, chronic mild stressors for four consecutive weeks. The open field and sucrose consumption tests were used to measure depression.</td>
<td>DBS of the LHb improves depressive-like symptoms in rats. The rats had elevated numbers of crossings and rearing during the open-field test in DBS-treated rats. Norepinephrine, dopamine, and serotonin were increased by DBS of the LHb. Limiting habenular hyperactivity reduces maternal separation depressive-like symptoms.</td>
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<td>Boulos et al, 2017</td>
<td>2017 Viral</td>
<td>Mice</td>
<td>Mice were separated from their parents, and mice with virally expressed inhibitors of the LHb showed fewer depressive symptoms.</td>
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<td>Savitz et al, 2011</td>
<td>Postmortem diencephalic samples</td>
<td>Volumetric analysis in postmortem samples.</td>
<td>Directional asymmetries were present in the volume of the human habenula. The LHb is larger on the left than in both sexes. The medial habenula shows left-right directional bias. Habenular laterality should be used in the context of health and illness. The mammillothalamic tract approximately marks the anterior-posterior coordinate of the anterior pole of the subthalamic nucleus in the anterior commissure-posterior commissure plane.</td>
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<tr>
<td>Hikosaka, 2010</td>
<td>Postmortem diencephalic samples</td>
<td>A total of 12 formalin-fixed brains were dissected to expose the medial diencephalic surface. Measurements were taken of the mammillothalamic and habenulo-interpeduncular tracts.</td>
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AMPK, adenosine monophosphate-activated protein kinase; DTI, diffusion tensor imaging; FA, fractional anisotropy; FG, fluorogold; HFS, high frequency stimulation; IL, infralimbic cortex; mTOR, mammalian target of rapamycin; STN, subthalamic nucleus; TCA, tricyclic antidepressant.
underwent DBS of the habenula were identified (Table 1). A PRISMA flow diagram is displayed in Figure 3.

As reflected in Table 1, a total of four studies had authors from multiple countries, whereas one study originated from China, and another from Germany. The trials took place from 2010 to 2020, with four occurring in or after 2019. Four studies targeted the habenula in general, whereas the remaining four targeted the LHb specifically. The four studies that targeted the habenula in general examined a variety of neuropsychiatric indications, including refractory depression, BD, OCD, and schizophrenia. One study investigated DBS of the habenula for the treatment of major depressive disorder (MDD). Details of patient outcomes are displayed in Table 2.

Quality assessment revealed one study with a high risk of bias because for a preintervention factor, no psychiatric history or complete history of psychiatric medications was provided. These could potentially be confounding factors of results. In addition, this was based on preliminary data only, with only one-month follow-up lowering postintervention quality scores. Five studies were rated as having a moderate risk of bias. In these studies, complete, detailed patient histories were provided. However, there was no way to control for bias in reporting results after intervention. It is possible that other negative or null outcomes were present but not published or reported in publications, creating a potential implication of postintervention bias.

DISCUSSION

The habenula is a bilateral nucleus and is located next to the dorsomedial thalamus where the striatal and limbic inputs meet, and it is thought to play a critical role in the forebrain control of serotonin and dopamine from the midbrain. In this review, the authors investigate the results of clinical studies on the use of DBS for neuromodulation of the habenula for a variety of neuropsychiatric indications.

Bipolar Disorder

Lithium/divalproex has been shown to affect the habenula size in patients experiencing BD. From a magnetic resonance imaging analysis of the habenula volume in patients with BD (74 controls, 15 medicated—lithium or divalproex, 22 unmedicated), patients with BD unmedicated for at least two months had smaller habenula...
<table>
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<tr>
<th>Author, year</th>
<th>Age</th>
<th>Procedure</th>
<th>Patients included</th>
<th>Disorder treated</th>
<th>Findings</th>
<th>Risk of bias</th>
</tr>
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<tbody>
<tr>
<td>Sartorius et al, 2010</td>
<td>64</td>
<td>Bilateral DBS</td>
<td>1</td>
<td>MDD</td>
<td>DBS resulted in a sustained remission of depressive symptoms in a patient who was resistant to treatment for 9 y and suffered from MDD for 46 y</td>
<td>Moderate</td>
</tr>
<tr>
<td>Kiening and Sartorius, 2013</td>
<td>N/A</td>
<td>Bilateral DBS</td>
<td>1</td>
<td>MDD</td>
<td>Patient improved more than 50% after 12 wk of DBS on a depressive symptom scale but suffered from a comparable relapse during a pacemaker exchange for infection</td>
<td>Moderate</td>
</tr>
<tr>
<td>Zhang et al, 2019</td>
<td>41</td>
<td>DBS</td>
<td>1</td>
<td>BD: depressive phase</td>
<td>Low-frequency (10-Hz) DBS was more effective than high-frequency (100-Hz) DBS at improving energy, sleep, quality of life, and physical, social, and occupational functioning. The authors commented on depression-phase symptoms only and not on manic symptoms.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Zhang et al, 2020</td>
<td>N/A</td>
<td>Bilateral DBS</td>
<td>6</td>
<td>5 BD: depressive phase: 1 unipolar MDD</td>
<td>HAM-D and MADRS scores showed significant declines from 24 and 31 to 14 and 17.3, respectively. PSQI mean scores decreased from 16.3 to 9.7. SDS mean scores also significantly decreased. This article commented on depression-phase symptoms only and not on manic-phase symptoms.</td>
<td>High</td>
</tr>
<tr>
<td>Zhang et al, 2020</td>
<td>30</td>
<td>Bilateral DBS</td>
<td>1</td>
<td>OCD</td>
<td>The severity of the patient’s OCD symptoms was reduced by 35% at 1-mo follow-up and was maintained at 12-mo follow-up as measured by the YBOCS-II</td>
<td>Moderate</td>
</tr>
<tr>
<td>Wang et al, 2020</td>
<td>26, 21</td>
<td>Bilateral DBS</td>
<td>2</td>
<td>Schizophrenia</td>
<td>Both patients experienced improvements in clinical symptoms during the first 6 mo of treatment. However, only 1 patient retained the clinical benefits at 12-mo follow-up with clinically significant improvements in the PANSS positive symptom score by 53.8%, negative symptom score by 31.7%, general psychopathology score by 20.8%, and total score by 31.7%. The other patient began to decline at 7-mo follow-up and had to be hospitalized at 10-mo follow-up.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Fiorillo et al, 2003</td>
<td>Mean age, 31 (range, 21–46)</td>
<td>Bilateral DBS</td>
<td>4</td>
<td>2 BD: 2 schizophrenia</td>
<td>Transient effects were found in 54% of patients of all patients who underwent stimulation. Of the total number of transient effects, patients had numbness (67%), heart rate changes (36%), pain (17%), and involuntary movements (8%) that were found to increase with voltage level. This article did not comment on improvement of depression phase or manic phase symptoms.</td>
<td>Moderate</td>
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N/A, not applicable.
volumes than healthy controls, whereas the medicated group with BD did not differ in habenula volume. Although an N-methyl-D-aspartate (NMDA) receptor signaling pathway has been posited as a potential culprit, the exact cause of the reduced habenula volume in unmedicated patients with BD remains unknown.

In terms of DBS, Zhang et al. in 2019 described the first case of refractory BD that was successfully managed with DBS of the habenula. Zhang et al. presented the case of a 41-year-old man who was diagnosed with bipolar I disorder and who had experienced manic and depressive episodes for more than 21 years. However, throughout the last four years, the patient’s BD symptoms could not be managed with conventional treatment. As a result, the patient was treated with habenula DBS at high frequency and ultimately displayed significant improvement at three-month follow-up, with a 46% decreased depression score. However, his clinical state later worsened, and at seven-month follow-up, DBS was turned off, which resulted in clinical improvement. One month later, DBS of the habenula was initiated at a lower frequency, which resulted in improved energy levels, sleep, and quality of life, and the patient continues to do well. These data suggest that low-frequency DBS of the habenula may be a useful therapy for chronic BD that is resistant to medical management, although long-term data have yet to be published.

In 2020, Zhang et al. presented an abstract that discussed five patients who had BD and were treated with DBS of the bilateral habenula. At one-month follow-up, the Hamilton Depression Rating Scale (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS) decreased significantly from 24 and 31 to 14 and 17.3, respectively. In addition, the Pittsburgh Sleep Quality Index (PSQI) significantly decreased from 16.3 to 9.7, and the Sheehan Disability Scale (SDS) also significantly decreased.

Depression

In 2007, Sartorius et al. proposed the LHb as a possible DBS target for depression and hypothesized that an overactivation of the habenula in depression leads to the downregulation of the serotonergic, noradrenergic, and dopaminergic pathways. High-frequency stimulation of the LHb was found to attenuate the rise of serotonin in the DRN, which led to higher serotonin levels in projection areas. DBS of the LHb in depressed rats showed increased concentrations of monoamines and significantly improved depressive-like symptoms. Furthermore, lesioning of the LHb in depressed rats resulted in decreased behavioral measures of depression.

In 2010, a case of bilateral habenula DBS was reported in a 64-year-old woman who suffered from MDD with a HAM-D rating of 45 (Hamilton Depression Rating Scale - 21) for 46 years and who was therapy-resistant to medication and electroconvulsive therapy for the last nine years. When programming this patient, stimulation at 5 V showed no improvement; however, full and stable remission (a HAM-D score of 3) was achieved when stimulation was increased to 10.5 V. The patient was reported to have a relapse after a bicycle accident and then regained effect with a HAM-D score of 0 after 12 weeks of stimulation. No adverse effects were reported, and normal cognitive functioning was verified by post-operative neuropsychologic testing. [18F] fluorodeoxyglucose-positron emission tomography during the final remission phase demonstrated a localized metabolic increase at the stimulation sites but no metabolic change in the LHb.

In 2013, Kiening et al. reported results on the second patient with bilateral LHb DBS for depression, who improved more than 50% after 12 weeks of DBS on a depressive symptom scale but suffered from a comparable relapse one week after a pacemaker exchange. They report similar experiences of rapid relapses and slow remission periods in patients treated with DBS of the subgenual cingulate cortex, which, they posit, is a function of slow changes in the neuroplasticity of these circuits. The authors note that the electrode trajectory should target the lateral habenular complex, which includes the stria medullaris apart from the LHB, to ensure that this tract also is stimulated. Long-term outcome data have yet to be published for these two case reports, and whether the habenula is an effective lasting target for DBS of patients with treatment-refractory depression remains inconclusive.

Obsessive-Compulsive Disorder

Although the pathophysiology of OCD remains incompletely understood, preclinical and clinical studies have discovered abnormal functioning in medial and orbital frontal-basal ganglia-thalamic circuits comprising dopamine and serotonin. Because the LHb is believed to play a central role in negative reward processing through dopaminergic communication with the basal ganglia, it has been studied as a potential treatment target for OCD.

In 2020, Zhang et al. published the first and only case report of a 30-year-old man with persistent and disabling OCD symptoms refractory to psychologic and pharmacologic treatments and to surgical interventions involving both capsulotomy and cingulotomy. The patient underwent bilateral HB DBS, and the severity of the patient’s OCD symptoms was reduced by 35% at one-month follow-up and was maintained at 12-month follow-up as measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS-II).

Schizophrenia

Schizophrenia, although not completely elucidated in terms of pathophysiology, is associated with dysfunction of the phasic dopamine release. The habenula inhibits the substantia nigra pars compacta and the ventral tegmental area (VTA), which play a central role in dopaminergic transmission. Anatomical modification of the habenula has been linked to schizophrenia because early computed tomographic study on postmortem human brain slices showed increased habenular calcification. In addition, postmortem immunocytochemistry demonstrated reduced capillary density in the HB of patients with schizophrenia and reduced density of neuron expressing ABCB1 (adenosine triphosphate-binding cassette transporter), whose malfunction also has been associated with schizophrenia.

In 2020, Wang et al. published their early experience with bilateral HB DBS in the clinical management of two male patients with severe, chronic, and treatment-resistant schizophrenia. The primary clinical outcome was the severity of the patients’ positive and negative symptoms, as assessed using the Positive and Negative Syndrome Scale (PANSS) total and scale scores. Although both patients experienced improvements in clinical symptoms during the first six months of treatment, only one patient retained the clinical benefits and reached a favorable outcome at 12-month follow-up with clinically significant improvements in the PANSS positive symptom score by 53.8%, negative symptom score by 31.7%, general psychopathology score by 20.8%, and total score by 31.7%. The other patient began to deteriorate at seven-month follow-up and had to be hospitalized at ten-month follow-up and
could no longer participate in the study. Although no convincing conclusions can be drawn from such a small study, the patient who achieved a favorable outcome presented with less severe symptoms and had a shorter duration of illness before initiating DBS therapy than the patient with an unfavorable outcome.31

Addiction
Substance abuse is a chronic disease with relapse rates that range between 56.8% and 81.8%, with significant public health implications and a paucity of approved therapies, particularly for stimulants.44,45 Because of its critical forebrain connections, the habenula has been investigated in its potential role to decrease addictive behavior.

Friedman et al22 used both high and low DBS frequencies in male Sprague Dawley rats. An electrode was implanted into the LHB of the rats, and the rats were trained to self-administer 0.25 to 1 mg/kg of cocaine for 21 days.47 Rats were treated with DBS while being allowed to have access to cocaine through self-administration.22 Friedman et al22 found a decrease in drug-seeking behavior during cocaine self-administration and extinction with normalization of the increases in NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors that were increased with cocaine administration. Interestingly, no significant effects in cocaine self-administration were found when only high-frequency stimulation was used (100 Hz).22 However, lower-frequency stimulation (10 Hz) increased the self-administration presses of cocaine.22 Friedman et al22 later discovered that a combination of alternating high- and low-frequency stimulation was able to reduce the lever presses for cocaine self-administration in the rats optimally. This was believed to occur because high-frequency input from the globus pallidus internus activates the LHB after unpleasant events.46 In contrast, low-frequency input from other brain circuits can inhibit the LHB after positive reward expectations.35 As a result, the use of low- and high-frequency stimulation DBS can simulate these input paths to the LHB. Therefore, a reward is expected because of the low-frequency DBS, but the expectation is terminated with the high-frequency DBS.

Lax et al14 found that cocaine self-administration had a dose-dependent reduction in connection between the LHB and the midbrain in male Sprague Dawley rats. In particular, high-dose cocaine led to fasciculus retroflexus degeneration, which is the main LHB efferent fiber.14 Furthermore, this shows that a reduced LHB inhibition of the mesolimbic system may be able to terminate the therapeutic effect that DBS of the LHB has on the maintenance, extinction, and relapse stages of addiction.14 As a result, the deterioration of the fasciculus retroflexus may have led to the nonresponse in rats that were able to self-administer cocaine in large doses (1.5 mg/kg).14 Taken together, the animal studies have demonstrated that DBS of the habenula can lessen the severity of cocaine addiction in rats. These results from animals suggest therapeutic potential of DBS in humans.

Obesity
In rodents, the medial habenula has been linked to obesity through the mechanism of overeating.47,48 The µ-opioid receptors were shown to preferentially bind to the medial habenula within rats with high weight gain.47 In terms of the LHB, glutamate decarboxylase 2 expression in mice was found to mark excitory from LHB neurons that lead to the raphe and pontine tegumentum. This finding further supports the role of the LHB in the reward mechanism.49 In addition, mouse models have indicated that a circuit between the hypothalamus and LHB has been implicated in the control of aversion50 by means of the transformation of neural stimuli into salient punishment-predictive cues.51 Projections of glutamatergic neurons from the lateral hypothalamic area to the LHB negatively regulate the consumption of palatable food.52 Accordingly, future clinical trials examining the use of DBS for obesity may target the habenula. However, it is important to note that further well-designed animal studies are required to supplement the existing base of evidence before this occurs in humans.

Limitations
Because of the very limited number of studies and the breadth of neuropsychiatric indications, reported outcomes are difficult to analyze and compare. Publication bias is of concern, given many of the included studies were case reports, potentially masking evidence against the habenula as a DBS therapeutic target. Because of the size and midline location of the habenula, it is difficult to target; thus, DBS will be more susceptible to imprecision. Surrounding structures may be stimulated instead, the closest of which is the mediodorsal nucleus of the thalamus.7 Statistically significant reductions in the volume of this structure have been associated with schizophrenia.53

CONCLUSIONS
The habenula is a novel target that could potentially aid in reducing neuropsychiatric symptoms, and further studies are indicated to better elucidate its role in treating refractory neuropsychiatric diseases. Existing anatomical and clinical data, however, suggest that the LHB can be considered in the investigation in select patients with refractory neuropsychiatric diseases, particularly in the burgeoning era of individual, circuit-specific DBS targeting in psychiatry.

Authorship Statements
Mickey E. Abraham was responsible for the study conception, data acquisition, analysis, interpretation, drafting the work, revising the work, and approving the final version of the work. Vera Ong was responsible for data acquisition, analysis, interpretation, drafting the work, revising the work, and approving the final version of the work. Nolan J. Brown was responsible for the study analysis, interpretation, drafting the work, revising the work, and approving the final version of the work. Elliot H. Choi was responsible for acquisition, analysis, revising the work, and approving the final version of the work. Nathan A. Shlobin was responsible for acquisition, analysis, revising the work, and approving the final version of the work. Shen Shahrestani was responsible for acquisition, analysis, revising the work, and approving the final version of the work. Alexander S. Himstead was responsible for acquisition, analysis, revising the work, and approving the final version of the work. Neal Patel was responsible for analysis, revising the work, and approving the final version of the work. Julian Gendreau was responsible for analysis, revising the work, and approving the final version of the work.
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How to Cite This Article

REFERENCES

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COMMENTS

There is much to be learned in the field of psychiatric neurosurgery—despite more than a hundred years of clinical experience, we still cannot figure out best surgical indications, we do not know appropriate surgical targets, and we do not possess reliable, safe, and effective means of controlling the symptoms or normalizing the pathological phenomena. In this regard, it becomes important to collect multiple anecdotal reports, summarize pros and cons for specific individual details, analyze unique aspects noted by different authors, and come up with potential directions for future research, especially when the subject of analysis is a very rarely used cerebral structure that is intricately involved in normal and pathological circuitry. I happen to share the authors’ enthusiasm about the potential role of the habenula in future neurosurgical interventions for a variety of psychiatric and behavioral disorders and look forward to seeing more clinical and laboratory research aimed at this promising target.

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The authors have done a systematic review of the literature on habenular nucleus DBS with regard to the clinical evidence accumulated thus far on the treatments of schizophrenia, depression, OCD, addiction, and obesity. Based on their search, which encompassed articles from 2007 to 2020, they found six studies (11 patients) of sufficient quality to be included in their review. Their conclusions seem warranted, but modest, given the small number of studies and patients included in these studies. This is a scholarly effort which may spur further thinking and studies on this previously underexplored target for DBS.

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