Deep brain stimulation for appetite disorders: a review

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The mechanisms of appetite disorders, such as refractory obesity and anorexia nervosa, have been vigorously studied over the last century, and these studies have shown that the central nervous system has significant involvement with, and responsibility for, the pathology associated with these diseases. Because deep brain stimulation has been shown to be a safe, efficacious, and adjustable treatment modality for a variety of other neurological disorders, it has also been studied as a possible treatment for appetite disorders. In studies of refractory obesity in animal models, the ventromedial hypothalamus, the lateral hypothalamus, and the nucleus accumbens have all demonstrated elements of success as deep brain stimulation targets. Multiple targets for deep brain stimulation have been proposed for anorexia nervosa, with research predominantly focusing on the subcallosal cingulate, the nucleus accumbens, and the stria terminalis and medial forebrain bundle. Human deep brain stimulation studies that focus specifically on refractory obesity and anorexia nervosa have been performed but with limited numbers of patients. In these studies, the target for refractory obesity has been the lateral hypothalamus, ventromedial hypothalamus, and nucleus accumbens, and the target for anorexia nervosa has been the subcallosal cingulate. These studies have shown promising findings, but further research is needed to elucidate the long-term efficacy of deep brain stimulation for the treatment of appetite disorders.

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Deep Brain Stimulation for Obesity

The prevalence of obesity across all age spectrums has greatly increased over the last few decades in both the developed and the developing world. 43, 44, 57 Obesity is defined as a body mass index (BMI) greater than or equal to 30, and morbid obesity is defined as a BMI greater than or equal to 40 or greater than 35 with comorbidities. In the United States, the prevalence of obesity in adults is 35.0% in men and 40.4% in women, with 7.7% of adults meeting the criteria for morbid obesity. 16 Morbid obesity is associated with a significantly impaired quality of life, multiple comorbidities, and premature death. 16, 43 Nonsurgical treatments for morbid obesity are associated with exceedingly high failure rates, while successful surgical options, such as gastric bypass and sleeve gastrectomy, come with significant morbidity and demonstrate considerable relapse and failure rates. 7, 9, 18 Because of its safety profile and adjustability, DBS has emerged as a potential intervention for morbid obesity.

Physiology and Targets

Obesity is the result of an incredibly complex interplay among environmental, genetic, homeostatic, and hedonic factors. Ultimately, obesity is a problem of energy...

ABBREVIATIONS AN = anorexia nervosa; BMI = body mass index; DBS = deep brain stimulation; fMRI = functional MRI; LH = lateral hypothalamus; MDD = major depressive disorder; NAc = nucleus accumbens; OCD = obsessive-compulsive disorder; VMH = ventromedial hypothalamus.


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imbalance, with a net positive energy balance over time. Much of the control over the process of balancing energy originates within the central nervous system. Numerous DBS targets for obesity have been proposed; however, this review focuses on the 3 targets that have emerged as the most promising and that are the most studied: the lateral hypothalamus (LH), the ventromedial hypothalamus (VMH), and the nucleus accumbens (NAc).

Lateral Hypothalamus

The LH is considered to be a small (6 × 6 × 3.5–mm) target within the hypothalamic nuclei, lying inferior to the fornix and superoposterior to the optic nerve and chiasm. The LH became classically known as the “feeding center” of the brain on the basis of several lesion studies that were performed midway through the previous century. These studies demonstrated that bilateral LH lesions in rats resulted in decreased food intake, weight loss, and decreased food-seeking behavior. Compared with sham-operated controls, rats with bilateral LH lesions gained significantly less weight with equal quantities of digested food, and they exhibited increased core body temperature. Subsequently, the LH was discovered to be the source of extensive projections of neurons containing 2 newly discovered neuropeptides: melanin-concentrating hormone and orexin. Both neuronal populations have broad projections throughout the central nervous system, and direct injection of either melanin-concentrating hormone or orexin into the ventricles will cause rats to feed, and these levels increase in rats during periods of starvation. Multiple early animal studies demonstrated that low-frequency stimulation of the LH resulted in an excitatory response of the fibers, with animals demonstrating food-seeking and food-hoarding behavior, increased gastrointestinal blood flow, and activation of vagal pathways. In 2007, Sani et al. reported on the use of high-frequency DBS of the bilateral LH in 16 rats that resulted in a 2.3% weight loss in stimulated rats and a 13.8% weight gain in unstimulated controls. In 2007, Sani et al. reported on the use of high-frequency DBS of the bilateral LH in 16 rats that resulted in a 2.3% weight loss in stimulated rats and a 13.8% weight gain in unstimulated controls.

The first pilot study of bilateral LH DBS for obesity in humans was performed in 2013 by Whiting et al., Table 1. Three patients who met the criteria for morbid obesity, who had had multiple unsuccessful attempts at lifestyle modification, and in whom bariatric surgery had failed underwent stereotactic DBS electrode placement bilaterally in the LH. The study was primarily focused on safety outcomes, and no serious adverse effects were observed during the mean follow-up of 35 months. Transient nausea, anxiety, and temperature change sensations were noted during programming changes but lasted less than 5 minutes. Throughout most of this pilot study, stimulation parameters were set at a frequency of 185 Hz and a pulse width of 90 μsec. The resting metabolic rate was tested systematically using monopolar stimulation at different voltages and electrode contacts to find the optimized stimulation parameters and contacts. Although the study was primarily focused on safety, early data on weight change showed a trend toward weight loss in 2 of the 3 patients at optimized parameters. Other studies are currently being completed that examine the effect of different frequencies and pulse widths on resting metabolic rate and sleep energy expenditure, and long-term studies are examining weight changes, effects on comorbidities, and the durability of resting metabolic rate changes.

Ventromedial Hypothalamus

The VMH is a 2 × 3 × 5–mm target posterior to the optic nerve, anterior to the mammillary body, and inferior to the anterior commissure. The VMH was classically referred to as the “satiety center” of the brain after animal lesion studies demonstrated that bilateral VMH lesions resulted in increased body lipid and insulin levels compared with those in controls and that bilateral VMH lesions resulted in metabolic hyperphagia and obesity. Electrical stimulation studies in rats demonstrated that low-frequency stimulation of the VMH at 60 Hz resulted in the disruption of feeding behavior. The results of these studies led to the design of experiments involving DBS of the VMH in animals. In one study, low-frequency DBS of the VMH (50 Hz) in minipigs resulted in decreased weight gain over time, while in a separate study, intraventricular DBS electrodes were placed adjacent to the VMH in monkeys, and stimulation at a low frequency (80 Hz) resulted in reduced body weight and body fat. Conversely, Lačan et al. found that high-frequency DBS (185 Hz) of the VMH in monkeys resulted in increased food intake.

The first report of a study of DBS in humans specifically for obesity was published in 2008 by Hamani et al., who treated a patient with morbid obesity (Table 1). The patient had no change in weight while undergoing high-frequency stimulation and demonstrated mild weight loss that was eventually regained while undergoing low-frequency stimulation. Interestingly, the patient demonstrated improved memory during stimulation, prompting divergent experiments investigating DBS for Alzheimer’s disease. No further studies in humans that examine DBS of the VMH for refractory obesity have been published to date.

Nucleus Accumbens

The NAc is an 8 × 6 × 6–mm region of the striatum located inferior to the anterior limb of the internal capsule, anterior to the preoptic area of the hypothalamus, and superolaterally to the optic nerve. The NAc is functionally divided into 2 subregions: the NAc shell, with broad projections primarily to the limbic system, and the NAc core, with projections primarily to the caudate and putamen, the globus pallidus, and the substantia nigra. Both subregions of the NAc consist substantially of neurons containing dopamine receptors, and both have been associated with reward pathways, with the NAc shell associated with motivation-based reward pathways and the NAc core associated with learning-based reward pathways.

With its complex involvement in reward, craving, anticipation, and withdrawal pathways, the NAc has emerged as a treatment target for obesity. Indeed, the effects on the NAc circuitry from excessive consumption of palatable foods are similar to the effects of drug abuse, so dysfunctional circuitry could lead to the outcomes observed with morbid obesity. Compared with normal-weight controls, obese patients demonstrate greater activation of the NAc and reward pathways when exposed to high-calorie foods.
Early animal studies demonstrated that NAc lesions in rats resulted in abolition or severe reduction in food-hoarding behavior.\textsuperscript{22} When the rats were treated with levodopa, hoarding behavior was restored, implicating the dopaminergic NAc pathways in these feeding-related behaviors. Halpern et al.\textsuperscript{20} examined the effects of DBS of the NAc in a rat model by placing bilateral electrodes in the NAc shell. They found that high-frequency stimulation (160 Hz) in diet-induced obese mice resulted in acute reductions in caloric intake and induced weight loss. Their study demonstrated that this change was mediated by a change in dopamine signaling involving dopamine D2 receptors.\textsuperscript{20} Interestingly, Wu et al.\textsuperscript{62} demonstrated by a case report for obsessive-compulsive disorder (OCD), depression, and Tourette syndrome.\textsuperscript{20} In a study by Mantione et al.,\textsuperscript{38} a woman had bilateral NAc DBS electrodes placed for treatment-refractory OCD and underwent high-frequency stimulation. Interestingly, Wu et al.\textsuperscript{62} demonstrated that mice exhibited appreciable local field potentials in the NAc during reward anticipation, such as food presentation, and that closed-loop stimulation of the NAc after the presentation of these triggers reduced binge-eating behavior.

The only published report of NAc DBS primarily for obesity in humans is a case report by Harat et al.,\textsuperscript{22} describing a woman with hypothalamic obesity after craniopharyngioma surgery (Table 1). She underwent implantation of bilateral NAc DBS electrodes, followed by chronic high-frequency stimulation for 14 months, and subsequently demonstrated a change in BMI from 52.9 to 48.2 with no major adverse effects.

Although no organized trials of DBS of the NAc for obesity have been published, the NAc is already a well-studied DBS target for obsessive-compulsive disorder (OCD), depression, and Tourette syndrome.\textsuperscript{20} In a study by Mantione et al.,\textsuperscript{38} a woman had bilateral NAc DBS electrodes placed for treatment-refractory OCD and underwent high-frequency stimulation. Interestingly, the patient also demonstrated baseline nicotine addiction and obesity, but with chronic high-frequency stimulation demonstrated smoking cessation and significant weight loss. This experience highlighted the common circuitry involved in dysfunctional reward pathways and supported the feasibility of DBS of the NAc for the treatment of obesity.\textsuperscript{38}

### Deep Brain Stimulation for Anorexia Nervosa

AN is a multifaceted, challenging disease defined as a restriction of energy intake relative to bodily requirements, leading to a relatively low body weight in association with a distorted body image and anxiety about weight gain.\textsuperscript{1} Young females have the highest prevalence rates, which are estimated to be 0.3% in this population.\textsuperscript{28} AN is associated with severe morbidity and mortality, and estimates in the medical literature have established AN as having the highest mortality rate of any psychiatric disease.\textsuperscript{3,24,53} The current mainstays of treatment involve diet and nutritional support, various forms of interventional therapy, and medical treatment of comorbidities, with patients with severe AN requiring admission to specialized inpatient units. Unfortunately, despite multiple intensive modalities of medical care and intervention, the rates of long-term treatment success and remission are relatively low.\textsuperscript{4,15,36} Because of the lack of consistently successful treatment strategies for AN, its strong association as a comorbidity with other psychiatric diseases, and the adjustability and safety profile of DBS, DBS has emerged as a potential intervention for AN.

### Physiology and Targets

Multiple imaging studies have demonstrated that persons with AN have dysfunctional appetitive behaviors and cerebral circuitry, related to both sensory processing and reward mechanisms.\textsuperscript{39} Cerebral blood oxygenation changes on functional MRI (fMRI) have shown that, when presented with pictures of high-calorie food, anorexic females have more extensive activation of the left insula, the anterior cingulate gyrus, and the amygdala and hippocampus compared with controls.\textsuperscript{12} Further fMRI studies demonstrated greater activation of the medial orbitofrontal and anterior cingulate cortex in anorexic individuals than in controls when presented with images of food.\textsuperscript{58} FDG PET sequences in anorexic female patients demonstrated hypermetabolism in the frontal lobe, amygdala and hippocampus, left insula, and left subcallosal gyrus and demonstrated hypometabolism in the parietal lobe compared with age-matched healthy controls.\textsuperscript{54} Because AN demonstrates many functional parallels to OCD and frequently co-occurs with it,\textsuperscript{8} similar dysfunctional circuitry and potential DBS targets have been proposed for these diseases.\textsuperscript{63} Current research predominantly focuses on the striatal terminalis and medial forebrain bundle, the NAc, and the subcallosal cingulate as DBS targets for AN.

### Human Studies

With the frequent overlap between AN, OCD, and major depressive disorder (MDD), there have been case re-

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**TABLE 1. Published reports of deep brain stimulation for the treatment of obesity in humans**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Pts</th>
<th>No. of Pts</th>
<th>Study Design</th>
<th>Target</th>
<th>Stimulation Parameters</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamani et al., 2008</td>
<td>Adult w/ morbid obesity</td>
<td>1</td>
<td>Case report</td>
<td>Ventromedial hypothalamus</td>
<td>Bilat, 2.8 V, 60 µsec, 130 Hz</td>
<td>Minimal long-term weight change; improved memory</td>
</tr>
<tr>
<td>Whiting et al., 2013</td>
<td>Adults w/ treatment-refractory obesity</td>
<td>3</td>
<td>Open-label trial</td>
<td>Lat hypothalamus</td>
<td>Bilat, variable voltage, 90 µsec, 185 Hz</td>
<td>No serious adverse effects; trend toward weight loss in 2/3 pts</td>
</tr>
<tr>
<td>Harat et al., 2016</td>
<td>Adult w/ iatrogenic hypothalamic obesity</td>
<td>1</td>
<td>Case report</td>
<td>Nucleus accum-bens</td>
<td>Bilat, 3.75 mA, 208 µsec, 130 Hz</td>
<td>At 14-mo follow-up, change in BMI (from 52.9 to 48.2); no major adverse effects reported</td>
</tr>
</tbody>
</table>

Pts = patients.
ports in the medical literature reporting on AN outcomes after DBS for OCD or MDD. McLaughlin et al. reported the case of a woman with refractory OCD and AN who underwent DBS of the ventral capsule and ventral striatum. With high-frequency stimulation, the patient reported subjective improvement in her AN symptoms. Blomstedt et al. reported on a woman with MDD and concurrent AN who underwent DBS of the bed nucleus of the stria terminalis. The patient demonstrated no change in BMI, but experienced subjective improvement in food and eating anxiety.

Other reports have focused on DBS specifically for the treatment of AN (Table 2). Lipsman et al. reported on the first Phase 1 trial of DBS of the subcallosal cingulate gyrus, specifically for treatment-refractory AN in 6 patients. Their results demonstrated an acceptable safety profile, with only 1 patient having a serious adverse event (seizure; Table 2). After 9 months at high-frequency stimulation, 3 of the 6 patients maintained a BMI greater than that at baseline. Additionally, 3 patients reported improvements in quality of life. These stimulation parameters resulted in the patient requiring no further interventions or hospitalizations for AN over the 2-year follow-up period.

In 2013, Lipsman et al. reported on the first Phase 1 trial of DBS of the subcallosal cingulate gyrus, specifically for treatment-refractory AN in 6 patients. Their results demonstrated an acceptable safety profile, with only 1 patient having a serious adverse event (seizure; Table 2). After 9 months at high-frequency stimulation, 3 of the 6 patients maintained a BMI greater than that at baseline. Additionally, 3 patients reported improvements in quality of life. This study was succeeded by a larger 1-year follow-up study in 2017 by Lipsman et al., involving 16 patients with treatment-refractory AN who underwent the same procedure (Table 2). With chronic stimulation, the patients in that study demonstrated a significant increase in average BMI, from 13.83 to 17.34. The authors found that DBS of the subcallosal cingulate was associated with significant improvements in depression, anxiety, and affective regulation. Additionally, changes in glucose metabolism on PET imaging were detected in the subcallosal and anterior cingulate, parietal lobe, and other regions of the brain associated with dysfunction in AN at 6 and 12 months of stimulation. Wu et al. also examined the effects of DBS in 4 patients with AN, but they used the NAc as their stimulation target (Table 2). They reported a mean increase of 65% in body weight in their patients (n = 4) after chronic high-frequency stimulation at a mean follow-up of 38 months. Further studies are needed to determine the long-term effects and durability of DBS for AN.

Conclusions

DBS has proven to be a safe, reversible, and highly efficacious treatment for a variety of neurological disorders, and it has been proposed as a treatment for refractory obesity and AN. Studies have demonstrated several potential central nervous system DBS targets for both disorders. The VMH, LH, and NAc have all been demonstrated to have elements of success as DBS targets in animal models of refractory obesity. One open-label trial of 3 patients undergoing LH DBS for refractory obesity has been performed; no serious adverse effects were found, and studies are ongoing to evaluate its effect on obesity. Larger studies examining the effects of DBS on these separate targets for refractory obesity are needed going forward. AN research has predominantly focused on the stria terminalis and medial forebrain bundle, the subcallosal cingulate, and the NAc as potential DBS targets. The largest trial, involving 16 patients undergoing DBS of the subcallosal cingulate for AN, demonstrated significant improvement in BMI and other psychological outcomes. These outcomes highlight the promise of DBS for the treatment of refractory AN, but further studies are needed to continue to elucidate its effects and long-term outcomes.
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