Deep brain stimulation for obesity or binge-eating behavior: an overview

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Obesity is a global epidemic, leading to huge burdens on both individuals and society. Non-invasive approaches, such as lifestyle modification or medication, have been regarded as a first-line treatment. However, these have shown only limited success. For patients with medically refractory obesity, surgical options (e.g., gastric bypass or sleeve gastrectomy) have been attempted, although they also have a high rate of recurrence and may cause nutritional complications. Beyond body weight itself or peripheral systems that control body weight, recent evidence has suggested that obesity or binge eating behavior is closely associated with the hedonic properties of highly palatable food, which is mediated by the dopamine system in the brain reward circuit. In this context, deep brain stimulation for medically refractory obese patients has gained attention as a novel treatment that challenges the traditional paradigm of treatment for obesity. In this review article, we summarize the evidence from animal experiments and human studies dealing with deep brain stimulation for obesity or binge-eating disorder. We also explain the theoretical background of obesity as it relates to the reward circuit and introduce current ongoing human trials for obesity.

KEY WORDS: Binge eating, Deep brain stimulation, Hypothalamus, Nucleus accumbens, Obesity, Reward

INTRODUCTION

Obesity is an increasingly prevalent condition, especially in developed countries, causing 3.4 million deaths per year worldwide [1]. According to a global national survey in 2014, there has been a 10% increase in overweight populations (body mass index [BMI] > 25 kg/m²) between 1980 and 2013. Furthermore, the number of children with overweight has been rapidly increasing up to 23% in developed countries, indicating a significant health concern [1,2]. Given the numerous comorbidities of obesity such as osteoarthritis, stroke, certain types of cancer, financial burdens affecting individuals and whole societies are also to be expected. The medical costs associated with obesity are estimated to have risen to $147 billion from $78.5 over the span of 10 years [2-4]. In the United States, if the current increase in the obese population continues, all adult Americans will be overweight by the year 2048 [5].

There are only limited treatment options available for obese patients. The current available anti-obesity drugs can be divided into two classes; central acting...
Review of DBS for obesity

and peripheral acting. However, owing to a number of factors including misuse of the agents, abusive commercialization of pharmaceutical galenic preparations and less emphasis on classic treatment counselling, the long-term effect of these anti-treatment drugs is controversial yet. Furthermore, the vast majority of these focus on body weight alone, leading to a high rate of treatment failure [6].

Bariatric surgery is usually reserved for patients with a BMI > 40 kg/m² or a BMI > 35 kg/m² in the presence of significant comorbidities and most commonly involves laparoscopic gastric banding or laparoscopic Roux-en-Y gastric bypass [6]. Although bariatric surgeries have been regarded as a primary weight loss strategy for medically refractory obese patients, it has various limitations, including a high incidence of both recurrence and complications [6,7]. Even if bariatric surgery leads to weight loss and improvement in morbidity reduction, considerable weight gain often recurs approximately 2 years after surgery with a failure rate of up to 46% [2]. Moreover, as Roux-en-Y gastric bypass surgery enables the bypass of 95% of the stomach, the entire duodenum, and 150 cm of the jejunum, the risk of micronutrient deficiency, such as in calcium and various minerals, is high and patients need to be treated with life-long supplementation [2]. Considering that the fundamental cause of obesity or binge eating behavior is related to psychiatric disease linked to the reward center of the brain, the limitation of gastric bypass surgery is apparent. The primary focus should be put on a more fundamental treatment that targets the cerebral networks of the reward system [2,6,7].

The present study has two purposes: 1) to review findings from the recent literature on deep brain stimulation (DBS) for obesity or binge eating behavior and 2) to introduce a persuasive theoretical hypothesis by which DBS works for obesity. It is not meant to be an extensive review of obesity, but rather a summary of contemporary theories and practical information, which stem from animal experiments, human studies, and ongoing human trials.

REWARD SYSTEM AND KEY STRUCTURES

Many cerebral regions are known to be involved in the mechanism of eating disorders [8]. It is widely accepted that there is “bottom-up” emotion generation emerging from subcortical, limbic neural structures and “top-down” emotion regulation by dorsal prefrontal cortical regions. An imbalance between these can result in abnormal behavior. Increased activity of the “bottom-up” stream, which means increased activity in emotion generation to external stimuli, may contribute to altered reward processing such as binge eating behavior [8,9]. Key neurotransmitter in this reward system is dopamine. The regulation of eating behavior or addiction is modulated by multiple peripheral and central systems that deliver information to the dopamine center in the reward system [10-15]. The brain dopamine reward circuitry increases the probability that behaviors that activate it (food consumption) will be repeated when encountering the same reinforcer [15]. Hence, with repeated access to highly palatable food, some individuals may exceed the inhibitory process that signals satiety and begin to compulsively consume large amounts of food, frequently leading to repulsion in this behavior [2,11-15]. Three cerebral structures have been identified through lesioning studies to have a critical role in the reward circuit, leading to excessive food consumption: the lateral hypothalamus (LH), nucleus accumbens (NA), and ventral tegmental area (VTA) [2,7]. We will discuss the individual structures in the next section.

THE LATERAL HYPOTHALAMUS, NUCLEUS ACCUMBENS, VENTRAL TEGMENTAL AREA

The LH has been shown to mediate appetitive and feeding-related behaviors [12]. GABAergic neurons from the LH disinhibit dopamine neurons in the VTA and result in increased dopamine levels in the NA, leading to motivated behaviors (Fig. 1A) [14]. As a response to this increase in dopamine levels in the NA, the lateral NA predominantly disinhibits dopamine neurons in the lateral VTA, increasing dopamine levels in the NA (indirect feedback). However, the medial GABAergic inhibitory pathway from the NA to dopamine neurons in the medial VTA is much stronger (direct feedback), thus resulting in the net inhibition of VTA dopaminergic neurons (Fig. 1B) and consequently leading to a decreased dopamine concentration in the NA [16]. This feedback loop between these three structures (LH-VTA-NA) has been widely accepted as a fundamental background in reward systems, especially for eating behaviors [16].

DEEP BRAIN STIMULATION TARGETS IN ANIMAL EXPERIMENTS

Previous findings from animal studies on DBS for obesity or binge eating behavior are summarized in Table 1 [11,17-24]. Many studies have confirmed that the NA can be divided into two substructures, core and shell, which both mediate reward cue-driven consumptive behaviors [25-27]. However, the effect of DBS in the NA core and shell is dissociable based on the aspects of motivated behavior, “wanting” vs. “liking” [28]. In a study to identify the differences in the effect on eating behavior between the two, stimulation of the NA core before binge eating (not during binge eating) induced a decrease in high-fat food intake, whereas stimulation of the NA shell during binge eating (not

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before) affected behavior [20]. Given that “wanting” is responsible for cravings (i.e., in anticipation before binge eating) and “liking” is the pleasurable feeling of using the potentially incentive substance (during binge eating), it is plausible that NA core stimulation might modulate the process of “wanting” and that the NA shell might be involved in the process of “liking.” The NA shell can further be divided into two sub-nuclei, based on their distinct functional role in food intake (medial NA shell vs. lateral NA shell) [21]. However, even if the same target of the NA shell is stimulated, conflicting results have also been reported: increased food intake in normal-weight rats following DBS of the medial NA shell but a decrease in food intake in obese rats [21,24,29]. Despite this inconsistency, these results indicate that the NA shell is associated with food intake and body weight, further highlighting the NA shell as an interesting target of DBS to modulate eating behavior [21]. As a potential mechanism by which DBS on the NA shell may modulate such behavior, Halpern et al. [11] suggested the hypothesis that DBS in the NA shell may lead to local release of dopamine, which in turn binds to dopamine-2-receptor (D2R), blocking the hedonic valence of the high-fat diet [24,30]. However, the efficacy was found to diminish with continuous stimulation. In addition, in some cases of behavioral context changes (e.g., other behaviors of palatable food consumption such as diet-induced obesity or a binge relapse model), DBS of the NA shell appears to be less effective [11,18]. With regard to this failure in a relapse model, Doucette et al. postulated that the decreased efficacy of NA DBS may stem from an increased motivation to consume the palatable food, which had been proven in many studies showing that “incubation of craving” during prolonged abstinence can drive a more enhanced response to specific material when animals are re-exposed to previously associated cues [18,31,32]. In addition, a recent study by Casquero-Vega et al. [17] supported a new hypothesis that NA DBS can also decrease metabolism in the striatum and thalamus, suggesting that this induced hypometabolism may alleviate the hyperactivated status of the striatum and thalamus, which is a characteristic pathology in obesity.

Given that the LH is an anatomical hub linking the arcuate nucleus in the ventromedial hypothalamus (VMH) (in which various peripheral signals are delivered through fenestrated capillaries) and multiple limbic structures, its effect on obesity or binge eating disorder has received significant attention [22]. Sani et al. [22] reported that stimulation of the LH leads to weight loss without any change in food or water intake, suggesting that LH stimulation may induce metabolic changes rather than modulate eating behavior. However, in other studies, LH stimulation showed different efficacies between diet-induced obese rats and normal rats [24]. Previ-

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**Fig. 1.** (A) Model representing the GABAergic projection from the LAT hypothalamus (LH) onto GABA cells in the ventral tegmental area (VTA). Activation of the GABAergic LH-VTA projection leads to disinhibition of VTA dopamine (DA) neurons, thereby increasing DA release in the nucleus accumbens (NA). (B) Model representing direct and indirect feedback loops in the VTA and NA. Since the MED GABAergic inhibitory pathway in the NA to DA neurons in the MED VTA is much stronger (direct feedback) than the LAT NA to VTA pathway, the activation of the NA to VTA GABAergic pathway results in net inhibition of VTA dopaminergic neurons. GABA_A represents GABA receptor subtype A. MED: medial, LAT: lateral.
Table 1. Summary of findings from previous animal experiments on DBS in obesity or binge eating models

<table>
<thead>
<tr>
<th>Study</th>
<th>Animal</th>
<th>Sample size</th>
<th>Disease</th>
<th>Devices (1. Electrode/2. Generator/3. Output monitor)</th>
<th>Target-coordinates (mm)</th>
<th>Parameter</th>
<th>Outcome measurement</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Doucette et al. [18] (2015)</td>
<td>Sprague-Dawley rats</td>
<td>12 (DBS) vs. 6 (control)</td>
<td>BE</td>
<td>1. Plastics, Roanoke 2. S11, Grass instruments 3. PSIU6, Grass Technologies</td>
<td>NA core, Bilateral; 1.2 (A), 2.8 (L), 7.6 (V) 4° from bregma</td>
<td>Monophasic, continuous 60 µsec, 50 Hz, 150 µA</td>
<td>1. Binge size change (%)</td>
<td>1. Reduction of binge size in DBS group</td>
<td>Relapse model; No significant improvement in binge size</td>
</tr>
<tr>
<td>Halpern et al. [11] (2013)</td>
<td>Mice (male, C57BL/6J)</td>
<td>NA shell (n = 12) vs. dorsal striatum (n = 11) vs. control (n = 7)</td>
<td>BE</td>
<td>1. Custom bipolar tungsten electrode 2. SD9 Square Pulse Stimulator, Grass Technologies 3. CT3684, Cal Test/TPS2000B, Tektronix</td>
<td>NA shell Unilateral; 1.34 (A), 0.6 (L), 4.25 (V) Dorsal striatum 1.34 (A), 1.5 (L), 2.2 (V) from bregma</td>
<td>Monophasic, continuous 60 µsec, 160 Hz, 150 µA</td>
<td>1. High-fat diet (kcal) 2. Activity 3. c-Fos-IR in the NAS and ILC 4. Pharmacological effect (D1R, D2R)</td>
<td>1. Decrease in high-fat diet intake 2. No activity change 3. Increased c-Fos-IR in the bilateral NA 4. Only D2R antagonist attenuated the effects of DBS</td>
<td>NA DBS can produce behavioral change (reducing high-fat diet intake) via the D2R pathway</td>
</tr>
<tr>
<td>Sani et al. [22] (2007)</td>
<td>Sprague-Dawley rats</td>
<td>8 vs. 8 (DBS vs. sham)</td>
<td>BE</td>
<td>1. 0.25 mm bipolar product (Plastic) 2. Medtronic products</td>
<td>LH Bilateral; 2.3 (P: bregma), 2 (L: sagittal), 8.6 (below dura)</td>
<td>Continuous 100 msec, 180–200 Hz, 2.0 V</td>
<td>1. Body weight 2. Food intake 3. Water intake</td>
<td>1. Significant weight reduction in stimulated rats 2. No change in food or water intake</td>
<td>Stimulation of LH might reduce metabolic rate, rather than modulating appetite control</td>
</tr>
<tr>
<td>Prinz et al. [21] (2017)</td>
<td>Sprague-Dawley rats (female)</td>
<td>6 vs. 6 (DBS vs. sham)</td>
<td>Normal</td>
<td>1. platinum/iridium wire with 70 µm diameter 2. Implantable stimulator 3. None</td>
<td>Medial NA shell; Unilateral; 1.44 (A), 3.0 (L), 7.3 (V) 18°</td>
<td>Biphasic 130 Hz, 100 µA for 7 days</td>
<td>1. Food/water intake 2. Weight gain 3. Behavior</td>
<td>1. High trend of an increase in weight gain in DBS group 2. No changes in food intake and behavior</td>
<td>Day time food intake &gt; night food intake (DBS group) Reduction of satiation</td>
</tr>
<tr>
<td>Zhang et al. [24] (2015)</td>
<td>Sprague-Dawley rats</td>
<td>1. DIO (DBS, n = 8) vs. control (sham, n = 8) 2. Normal (DBS, n = 8) vs. control (sham, n = 8)</td>
<td>Normal</td>
<td>1. CBCRJ30 (FHC) 2. Master 8 (AMPI) 3. None</td>
<td>Left NA shell; Unilateral; 1.2 (A), 0.7 (L), 7.4 (V) from bregma</td>
<td>90 µsec, 130 Hz, 500 µA</td>
<td>1. Body weight/food intake 2. D1/D2 receptor mRNA 3. DA/DOPAC</td>
<td>1. Significant weight loss and food intake reduction in DIO-DBS rats 2. Increased D2R mRNA expression in DIO-DBS rats 3. Increased dopamine levels in DIO-DBS rats but no significant change in DOPAC level was noted</td>
<td>DBS has effect only in DIO rats No significant change in weight loss (or food intake) and dopamine-related activity was noted in normal rats</td>
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<table>
<thead>
<tr>
<th>Study</th>
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<th>Parameter</th>
<th>Outcome measurement</th>
<th>Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torres et al. [23] (2012)</td>
<td>Monkeys (Macaca fascicularis)</td>
<td>4 (DBS) vs. 1 (sham)</td>
<td>Normal</td>
<td>VMH, Anterior to 3rd ventricle; Unilateral</td>
<td>30–130 Hz</td>
<td>Body weight and body fat</td>
<td>1. Significant reduction in body weight and body fat in DBS monkeys</td>
<td>2. No significant change in fat intake during stimulation</td>
<td>3. No change in glucose or leptin level during stimulation</td>
</tr>
<tr>
<td>Oterdoom et al. [20] (2020)</td>
<td>Wister rats</td>
<td>7 (NA core) vs. 7 (NA lateral shell) vs. 7 (NA medial shell)</td>
<td>BE</td>
<td>NA core vs. NA shell; Coordinates were not specified; Unilateral</td>
<td>60 μsec, 140, 50, 10 Hz, 250 μA (or 150 μA in cases with side effects)</td>
<td>High-fat food intake</td>
<td>NA core–stimulation before binge eating produced significant decrease in high-fat food intake</td>
<td>NA lateral shell–stimulation during binge eating led to suppression of high-fat food intake</td>
<td>Different mechanism on binge eating between NA core and NA shell; wanting vs. liking Stimulation of medial NA shell led to major side effect (e.g., fear and escape behavior) Over-activated striatum and thalamus in obese rats can be counteracted by NA DBS since it reduced glucose metabolism in the striatum and thalamus No significant weight loss in DBS rats can indicate that NA-DBS cannot resolve imbalance caused by the lack of leptin signaling in the hypothalamus</td>
</tr>
<tr>
<td>Casquero-Veiga et al. [17] (2018)</td>
<td>Zucker rats</td>
<td>6 (NA core) vs. 9 (sham)</td>
<td>Obesity model (leptin-resistant model)</td>
<td>NA core; 1.2 (P), 1.5 (L) from bregma, –8.2 from dura; Unilateral</td>
<td>Biphasic, continuous, 100 μsec, 130 Hz, 150 μA</td>
<td>1. Glucose metabolism using FDG-PET 2. Weight 3. Food and water intake</td>
<td>1. Alteration in glucose metabolism in DBS rats; decreased metabolism in the NA, thalamic and pretectal nuclei, and increased metabolism in the cingulate-retrosplenial-parietal association cortices 2. No significant change in weight and food intake.</td>
<td>3. No significant change in glucose or leptin level during stimulation</td>
<td>4. Increased velocity during stimulation</td>
</tr>
</tbody>
</table>
### Table 2. Summary of previous studies on DBS in obese humans

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Devices (1. Electrode/2. Generator)</th>
<th>Target+coordinates (mm)</th>
<th>Parameter</th>
<th>Outcome measurement</th>
<th>Conclusion</th>
<th>Significance or comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whiting (2013) et al. [44]</td>
<td>n = 3</td>
<td>1. Model 3389 (Medtronic) 2. Soletra (Medtronic)</td>
<td>LH; Bilateral; 6.5 (L), 3 (I) to intercommissural line, 4.5 (P) to AC ± adjustment in relation to fornix</td>
<td>Monopolar or bipolar; 90 µsec; 185 Hz</td>
<td>1. Psychological tests 2. Biochemical analysis 3. Energy metabolism 4. Body weight</td>
<td>1. Improvement in Binge Eating score (1/3), cognitive restraint subscale (1/3), hunger scale (2/3), body shape questionnaire (2/3) 2. No changes in biochemical analysis 3. Significant increase in RMR 4. Significant weight loss in 2/3 and stable weight in 1/3</td>
<td>Parameters that appeared to augment RMR induce significant weight loss in 2/3 patients Contact 1 (most closely located to mid-LH) increased RMR in 2/3 Contact 3 produced increased activity and increased arousal in all patients No significant adverse effects</td>
</tr>
<tr>
<td>Whiting et al. [45] (2019, follow-up study)</td>
<td>n = 2 (one patient was excluded due to lead breakage)</td>
<td>1. Model 3389 (Medtronic) 2. Soletra (Medtronic)</td>
<td>LH; Bilateral</td>
<td>Various settings were tested to identify optimal setting</td>
<td>1. Optimal setting for increasing RMR</td>
<td>Patient 1: contact 2 with pulse width of 60 msec and a frequency of 185 Hz Patient 2: contact 0 with pulse width of 90 msec and a frequency of 60 Hz</td>
<td>This different optimal setting might indicate the activation of different nuclei and regions Long-term investigations of weight loss and metabolic rate at optimized settings are mandatory</td>
</tr>
<tr>
<td>Mantione et al. [46] (2010)</td>
<td>n = 1 (OCD patient with obesity; BMI 37 kg/m² [107 kg])</td>
<td>1. Model 3389 (Medtronic) 2. Soletra (Medtronic)</td>
<td>NA; Bilateral</td>
<td>Monopolar; 90 msec; 185 Hz; 3.5 V</td>
<td>1. Various psychiatric batteries 2. Weight loss 3. Smoking cessation</td>
<td>1. Significant improvement in various tests for OCD, depression, and anxiety 2. Significant reduction in weight 3. Success in smoking cessation</td>
<td>Compulsions, smoking, and excessive food intake have a shared pathophysiology that can be improved by NA modulation</td>
</tr>
<tr>
<td>Harat et al. [47] (2016)</td>
<td>n = 1 (hypothalamic obesity due to earlier craniopharyngioma surgery)</td>
<td>Not shown</td>
<td>NA; Bilateral</td>
<td>208 µsec; 130 Hz; 2 mA (increases to 3.5 mA)</td>
<td>1. Various psychiatric tests 2. Weight control</td>
<td>1. Significant improvement in various psychiatric tests 2. Significant weight reduction</td>
<td>Modulation of the immediate brain reward system can treat hypothalamic obesity</td>
</tr>
</tbody>
</table>

ous studies have shown that impaired dopamine neurotransmission in diet-induced obese leads more obsession with high-energy food to compensate for the weak dopaminergic input and this altered system of dopamine neurotransmission in obesity is believed to result in this difference [24,33,34]. Consistent with this, Zhang et al. [24] reported that DBS of the LH can induce an anorexic effect caused by the activation of D2Rs only in diet-induced obese rats (not in normal rats), implying that DBS-induced higher upregulation of dopamine can account for this selective efficacy.

In addition to these targets directly related to the reward circuit, it is worth noting that neuromodulation of the VMH can also lead to weight reduction [2,10,13]. The VMH, which contains the ventromedial nuclei and arcuate nuclei, is a critical structure in regulating glucose levels and energy homeostasis [35]. There is a long-lasting consensus suggesting that the VMH can reduce weight gain by altering the metabolic rate, rather than affecting eating behavior [36,37]. Being modulated by positive signals of nutritional resources such as glucose (insulin) and leptin, the VMH not only reduces hepatic glucose output and increases peripheral glucose metabolism but also regulates appetite regulation as the satiety center of the brain [2,13]. The interaction between the VMH and structures of the reward system is schematically depicted in Fig. 2. Receiving projections from brain regions that maintain homeostasis (VMH), nuclei in the LH send projections to the reward center (VTA and NA) where they promote motivated behaviors [38]. Accordingly, in contrast to the mechanism related to dopamine levels in the reward system when the LH or NA is stimulated, the effect of VMH stimulation is likely associated with hypermetabolism, which increases basal energy consumption [23,39]. In a study by Torres et al. [23], a significant reduction in body weight and body fat was observed without any changes in hormone levels after chronic DBS stimulation of the VMH. In addition, an increase in animals’ movement velocity facilitating a higher metabolic rate during acute stimulation was noted. The authors also suggested that chronic DBS was effective only at 80 Hz stimulation, which might indicate selective inhibition of the orexigenic LH [23]. In addition, low-frequency DBS of the VMH can induce a significant reduction in weight gain without any behavioral change in minipigs, providing preclinical evidence in support of low-frequency VMH DBS as a treatment for obesity [19].

DEEP BRAIN STIMULATION FOR HUMANS WITH OBESITY OR BINGE EATING DISORDER

Ventromedial hypothalamus

The findings of recent studies dealing with DBS for humans are summarized in Table 2 and 3. Since a growing body of evidence has revealed that posterior hypothalamic DBS can induce weight loss in various diseases (i.e., cluster headache and refractory aggressiveness disorder), bilateral VMH DBS has emerged as a potential intervention for patients who fail bariatric surgery or for those preferring a reversible surgery [40-42]. In a study by Hamani et al. [41], morbidly obese patients treated with bilateral ventral hypothalamic DBS showed a 6% weight loss over 5 months with low-frequency stimulation, without any change in behavior. Currently, a single-cohort, open-label, and non-masked study of DBS of the VMH with low frequency (50 Hz) is ongoing. The role of

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**Fig. 2.** Interaction between the ventromedial hypothalamus (VMH) and structures of the reward system. LH: lateral hypothalamus, VTA: ventral tegmental area, NA: nucleus accumbens.
VMH DBS in refractory obese patients will be elucidated in the near future in the BLESS trial (NCT 02232919) (for more detailed information, see Table 3) [43].

### Lateral hypothalamus

The first pilot study of LH DBS for obesity was published in 2013 [44]. In a pilot study in which bilateral DBS electrodes were implanted in the LH of three obese patients who showed no improvement after bariatric surgery, significant weight loss with increased resting metabolic rate (RMR) was observed in two of these patients. Since the DBS effect on RMR was observed at contact 1 of model 3389 (Medtronic, Inc., Minneapolis, MN, USA), which was located more closely to the mid-LH, the authors postulated that the nearby nuclear structures around the mid-LH might play a critical role in the regulation of metabolic rate. However, in a follow-up study to identify optimal stimulation settings for increasing RMR, opposite DBS settings between two participants for the maximal increase in RMR were found: high-frequency of 185 Hz vs. low-frequency of 60 Hz [45]. This difference is assumed to be caused by different regions being activated by LH stimulation, suggesting that long-term investigation of weight loss and RMR at the optimized DBS settings is mandatory in each LH-DBS patient [45].

### Nucleus accumbens

During the treatment of a patient for medically refractory obsessive-compulsive disorder with DBS of the NA, a non-intended reduction in food intake was observed [46]. Although a sustained weight loss occurred 10 months after DBS surgery when most of her obsessive-compulsive disorder symptoms had disappeared, this case report suggests the possibility that compulsion, addiction, and food consumption have a shared pathophysiology in the reward circuit and that these behavioral disorders can be treated with neuro-modulation of the NA. In the case of hypothalamic obesity patients, bilateral NA DBS also showed a significant effect on weight reduction with improvement in various psychiatric tests [47].

However, since the effects of DBS on excessive food intake may not be sustained over time and may even affect other social behaviors, closed-loop NA DBS, in which stimulation is delivered only when specific physiological fluctuations associated with abnormal behavior are detected in the NA, has been receiving significant attention. A randomized, early feasibility study of closed-loop NA DBS was designed to study this in more detail (DBSLOC; NCT 03868670, currently recruiting) [48].

### CONCLUSIONS

Although the exact mechanism to explain the effects of DBS on obesity or binge eating behavior has not been elucidated, an increasing number of studies have consistently revealed promising results on the clinical utility of DBS for medically refractory obesity. The currently ongoing human trials are expected to further elucidate the role of neuromodulation in the treatment of obesity. Furthermore, other novel less-invasive methods such as optogenetics will hopefully emerge as an effective treatment in the near future.

### CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Table 3. Ongoing trials of DBS for patients with obesity

<table>
<thead>
<tr>
<th>Study</th>
<th>RCT numbers</th>
<th>Inclusion &amp; estimated sample size</th>
<th>Target</th>
<th>Parameters</th>
<th>Outcome measurements</th>
<th>Current status</th>
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<tbody>
<tr>
<td>De Salles et al. [43] (BLESS study, 2018)</td>
<td>NCT 02232919</td>
<td>BMI &gt; 40 kg/m² or &gt; 35 kg/m² with therapeutic failure Sample size: 6 patients</td>
<td>VMH; Bilateral</td>
<td>Low frequency (50 Hz)</td>
<td>1. Various psychiatric batteries 2. Weight changes 3. Indirect calorimetry and dual-energy X-ray absorptiometry (DEXA 62) 4. Food intake</td>
<td>Recruited</td>
</tr>
<tr>
<td>Wu et al. [48] (DBSLOC, NCT 03868670 2020)</td>
<td>BMI 40–60 kg/m² Sample size: 6 patients</td>
<td>NA; Bilateral</td>
<td>RNS® system (closed-loop DBS); Stimulation setting is not specified.</td>
<td>1. Adverse events 2. Decrease in loss of control episodes</td>
<td>Recruiting</td>
<td></td>
</tr>
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</table>

DBS: deep brain stimulation, RCT: randomized controlled trial, BMI: body mass index, VMH: ventromedial hypothalamus, NA: nucleus accumbens.
REFERENCES


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