Deep brain stimulation for obesity: past, present, and future targets

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The authors review the history of deep brain stimulation (DBS) in patients for treating obesity, describe current DBS targets in the brain, and discuss potential DBS targets and nontraditional stimulation parameters that may improve the effectiveness of DBS for ameliorating obesity. Deep brain stimulation for treating obesity has been performed both in animals and in humans with intriguing preliminary results. The brain is an attractive target for addressing obesity because modulating brain activity may permit influencing both sides of the energy equation—caloric intake and energy expenditure.

http://thejns.org/doi/abs/10.3171/2015.3.FOCUS1542

KEY WORDS deep brain stimulation; eating disorders; compound obesity; addiction; incentive salience; functional neurosurgery

Obesity is often defined as a body mass index (BMI) of > 30 kg/m², with a healthy BMI ranging from 18.5–24.9 kg/m². Using this definition, the WHO estimates that approximately 600 million people worldwide are obese. Sedentary lifestyles, urbanization, genetics, and an abundance of processed, high-calorie foods have contributed to a 4-fold increase in the prevalence of obesity in many countries across the world over the past 3 decades. The risks for increased morbidity and mortality rates associated with this condition, as well as the immense burden on health care systems coping with an increasing number of obese individuals, are at an all-time high and will likely worsen in years to come. For example, in the United States, the prevalence of obesity in adults has increased by nearly 50% in the past 2 decades. Moreover, this increase approaches 300% in American children. With 17% of adolescents being obese, and with 44% of those adolescents having metabolic syndrome, the prevalence of chronic diseases and burdensome pressures on health care systems will inevitably surge in the coming decades. Because of the consequences of this pandemic for society, investigators have intensified programs geared toward alleviating the burden of this debilitating disease.

Thanks to recent advances in molecular genetics and functional neuroimaging, functional neurosurgery is one of the most recently developed tools used to treat morbid obesity. Deep brain stimulation (DBS) in particular has been shown to improve symptoms in neurological disorders such as Parkinson’s disease, essential tremor, and dystonia in both adults and children. Additionally, increasing evidence points to DBS as an effective modality in the treatment of neuropsychiatric and degenerative disorders such as Tourette’s syndrome, obsessive-compulsive disorder (OCD), Alzheimer’s disease, and depression.

Leading theories for how DBS effects beneficial treatment outcomes suggest that it may disrupt abnormal oscillations in brain signaling and restore normal synchronization and coupling between various areas of the brain. As such, DBS targets for most currently treated disorders are not limited to one area because stimulation...
of several different targets may yield similar therapeutic efficacy. As currently used, DBS is effective when administered at what is considered high-frequency stimulation (HFS; that is, at > 100 Hz); however, there is evidence that the parameters of stimulation used in treating movement disorders may not be optimal for treating diseases such as obesity. In addition, targeting several brain structures with DBS to treat neuropsychiatric disorders has been shown to engender weight loss and reduce addiction, lending further evidence to the notion that multinodal circuits rather than a localized area of the brain are involved in many of these disorders. In this review, we discuss the targets and outcomes of DBS for managing obesity and the progression of the field. We also review the neurobiology and molecular physiology indicating potential novel targets in humans and discuss recent animal DBS and human functional imaging and neuropsychiatric studies.

**Past and Present DBS Targets for Obesity**

**Ventromedial Hypothalamus**

In 2008, Hamani and colleagues implanted bilateral DBS electrodes into the ventromedial hypothalamic VMH of a morbidly obese man who did not wish to undergo gastric bypass surgery because he knew he would still have the desire to eat. Stimulation of the VMH in this patient produced several unexpected side effects, including déjà vu and feelings of being in an alternate environment, yet had no effect on appetite. Confirming that stimulation of the VMH leads to undesirable effects, Wlent et al. reported that DBS induced panic attacks in a graded manner during HFS of the VMH, demonstrating that its stimulation causes adverse psychogenic manifestations. Since publication of these results, no additional trials involving DBS of the VMH have been reported.

**Lateral Hypothalamic Area**

In an FDA-approved pilot study by Whiting et al. to determine the safety of DBS of the lateral hypothalamic area (LHA), 3 morbidly obese patients in whom gastric bypass surgery had failed to control their condition underwent bilateral DBS of the LHA. While undergoing HFS of the LHA over 4 consecutive days, the patients were placed in a metabolic chamber that measured energy expenditure through gas exchange. The resting metabolic rate increased in 2 of the 3 patients during the treatment, and all 3 individuals reported a decreased urge to eat, as well as increased energy levels during active stimulation. These feelings reproducibly waned when the stimulation ceased. Follow-up examinations at 9 and 11 months under optimized settings indicated a weight loss of 12.3%–16.4% in 2 patients, and a 0.9% weight loss at the 16-month follow-up in the third patient. Although these reductions in weight were modest, defining effective outcomes by using absolute measures may be misleading for several reasons. For instance, more accurate measures of obesity exist, including body shape, BMI, waist-to-hip ratio, waist circumference, waist-to-stature ratio, and fat distribution, each of which predicts and reflects the associations to other medical comorbidities. Two-year follow-up metabolic analysis is currently ongoing in these 3 patients.

**Future DBS Targets for Obesity**

Serendipitous outcomes after DBS of various targets for the treatment of neuropsychiatric diseases, such as OCD and Tourette’s syndrome, has led researchers to investigate the role of various nuclei in the treatment of obesity. The brain circuits responsible for cravings associated with obesity due to overeating or with drug addiction share extensive overlap. Perhaps the most convincing account of such overlap was demonstrated by Mantione et al., who reported that stimulation of the nucleus accumbens (NAc) in a patient with OCD led to weight loss and enabled him to quit his long-standing nicotine habit. Similarly, other researchers documented remission of alcohol dependency in a patient who underwent DBS of the NAc for severe anxiety. In addition to such coincidental outcomes in DBS treatments of patients, animal models and advances in functional neuroimaging, molecular genetics, and neurobiology have yielded insight into targets whose stimulation could be of potential benefit in the obesity treatments based on DBS, and these will be discussed in the following.

Three broad categories of circuits are described below, each with unique, as well as with overlapping, roles in eating behaviors. The 3 categories are further subdivided into primary anatomical and physiological nodes. These target nodes are summarized in Table 1.

**Reward Circuitry, Cravings, and Addiction**

**Nucleus Accumbens**

The NAc is functionally divided into core and shell, the latter of which has been the primary focus of DBS. Studies using animal models of DBS have reported that the NAc affects activity in several brain centers involved in neuropsychiatric disorders. Electrical stimulation of the NAc in humans is safe and feasible, as demonstrated by studies in which the NAc was targeted for treating OCD, depression, Tourette’s syndrome, or alcoholism. Besides coincidental weight loss observed in a study in which the NAc was targeted to treat a different neuropsychiatric disorder, robust animal data support the NAc as a potential target for DBS in people with obesity.

For example, dopamine (DA) levels in the NAc of mice significantly decrease after highly palatable foods are removed from their diets. Furthermore, rodent NAc-lesioning models indicate significant reductions in weight and in binge-eating and food-hoarding behaviors. Activity in the NAc is increased in individuals who imagine eating highly palatable foods, and visual cues disproportionately stimulate the reinforcement circuits in obese and leptin-deficient individuals in anticipation of these visualized rewards. Interestingly, both HFS and low-frequency stimulation (≤ 50 Hz) effectively stimulate the NAc. As shown by Hamilton et al., stimulating the NAc with both DBS modalities attenuates drug-seeking behavior in rodents. In addition, activation of cannabinoid receptors in the NAc shell of rodents induces the expression of genes that are associated with increased food intake.

**Subgenual/Subcallosal Cingulate Cortex**

Several trials involving DBS of the subcallosal cin-
TABLE 1. Potential DBS targets for treating obesity

<table>
<thead>
<tr>
<th>Predominant Role in Obesity</th>
<th>Target</th>
<th>Key Modulatory Components &amp; Pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integration of nutritional status &amp; energy state</td>
<td>LHA (feeding center), VMH (satiety center), area postrema, &amp; NTS</td>
<td>Orexins, MCH, NPY, leptin, insulin, glucose, amino acids, POMC, CART, &amp; AGRP: mediators integrating the satiety &amp; feeding centers w/ the reward system. Area postrema associated w/ variations in meal sizes in rat models. NTS is primary satiety relay center to CNS from GI tract.</td>
</tr>
<tr>
<td>Hedonic food drive/incentive salience; primary limbic &amp; striatal structures</td>
<td>NAc,* VMPFC (medial OFC, SCC, anterior cingulate), DMmc, GP,* STN,* ALIC,* VPT, SNpr, AI, &amp; FO</td>
<td>Input from various homeostatic nuclei w/ integration into reward center (primarily DA mediated).</td>
</tr>
<tr>
<td>Cognitive control of feeding</td>
<td>dIPFC, LOFC, DMPc, &amp; VAT</td>
<td>Associative system responsible for executive decisions involved in eating habits &amp; nutritional valuation.</td>
</tr>
<tr>
<td>Integration of food-seeking behavior w/ caloric needs</td>
<td>PPN, IdTA, SI, &amp; median eminence</td>
<td>Peripheral integration of feeding control, primarily ACh-mediated influence on DA &amp; Glu signaling. Connectivity w/ hypothalamus.</td>
</tr>
<tr>
<td>Others</td>
<td>ST &amp; amygdala</td>
<td>Connections to limbic circuits (SCC, NAc shell) and LHA. Integration of associative, homeostatic, and reward mechanisms.</td>
</tr>
<tr>
<td>ITP</td>
<td></td>
<td>Connections via amygdalofugal pathway to &amp; from DMmc/Si.</td>
</tr>
<tr>
<td>LHB*, MHB*, &amp; SMT*</td>
<td>Limbic/BG input, output to DRN. Integration of reward w/ cognition &amp; emotion (VBDM), implicated in depression &amp; obesity.</td>
<td></td>
</tr>
</tbody>
</table>

ACh = acetylcholine; AGRP = agouti-related peptide; AI = anterior insula; ALIC = anterior limb of internal capsule; BG = basal ganglia; CART = cocaine- and amphetamine-regulated transcript; dlPFC = dorsolateral prefrontal cortex; DMmc = dorsomedial magnocellular thalamus; DMpc = dorsomedial parvocellular thalamus; DRN = dorsal raphe nucleus; FO = frontal operculum; GI = gastrointestinal; Glu = glutamate; GP = globus pallidus internus; ITP = inferior thalamic peduncle; IdTA = lateral dorsal tegmental area; LOFC = lateral orbitofrontal cortex; MCH = melanin-concentrating hormone; MHb = medial habenular nucleus; NPY = neuropeptide Y; NTS = nucleus of tractus solitarius; POMC = pro-opiomelanocortin; PPN = pedunculopontine nucleus; SI = substantia innominata; SMT = stria medullaris of thalamus; ST = stria terminalis; STN = subthalamic nucleus; VAT = ventral anterior thalamus; VBDM = value-based decision making; VPT = ventral posterior thalamus.

Asterisks indicate critical targets for obesity. *This brain region involves both limbic and cognitive circuits.

Deep brain stimulation targets for obesity

Table: Potential DBS targets for treating obesity

The anterior insula and frontal operculum are 2 areas that are involved in both food cravings and anticipatory food reward. Functional neuroimaging studies have reported hyperactivity in the anterior insula, as well as in other areas described below, in individuals who are obese. Addiction studies have identified a strong correlation between insular hyperactivity and addiction, suggesting that the insula could be a DBS target in obese patients who have eating habits resembling an addiction. In contrast, hypoactivity in the frontal operculum (and in the lateral OFC and striatum) observed in individuals who imagine consuming highly palatable foods is a predictor of future weight gain in some of these individuals.

Ventral Striatum, Dorsal Striatum, and Other Limbic System Nodes

Although the hypothalamus has long been known to govern homeostatic control of eating, recent evidence suggests that the striatum initiates the initial drive or motivation to seek nutrition. The ventral striatum (VS) is involved in those DA pathways dysregulated in obesity that are related to pleasure, reward, and addiction; normally, these phylogenetically preserved pathways may provide the impetus to invest energy into seeking out food. Once the homeostatic aspect of the VS activates food-seeking behavior, it uses outputs from the dorsal striatum to other areas that couple goal-directed behavior to motor responses. The hedonic aspect of obesity, also known as incentive salience, is a product of this circuit’s maladaptation. Interestingly, recent data suggest that certain hormones involved in feeding (insulin, ghrelin, and leptin) directly alter DA activity to increase or decrease feeding behaviors.

Teegarden et al. provided evidence of the adverse and maladaptive consequences of obesity by demonstrating that rodents are willing to be exposed to an adverse environment and to forgo some foods in order to obtain a more palatable meal. The reward of eating highly palatable foods has been repeatedly linked to the limbic system. It therefore follows that DBS at varying points along the circuit should counteract the hedonic drive to eat. In particu-
lar, such targets would prove most useful in individuals who have developed aberrant DA signaling in structures that have been physiologically altered after years of exposure to highly palatable foods.\textsuperscript{32}

Using functional MRI, Stice et al. not only demonstrated increased DA activity in the frontal operculum, lateral OFC, and striatum when human subjects thought of consuming highly palatable foods, but also that these altered DA activities help predict individuals at risk for future weight gain.\textsuperscript{88} Further support of the DA dysregulation theory in obesity comes from molecular studies that indicated that a decreased striatal DA\textsubscript{1} receptor availability is proportional to changes in BMI in obese individuals.\textsuperscript{100} Additional potential DBS targets along the limbic circuit include the anterior limb of the internal capsule, the ventromedial caudate and ventromedial prefrontal cortex (PFC) (including the medial OFC, and anterior cingulate), the putamen and ventral pallidum, the dorsomedial magnocellular thalamus, the hippocampus and subthalamic nucleus, the ventral posterior thalamus and ventral tegmental area (VTA), and the substantia nigra pars reticulata.

While the signaling cascades involved in the limbic system traverse many nodes, it is likely that only a handful of these nodes may be useful targets for DBS. For example, among several areas implicated in food cravings and reward, the OFC, amygdala, and striatum appear to encode the reward value of food.\textsuperscript{22,85,88} A recent pilot study verified the safety and feasibility in accurately targeting the VS in patients with OCD,\textsuperscript{89} supporting the safety and accessibility of the VS as a potential DBS target for treating obesity.

An interesting effect produced through stimulation of the VS is smiling and laughter, which highlights the involvement of emotional components in certain types of obesity. It reaffirms that eating disorders are linked to emotions; therefore, if stimulation affects mood, it may affect eating as well, and vice versa. In addition to being the primary reward center involved in DA transmission, the VTA (and NAc) have increased activity associated with cravings in response to nutrients such as lipids and sugars.\textsuperscript{97} Indeed, there is a growing consensus that targeting areas such as the VTA, NAc, and SCC could produce successful clinical outcomes in DBS for obesity.\textsuperscript{40,90}

Satiety Signaling

Ventromedial Hypothalamus

Lesioning (or HFS) of the well-known “satiety” center, the VMH, diminishes feeding in animal models.\textsuperscript{33,41,75} Kullmann and colleagues recently showed how the LHA and VMH are functionally connected to other brain regions in both healthy-weight and obese individuals.\textsuperscript{46} The authors reported that the LHA network was more robustly connected to the anterior cingulum, dorsal striatum, and frontal operculum, while the VMH made stronger connections to the medial OFC and the NAc. These observations suggest that food-mediated activation of components of the dopaminergic reward system affect the VMH and LHA differently and that stimulation of the VMH and stimulation of the LHA activate distinct circuits. The VMH is smaller and more challenging to access than the LHA, and previous trials involving VMH stimulation resulted in side effects due to spread of current to adjacent nuclei.\textsuperscript{26,105} With the advent of new DBS technologies\textsuperscript{29,58} more precise targeting of the VMH with smaller microcontacts to reduce the spread of current could lead to a resurgence in the interest of targeting the VMH for obesity treatment.

Amygdala, Stria Terminalis, and Inferior Thalamic Peduncle

Orexinergic neurons (ONs), located primarily in the LHA, have long been known to modulate feeding behavior through homeostatic and associative mechanisms.\textsuperscript{80,103} Recent rodent studies have unveiled novel downstream effects of ONs. The amygdala is the prime target of the LHA ONs, and the striatal terminals account for much of the connectivity between the amygdala and the VMH.\textsuperscript{8,103} Findings in many animal models have implicated this major pathway in the valuation of highly palatable foods.\textsuperscript{97,103} Certain neuropeptides of the ONs, such as orexins, have also been shown to be linked to drug seeking and addiction, including food addictions that contribute to obesity.\textsuperscript{14,103} Furthermore, ONs respond not only to internal energy states, but also to external food-related cues, particularly when they override satiety.\textsuperscript{103} Another major modulatory nucleus of thalamocortical projections to and from the OFC is the inferior thalamic peduncle, which lies in close proximity to the striatal terminalis and has been shown to elicit behavioral modifications in patients who have had DBS of the inferior thalamic peduncle for treating OCD.\textsuperscript{37}

Energy Homeostasis and Nutritional Gauging

Habenula and Stria Medullaris of Thalamus

The lateral habenula (LHb) regulates several essential physiological features, such as sleep patterns and responses to stress and pain, and it also plays a critical role in the neurobiological underpinnings of several psychiatric illnesses.\textsuperscript{32,109} By integrating DA-reward pathways (via the stria medullaris of thalamus) with cognitive processes and emotion (that is, via connections to, and modulation of, serotonergic output of the dorsal raphe nucleus),\textsuperscript{109} the LHb participates in motivational or value-based decision making.\textsuperscript{32,34} Nonhuman primate models have provided insight into the major reward inputs of the LHb, which are likely also present in humans. By stimulating varying areas of the striatum and globus pallidus, Hong and Hikosaka identified alternating excitatory and inhibitory inputs to the LHb from the basal ganglia.\textsuperscript{74}

Interestingly, rodent obesity models implicate the medial habenula in diet-induced obesity.\textsuperscript{86} Smith et al. have postulated a homeostatic mechanism that normally limits overeating (and eventual obesity) as a behavior that is mediated through the medial habenula.\textsuperscript{86} The LHb is currently a DBS target of interest in patients with severe refractory depression,\textsuperscript{32,83} and its role in value-based decision making may potentially have significant implications for using it as a target in DBS to treat obesity.

Area Postrema and Nucleus of Tractus Solitarius

Orexins and melanin-concentrating hormone are produced in the LHA and mediate feeding behavior in differ-
ent ways.\textsuperscript{50,83} Findings in animal models indicate that the area postrema and the nucleus of tractus solitarius have links to the LHA indirectly through the orexin-mediated pathways and that the hyperphagic effects of melanin-concentrating hormone rely on stimulation of the forebrain, whereas those of orexin-A and also of neuropeptide Y do not.\textsuperscript{5,31} Additionally, the area postrema and nucleus of tractus solitarius have effects on meal size, but not on meal frequency.\textsuperscript{1} The area postrema and the nucleus of tractus solitarius both promote orexin-mediated feeding behaviors, suggesting that they represent a robust link to the feeding centers in the LHA. The nucleus of tractus solitarius is the primary satiety relay center to the CNS from the gastrointestinal tract via N-methyl-D-aspartic acid (NMDA) receptor–mediated activation by vagal afferents,\textsuperscript{9,13,36,94} making DBS of this region an attractive proposition. In addition, some neurons within the nucleus of tractus solitarius selectively respond to essential amino acids according to various nutritional states.\textsuperscript{97} Because both of these structures are surrounded by critical structures of the brainstem, cannulating them may increase the risk for injury of the critical structures, which may account for a lack of interest in this procedure.

**Conscious Rationalization of Food-Eating Behavior**

**Cognitive Circuit Targets**

The limbic system is largely responsible for the emotional and rewarding components of eating,\textsuperscript{50,80} and the cognitive, or “associative,” loop is mainly engaged in the processes involved in the conscious decisions about eating.\textsuperscript{80} The cognitive loop may be responsible for overriding the reward aspect of eating and may be dysfunctional or overcome by the limbic system in obese individuals who overeat because of a lack of self-control.\textsuperscript{36,90} Candidate DBS nodes in these regions for treating obesity include the dorsolateral PFC, dorsomedial parvocellular thalamus, globus pallidus internus, lateral OFC, and ventral anterior thalamus. Multiple imaging studies have indicated that obese individuals have increased responses to food in areas such as the striatum, operculum, and medial OFC and decreased responses in regions involved in inhibitory control, such as the PFC.\textsuperscript{28,46,79}

**Additional Brain Targets**

Nicotinic and muscarinic acetylcholine signaling is largely responsible for learned maladaptive behaviors, including overeating.\textsuperscript{72} The long-term modulatory activity of acetylcholine accounts for the regulatory release of, and responsiveness to, the more acute functions of other neurotransmitters (namely DA and glutamate) implicated in the central dysregulation observed in obesity.\textsuperscript{6,10,63,22,74,107,108} The neuromodulatory effects of acetylcholine on these other circuits and its significant role in coordinating food-seeking behavior and caloric needs\textsuperscript{39} all suggest cholinergic signaling as another potential avenue of DBS treatment. Various nuclei related to the peripheral integration of feeding control exhibit abrupt adaptation in response to environmental cues.\textsuperscript{71,72} The laterodorsal tegmental and pedunculopontine areas are prime examples of such targets and supply cholinergic input to the hypothalamus,\textsuperscript{24,138} and DBS of the pedunculopontine areas was accomplished in 2 patients with progressive supranuclear palsy.\textsuperscript{50}

A source of cholinergic signaling and an area that has been safely targeted in the treatment of individuals with cognitive decline\textsuperscript{6,44} is the nucleus basalis of Meynert. The potentiating effects of these cholinergic pathways are partially responsible for the learned behaviors and adaptive changes associated with eating disorders, which makes these pathways strong candidates for DBS in the treatment of obesity. Other examples of nodes with functional connectivity to the hypothalamus through cholinergic signaling include the substantia innominata, which is activated by food presentation in primates subjected to fasting\textsuperscript{72,77} and the median eminence, which releases corticotropin-releasing hormone, leading to downstream effects on metabolism.\textsuperscript{72}

**Discussion**

**Compound Obesity**

Compound obesity is defined here as obesity due to the maladaptive processes produced by dysfunction in one or more signaling pathways, for example, in those originating from the LHA and leading to a domino effect resulting in aberrant signaling in multiple circuits and nodes. This irregular signaling leads to dysregulation of the limbic and associative circuits involved in the hedonic and homeostatic aspects of food-seeking behaviors. Examples of this type of dysregulation in obesity may include those arising from genetic defects in the insulin pathway or from nutritional deficiency, leading to increased food consumption to counteract the underlying signaling defects. In this setting, hyperphagia might lead to increased activity in the dopaminergic reward system, which has roles in addiction and craving not only for drugs, but also for lipids and sugars.\textsuperscript{99}

**Multiplicity**

Last, we propose a multipronged approach to the treatment of compound obesity with DBS. Given the high number of connections among the various nuclei associated with obesity, simultaneous DBS of more than one brain target has shown some efficacy in patients with co-occurring essential tremor or with Parkinson’s disease.\textsuperscript{1,2,11,96} Therefore, because compound obesity by definition is the result of a malfunction in more than one bodily system, effective treatment of this condition likely requires modulation at both individual and multiple nodes. Concomitant stimulation of the LHA and NAc, ventromedial PFC, or of various combinations thereof may be beneficial in patients with a long history of compound obesity and whose neural networks have structurally and functionally adapted to the disease through long-term plasticity.

The LHA remains the primary DBS target for treating obesity because the LHA is the central hub for all circuits involved in the drive to eat.\textsuperscript{30,97,103} In addition to the robust connectivity between the LHA and the limbic system, data supporting it as a DBS target include the modulatory effects of DBS on the resting metabolic rate in patients,\textsuperscript{104} the recent discovery of amino acid–sensing pathways that connect the stomach to the LHA,\textsuperscript{47} and the discovery of...
obesity-related genes expressed exclusively by ONs in the LHA. Because the ONs of the LHA control diet-induced thermogenesis, reward circuits, energy homeostasis, and satiety, the LHA continues to be the target of choice for addressing obesity due to metabolic dysregulation (in peripheral and central areas), genetics, or food addiction.

Rapid technological and engineering advances are molding the future of DBS. The availability of new electrodes is popularizing systems with constant current (as opposed to constant voltage, regardless of impedance), directional or steerable current, and closed-loop devices that activate via aberrant signaling when needed. These advances are contributing to improved outcomes and new applications for DBS. Adoption of DBS by multidisciplinary teams responsible for the treatment of various neuropsychiatric disorders continues to increase, and the number of prospectively controlled trials for these disorders is also increasing. Although many clinicians are aware of the life-changing effects of neuromodulation, reports of the placebo effects of DBS (up to 39%) likely contribute to the reluctance of skeptical practitioners to accept this intervention as valid and effective. The community must therefore remain steadfast in the objective and accurate reporting of the clinical benefits and possible shortcomings that such surgeries may yield.

Conclusions

Electrical stimulation of various combinations of brain targets may ultimately improve willpower, decrease hedonic drive, increase metabolic rate, and enhance or inhibit, as necessary, the functionality of those nodes and pathways that are altered in individuals with obesity. Although many imaging, molecular, and animal studies implicate various neural nodes in modifying the pathogenesis of obesity, DBS of the LHA remains the neurosurgical treatment of choice in the treatment of this disease.

References

Hauptman JS, DeSalles AA, Espinoza R, Sedrak M, Ishida
Hong S, Hikosaka O: Diverse sources of reward value signals in the basal ganglia nuclei transmitted to the lateral habenula in the monkey. Front Hum Neurosci 7:778, 2013
Kaizer RR, da Silva AC, Morsch VM, Corrêa MC, Schet-
Müller UJ, Sturm V, Voges J, Heinez HJ, Galazky I, Hel-
70. Pérez-Morales M, López-Colomé AM, Méndez-Díaz M, Ruiz-Contreras AE, Prospéro-García O: Inhibition of diacylglycerol lipase (DGAL) in the lateral hypothalamus of rats prevents the increase in REMs and food ingestion induced by PAR1 stimulation. *Neurosci Lett* 578:117–121, 2014
92. Teegarden SL, Scott AN, Bale TL: Early life exposure to a high fat diet promotes long-term changes in dietary preferences and central reward signaling. *Neuroscience* 162:924–932, 2009


Author Contributions

Conception and design: Dupré, Whiting. Acquisition of data: Dupré. Analysis and interpretation of data: Dupré. Drafting the article: Dupré. Critically revising the article: Tomycz, Oh. Reviewed submitted version of manuscript: all authors. Administrative/technical/material support: Whiting. Study supervision: Whiting.

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