Class II obesity (BMI 35–40 kg/m²) and class III obesity (BMI > 40 kg/m²) are serious medical conditions with an increasing global prevalence. Current estimates in the adult population in western countries vary from 3% to 8.5% for class II, and 1%–3.1% for class III obesity, depending on geographical region. These numbers continue to increase. There is an increased mortality rate when BMI rises above 30, with a decreased life expectancy of 10 years in class III obesity. Furthermore, obesity has a significant negative impact on quality of life. Weight loss improves quality of life and reverses comorbidities, such as dyslipidemia and diabetes mellitus. Success rates for various interventions that aim to re-

Therapeutic potential of deep brain stimulation of the nucleus accumbens in morbid obesity

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OBJECTIVE Morbid obesity is a growing problem worldwide. The current treatment options have limitations regarding effectiveness and complication rates. New treatment modalities are therefore warranted. One of the options is deep brain stimulation (DBS) of the nucleus accumbens (NAC). This review aims to summarize the current knowledge on NAC-DBS for the treatment of morbid obesity.

METHODS Studies were obtained from multiple electronic bibliographic databases, supplemented with searches of reference lists. All animal and human studies reporting on the effects of NAC-DBS on body weight in morbidly obese patients were included. Articles found during the search were screened by 2 reviewers, and when deemed applicable, the relevant data were extracted.

RESULTS Five relevant animal experimental papers were identified, pointing toward a beneficial effect of high-frequency stimulation of the lateral shell of the NAC. Three human case reports show a beneficial effect of NAC-DBS on body weight in morbidly obese patients.

CONCLUSIONS The available literature supports NAC-DBS to treat morbid obesity. The number of well-conducted animal studies, however, is very limited. Also, the optimal anatomical position of the DBS electrode within the NAC, as well as the optimal stimulation parameters, has not yet been established. These matters need to be addressed before this strategy can be considered for human clinical trials.

https://thejns.org/doi/abs/10.3171/2018.4.FOCUS18148

KEYWORDS obesity; food addiction; deep brain stimulation; nucleus accumbens; reward
TABLE 1. Electronic databases and other resources

<table>
<thead>
<tr>
<th>Resource</th>
<th>Date of Search/Last Issue Searched</th>
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<tbody>
<tr>
<td>Cochrane Library</td>
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<tr>
<td>EMBASE</td>
<td>Issue 1/2018</td>
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<tr>
<td>MEDLINE</td>
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<td>psycINFO</td>
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<td>CINAHL</td>
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<tr>
<td>Gray literature</td>
<td>Until 1/1/2018</td>
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<td>AMED</td>
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<tr>
<td>Web of Science Proceedings</td>
<td></td>
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<tr>
<td>Ongoing trials</td>
<td>Until 1/1/2018</td>
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<tr>
<td>Australian New Zealand Clinical Trials Registry</td>
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<tr>
<td>ClinicalTrials.gov</td>
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<td>EU Clinical Trials Register (EU-CTR)</td>
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<td>ISRCTN</td>
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<tr>
<td>Brazilian Clinical Trials Registry (ReBec)</td>
<td></td>
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<tr>
<td>Chinese Clinical Trial Registry, 31 March 2014</td>
<td></td>
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<tr>
<td>Clinical Trials Registry—India, 31 March 2014</td>
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<tr>
<td>Clinical Research Information Service—Republic of Korea</td>
<td></td>
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<tr>
<td>Cuban Public Registry of Clinical Trials</td>
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<td>German Clinical Trials Register</td>
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<td>Iranian Registry of Clinical Trials</td>
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<td>Japan Primary Registries Network</td>
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<td>Pan African Clinical Trial Registry</td>
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<td>Sri Lanka Clinical Trials Registry</td>
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<td>The Netherlands National Trial Register</td>
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<td>Thai Clinical Trials Register (TCTR)</td>
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due BMI has a large interindividual variability. This variability underlines the fact that causes for obesity are multifactorial. Compared to behavioral and pharmacological interventions, bariatric surgery (BS) is currently the most effective treatment in severe obesity. BS results in weight loss ranging from 20% to 60% of total body weight with a concomitant improvement in morbidity. However, 20%–40% of patients undergoing BS fail to lose sufficient weight or regain weight after initial weight loss, which may be attributed to personality traits and pathological eating behavior.

More knowledge about neurobehavioral mechanisms causing morbid obesity is needed to develop tailored therapies adjustable for individual patients. Development of new treatment strategies for obesity cannot remain “brainless.” In the brain, the nucleus accumbens (NAC) is an anatomical structure located in the ventral striatum that plays a major role in the reward system. The NAC regulates motivation and action. Hyperactivity of the NAC has been established to play a role in obesity, ingestion, and reward-related learning: showing pictures of high-caloric food induces activation of the NAC in humans. This activation is more prominent in obese subjects compared to nonobese subjects in a fasted state. After testing, patients with activated NAC are more likely to eat. In a fed state, the NAC remains more active in obese persons.

In certain cases, obesity may develop as a form of addiction much like other addiction disorders, such as alcohol, drugs, and gambling. The incentive sensitization theory, which was developed in the context of drug addiction, states that food cues can play a role in visual attraction and strengthen the desire to eat. This effect is stronger in overweight persons. The NAC plays a major role in incentive sensitization in drug addiction.

The NAC has already proven to be a successful target of deep brain stimulation (DBS) for other neuropsychiatric diseases and this review aims to summarize the available evidence regarding a potential role for DBS of the NAC in the treatment of obesity.

Methods

Sources of potentially relevant records were identified (Table 1). A query to extract relevant records from these resources was formulated (Table 2). Retrieved records were screened by title, abstract, and full text when deemed potentially applicable and relevant data were extracted. Any report on the effect of DBS of the NAC in human or animal subjects on body weight change or caloric intake was included, if an English abstract was available. References of relevant original articles and reviews were checked for additional relevant papers.

Results

Searching the different databases according to the aforementioned strategy yielded 28 records in Medline, 54 records in Embase, 68 records in Web of Science (WOS), 5 records in the Cochrane Library, 16 records in the International Clinical Trials Registration Platform (ICTRP), and 3 records in a combined search of the Allied and Complementary Medicine (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and psycINFO databases. After screening these articles for title, abstract, full text, and filtering duplicates, 5 relevant papers discussing animal experimental data, 3 case reports, and 3 relevant reviews were identified. Two human trials in progress were identified investigating DBS for obesity. The references of the original articles and relevant reviews were checked for relevant papers, which yielded no additional studies (Fig. 1).

Animal Experimental Data

The animal experimental data are summarized in Table 3. In rodents, the NAC is divided into three functionally distinct subregions, i.e., the core, the lateral shell, and the medial shell, but in humans these anatomical subdivisions are controversial.

Halpern et al. investigated the effects of DBS of the left NAC shell on obesity in mice. Eight mice were put on a high-fat diet for 16–20 weeks and then grouped into 4 weight-matched pairs. After stabilization of body weight and caloric intake, half of the mice were put on a 4-day trial of continuous high-frequency stimulation (150 μA,
60 μs, 160 Hz) and compared to their matched controls regarding weight and intake. A crossover trial was performed afterwards. Video monitoring revealed no signs of motor side effects that could affect the ability to eat. A significant decrease from baseline body weight was detected after DBS.

These authors also investigated the effects of DBS of the left NAC on binge eating in 10 mice. The electrode was placed in the NAC shell of 8 mice, and in the NAC core of 2 mice. The mice were put on a limited access protocol to high-fat food, known to induce binge eating. After stabilization of binge size, a protocol was started with high-frequency stimulation on alternating days (150 μA, 60 μs, 160 Hz). Video monitoring revealed no signs of motor side effects that could affect the ability to eat. The number of calories consumed during the binge was significantly lower on days with stimulation in the mice with NAC shell stimulation, compared to days without. No significant effects were found in the 2 mice with NAC core stimulation.

van der Plasse et al. tested the effect of DBS of the lateral NAC shell, medial NAC shell, and NAC core on sucrose preference, food intake, and motivation to respond for sucrose under a progressive ratio schedule for reinforcement in rats. The groups consisted of 23 medial NAC shell, 20 lateral NAC shell, and 21 NAC core rats. Outcomes were compared intraindividually to the baseline situation (implantation, connection to the wiring system without stimulation) and within groups. Stimulation intensity was varied, while frequency and pulse duration were kept stable at 130 Hz and 60 μs. Stimulation at 100 μA in the medial NAC shell increased intake of normal chow. Stimulation at 100 μA in the lateral NAC shell reduced the number of sucrose rewards obtained during the progressive ratios. For the lower intensities, no effects were observed. There was no influence of stimulation on sucrose preference. No effects were observed during core stimulation.

Zhang et al. evaluated the effect of DBS of the NAC shell on intake and weight gain in rats on a high-fat diet. Sixteen rats were put on a high-fat diet leading to diet-induced obesity and 16 received normal chow. All rats were implanted with left-sided medial shell electrodes, but only half of the animals in each group received stimulation.

TABLE 2. Applied search strategy

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<thead>
<tr>
<th>Database</th>
<th>Search Strategy</th>
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<tr>
<td>Embase</td>
<td>striat*:ab,ti OR accumbens:ab,ti OR nacc:ab,ti OR nac:ab,ti OR acb:ab,ti OR na:ab,ti AND (dbs:ab,ti OR ‘deep brain stimulation’:ab,ti) AND (obesit*:ab,ti OR overweight:ab,ti OR weight*:ab,ti OR intake:ab,ti OR eat*:ab,ti) AND [embase]</td>
</tr>
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</table>
Stimulation settings were 500 μA, 130 Hz, and 90 μs. The stimulated normal chow rats did not alter their caloric intake or their weight gain compared to their sham controls, but the animals with diet-induced obesity showed a clear decline in caloric intake and weight gain as compared to their controls.

Doucette et al.21 investigated the effect of bilateral high-frequency stimulation of the NAC core on binge size in a rat model for both “chronic” and “relapse to chronic” binge eating. Rats were placed on a diet to induce binge eating. Rats received either active or sham stimulation. After testing in the “chronic” binge eating state they did not engage in binge sessions for a month. Binge sessions were resumed (relapse to chronic) and active and sham stimulation states were applied again. Binge size was significantly reduced in the chronic binge eating state, but not in the “relapse to chronic” state following stimulation.

Wei et al.67 implanted right-sided unilateral electrodes in either the NAC shell (n = 10) or NAC core (n = 10) of rats. High-frequency stimulation in the shell, but not the core, induced decreased high-fat food intake during and after stimulation. In this experiment, a recording electrode was concomitantly placed in the lateral hypothalamic area. Nearly all lateral hypothalamic neurons were inhibited during high-frequency stimulation of the NAC shell, whereas the firing rate of the lateral hypothalamic neurons was hardly influenced during high-frequency stimulation of the NAC core. In a microdialysis study, this group showed that high-frequency stimulation of the NAC shell, but not the NAC core, induced increased γ-aminobutyric acid (GABA) levels in the lateral hypothalamic area during and after stimulation.

Even though the number of preclinical studies is limited, and study objectives and methods vary, common denominators can be identified. High-frequency stimulation of the NAC shell has a consistent effect of reduction of food intake and weight (gain) on animals with the various baseline conditions: obesity,27,73 binge eating,8 normal diet,63 and food deprivation.68 There is one exception in which high-frequency stimulation of the lateral NAC shell led to an increase of normal chow in rats on a regular diet.63 There is no effect of NAC core stimulation in all baseline conditions18,21,27,68 except for a reduction on binge size in one experiment.21 However, this effect diminished after a 1-month period in which binge sessions were interrupted.21 Taken together, these studies indicate that the effect of high-frequency stimulation of the NAC shell, especially the medial shell, is the most effective part of the NAC to treat obesity in animal experiments. There is no difference in the effect of uni- or bilateral high-frequency stimulation.

Case Reports

The case reports are summarized in Table 4. Mantione et al.45 reported a case of a 47-year-old woman with nicotine dependence and obesity, who was treated with bilateral NAC DBS for therapy refractory obsessive-compulsive disorder (OCD). With a weight of 107 kg and a length of 1.70 m, her BMI was 37 kg/m². Stimulus parameters were 3.5 V, 90 μs, and 185 Hz. In the first 10 months after implantation she gained weight and reached a BMI of 39 kg/m². After this period when most of her OCD symptoms had significantly improved, she chose to quit smoking and lose weight. She succeeded at both, losing 44 kg resulting in a BMI of 25 kg/m². She maintained this weight at the 2-year follow-up.

Harat et al.67 reported a 19-year-old woman steadily gaining weight after having undergone craniopharyngioma surgery. When she weighed 151.4 kg, she underwent

<table>
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<tr>
<th>TABLE 3. Summary of animal experimental data</th>
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<tbody>
<tr>
<td>Authors &amp; Year</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Halpern et al., 2013</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Van der Plasse et al., 2012</td>
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<td>Zhang et al., 2015</td>
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<td>Doucette et al., 2015</td>
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<tr>
<td>Wei et al., 2015</td>
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All subjects were rodents. In all experiments high-frequency stimulation was applied.

* Mice.
† Rats.
implantation with a bilateral NAC DBS system. After 3 months of stimulation, she had lost 19.6 kg, reaching a BMI of 46.2 kg/m². Tronnier et al. present a case of a 40-year-old woman who was treated with NAC-DBS to treat severe depression as a primary goal and obesity (BMI 66 kg/m²) as a secondary goal. She underwent gastric bypass surgery 6 months before DBS. She lost 1.75 kg/month afterwards. This rate accelerated to 2.85 kg/month after DBS.

Human Trials in Progress

Two human trials in progress were identified. One is titled “Deep Brain Stimulation For Morbid, Treatment-Refractory, Obesity” (clinicaltrials.gov identifier: NCT01512134). This trial is a safety and efficacy study. It included 5 patients at least 24 months after gastric bypass surgery without evidence of a sustained improvement in BMI for at least 6 months. The intervention tested is DBS, but the target area is not specified. The primary outcome is percentage of excess weight loss. The study is completed, but no results are published to date. The second study is titled “PINS Stimulator System for Deep Brain Stimulation For Morbid, Treatability-Refractory, Obesity” (clinicaltrials.gov identifier: NCT02254395). This Phase 1 study aims to enroll 8 morbidly obese (BMI > 40 kg/m²) patients for DBS. However, the target is not specified and the study is not yet recruiting.

Reviews

Three reviews were conducted, two by Halpern et al. and one by Betry et al. These reviews yielded no additional relevant original research papers. Their overall conclusion was that the NAC is a potential target for DBS in the treatment of therapy-refractory obesity. These reviews were all published more than 5 years ago.

Discussion

The rationale for NAC stimulation to target eating disorders is based on the established role of the NAC in ingestive behavior and on the accumulating evidence that obesity, at least in part, can be considered the result of addictive behavior toward food. The latter is relevant because positive results of NAC-DBS for compulsions and addiction are increasingly available.

The NAC and the Reward Circuitry

The NAC is part of the so-called reward circuitry. The term “reward” as used in scientific literature may designate: 1) pleasure or hedonia, 2) appetitive motivation, and 3) reinforcement. These are discrete entities that do not need to coincide. Focusing on motivated behavior, different aspects can be dissociated through neurochemical or other manipulations, such as “wanting” vs “liking,” or “preparatory/appetitive” vs “consummatory.”

Anatomically, reward is mediated by a corticobasal ganglia network in which the basal ganglia fulfill the role of a “motivation-to-movement” interface. The NAC receives its inputs primarily from the olfactory and visceral-associated insula, from the ventromedial prefrontal cortex, and most likely from the medial prefrontal cortex on the one hand, and from the amygdala and the hippocampus on the other. These projections synapse on single fast-spiking GABAergic interneurons, which are believed to integrate the different cortical inputs before the information is transferred to the medium spiny projection cells. Output is delivered mainly to the pallidum and the midbrain (ventral tegmental area and medial substantia nigra) and to a lesser extent to the lateral hypothalamus and the extended amygdala.

The NAC and Its Relation to Ingestive Behavior and Obesity

There is an association between activity and manipulation of activity in several subregions of the NAC and ingestive behavior in rodents. Upon presentation of a conditioned stimulus (a retractable lever) associated with sucrose delivery, a subpopulation of neurons in the NAC exhibits increased firing, while other subpopulations of neurons show suppressed activity compared to baseline. This activity is associated with approach behavior to the stimulus and is not present upon presentation of a comparable cue (another lever) unrelated to sucrose delivery. These cue-related neural responses may represent neural responses in the human reward circuitry and model the compulsive nature of addiction in humans.

In the anterior NAC, multiple sites have been identified that show a decreased activity just before and during feeding. Stimulation at these sites at 15 or 40 Hz disrupts licking of water with or without sucrose. Neuroimaging studies show a relationship between activation of the NAC and obesity. Several studies show an increased activation of the NAC in obese individuals in response to food stimuli. A comparison of 12 age- and sex-matched individuals with and without obesity showed an increased activation of the NAC in the obese individuals in response to both pleasant and unpleasant taste sensations. Obese women exhibit greater activity in the NAC in response to food stimuli compared to age- and sex-matched controls. These findings support the notion that the NAC may play a role in the development and maintenance of obesity.”

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Primary DBS Indication</th>
<th>Intervention</th>
<th>Weight Loss</th>
</tr>
</thead>
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<tr>
<td>Mantione et al., 2010</td>
<td>47, F</td>
<td>OCD</td>
<td>Bilat NAC</td>
<td>44 kg, BMI reduced from 39 kg/m² to 25 kg/m²</td>
</tr>
<tr>
<td>Harat et al., 2013</td>
<td>19, F</td>
<td>Obesity after craniopharyngioma surgery</td>
<td>Bilat NAC</td>
<td>19.6 kg, BMI reduced from 53 kg/m² to 46 kg/m²</td>
</tr>
<tr>
<td>Tronnier et al., 2018</td>
<td>40, F</td>
<td>Depression</td>
<td>Bilat NAC</td>
<td>30 kg, weight loss (1.75 kg/month) after gastric bypass surgery, which accelerated after DBS (2.85 kg/mo)</td>
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to high-calorie food items than do healthy-weight control subjects. In a cohort of 58 first-year female students, higher activation at baseline in the left NAC upon presentation of an image of palatable food was associated with increased weight gain after 6 months. Higher activity of the NAC in response to food images in obese individuals at the start of a weight loss program is predictive of less weight loss after 9 months. Thus, a higher activity in the NAC in response to food stimuli is a characteristic of the obese state and is predictive of weight gain.

**Obesity: An Addiction to Palatable Food?**

The preclinical evidence of addictive properties of food is numerous. A recent review summarizes the evidence from animal experimental research showing that the neurochemical and behavioral effects of intermittent and excessive sugar intake resemble those of other known substance addictions. Fat also induces behavioral and chemical alterations related to addiction, although the typical opioid-like withdrawal is not observed in rats, in contrast to sugar.

Clinical data are also becoming increasingly available, most notably in the weight-loss surgery population. Patients in whom BS fails report an unchanged daily intake of food. After gastric bypass surgery 25%-39% of patients report “loss of control” eating behavior, which is associated with less weight loss. Approximately half of the people seeking medical attention for the treatment of their obesity meet the criteria for binge-eating disorder. This subpopulation loses less weight after BS. This supports the view that especially refractory cases of obesity could be attributed to some form of food addiction.

**DBS of the NAC and Addiction**

DBS of the NAC has positive effects on several forms of compulsive behavior. Experiments in rats show a reduction of addictive behavior related to alcohol and cocaine. Some clinical evidence indicates a favorable outcome of DBS with regard to compulsions in patients with obsessive-compulsive behavior. Furthermore, beneficial effects were reported in a case series with positive effects on alcoholism.

**Current Evidence for DBS of the NAC in Obesity**

From a theoretical point of view the NAC makes a suitable target for DBS in the treatment of obesity, especially the forms related to food addiction. There are, however, only 5 animal experimental papers actually testing this concept. This leaves many questions still unsolved. In the study by Halpern et al. only two subjects received stimulation of the NAC core, which is insufficient to make a statement with regard to the effectiveness of stimulation in this region. Furthermore, only one frequency profile was used. It is known that the effects of stimulation may differ depending on the frequency used, and some effects on feeding behavior have been reported at stimulation at lower frequencies. In the first experiment, stimulation was only performed over a 4-day course, and even over this period the effect seemed to diminish over time. This leaves the long-term effects of DBS questionable, especially because relapse is a challenge in the treatment of obesity.

Zhang et al. observed a strong effect on weight gain but did not monitor for side effects. Because the basal ganglia plays an important role in locomotion, it would be warranted to monitor for such side effects. Furthermore, it is well investigated that manipulations particularly in the caudal medial shell can induce fearful antipredator behavior. These occur generally between 0.48 and 1.4 mm ahead of bregma. Because the anterior location of the electrodes in these experiments was 1.2 mm, the possibility of such an undesirable mechanism of weight loss cannot be ruled out. The third animal experimental paper by van der Plasse et al. assessed influence of NAC-DBS on intake in lean rats and found no significant effects. This finding is supported by the findings of Zhang’s group: no effects of stimulation were observed in the lean rats. One of the hypotheses on the mechanism of action of DBS is a disruption of pathological oscillations to restore rhythmic activity and synchronization. In the absence of a pathological condition in lean rats, there are no pathological oscillations that can be modulated by DBS and these results can therefore not be extrapolated to the obese population. However, the decreased motivation to work for a sucrose reward does support the view that DBS of the NAC could modulate a dysfunctional reward mechanism in food addiction.

Results of the study by Doucette et al. are consistent with the experiments by Halpern et al. Apart from the limitations that are thoroughly discussed in the paper (e.g., unequal group sizes at completion) the fact that the stimulation period was limited to the binge session needs to be addressed. Reduction of binge size might therefore be attributed to (motor) side effects and not to the actual alternation of the reward circuitry in the brain.

Wei et al. show that NAC shell (but not NAC core) stimulation inhibits palatable food consumption after food deprivation. The suggested underlying mechanism is that stimulation of the shell’s GABAergic projections to the lateral hypothalamic area decreases the perceived reward value of that food and therefore may disturb the process of developing obesity.

Three case reports describe weight loss in obese patients following bilateral high-frequency stimulation of the NAC. However, two of the patients represent very specific subpopulations—obesity with a possible relationship to OCD and hypothalamic obesity—of the total obese population. The third patient suffered from depression. She underwent BS and DBS was performed before peak weight loss was to be expected (18 months after BS). A marked accelerated weight loss is reported after DBS. This may have been due to a dual effect of both treatments. Thus, these studies report on promising observations. However, because of their nature as single case reports, their value is limited.

**Conclusions**

With the increasing incidence of morbid obesity and the significant failure rates of current treatment modalities, new treatment strategies are warranted. The large interin-
individual variability in success rates for various interventions emphasizes the fact that causes for obesity are multifactorial. Animal experimental data and anecdotal case reports show promising results of DBS of the NAC in the treatment of obesity. The number of well-conducted animal studies, however, is very limited and the optimal anatomical target within the NAC and stimulation parameters have not been established. These matters need to be addressed before this strategy can be considered for clinical trials in humans. Multidisciplinary cooperation between clinicians (obesity specialists, endocrinologists, bariatric surgeons, psychiatrists, psychologists, neurophysiologists, and neurosurgeons) and preclinicians is warranted to address these issues and refine patient selection for clinical trials in DBS for obesity.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Oterdoom, G van Dijk. Acquisition of data: Oterdoom, G van Dijk, Verhagen. Analysis and interpretation of data: Oterdoom, G van Dijk. Drafting the article: Oterdoom, G van Dijk. Critically revising the article: all authors. Reviewed submitted version of manuscript: Oterdoom. Approved the final version of the manuscript on behalf of all authors: Oterdoom. Administrative/technical/material support: Oterdoom. Study supervision: JMC van Dijk.

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