Deep brain stimulation for anorexia nervosa treatment

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Targets

Deep brain stimulation (DBS) has emerged as a potential anorexia nervosa treatment for severe, treatment-resistant cases. While research is still in early stages, certain brain regions have been identified as promising targets for DBS in the treatment of AN, based on the brain circuits involved in mood regulation, reward, and cognitive control.

Here are the primary DBS targets currently being explored for anorexia nervosa:

1. **Subcallosal Cingulate (SCC) / Brodmann Area 25**

1. **Why it's targeted**: The SCC is involved in mood regulation and is often hyperactive in patients with mood disorders such as depression and anxiety, which commonly co-occur with anorexia nervosa.
2. **Evidence**: DBS of the SCC has shown promise in improving mood symptoms in AN patients, which can help reduce the emotional and cognitive rigidity that drives disordered eating behaviors.

2. **Nucleus Accumbens (NAcc)**

1. **Why it’s targeted**: The NAcc is a key part of the brain's reward circuitry and is involved in the regulation of motivation, pleasure, and reward processing. Individuals with anorexia often experience altered reward responses to food.
2. **Evidence**: Targeting the NAcc with DBS may help correct dysfunction in reward processing, potentially improving motivation to eat and reducing compulsive exercise or restrictive behaviors.

3. **Ventral Striatum**

1. **Why it’s targeted**: The ventral striatum, which includes the NAcc, is crucial in the reward system and decision-making. Alterations in the reward system, particularly with regard to food, are thought to contribute to the development and maintenance of anorexia.
2. **Evidence**: Some studies suggest that DBS to this area may reduce obsessional thoughts about food and body image and help regulate abnormal reward processing.

4. **Hypothalamus**

1. **Why it’s targeted**: The hypothalamus regulates hunger and satiety and plays a critical role in maintaining energy balance. Disruption of hypothalamic signaling is thought to contribute to the severe weight loss seen in anorexia.
2. **Evidence**: While less common than the other targets, hypothalamic DBS has been considered as a way to address the physiological disruptions in hunger and metabolism in AN.

5. **Dorsal Anterior Cingulate Cortex (dACC)**

1. **Why it’s targeted**: The dACC is involved in cognitive control, decision-making, and emotional regulation. Many patients with anorexia nervosa display cognitive rigidity and difficulty adapting to changing circumstances or recognizing healthy food choices.
2. **Evidence**: DBS targeting the dACC may help enhance cognitive flexibility and reduce obsessive, compulsive behaviors related to food and weight control.

6. **Insula**

1. **Why it’s targeted**: The insula is involved in interoceptive awareness—how one senses internal bodily states, including hunger and fullness. People with anorexia nervosa often have altered interoceptive awareness, making it difficult for them to accurately perceive hunger or satiety cues.
2. **Evidence**: DBS targeting the insula may help restore more normal interoceptive awareness, improving the ability to recognize hunger and satiety, which could aid in recovery.

Kohara et al. introduced the results of representative studies that investigated functional neurosurgery for AN [1].

Eight patients with severe, chronic, treatment-resistant AN received DBS either to the nucleus accumbens (NAcc) or subcallosal cingulate (SCC; four subjects on each target). A comprehensive battery of neuropsychological and clinical outcomes was used before and 6-month after surgery.

Although Body Mass Index (BMI) did not normalise, statistically significant improvements in BMI, quality of life, and performance on cognitive flexibility were observed after 6 months of DBS. Changes in BMI were related to a decrease in depressive symptoms and an improvement in memory functioning.

These findings, although preliminary, support the use of DBS in AN, pointing to its safety, even for cognitive functioning; improvements of cognitive flexibility are reported. DBS seems to exert changes on cognition and mood that accompany BMI increments. Further studies are needed better to determine the impact of DBS on cognitive functions [2].

Oudijn et al. first target DBS in AN at the ventral anterior limb of the capsula interna (vALIC), part of the reward circuitry. vALIC-DBS showed strong and long-lasting effects in obsessive-compulsive disorder (OCD). We hypothesized that, due to the clinical and neurobiological similarities between AN and OCD, vALIC-DBS may exert comparable effects in treatment-refractory AN. We included a sample of patients with exceptionally severe AN [3].

Ethics

Aydin et al. explores the clinical efficacy and ethical considerations of DBS in treating these disorders. While DBS has shown substantial promise in alleviating symptoms and improving quality of life, it raises ethical challenges, including issues of informed consent, patient selection, long-term management, and equitable access to treatment. The irreversible nature of DBS, potential adverse effects, and the high cost of the procedure necessitate a rigorous ethical framework to guide its application. The ongoing evolution of neuromodulation requires continuous ethical analysis and the development of guidelines to ensure that DBS is used responsibly and equitably across different patient populations. This paper underscores the need for a balanced approach that integrates clinical efficacy with ethical considerations to optimize patient outcomes and ensure sustainable practice [4]

The use of **deep brain stimulation (DBS)** for treating **anorexia nervosa (AN)** raises several important ethical considerations. Given that DBS is an invasive neurosurgical procedure and that anorexia nervosa often affects young individuals with complex psychological and physical issues, its use must be carefully evaluated from an ethical standpoint. Here are some of the key ethical concerns:

1. **Informed Consent**

1. **Capacity to consent**: Anorexia nervosa can impair decision-making abilities, especially in severe cases, where malnutrition may impact cognitive function. This raises concerns about whether patients are truly able to provide informed consent for an invasive procedure like DBS.
2. **Coercion and autonomy**: Given the severity and chronic nature of anorexia, patients may feel desperate for treatment, potentially leading to concerns about **coercion**. They may consent to DBS under the belief that there are no other viable options left, complicating the concept of fully voluntary consent.

2. **Risk vs. Benefit**

1. **Invasiveness of DBS**: DBS involves surgery to implant electrodes in the brain, which carries risks such as infection, hemorrhage, or neurological complications. Given these risks, it is crucial to weigh the **potential benefits** of the procedure (such as symptom improvement) against the **risks of harm** to the patient.
2. **Uncertainty of outcomes**: While DBS has shown promise for treatment-resistant depression and obsessive-compulsive disorder, its efficacy in anorexia nervosa is still experimental. The unpredictability of the treatment's success raises ethical questions about whether it should be used outside of strictly controlled research settings.

3. **Patient Vulnerability**

1. **Age and developmental stage**: Anorexia nervosa often begins in adolescence, a period of heightened psychological vulnerability. Using DBS on younger patients raises concerns about subjecting still-developing brains to invasive interventions, especially given the potential long-term effects of brain stimulation.
2. **Chronic nature of anorexia**: Patients with severe, chronic anorexia nervosa may have exhausted many treatment options, increasing their vulnerability to seeking drastic solutions like DBS, even if the evidence for its efficacy is limited.

4. **Effect on Identity and Autonomy**

1. **Neuroethical concerns**: DBS has the potential to alter emotional and cognitive functions. This raises questions about whether the treatment could affect patients' sense of identity, autonomy, and authenticity. For example, if DBS changes behavior or personality traits, it may conflict with patients' self-perception or values, especially if the changes are unintended or undesired.

5. **Nonmaleficence and Beneficence**

1. **Do no harm**: The ethical principle of nonmaleficence (doing no harm) demands that DBS not expose patients to unnecessary risk or harm, particularly when less invasive treatments are still viable.
2. **Best interests of the patient**: The principle of beneficence requires that DBS be offered only if there is a reasonable expectation that it will significantly benefit the patient, improving quality of life and not merely prolonging suffering. This is especially important for treatment-resistant anorexia nervosa, where patients often experience years of failed interventions.

6. **Alternative Treatments**

1. Before resorting to DBS, all less invasive and better-established treatments, including psychotherapy, nutritional counseling, family therapy, and pharmacological interventions, should be fully explored. If DBS is being considered, it should only be for the most **treatment-resistant cases** where other interventions have failed, and where the patient is at significant risk due to the chronic nature of the disorder.

7. **Research Ethics and Experimental Use**

1. **Experimental status**: DBS for anorexia nervosa is still experimental, and as such, its use should be conducted within the context of rigorous clinical trials with robust ethical oversight. The primary goals should include understanding the safety, efficacy, and long-term impact of the treatment on patients with severe anorexia.

2. **Patient selection**: Selecting appropriate patients for DBS trials is critical to ensure that only those who genuinely meet criteria for treatment resistance and are suitable candidates (e.g., with severe, chronic illness) are included, to avoid exposing patients to unnecessary risks.

8. **Quality of Life vs. Symptom Reduction**

1. **Holistic approach**: Even if DBS reduces symptoms of anorexia (e.g., restrictive eating), there is no guarantee it will improve overall quality of life. Ethical considerations must extend beyond symptom management to include psychological well-being, social functioning, and the patient’s overall sense of life satisfaction.

Conclusion: Deep brain stimulation holds potential as a **last-resort** treatment for severe, treatment-resistant anorexia nervosa, but its use involves significant ethical considerations. Careful attention must be paid to the patient's capacity to consent, the risks and benefits of the procedure, and the overall aim of improving the patient's well-being. DBS should only be considered after all other treatments have failed and within ethically conducted clinical trials that prioritize patient safety and autonomy.

Systematic Reviews

DBS has been studied in patients with anorexia nervosa (AN) Several stimulation locations have been tested without a clear indication of the best region. In a systematic review and network meta-analysis, Shaffer et al. used patient-level data to identify stimulation targets with the greatest evidence for efficacy in increasing body mass index (BMI).

A systematic search was performed on or before August 4, 2022, using PubMed/MEDLINE, Ovid, and Scopus. Articles were included if patient-level data were presented, patients were diagnosed with AN and treated with DBS, and 6 months or more of postoperative follow-up data were reported. Quality and risk of bias were assessed with the NIH assessment tools. Patient data were collected and stratified by stimulation location. A network meta-analysis was performed. This review was written in accordance with PRISMA guidelines for systematic reviews.

Eleven studies consisting of 36 patients were included. The mean age and BMI at the time of surgery were 38.07 (SD 11.64) years and 12.58 (SD 1.4) kg/m2, respectively. After 6 months of DBS, a significant difference in percentage change in BMI was found between the nucleus accumbens and subcallosal cingulate cortex (SCC) (SMD 0.78; 95% CI 0.10, 1.45) and between the SCC and ventral anterior limb of the internal capsule (SMD -1.51; 95% CI -2.39, -0.62). Similarly, at 9-12 months, a significant difference in percentage change in BMI was found between the SCC and ventral anterior limb of the internal capsule (SMD -1.18; 95% CI -2.21, -0.15). With hierarchical ranking, this study identified SCC as the most supported stimulation location for BMI change at 6 and 9-12 months (P-scores 0.9449 and 0.9771, respectively).

Several DBS targets have been tested for AN, and this study identified the SCC as the most supported region for BMI change. However, further studies with blinded on/off periods are necessary to confirm this finding [5)].

Murray et al. conducted a systematic review of 20 trials of neurosurgical and neuromodulatory treatments for AN, including neurosurgical ablation, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS). Overall, there is evidence to support the role of stereotactic ablation and DBS in the treatment of AN. In contrast, results for rTMS and tDCS have been modest and generally more mixed. Neurosurgical treatment may offer important new avenues for the treatment of AN. Additional randomized clinical trials with comparable patient populations will be needed, in which change in affective, cognitive, and perceptual symptom phenomena, and interrogation of targeted circuits, pre- and post-intervention, are carefully documented [6)]

Prospective cohort studies

Sixteen participants, including eight patients with anorexia nervosa and eight controls, underwent baseline T1-weigthed and diffusion tensor imaging (DTI) acquisitions. Patients received DBS targeting either the subcallosal cingulate (DBS-SCC, N = 4) or the nucleus accumbens (DBS-NAcc, N = 4) based on psychiatric comorbidities and AN subtype. Post-DBS neuroimaging evaluation was conducted in four patients. Data analyses were performed to compare structural connectivity between patients and controls and to assess connectivity changes after DBS intervention.

Baseline findings revealed that structural connectivity is significantly reduced in patients with AN compared to controls, mainly regarding callosal and subcallosal white matter (WM) tracts. Furthermore, pre- vs. post-DBS analyses in AN identified a specific increase after the intervention in two WM tracts: the anterior thalamic radiation and the superior longitudinal fasciculus-parietal bundle.

This study supports that structural connectivity is highly compromised in severe AN. Moreover, this investigation preliminarily reveals that after DBS of the subcallosal cingulate and nucleus accumbens in severe AN, there are white matter (WM) tracts modifications. These microstructural plasticity adaptations may signify a mechanistic underpinning of DBS in this psychiatric disorder [7)]

Case reports

Lin et al. reported the long-term safety and efficacy of rescue bilateral anterior capsulotomy after the failure of bilateral nucleus accumbens (NAcc)-DBS in an 18-year-old female patient with life-threatening and treatment-resistant restricting subtype AN. Improvements in the neuropsychiatric assessment were not documented 6 months after the NAcc-DBS. Rescue bilateral anterior capsulotomy was proposed and performed, resulting in a long-lasting restoration of body weight and a significant and sustained remission in AN core symptoms. The DBS pulse generator was exhausted 2 years after capsulotomy and removed 3 years postoperatively. No relapse was reported at the last follow-up (7 years after the first intervention). From this case, we suggest that capsulotomy could be a rescue treatment for patients with treatment-resistant AN after NAcc-DBS failure. Further well-controlled studies are warranted to validate our findings [8)].

A 42-year-old woman suffering from chronic AN of the bulimic subtype shows a 46.9% weight gain and a subjective increase in quality of life, 12 months after bilateral nucleus accumbens (NAcc) DBS implantation. No improvement in comorbid depression could be achieved. DBS of the NAcc is a treatment option to be considered in severe AN when conventional treatment modalities recommended by evidence-based guidelines have not been able to bring lasting relief to the patient's suffering [9].

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