Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial

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Summary

Background Anorexia nervosa is a life-threatening illness. Brain circuits believed to drive anorexia nervosa symptoms can be accessed with surgical techniques such as deep brain stimulation (DBS). Initial results suggest that DBS of the subcallosal cingulate is safe and associated with improvements in mood and anxiety. Here, we investigated the safety, clinical, and neuroimaging outcomes of DBS of the subcallosal cingulate in a group of patients during 12 months of active stimulation.

Methods We did this prospective open-label trial at the Department of Surgery of the University of Toronto (Toronto, ON, Canada). Patients were eligible to participate if they were aged 20–60 years and had a diagnosis of anorexia nervosa (restricting or binge–purging subtype) and a demonstrated history of chronicity or treatment resistance. Following a period of medical stabilisation, patients underwent surgery for DBS and received open-label continuous stimulation for the entire 1 year study duration. The primary outcome was safety and acceptability of the procedure. The secondary outcomes were body-mass index (BMI), mood, anxiety, affective regulation, and anorexia nervosa-specific behaviours at 12 months after surgery, as well as changes in neural circuitry (measured with PET imaging of cerebral glucose metabolism at baseline and at 6 and 12 months after surgery). This trial was registered with ClinicalTrials.gov, number NCT01476540.

Findings 16 patients with treatment-refractory anorexia nervosa were enrolled between September, 2011, and January, 2014, and underwent DBS of the subcallosal cingulate between November, 2011, and April, 2014. Patients had a mean age of 34 years (SD 8) and average illness duration of 18 years (SD 6). Two patients requested that their devices be removed or deactivated during the study, although their reasons for doing so were poorly defined. The most common adverse event was pain related to surgical incision or positioning that required oral analgesics for longer than 3–4 days after surgery (five [31%] of 16 patients). Seven (44%) of 16 patients had serious adverse events, most of which were related to the underlying illness, including electrolyte disturbances. Average BMI at surgery was 13·83 (SD 1·49) and 14 (88%) of the 16 patients had comorbid mood disorders, anxiety disorders, or both. Mean BMI after 12 months of stimulation was 17·34 (SD 3·40; p=0·0009 *vs* baseline). DBS was associated with significant improvements in measures of depression (mean Hamilton Depression Rating Scale scores 19·40 [SD 6·76] at baseline *vs* 8·79 [7·64] at 12 months; p=0·00015), anxiety (mean Beck Anxiety Inventory score 38·00 [15·55] *vs* 27·14 [18·39]; p=0·035), and affective regulation (mean Dysfunction in Emotional Regulation Scale score 131·80 [22·04] *vs* 104·36 [31·27]; p=0·019). We detected significant changes in cerebral glucose metabolism in key anorexia nervosa-related structures at both 6 months and 12 months of ongoing brain stimulation.

Interpretation In patients with chronic treatment-refractory anorexia nervosa, DBS is well tolerated and is associated with significant and sustained improvements in affective symptoms, BMI, and changes in neural circuitry at 12 months after surgery.

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Introduction

Anorexia nervosa is common, highly challenging, and associated with the highest mortality rate of any psychiatric disorder.[1] Prevalence approaches 0·5% in the general population worldwide, with adolescent girls accounting for the largest proportion of cases.[2] For many patients, anorexia nervosa is a diagnosis of adolescence but an illness of adulthood, with initial presentations occurring in their teens and 20s, but the illness continuing well into the adult years.[3] Anorexia nervosa is an eating disorder marked by a pervasive preoccupation with bodyweight, shape, and size, leading to maintenance behaviours, such as caloric restriction and exercise, in an effort to maintain a low body-mass index (BMI).[4] The challenges associated with anorexia nervosa are many, including frequent denial of the disorder by the patient, and subsequent failure to obtain or seek medical attention despite

Research in context

Evidence before this study

We searched PubMed on Nov 18, 2016, using the term "anorexia nervosa" combined with "neurosurgery", "deep brain stimulation", "brain stimulation", and "neuromodulation". We limited our results to peer-reviewed articles about deep brain stimulation (DBS) in human beings, and excluded lesional studies and preclinical and animal models of anorexia nervosa. Without applying date or language restrictions, we found one clinical trial investigating the use of transcranial magnetic stimulation in anorexia nervosa and one trial of DBS in anorexia nervosa, which was our own trial published in 2013. We further identified three articles: a case report of DBS of the subcallosal cingulate for anorexia nervosa, a case report of DBS of the ventral striatum in patients with treatment-refractory major depression and obsessive-compulsive disorder, and a clinical study of DBS of the nucleus accumbens in four adolescents with acute anorexia nervosa. In the field of neuromodulation for anorexia nervosa, whether invasive or non-invasive, little progress has been made in terms of published, peer-reviewed studies since the publication of our pilot trial in 2013.

Added value of this study

Our trial is, to our knowledge, the largest and most comprehensive study investigating DBS in patients with chronic treatment-refractory anorexia nervosa, and is among the largest studies to examine the effect of DBS on a primary psychiatric disorder. Our study provides safety and clinical data up to 1 year after device implantation and tracks the effect of brain stimulation on key limbic structures over time by use of longitudinal functional imaging. We found that in some patients with highly refractory anorexia nervosa, DBS is a safe and effective treatment, with evidence of improvements in primary and comorbid symptoms and reversals of known metabolic disturbances in anorexia-related brain circuits.

Implications of all the available evidence

Anorexia remains the psychiatric disorder with the highest mortality rate, and there is an urgent need to develop safe, effective, evidence-driven treatments that are informed by a growing understanding of brain circuitry. Our findings emphasise the need for continued research into novel neuromodulation strategies for anorexia nervosa, and for psychiatric disorders more broadly.

severe illness, as well as high rates of comorbidity with mood and anxiety disorders.[5,6]

Few effective and enduring treatments are available for refractory anorexia nervosa, with conventional treatment failing to elicit a response in about 50% of patients.[7,8] Acutely ill patients are admitted to specialised inpatient units for nutritional support, medical stabilisation, and behaviour interruption programmes, whereas patients with chronic disease are typically managed as outpatients, often with concomitant medical treatments. Several novel programmes, including family and interpersonal therapies, have been developed to address illness-maintaining thoughts and behaviours, and some of these have been associated with clinically significant long-term responses.[9,10] No medical treatments have been shown to be effective at achieving and sustaining remission in anorexia nervosa. Malnutrition and comorbid depression and anxiety compound the challenges of medical treatments, leading to high rates of attrition from inpatient programmes, and contributing to high rates of chronic illness, treatment resistance, and suicide.[11]

Advances over the past two decades have led to an improved understanding of the neural circuitry of anorexia nervosa. Structural and functional imaging have implicated key anatomical structures in its pathophysiology compared with healthy controls and remitted patients. Such results help to explain the highly heterogeneous nature of the illness and its high rate of comorbidity with other axis I disorders. For example, the subcallosal cingulate cortex, which has been implicated in major depressive disorder[12] and is a key affective regulatory node,[13] has been shown to have altered serotonin binding in acutely ill patients with anorexia.[14] Structures crucial to reward and perceptual pathways, such as the ventral striatum and temporoparietal junction, have also been implicated in imaging studies, suggesting dysfunction across multiple overlapping circuits.[15,16] Current conceptions of anorexia circuitry therefore posit the existence of key modulatory centres, including the insula and subcallosal cingulate, which modulate top-down and bottom-up effects on cognition and overt behaviour.[17] Such models provide the rationale for targeted surgical interventions such as deep brain stimulation (DBS) in patients with highly refractory anorexia nervosa.

DBS is a surgical procedure involving the implantation of typically bilateral electrodes in key structures believed to drive pathological activity. DBS within the dysfunctional motor circuits of Parkinson's disease, dystonia, and essential tremor is safe and highly effective at controlling disabling motor symptoms.[18] Such results have led to strong interest in use of DBS in other circuit-based disorders, such as major depression and anorexia nervosa, which feature affective, reward, and general limbic dysfunction. A prerequisite for a trial of DBS is the association of clinical symptoms with specific circuits and the surgical accessibility of circuit nodes.

In a previous phase 1 pilot trial,[19] we showed that DBS of the subcallosal cingulate in anorexia nervosa was safe in a small group of patients with highly refractory disease and was associated with improvements in