Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: a phase 1 pilot trial

Nir Lipsman, D Blake Woodside, Peter Giacobbe, Clement Hamami, Jacqueline C Carter, Sarah Jane Norwood, Kalam Sutandar, Randy Staab, Gavin Elias, Christopher H Lyman, Gwenn S Smith, Andres M Lozano

Summary

Background Anorexia nervosa is characterised by a chronic course that is refractory to treatment in many patients and has one of the highest mortality rates of any psychiatric disorder. Deep brain stimulation (DBS) has been applied to circuit-based neuropsychiatric diseases, such as Parkinson’s disease and major depression, with promising results. We aimed to assess the safety of DBS to modulate the activity of limbic circuits and to examine how this might affect the clinical features of anorexia nervosa.

Methods We did a phase 1, prospective trial of subcallosal cingulate DBS in six patients with chronic, severe, and treatment-refractory anorexia nervosa. Eligible patients were aged 20–60 years, had been diagnosed with restricting or binge-purging anorexia nervosa, and showed evidence of chronicity or treatment resistance. Patients underwent medical optimisation preoperatively and had baseline body-mass index (BMI), psychometric, and neuroimaging investigations, followed by implantation of electrodes and pulse generators for continuous delivery of electrical stimulation. Patients were followed up for 9 months after DBS activation, and the primary outcome of adverse events associated with surgery or stimulation was monitored at every follow-up visit. Repeat psychometric assessments, BMI measurements, and neuroimaging investigations were also done at various intervals. This trial is registered with ClinicalTrials.gov, number NCT01476540.

Findings DBS was associated with several adverse events, only one of which (seizure during programming, roughly 2 weeks after surgery) was serious. Other related adverse events were panic attack during surgery, nausea, air embolus, and pain. After 9 months, three of the six patients had achieved and maintained a BMI greater than their historical baselines. DBS was associated with improvements in mood, anxiety, affective regulation, and anorexia nervosa-related obsessions and compulsions in four patients and with improvements in quality of life in three patients after 6 months of stimulation. These clinical benefits were accompanied by changes in cerebral glucose metabolism (seen in a comparison of composite PET scans at baseline and 6 months) that were consistent with a reversal of the abnormalities seen in the anterior cingulate, insula, and parietal lobe in the disorder.

Interpretation Subcallosal cingulate DBS seems to be generally safe in this sample of patients with chronic and treatment-refractory anorexia nervosa.

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Introduction Anorexia nervosa has a mortality of 6–11% and is among the most challenging psychiatric disorders to treat.1 With an estimated prevalence of 0.3–0.9%, it is typically diagnosed in female young adults aged 15–19 years, and is among the most common psychiatric disorders in this age group.2,3 Anorexia nervosa is characterised by a refusal to maintain a healthy body weight, a persistent fear of gaining weight, a relentless drive for thinness, and preoccupations with body image and self-perception.4 Psychological factors, such as perfectionism, anxiety, affective dysregulation, and reward processing abnormalities, have been proposed as prominent perpetuating, and causal, factors in the disorder.5–10

Treatment strategies used currently are aimed at the acute and chronic stages of the illness. Acute care entails medical stabilisation (such as the correction of electrolyte abnormalities or cardiac problems) in severely underweight and metabolically unstable patients. Rapid fluctuations in weight, severe restriction, and binging and purging behaviour are associated with serious medical complications, which can lead to cardiac arrhythmias and musculoskeletal and neurological symptoms.11 Intensive treatment, in inpatient or outpatient settings, focuses on behavioural change and on addressing underlying and disease-maintaining factors.12 Anorexia nervosa is usually a chronic illness, with a waxing and waning course. Up to 20% of patients derive no sustained benefit from available treatment programmes and are at risk for premature death.13 Despite decades of investigation, the factors associated with mortality and progression to chronic illness are poorly understood.

The circuitry and biology of anorexia nervosa are areas of active investigation, with most disease models focused on structures that underlie pathological mood, anxiety, reward, body perception, and interoception.14
Much of this work is driven by neuroimaging, which has been used to show both structural and functional differences between patients with anorexia nervosa and healthy controls. The most consistent features are parietal area hypometabolism and limbic circuit dysfunction, including increased activity and decreased 5-HT2A binding in the subcallosal area, a region that is known to be important in mood regulation, which emphasises the importance of perceptual and mood disturbances in the disorder.

Deep brain stimulation (DBS) is a neurosurgical procedure that has been used for more than 25 years to modulate the activity of dysfunctional brain circuits. It has proved effective and safe in patients with Parkinson’s disease and essential tremor and its use has now been extended to other circuit-based neuropsychiatric disorders, such as major depression, obsessive–compulsive disorder, Tourette’s syndrome, and Alzheimer’s disease. DBS is a non-lesional and adjustable procedure that exerts its effect both locally and remotely, across monosynaptically and polysynaptically linked networks.

We selected the subcallosal cingulate as a target for DBS in anorexia nervosa because: imaging studies show similar patterns of activity in the subcallosal cingulate region and in its afferent and efferent projections in patients with anorexia nervosa as are seen in patients with depression; anorexia nervosa and mood and anxiety disorders are often comorbid, with similar anatomical structures and circuits implicated (results of several studies have also shown that treatment of weight alone in patients with anorexia nervosa leads to faster relapse, whereas

Panel 1: Inclusion and exclusion criteria

Inclusion criteria

• Female or male patients aged 20–60 years
• Diagnosis of anorexia nervosa, restricting or binge-purging subtype, as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)
• Chronicity or treatment resistance shown by some or all of:
  • A pattern of 3 years’ duration of relentless unresponsiveness to repeated voluntary hospital admissions, characterised by failure to complete treatment or immediate weight relapse after treatment
  • A pattern of increasing medical instability, accompanied by refusal to participate in or a pattern of poor response to intensive expert treatment and increasing medical acuity, lasting at least 2 years and including at least two episodes of involuntary feeding
  • A pattern of chronic stable anorexia nervosa that has lasted at least 10 years
• Able to provide informed consent
• Able to comply with all testing, follow-ups, and study appointments and protocols

Exclusion criteria

• Any past or present evidence of psychosis
• Active neurological disease such as epilepsy
• Alcohol or substance dependence or abuse in the previous 6 months, excluding caffeine and nicotine
• Any contraindication to MRI or PET scanning
• Likely to relocate or move during the study’s 1-year duration
• Body-mass index less than 13
• Presence of cardiac arrhythmias or other cardiac, respiratory, renal or endocrine disorders, as a result of anorexia nervosa or not, that will result in substantial risk from a surgical procedure
• Pregnancy
Methods

Patients and study design

Inclusion and exclusion criteria for this study are listed in panel 1. Patients were identified through the eating disorders programme at Toronto General Hospital (Toronto, ON, Canada) and through community referrals to the study. Our intent was to offer this procedure only to patients who might be expected to continue with a chronic illness or die a premature death because of the severity of their illness. No established, consensus operational criteria exist to identify treatment-refractory patients with anorexia nervosa. Accordingly, we developed a set of criteria (panel 1) to select such patients for the study. After initial screening for eligibility and team discussion, patients were referred to a non-study-affiliated psychiatrist for independent assessment of the diagnosis, treatment refractoriness, study eligibility, and review of capacity to consent.

Once enrolled, patients underwent baseline psychometric assessments with depression, anxiety and eating disorder inventories: Hamilton rating scale for depression,17 Beck depression inventory (BDI),18 and Yale–Brown obsessive compulsive scale (YBOCS).19 Yale–Brown–Cornell eating disorder scale in women (YBC-EDS).20 and quality of life scale.20 Patients also underwent neuro-imaging with MRI and 18F-fluorodeoxyglucose (18F-FDG) PET, and an anaesthesia consultation for assessment of fitness for surgery. Preoperative body-mass index (BMI) was recorded for all patients, and baseline BMIs were calculated on the basis of medical records, patient interviews, and weight diaries.

This study was approved by the research ethics board at the University Health Network, University of Toronto, and all patients provided written informed consent.

Surgery

On the morning of surgery, a stereotactic frame was applied to patients and MRI was used to select the anatomical target, which was a white matter bundle immediately below the genu of the corpus callosum. This site has previously been used for DBS in patients with depression.21 The procedure was done under local anaesthesia, with the patients fully awake. Bilateral burr holes were drilled, and electrodes (model 3387, Medtronic, Minneapolis, MN, USA) inserted under fluoroscopic guidance (figure 1). Each of the electrode contacts was stimulated to check for spontaneous reports of mood or anxiety changes or adverse effects. Several patients reported acute responses to blinded stimulation, described in further detail in the appendix. An intraoperative anorexia nervosa rating scale, designed by the research team to probe changes in cardinal symptoms with stimulation, was also administered at individual contacts, with frequency and amplitude kept constant (appendix pp 4–5). Responses were noted and videotaped for subsequent analysis.

Once testing was complete, the electrodes were internalised and connected to a subcutaneously implanted pulse generator placed below the right clavicle, with the patient under general anaesthesia. Patients underwent structural MRI for electrode position confirmation on the first postoperative day and were discharged from hospital with the stimulator off.

<table>
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<th>Patient</th>
<th>Sex</th>
<th>Age at disease onset (years)</th>
<th>Age at surgery (years)</th>
<th>Duration of illness (years)</th>
<th>Anorexia subtype</th>
<th>BMI (historical low)</th>
<th>Psychiatric comorbidities</th>
<th>Psychiatric drugs at surgery</th>
<th>Number of acute inpatient admissions</th>
<th>Medical complications</th>
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<td>Purge</td>
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<td>Quetiapine, lorazepam, sertraline</td>
<td>&gt;10</td>
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<td>Binge-purge</td>
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<td>Fluoxetine, quetiapine</td>
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<td>0†</td>
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</table>

BMI=body-mass index. MDD= major depressive disorder. OCD= obsessive-compulsive disorder. SUD= substance use disorder. PTSD= post-traumatic stress disorder. *Substance use disorder in remission for 6 months before study enrolment. †Remote inpatient admission as a teenager for chronic treatment, not medical stabilisation.

Table 1: Demographic characteristics
Follow-up
Patients were seen 10 days after discharge for device activation. Initial stimulating contacts were either those that elicited the most substantial acute mood and anxiolytic responses in the operating room or were the closest to the anatomical subcallosal cingulate on postoperative MRI. We started all patients at an amplitude of 3·5 V, pulse width 90 μs, and frequency 130 Hz. Stimulation settings were changed on the basis of patient and physician feedback. Frequency and pulse width remained unchanged for the duration of the study, with amplitudes ranging from 5 to 7 V in all patients. No drug changes were made in the first 3 months after surgery. Psychometric assessments were repeated at 1, 3, and 6 months after device activation. ¹⁸F-FDG PET and structural MRI were repeated at 6 months after activation. Weight was recorded and BMI calculated at 2, 3, 6, and 9 months after activation.

Since this was a pilot study, primary outcome measures were adverse events associated with surgery and those related to acute and chronic stimulation. Adverse events were monitored for at every study visit. Secondary outcomes related to weight (BMI) and mood and anxiety measures (BDI, BAI, HAMD, YBOCS, YBC-EDS).

PET image acquisition and analysis
PET scans with ¹⁸F-FDG to measure regional cerebral glucose metabolism were acquired preoperatively and after 6 months of continuous DBS. Composite images that combined data from all six patients were produced and analysed. PET acquisition and analysis was done as described in previous publications, and are further outlined in the appendix. This trial is registered with ClinicalTrials.gov, number NCT01476540.

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Six patients were enrolled in this pilot trial (table 1). All patients were female and had a mean age at surgery of 38 years (SD 11). All patients met DSM-IV-TR criteria for anorexia nervosa, with an average age at diagnosis of 20 years, and a mean duration of illness of 18 years (SD 11) before DBS surgery. Five patients had a history of recurrent acute hospital admissions for medical stabilisation, with four of these patients having had ten or more admissions. After study enrolment, all patients needed some form of medical stabilisation before surgery; this consisted of either inpatient treatment or close outpatient follow-up to ensure that they continued to meet the study entrance criteria. All patients except one, the oldest, had comorbid psychiatric disorders, with major depressive disorder and obsessive–compulsive disorder being the most common. At enrolment, all patients currently, or had previously, had several medical complications directly related to anorexia nervosa (table 1).

Surgery was generally well tolerated, but was associated with several adverse events (table 2). The average length of hospital stay after surgery was 1–3 days, with four of the six patients discharged on the first postoperative day. Serious adverse events were classified as either study-related or non-study-related. One study-related serious adverse event occurred—a seizure after DBS programming in patient 5 whose operation had been done...
about 2 weeks previously, and who was having a substantial metabolic derangement. The DBS device was turned off, and was reactivated 1 week later. The patient had no history of seizures and no seizure recurrence during follow-up. Several serious adverse events were unrelated to treatment and were attributed to the underlying illness, including metabolic aberrations and cardiac arrhythmias. Intraoperatively, one patient had a self-limiting panic attack during drilling of the skull, and one had a cardiac air embolus that resolved within 5 min after repositioning of the operating table. Three patients complained of pain (table 2).

To obtain an adequate estimate of baseline BMI, we reviewed medical records for the 5–7 years before study enrolment, interviewed patients, and examined their weight diaries. This investigation revealed a mean baseline BMI of 13.7 (SD 1.4) for the six enrolled patients. At the initial study screening visit, which took place within 6–8 weeks of surgery, most patients (1, 2, 3, 4, and 5) had recently been attending inpatient treatment, which had resulted in some weight gain. This patient group is typically in and out of hospital, dependent on their physical condition, with resultant fluctuations in weight. As such, mean preoperative BMI was 16.1 (1.5), a value substantially higher than the typical baseline BMI for such patients (figure 2).

At 2 months after surgery, all patients had lost weight from their preoperative BMI (figure 2). This fall might represent a regression towards the baseline, as would be expected from the natural history of the illness, since the preoperative BMI was probably an artifact of recent inpatient treatment. At 3 months, however, this pattern began to reverse, with five of the six patients having gained weight or stabilised relative to 2 months after the operation. Two patients (1 and 5) were after 6 months at a BMI greater than that at the time of surgery; at 9 months, three patients (1, 2, and 5) were maintaining BMIs that were higher than those at baseline (figure 2). For all three of these patients, this was the longest period of sustained increase in BMI since the onset of their illness. The remaining three patients had BMIs at 9 months that were virtually unchanged from their historical baseline (within 0.3 points), which suggests that DBS had no apparent effect, positive or negative, on these patients’ weights.

Mood ratings, as assessed by both physicians and patients, showed changes after initiation of stimulation (table 3, figure 3). The mean preoperative HAMD score (Continues in next column)
for all six patients had fallen by about 5 points at 3 months and about 7 points at 6 months. At baseline, four patients (1, 2, 3, 5, and 6) had met clinical criteria for obsessive-compulsive disorder at baseline, and three of these (2, 5, and 6) were clinical responders at 6 months, defined as a reduction in YBOCS scores of more than 35%. Subjective anxiety measures were also much reduced at 6 months—mean BAI scores fell by about 10 points (figure 3). Eating-disorder-specific attitudes were assessed preoperatively and postoperatively. Scores related to food and weight preoccupations and eating disorder rituals were reduced during the course of the study (table 3, figure 3).

The mean quality of life score for all patients at baseline was 57.3 (SD 25.6) and had improved to 65.8 (SD 20.1) at 6 months (individual patient data are in the appendix). For the three patients who saw improvements in BMI, mean quality of life improved from 43.0 (SD 10.0) at baseline to 60.0 (SD 7.5) at 6 months. For the other three patients, mean quality of life scores were unchanged between baseline and 6 months (71.7 [SD 30.4] vs 71.7 [SD 29.1]).

With respect to the PET scan results, the voxel-wise analyses of the standardised-uptake-value data revealed changes in cerebral glucose metabolism after 6 months of DBS (figure 4, appendix p 7). Metabolism was decreased in the anterior cingulate (Brodmann area [BA] right 24, 25), medial frontal gyrus (left BA 6, right BA 9), bilateral insula (BA13), left caudate, left claustrum, and left cerebellum (culmen, vermis, and declive). Metabolism was increased in posterior cortical regions, the right middle and right inferior temporal gyrus (BA 21, 20), left post-central gyrus (BA 1), right precuneus (BA 7), right supramarginal gyrus (BA 40), right inferior parietal lobule (BA 40), and left cuneus (BA 19).

Discussion

DBS in this group of six patients with chronic and treatment-refractory anorexia nervosa was generally safe. All our patients had longstanding, life-threatening disease; five had a history of emergency admissions to intensive care, and four had needed to be surgically fed in the past. At 9 months no deaths, strokes, infections, or serious device-related complications had occurred (table 2). One unanticipated adverse event was a seizure that followed device programming, which occurred in the context of a severe metabolic derangement. Other serious adverse events were related to the underlying illness and were treated promptly and appropriately. Although our experience is limited to six patients, the complication profile of DBS in this population can thus far be presumed to be low.

No previous studies of DBS in patients with chronic, treatment-refractory anorexia nervosa have been reported (panel 2). Previously published work is limited to two
case reports, and a study of DBS in acutely ill adolescents with the disorder. For our trial, we did not operate on patients younger than 20 years or with a BMI less than 13, and further required a history of long-standing, treatment-refractory anorexia nervosa.

DBS was associated in some patients with positive effects on BMI, mood, anxiety, and brain metabolism. Clinically, three of the six patients showed a change in the natural history of their disorder, achieving a sustained increase in BMI over a period of at least 3–6 months, for the first time in the course of their illness. These changes were further accompanied in these patients by subjective improvements in quality of life. The clinical and imaging findings are especially striking in view of the chronicity, severity, and life-threatening nature of the disorder in these patients, whose combined histories included almost 50 hospital admissions.

Assessment of weight or BMI is an obvious target in a study of this type. However, the natural history of chronic anorexia nervosa means that many changes in weight take place with time, which are related to emergency medical admissions, voluntary admissions, and frequent episodes of precipitous weight loss. As a result, identification of a baseline BMI and definition of weight change is complex in this patient group. Since no established mechanism exists for this purpose, we did the most comprehensive assessment possible and obtained all available data.

Although weight cannot be ignored, for this group of patients attempts to identify whether the overall course of the illness is changing might be a more realistic approach to assess the effectiveness of DBS. For example, patients with substantial improvements in their affective regulation might have reductions in impulsive behaviours and improved relationships with others that allow an improved response to standard treatments that are heavily weighted towards psychotherapy. In view of the high risk of death in the patient population being studied, and the patients’ well-established failure to respond to standard treatments, a shift towards being able to make use of such treatments, or an apparent switch to a more stable form of the illness, would represent a major step forward in this particular patient group.

All six patients had lost weight relative to baseline at 2 months after surgery. At 9 months, however, three patients were maintaining BMIs that were higher than those at baseline, and three showed effectively no change in BMI relative to baseline (figure 2). The initial weight loss argued against a primary effect of DBS on hunger, appetite, or metabolic rate. It also suggests that there is little in the way of a placebo-related benefit to the surgery. Instead, the pattern seen could indicate the effect of mood and anxiety control on anorexia nervosa-related thoughts and behaviours, and hence BMI. Previous work with DBS in dystonia and mood and anxiety disorders has shown that the benefits of stimulation are delayed and progressive, and that they follow a pattern of a latency of 2–3 months. This length of time is similar to the inflection point in mean BMI at 2 months seen in our study in patients with anorexia nervosa, which tracked with improvement in mood, as shown by reductions in HAMD and BDI scores at 3 months.
The presence of untreated mood and anxiety symptoms portends a worse prognosis and increased frequency of relapse in anorexia nervosa. The substantial reductions in HAMD scores at 6 months in our patient group accord with previously reported effects of limbic system DBS on depression, in which typically 50–60% of patients responded to treatment. The additional effect on anxiety, shown by substantial reductions in YBOCS and BAI scores, suggests a broader effect of subcallosal cingulate activity on affective regulation. The tandem mood and anxiety effects of subcallosal cingulate DBS suggest that the clinical effect seen in these patients might be mediated by a restoration of affective equilibrium to a previously dysregulated state, rather than the treatment of a depression. In this way, DBS that is associated with improved mood, anxiety, and affective regulation could disrupt important illness-maintaining factors, and could represent a foot-in-the-door technique for patients with highly refractory disease. The finding of improvements in mood and anxiety in patients who were still underweight is especially striking, in view of the well known poor response of underweight patients to conventional pharmacotherapies or psychotherapies.

The imaging results from our study show that subcallosal cingulate DBS has network-wide effects, and that it affected structures directly implicated in anorexia nervosa, including the anterior cingulate, insula, and parietal lobe. Our results, based on composite scans from all six patients, show that DBS of the subcallosal cingulate area in patients with anorexia nervosa produces decreased subcallosal cingulate and medial frontal activity and increased parietal activity, similar to the changes seen with stimulation of this area in patients with treatment-resistant major depression. This similarity suggests that, independent of the diagnosis, stimulation of this same target can lead to fairly stereotypical cerebral metabolic changes. Reduced subcallosal cingulate and insula activity and enhanced parietal activity have also been linked to clinical improvements in depressed mood after pharmacological, psychotherapeutic, and simulation-based treatments. Consistent with these findings, we noted similar patterns of changes in glucose utilisation in the same regions in our patients as a group, together with substantial improvements in depression ratings at 6 months after initiation of DBS. Such findings provide additional evidence for the effect of the subcallosal cingulate on downstream limbic structures, and for its putative role in the regulation of negative affect.

Metabolic activity in the insula was reduced bilaterally in our patients after 6 months of DBS. The insula features prominently in present models of anorexia nervosa because of its role in fear–anxiety circuitry, taste sensation, and monitoring of one’s internal environment, all of which are known to be dysfunctional in patients with the disorder. Although the clinical correlates of insular modulation are unclear, a possible result might be to offset over-vigilance to internal milieu.

Body and weight distortions are defining features of anorexia nervosa and have been linked to parietal lobe dysfunction. Results of several studies have shown that parietal glucose hypometabolism and hypoperfusion are consistent features of patients with anorexia nervosa compared with healthy, age-matched controls. Our composite PET results show that chronic subcallosal cingulate DBS leads to increases in glucose metabolism in the parietal lobe, which suggests that remote, disease-relevant structures might be modulated with stimulation.

One enrolled patient (4) saw no substantial changes in BMI or psychometric scores during the course of the trial. Two additional patients (3 and 6) saw no changes in BMI at 9 months, but did see some improvements in mood or obsession and compulsion scores at 6 months. The number of patients is too small to speculate about possible predictors of treatment response or the characteristics of responders compared with non-responders, both of which remain questions for future investigation.

Our study has some important limitations. First, the small number of enrolled patients limits its generalisability. Six patients is, however, within range of several pilot trials of DBS for novel indications, and represent a balance between the search for effectiveness with feasibility and safety considerations. A second limitation stems from that fact that all stimulation was open-label, with both the patient and the research team aware of the stimulation settings. The chronicity and resistant nature of the illness in our patient population, and the durability of the response in those who responded, speaks against the possibility of a placebo effect, although such an effect cannot be excluded definitively without further, blinded, sham-stimulation-controlled investigation. For this pilot trial, safety was the main concern, and we could not justify masking interventions from patients or clinicians at this stage.

Contributors NL, AML, and DBW conceived of the study and its initial design. DBW, KS, JCC, SJN, PG, and RS did baseline and follow-up psychometric assessments, clinical psychiatry and psychology follow-ups, and provided support with study design. NL, CH, and AML did the surgical operations and the neurosurgical follow-ups. CH prepared figure 1. GE assisted with data collection and analysis of data and with the preparation of the results and the appendix. CHL and GSS analysed the PET imaging data and created figure 4 and the supplementary table in the appendix. All authors contributed to and edited the report. All authors approved the report before submission.

Conflicts of interest NL, DBW, JCC, SJN, KS, RS, GE, CHL, and GSS declare that they have no conflicts of interest. PG and CH are consultants for St Jude Medical, Medtronic and Boston Scientific, and holds intellectual property related to brain stimulation for depression.

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References
DBS for treatment-refractory anorexia nervosa

Although early treatment of adolescents with anorexia nervosa—through mobilisation of the family to restore normal eating and weight—is successful in 30–60% of patients,1 in those with an illness duration of longer than 3 years (as is often the case in adult patients) change is more difficult.2 Even with the best available psychological treatments, outcomes in those with an established form of the illness are generally poor.3

In The Lancet, Nir Lipsman and colleagues4 report the use of deep brain stimulation (DBS) for the treatment of people with severe and enduring anorexia nervosa. In this phase 1 study of six patients, the subcallosal cingulate, an area that has previously been targeted in DBS treatment of resistant depression, was the target for stimulation. In terms of safety, one patient had a serious adverse event—a seizure after DBS programming, 2 weeks after surgery. However, this event was in the context of a serious, illness-related metabolic problem. The device was switched off and restarted after 1 week, with no further problems. Intraoperatively, one patient had a panic attack and another had an air embolus, both of which were managed. The results also showed some early promise for the procedure, with three of the six patients showing improvements in their physical status—benefits that seemed to be mediated by improvements in mood and anxiety rather than caused by a direct effect on appetite. However, this finding should be interpreted with caution, since the study was not powered to assess efficacy.

Resistance to treatment beyond a crucial window for intervention might in part be caused by the effect of starvation on the brain, especially during its development in adolescence. Components of executive function, including decision making, social communication, and new learning are impaired by low weight, and because these are integral to the psychological treatments that are usually used in patients with anorexia nervosa, treatment becomes more difficult the more the illness becomes embedded.

The six patients in Lipsman and colleagues’ trial belong to the sizeable minority of patients who have a severe and enduring form of anorexia nervosa, for whom eating and weight gain are extremely aversive and food restriction and other weight-loss behaviours have become pathologically rewarding. Such patients tend to have severe physical and psychological comorbidities and often need long-term inpatient care. Unsurprisingly, they are the subgroup of patients with the highest rate of death from either physical complications or suicide.5,6 A report7 from Australia estimated the effect of eating disorders on productivity in the country as AUS$15·1 billion in 2012, which is similar to the estimated economic costs of anxiety and depression. Thus the personal and social costs of eating disorders in general are large, and nowhere are these more evident than in patients with severe and enduring anorexia nervosa. New effective treatments for these patients are sorely needed.

Recent work has contributed to the development of a neurological understanding of eating disorders.8,9 This approach opens the way to treatments targeted at dysfunctional neurocircuits and could potentially circumvent the need to work through top-down processes that are disabled by secondary starvation deficits (loss of brain substance with functional problems—eg, in social cognition). DBS is a targeted, minimally invasive neurosurgical procedure that has been successfully used to treat severe movement disorders.10 Importantly, the procedure is adjustable and largely reversible, and is increasingly being used in carefully selected cases of severe, treatment-resistant neuropsychiatric disorders such as depression, obsessive-compulsive disorder, and addictions. These disorders all have aetiological and clinical overlaps with anorexia nervosa. Different potential brain targets for the application of DBS in these disorders are being explored in animal and human studies. For example, for obsessive–compulsive disorder, DBS of the ventral striatum, nucleus accumbens, and subthalamic nucleus have all been used with some beneficial effect in patients.11 The importance of the subthalamic nucleus for the control of eating is shown by the emergence of binge eating as a possible side-effect of DBS in that region for the treatment of Parkinson’s disease.12 In rats, DBS of subregions of the nucleus accumbens shell independently modulated food intake and the motivation to work for palatable food.13 Preliminary results from China with DBS of the nucleus accumbens in adolescents with severe anorexia nervosa suggest that targeting this area might be of benefit.14
Many open questions remain in relation to use of DBS in anorexia nervosa, including the choice of targets, mechanisms of action, and practical issues such as patient selection and acceptability of the treatment to patients and their families. Nonetheless, the findings of this proof-of-concept study are promising and will give hope to patients with especially pernicious forms of the disorder and their families. The fact that the procedure was associated in some patients with improvements in affective and obsessional symptoms is of key importance, since such improvements will go some way towards reassuring patients that DBS is not just another treatment designed to fatten them up without making them feel better.

*Janet Treasure, Ulrike Schmidt
Section of Eating Disorders, Institute of Psychiatry, King’s College London, London SE5 8AF, UK
janet.treasure@kcl.ac.uk

We declare that we have no conflicts of interest.