Neurosurgery for severe anorexia nervosa

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Abstract

Anorexia nervosa (AN) is primarily a mental disorder, characterised in modern society by disturbed attitudes towards weight, body shape and calorie balance. In earlier eras, anorexia did exist but religious or other values, rather than body image concerns, underlaid the obsessive-compulsive features. Serious physical and psychological complications cause high levels of disability and mortality. Early psychological intervention improves outcomes, but 20% develop severe and enduring symptoms and it has the highest mortality rate of any psychiatric disorder. AN has a biological component and shares significant genetic and neural network abnormalities with other mental illnesses, especially with obsessive-compulsive disorder (OCD). Functional neurosurgery, including stereotactic ablation (SA) and deep brain stimulation (DBS), are low-risk interventions that disrupt abnormal synchronised activity in neural circuits. Primarily used in movement disorders, these interventions are increasingly used in mental disorders, with evidence of efficacy from multiple randomised controlled trials in OCD and Gilles de la Tourette syndrome. Open-label studies of SA and DBS for AN report a large positive effect size on core psychopathology, quality of life and body mass index, sustained over many years. Early comorbid OCD symptoms and restricting AN subtype may be good prognostic predictors of response. Several surgical, psychological, logistical and financial factors may favour SA over DBS. However, the available evidence is limited and further studies are required to determine patient perception of, selection for and response to neurosurgery. AN is a potentially rewarding area for greater collaboration between eating disorders experts and functional neurosurgeons and offers hope to severely affected patients who have run out of treatment options.

Abbreviations: AN = anorexia nervosa; BMI = body mass index; DBS = deep brain stimulation; EDE = eating disorders examination; FUS = focused ultrasound; GK = gamma knife; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Rating Scale; OCD = obsessive-compulsive disorder; PD = Parkinson disease; SA = stereotactic ablation; SCC = subcallosal cingulate gyrus; VC/VS = ventral capsule/ventral striatum; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale

Introduction

Anorexia nervosa (AN) is an eating disorder characterised by disturbed attitudes towards weight, body shape, eating and calorie balance. This drives severe weight loss behaviours, such as dietary restriction, purging and excessive physical activity. Although adolescent girls and young women are particularly at risk, the condition can affect anyone, regardless of age, sex, culture or race.

AN is primarily a mental disorder with marked disturbance of cognitive and emotional functions. It often follows a protracted or relapsing course, leading to serious physical and psychological complications and comorbidities, and causes high levels of disability and mortality. AN leads to a poor quality of life, disrupted relationships, emotional distress, social isolation and economic disadvantage. Young people may experience pubertal delay and disruption to education. Post-pubertal women are usually amenorrhoeic, with risk of osteoporosis as well as fertility issues. AN places a heavy burden on individuals, families and society (1, 2).

In high-income countries, the reported lifetime prevalence of AN in the general population is around 1% in women and <0.5% in men (3). Accurate point prevalence is estimated as 0.3% to 0.5% in adults but relies on data from individuals who present to health services (4). AN typically begins in early-to-mid adolescence but can emerge at any age. In adults, females are eight times more likely to be affected, recovery rates are lower and mortality rates are higher (5).

Treatment and prognosis: Early intervention improves outcome. Many factors affect AN management and prognosis, including age of onset, severity of malnourishment and comorbidities such as depression, anxiety or trauma. Established treatments include psychological and family-based interventions and nutritional support, with escalating levels of outpatient and inpatient care. There is limited high-level evidence on the effectiveness of pharmacological therapies (2). With the best available medical and psychological treatment for AN, around 50% recover and 30% show some improvement. However, 20% remain chronically ill and develop a severe and enduring form of the illness that is particularly hard to treat. Severe enduring eating disorders have been characterised as "SEED" or "SEAN" (severe and enduring AN) (5, 6). However, the implication of a poor or even terminal prognosis could lead to a sense of hopelessness in both patients and clinicians. As a result, these terms have been assertively challenged by many professionals and by people with a lived experience of eating disorders.

Mortality: AN has the highest mortality rate of any psychiatric disorder. This is partly caused by its physical complications, and partly an increased suicide rate, accounting for 20% to 40% of deaths (7). A meta-analysis of 36 studies reported a standardised mortality ratio of 5.9 (95% confidence interval: 4.2–8.3) (8). Another study based on 119 study series (n = 5,590 patients) found a significant effect of duration of illness (n = 3,147), with 9.4% mortality in those with >10 years duration (5).

Health economics: Calculating the economic burden of AN on healthcare systems is complex. A recent systematic review placed the mean annual healthcare costs between €2,993 to €55,270 per patient (9). Economic evaluation of treatment in the UK revealed a cost of £34,531 (SD, £52,430; range, £86,000–£282,508) per patient for inpatient care (n = 47) and £40,794 (SD, £63,652; range, £1,483–£274,838) per patient for outpatient care (n = 43) over a two-year period between the years 2000 and 2003 (10).

The biological aetiology of anorexia nervosa

There is mounting evidence that AN has a biological aetiology as well as a psychological one. AN has a strong familial tendency that is absent in adoptive siblings. Female relatives of an affected individual are up to 11 times more likely to develop AN. Furthermore, twin studies show heritability estimates of 0.48 to 0.74. This remains true even in twins reared apart, eliminating the influence of environmental factors (11). A genome-wide study identified eight risk loci, pointing to a biological component to AN (12).

Significant genetic correlations exist with other psychiatric disorders or traits, by far the highest with obsessive-compulsive disorder (OCD), but also with anxiety disorders and major depression. AN also shares phenotypic similarities with these conditions; for example, individuals with AN and OCD exhibit cognitive inflexibility with decreased set-shifting ability and perseverative cognitive style (13, 14). A large population based, multi-generational and twin study found that females with OCD had a 16-fold increased chance of having a comorbid diagnosis of AN. Moreover, first- and second-degree relatives of patients with OCD had an increased risk of AN (15).

Yet another commonality between OCD and AN is dysfunction in emotive and reward/punishment brain networks (16). Brain connectivity studies in AN have shown increased structural and functional connectivity in a reward-related network connecting ventral striatum to orbito-frontal cortex (via the anterior limb of the internal capsule). This abnormality persisted even following weight restoration (17). Similar network dysfunction was also demonstrated in another multimodal MRI connectivity analysis (18).

Functional neurosurgery in neurological disorders

Stereotactic ablation (SA) and deep brain stimulation (DBS) are established surgical treatments that effectively treat the symptoms of several neurological disorders such as Parkinson disease (PD), dystonia and tremor (19). The hypothesis driving such approaches is that pathological changes within the brain result in maladaptive neural circuits that "drive" specific symptoms, impacting on everyday function and reducing quality of life (20).

SA is traditionally performed using radiofrequency ablation. During this procedure, a stereotactic frame is used to guide a radiofrequency probe to the target via a small burrhole. A tiny volume of brain tissue around the tip of the probe is then coagulated using a high-frequency electrical current (Figure 1A; Box 1). Alternatively, incisionless methods can be employed to make stereotactic lesions, such as

Box 1. Patient experience during radiofrequency ablation

"Radiofrequency ablation" is a relatively simple procedure for expert brain surgeons and is done under a local anaesthetic. This means the patient can chat with the friendly neurosurgical team throughout the procedure.

The team infiltrates some local anaesthetic into the scalp and after a few minutes they attach the frame – a "stereotactic frame" – to the patient's head using surgical screws. This can feel a bit uncomfortable but is not painful. People say that the applied frame feels "like a tight hat". This is followed by an MRI scan. This process of attaching the frame and completing the scan takes about 30 minutes. Now we are ready for the actual surgery.

The surgeon makes a scalp incision around 3 cm long, about 2 cm behind the hairline and 4 cm to one side. The hair can be parted to allow the incision and no shaving is required. Next, a small hole is made in the skull using a neurosurgical drill that takes less than a minute. This is usually referred to as a "burrhole". This is like being at a good dentist in that the patient hears the noise and feels some vibration, but there is no pain.

The frame now guides the surgeon's probe to the exact part of the brain identified on the MRI. A high-frequency electrical current is then used to make the lesion. Since the brain has no sensory nerve endings, the patient feels nothing at all. The probe is removed and the procedure repeated on the other side. Now that the main business of the procedure is done, the surgeon uses small titanium plates to cover the burrholes and closes the scalp incisions with stitches or staples.

Finally, another MRI scan is performed to check that all is well, and the frame is removed. The marks of the frame attachment heal and disappear in about a week. The operation itself takes about three quarters of an hour, so even with the MRI scans and preparations, the whole process only takes about three hours in total.

Neurosurgery under local anaesthesia sounds like a daunting prospect and it is certainly not undertaken without careful consideration and meticulous attention to surgical technique. However, patients often comment afterwards that the experience was less traumatic than having a tooth filled. This is because the top of the head is much less sensitive than the mouth and has far fewer nerve endings.

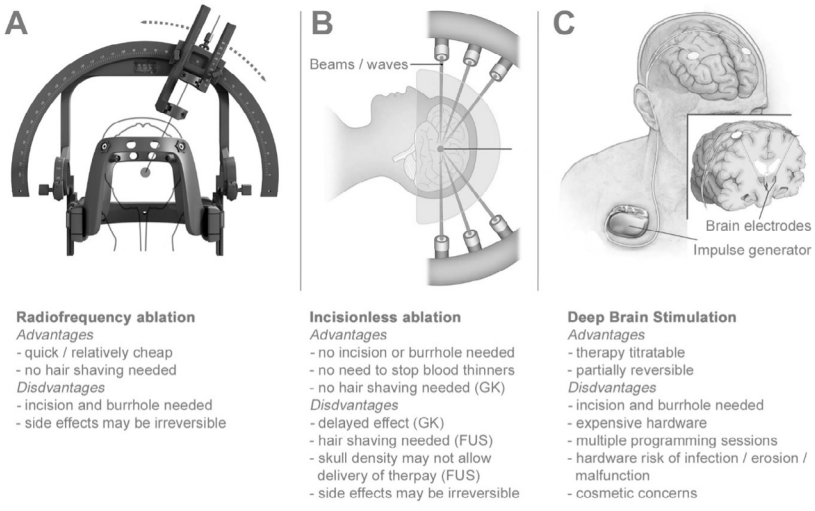

Figure 1. Principles of functional neurosurgery.

A. A stereotactic frame allows calculation of geometric coordinates of a visualised anatomical structure on specific MRI sequences. A minimally invasive approach then allows precise delivery of a radiofrequency probe to the desired anatomical location. A tiny volume of brain tissue around the tip of the probe is coagulated using a high-frequency electrical current.

B. Incisionless methods can be employed to make stereotactic lesions. MRI is again used to visualise the anatomical target. Focused gamma knife waves (from numerous radioactive cobalt sources) or ultrasound waves (from numerous piezoelectric crystals) deposit energy in the target, resulting in formation of a precise lesion.

C. Deep brain stimulation involves implanting brain electrodes that are connected to an internal impulse generator to drive a small high-frequency electrical current that disrupts neural transmission in adjacent brain tissue.

Abbreviations: FUS = focused ultrasound; GK = gamma knife.

gamma knife and MR-guided focused ultrasound (Figure 1B). DBS requires permanent implantation of brain electrodes and an impulse generator that drives a small high-frequency electrical current (Figure 1C). This effectively disrupts neural transmission in adjacent brain tissue and has the added benefit of a degree of reversibility. Each approach has specific advantages and disadvantages that are reviewed in Figure 1.

The same anatomical target can be used to alleviate a specific set of symptoms, regardless of the aetiopathogenesis of the disease itself. An example of this is the efficacy of SA or DBS of the motor nucleus of the thalamus on tremor, whether caused by cerebellar dysfunction (essential tremor), basal ganglia dysfunction (PD) or midbrain dysfunction (for example, Holmes tremor) (Figure 2).

Why consider neurosurgery in mental disorders?

As with some neurological disorders, many mental disorders are increasingly recognised as the product of abnormal activity within brain circuits (21). Class I evidence from multiple randomised, controlled trials supports the use of neurosurgical approaches in the treatment of some mental disorders, including OCD and Gilles de la Tourette syndrome (22-25). As with neurological movement disorders, there is some evidence to suggest that neurosurgery for mental disorders is a symptomatic treatment, regardless of the underlying diagnosis. For example, a recent meta-analysis of lesional neuropsychiatry revealed that anterior capsulotomy (disruption of the anterior limb of the internal capsule) resulted in a large and significant reduction in anxiety, regardless of the underlying psychiatric diagnosis (26).

How safe is stereotactic functional neurosurgery?

On the one hand, many non-specialists underestimate the physical and psychosocial dangers of AN. Imaging and other studies have demonstrated structural and functional damage to the starved brain (27). On the other hand, non-surgeons often overestimate the risk of modern neurosurgery. The most devastating complication in functional neurosurgery is haemorrhage leading to neurological deficit or death. However, this is exceedingly rare. Infection is exceptional in lesioning procedures; however, in DBS, the hardware may need to be explanted, leading to withdrawal of therapy. In a recent publication from our own institution, 4 of 650 DBS patients (0.6%) suffered transient neurological symptoms secondary to intracranial haemorrhage. Infection led to hardware removal in 21 of 650 patients (3.2%). Importantly, mortality was zero (28).

Psychiatrists are often concerned about the possible psychological sequelae of stereotactic ablative functional neurosurgery. Although data are scarce, several studies have compared detailed neuropsychology battery test results before and after SA for depression. All studies concluded that neurocognitive and personality testing were not significantly different at follow-up (29-32). Another study reported long-term improvements in fluency, inhibition function, set-shifting, decision-making and IQ scores in patients undergoing capsulotomy for OCD (33).

Should we consider neurosurgery in anorexia nervosa?

Anorexia is a pressing healthcare issue in dire need of novel treatments, especially for patients with longstanding illness. Campaigners and compassionate service providers will no longer tolerate a passive stance to such conditions and are demanding appropriate interventions. There is reluctance on both sides to enforce multiple admissions for the individual at exceedingly high financial cost. Despite such intensive interventions, recovery rates remain low at this stage of the disorder. This is exacerbated by difficulties gaining access to eating disorders services in the UK and

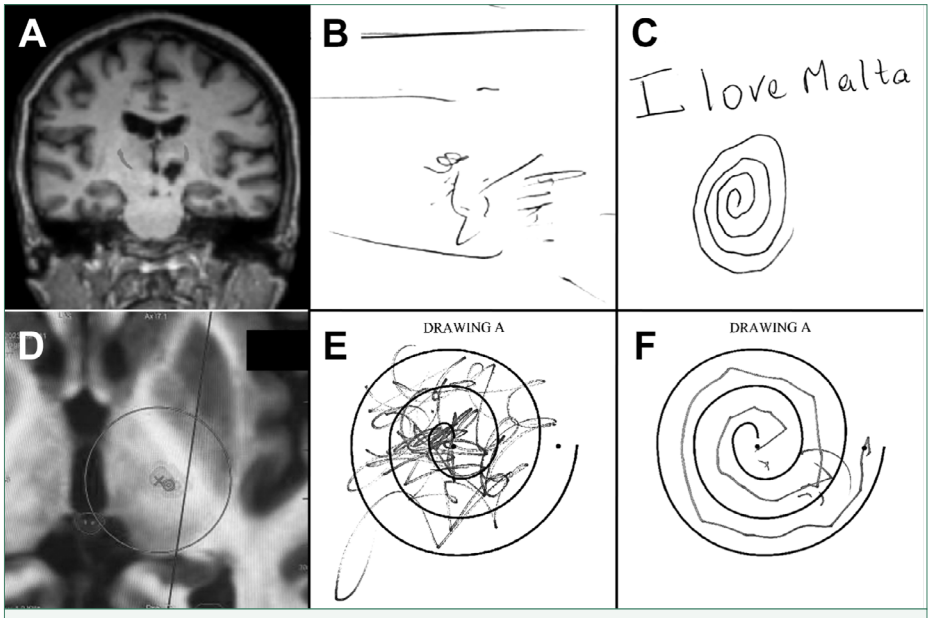

Figure 2. Using the same anatomical target in functional neurosurgery can treat specific symptoms, irrespective of the underlying pathology or surgical method.

Top row: Patient with Holmes tremor.

A. Coronal T1-weighted MRI showing left midbrain/thalamic cavernoma. **B.** Handwriting before surgery where the patient had difficulty keeping the pen in contact with the paper because of severe "flapping" tremor **C.** Handwriting after left radiofrequency thalamotomy.

Bottom row: Patient with severe essential tremor.

D. Axial FAT1 MRI showing planning of left focused ultrasound thalamotomy. **E.** Handwriting before surgery where the patient had difficulty following an Archimedes spiral because of severe tremor **F.** Handwriting after left focused ultrasound thalamotomy.

comparable nations. Meaningful improvement in the most severely affected individuals could break this cycle, improve quality of life and reduce the high mortality and morbidity associated with this condition.

As discussed above, there is an undeniable biological contribution to the aetiology of AN and considerable overlap with other psychiatric disorders, especially with OCD. A recent systematic review concluded that the obsessive-compulsive symptoms in AN are phenomenologically similar, though not identical to OCD alone (34). This is reinforced by genetic findings in the two disorders that were found to relate to the same areas of the brain (35). Therefore, the evidence-based success of neurosurgery in patients with severe refractory OCD gives hope that similar results may be achievable in AN, especially in patients with comorbid OCD symptoms. Moreover, the high mortality in individuals with AN on the extreme end of the clinical spectrum, combined with the relatively low risk of neurosurgical intervention, makes the option of neurosurgery particularly relevant.

What is known about stereotactic ablation for anorexia nervosa?

Stereotactic capsulotomy and stereotactic anterior cingulotomy are neurosurgical procedures performed for severe refractory OCD (Figure 3A and 3B). In patients who respond, reduction in anxiety and improvement in mood are accompanied by an improvement in the Yale-Brown Obsessive Compulsive Score (Y-BOCS), breaking the OCD cycle. Since stereotactic interventions are symptomatic therapies, this raises the hope that capsulotomy in individuals with AN, who also suffer from symptoms of OCD and anxiety, may lead to reduction in obsessive thoughts and anxiety pertaining to food and body image. Together with improvement in mood, this may provide numerous mechanistic opportunities to break the "anorexia cycle".

In a serendipitous observation, a patient with OCD, who also had AN, underwent bilateral anterior capsulotomy and reported significant improvement in both conditions (36). A more recent report of bilateral lesioning of the anterior capsule, cingulum and nucleus accumbens in a patient with comorbid AN and OCD resulted in improvement in both conditions (37). Notable in both reports is that gain in weight was accompanied by improvement in the underlying psychopathology (Box 2).

The largest dataset available is from an open-label study in 74 patients who underwent anterior capsulotomy for AN in Shanghai. Average (SD) body

Box 2. Outcome measures in anorexia nervosa

Outcome measurement in AN is challenging in areas of qualitative experience. Mental health professionals are still working to develop, validate and improve measures. These often involve self-rated or observer-rated questionnaires, and there is all too little uniformity across studies in their use. Since AN involves, at its core, an inability to tolerate a healthy body weight, it is convenient to use body mass index (BMI) as both a measure of how close to a healthy weight the psychopathology permits as well as a measurement of physical benefit. There is considerable evidence that nutritional recovery from starvation is essential – though not always sufficient – for psychosocial recovery from AN.

One limitation to the use of BMI in AN is that most good inpatient centres can impose weight gain on patients, using the Mental Health Act if necessary. Such weight gain may be transient and is not, in this case, an index of psychological recovery, or indeed of physical safety, if only short-lived. The best research therefore uses both BMI and symptom questionnaire measures in evaluation and pursues long-term follow-up.

mass index (BMI) improved from 13.6 (1.6) to 18.2 (3.4), p < 0.001, at 12 months and 19.3 (3.6) kg/m2, p < 0.001, at 36 months after surgery. Significant improvements were also noted in anxiety as measured by scores on the Hamilton Anxiety Scale (HAM-A) from 21.6 (7.0), p < 0.001, to 13.1 (8.3) at 12 months and 12.3 (9.3), p < 0.001, three years after surgery. Improvement was also seen in mood, with mean Hamilton Depression Rating Scale (HAM-D) scores improving from 27.7 (11.1) to 16.9 (12.2), p = 0.001, at 12 months and 16.6 (13.9), p < 0.001, at 36 months after surgery. Long-term adverse events were disinhibition (6 patients), memory loss (3 patients), and lethargy (4 patients), although the severity of these was not described. Once again, weight gain improved together with the underlying psychopathology (38).

Incisionless neurosurgery for AN is in its infancy. A Madrid group has reported 40% improvement in BMI and 30% improvement in health-related quality-of-life scores after gamma knife anterior cingulotomy in six patients with AN (39). As yet, there are no publications on MR-guided focused ultrasound for AN. The need to undergo a complete head shave prior to focused ultrasound treatment may be problematic for individuals with significant body image concerns.

What is known about deep brain stimulation for anorexia nervosa?

Open-label pilot studies of DBS in AN have had some promising results. A recent meta-analysis identified four clinical studies with ≥4 participants. The anatomical targets used include the subcallosal cingulate gyrus (SCC) and the ventral capsule/ventral striatum (VC/VS) (a similar anatomical target to that used in capsulotomy) (Figure 3C).

In a study from Toronto, 16 patients with "treatment-refractory anorexia nervosa" underwent SCC DBS (40). One year after surgery, average BMI improved from 13.8 (1.5) to 17.3 (3.4) kg/m2, p = 0.0009. Moreover, there were significant improvements in anxiety (mean (SD) Beck Anxiety Inventory scores, 38.0 (15.6) vs. 27.1 (18.4), p = 0.035) and mood (mean HAM-D scores, 19.4 (6.8) to 8.8 (7.6), p = 0.00015) (40). The same group has recently published longer-term outcome data in 22 patients with DBS for AN. Two patients died of complications of AN and there were several serious adverse events related to DBS, including seizures (n = 4) and surgical infections leading to hardware removal (n = 3). In the 15 patients who had ≥3 years of follow-up, mean BMI increased significantly from 14.0 at baseline to 16.3 kg/m2 (p = 0.003). However, significant psychometric improvement was not maintained at cohort level (41).

A Spanish (Barcelona and Madrid) group have presented early open-label data in eight patients with AN who underwent DBS of either the SCC (n = 4) or VC/VS (n = 4). When examining preliminary results after six months, there was a significant increase in BMI (p = 0.02) in patients who did not undergo preoperative inpatient care to raise BMI.Across all participants, the authors also observed significant improvement in SF-36 quality-of-life scores (p = 0.03). Three of the eight patients suffered cutaneous complications that required further surgical intervention. This study represents the initial phase of a planned randomised, double-blind, controlled crossover clinical trial and longer-term data are eagerly awaited (42).

The Shanghai group that reported on capsulotomy for AN have also published their experience with 28 women with AN undergoing VC/VS DBS. They noted significant improvements in BMI and psychopathology after six months that were maintained at two-year follow-up. BMI improved from 13.0 (1.9) to 17.7 (3.5) kg/m2 (p < 0.001), Y-BOCS from 20.5 (8.9) to 13.0 (9.6) (p < 0.001), HAM-A from 21.4 (8.5) to 12.6 (6.5) (p < 0.001) and HAM-D from 26.9 (12.0) to 15.9 (12.3) (p < 0.001). DBS was more effective for weight restoration in the restricting AN subtype than for the binge/purge subtype. The device had to be explanted in one patient (43).

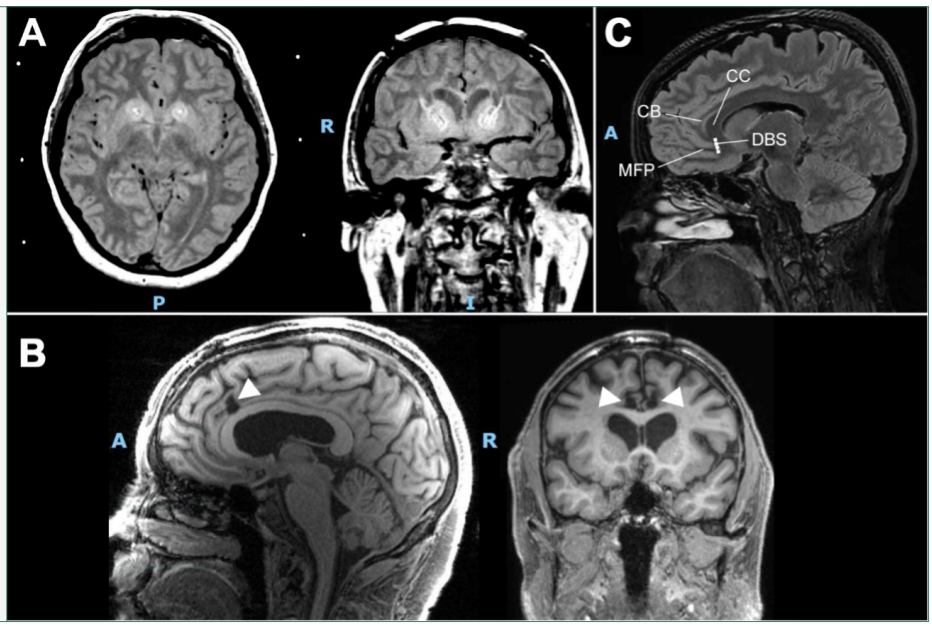

Figure 3. MRI after neurosurgery for mental disorders

A. Axial and coronal proton density–weighted MRI immediately after bilateral radiofrequency anterior capsulotomy. The hyperintense signal is mostly oedema and the permanent lesions are only around 3 mm in diameter.

B. Sagittal and coronal T1-weighted MRI, one year after radiofrequency anterior cingulotomy (arrowheads).

C. Sagittal MRI (fluid-attenuated inversion recovery) showing corpus callosum (CC), cingulate bundle (CB), medial frontal projection (MFP) and stylised deep brain stimulation lead (DBS) in the subcallosal cingulate gyrus, spanning both CB and MFP.

A further study from Amsterdam reported on four patients with AN who underwent VC/VS DBS. After 12 months, mean BMI improved from 12.5 (1.7) to 17.8 (1.7) kg/m2 ($p = 0.028$). This was accompanied by significant improvement in psychopathology, including "preoccupation and rituals" and "restraint and eating concern". Mood also improved significantly with changes in the HAM-D and HAM-A scales of 36.7% and 47.9%, respectively. Two hypomanic episodes were reported as serious adverse events that were probably related to the intervention. The authors, a very experienced group in DBS for OCD, commented on the challenging nature of performing a DBS study in AN patients, and reported several severe adverse events, including "transient hypomanic and impulsive symptoms … and self-destructive behaviour" (44).

After collating the results of these four studies (n = 56), a recent meta-analysis concluded that DBS had a significant positive effect on BMI with a large effect size and without heterogeneity. DBS also had a significant beneficial effect on psychopathology, including eating disorder symptoms ($p = 0.006$), depression ($p < 0.001$), OCD symptoms ($p < 0.001$), anxiety ($p < 0.001$) and quality of life ($p < 0.001$). There was no suggestion of publication bias. The authors concluded that DBS can be an effective last-resort treatment option in selected cases of severe treatment-refractory AN, under strict monitoring and scientific evaluation of the effects (45).

Following the above meta-analysis, a further study of VC/VS DBS was published by the Oxford group in seven patients with AN. During an initial 12-month open-label period, three of seven patients had a positive response (defined as >35% improvement in the Eating Disorders Examination (EDE) score). Responders also experienced significant reductions in depression and anxiety scores. However, there were no significant changes in BMI. No serious adverse events were reported. This study also included a two-week double-blind, randomised, crossover study at the end of the open-label period with stimulation on/off. However, the short crossover period, small study size and relatively low initial response rate compared to other DBS studies make these findings difficult to interpret. Interestingly, the authors noted that the three responders had early-onset comorbid OCD and, for them, DBS "was experienced as a game-changing intervention" (46).

Stereotactic ablation after failed deep brain stimulation for anorexia nervosa

The Shanghai group have published an interesting case report where a patient with life-threatening, treatment-resistant restricting-subtype AN did not respond to VC/VS DBS. The DBS system was explanted and "rescue" bilateral anterior capsulotomy was performed. The was followed by long-lasting restoration of body weight (BMI 13.3 to 22.1 kg/m2) and significant sustained remission in psychopathology and quality-of-life scores after seven years of follow-up. This individual also suffered from extreme comorbid OCD with Y-BOCS II scores falling from 46/50 prior to capsulotomy to 0/50 at long-term follow-up (47).

Ethical concerns with neurosurgery for anorexia nervosa

Functional neurosurgery should only be performed within the context of an experienced multidisciplinary team. In the case of AN, it is essential that this includes a functional neurosurgeon and a specialist eating disorders psychiatrist. Ensuring an individual has capacity and provides informed consent are essential aspects of any medical intervention. However, there are additional concerns in AN. There are deep cultural taboos against interfering with the mind and brain, and the profession of psychiatry still carries a burden of shame for having inflicted crude frontal lobotomies on psychiatric patients. Some individuals may not want to undergo SA because of its perceived irreversibility and their continuing ambivalence about losing their drive to lose weight; others may not wish to have an implanted device that may be seen as a form of "physician control" (48, 49). Moreover, surgery for mental disorders should only be performed in carefully selected patients within a framework of strong clinical governance and safeguarding (50). In England, mental health legislation ensures that every patient is reviewed by the Mental Health Board of the Care Quality Commission prior to undergoing surgery (51). This process ensures that vulnerable patients can provide consent, are fully informed of the potential risks and benefits and have symptoms refractory to other therapies that are severe enough to warrant a neurosurgical intervention.

Should we consider stereotactic ablation over deep brain stimulation in severe anorexia nervosa?

Although there are no "head-to-head" studies of SA and DBS in AN, there is some suggestion that SA may be preferable to DBS. Practically all the evidence for neurosurgery in AN is from open-label, uncontrolled studies. Nevertheless, the ultimate effect size on BMI is impressive. The largest study of capsulotomy in AN reported a mean improvement in BMI of 41.9% at three-year follow-up (n = 74) (38). A systematic review of DBS for AN calculated a mean improvement of 24.8% after a mean follow-up of 17 months (n = 118) (52). To put this into perspective, the highest level of evidence for pharmacotherapy in AN, a randomised controlled trial of olanzapine versus placebo, showed a mean BMI increase of 6.3% over four months, with no data available on longer follow-up (53). Of course, one cannot directly compare the results of randomised controlled drug studies with open-label trials of neurosurgical interventions, where the placebo effect is likely to be high. This is especially true of DBS that involves not only surgery, but multiple programming sessions. However, the effect size of capsulotomy on BMI appears to be even larger than DBS and is worthy of further investigation. A single head-to-head comparison exists in the form of a case report where capsulotomy led to significant long-term improvement of core AN symptoms and BMI after VC/VS DBS failed to make an impact (47).

Importantly, the evidence accumulated so far suggests that both neurosurgical interventions are accompanied by improvement in the underlying psychopathology, including anxiety, obsessive thoughts and compulsive behaviours. These lead to significant and sustained improvements in quality of life.

Reported deaths are limited to DBS patients (albeit not shown to be related to the intervention) suffering from erosion, infection, hypomania and seizures – complications that have not been reported and are unlikely to occur after stereotactic capsulotomy. On the other hand, 18% of patients undergoing capsulotomy reported some degree of disinhibition, memory loss or lethargy.

Other important aspects to be considered include the following.

Surgical factors: SA can be performed under local or general anaesthesia whereas DBS requires general anaesthesia for implantation of the cables and pulse generator. Patients with long-term AN often suffer from numerous cardiovascular, endocrine and metabolic abnormalities that increase the risk of general anaesthesia (2). Moreover, the thin skin and delicate tissues covering implanted DBS hardware is more likely to lead to erosion and infection, as is evident from published studies of DBS for AN.

Psychological factors: Body image concerns related to surgery are less likely with ablation as the scalp incisions are hidden behind the hairline. On the other hand, implanted hardware is likely to be visible and palpable through thin skin and scars on the chest wall are required for the implantable pulse generator. Adverse neuropsychological effects may occur with either procedure and could be permanent with ablation. However, the evidence available suggests that these are unlikely. DBS may also raise concerns about the potential for symptom rebound if DBS therapy is withdrawn because of hardware malfunction or infection requiring removal.

Cost and logistics: The cost of DBS is much higher than for ablation. A bilateral DBS implant with a rechargeable pulse generator can cost >£20 000 in hardware alone. Moreover, a specialised nurse or neuromodulation consultant is required to programme the DBS system over multiple sessions. This can be costly and time-consuming, even when programming patients undergoing "routine" DBS for PD, placing a significant load on already stretched healthcare systems. Finally, experienced DBS teams are rarely co-located with eating disorder specialists. Visiting different hospital settings can be a significant burden on patients. On the other hand, SA is a one-off procedure that is much faster and cheaper than DBS and does not require regular additional visits to the neurosurgeon/neuromodulation specialist over and above those to the eating disorder specialist.

Although there are many reasons why we should consider SA in long-term AN, ethical research into all promising therapies should be encouraged as each will have potential advantages and disadvantages. Ultimately, well-informed adult participants with capacity should be free to decide whether they wish to undergo a particular procedure and/or participate in an ethically approved research project.

Which anorexia nervosa patients should we consider for neurosurgery?

At the current stage of knowledge, neurosurgery should be restricted to adult patients with severe and enduring AN who have the capacity to provide informed consent. The criteria for severity and duration should be agreed by eating disorders experts with reference to the patient's age, length of illness and treatment history. There should be evidence of repeated unsuccessful previous treatments, with failure to improve or rapid relapse post-intervention. Treatments should have included courses of intensive specialist eating disorder inpatient treatment, both voluntary and compulsory, focusing on refeeding; and evidence-based specialist psychotherapies. To improve the chance of response, the available data suggests that comorbid OCD symptoms may be a predictor of good outcome. Patients with medical conditions that substantially increase the risk of a neurosurgical procedure should be excluded. It goes without saying that surgery should be undertaken only in highly reputable specialist centres with a good track record of surgery for psychiatric disorders, and in the context of ethical research protocols.

Limitations

The overall number of reported patients who have undergone functional neurosurgery for AN is relatively small. Moreover, the bulk of the data available for stereotactic capsulotomy in AN derives from a single relatively large study from Shanghai. It remains to be seen whether these results can be reproduced by other centres.

Conclusion

AN is a pressing healthcare issue in dire need of novel treatments, particularly when it has become chronic with associated severe psychosocial and psychical disability. Difficulty gaining access to eating disorder services is exacerbated by the high need for multiple admissions for the individual at exceedingly high cost. Despite intensive interventions, recovery rates remain low. Meaningful improvement in the most severely affected individuals could break this cycle, improve quality of life and reduce the high mortality and morbidity associated with this condition. Functional neurosurgery for AN seems promising but there is much scope and need for further research. It is not yet clear how patients, carers and clinicians will perceive the idea of different neurosurgical procedures for AN. Patient selection criteria will need to be developed and refined. Although several outcome measures have been used, clear definitions of response

and remission in AN remain elusive.

Over the past century, patients with movement disorders have benefitted greatly from collaboration between neurologists and neurosurgeons. Patients with mental disorders should also benefit from increased collaboration between the clinical neurosciences. The available evidence is far from conclusive. However, it suggests that AN is a potentially rewarding area for greater collaboration between functional neurosurgeons, psychiatrists specialising in eating disorders and their patients.

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Declarations of interest

Ludvic Zrinzo acts as a consultant for Medtronic, Boston Scientific, and Insightec.

Jane Morris has written and edited books on eating disorders for CUP and Springer.

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