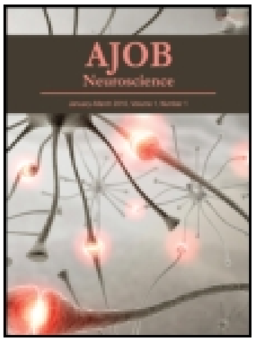

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Target Article

An Ethical Evaluation of Stereotactic Neurosurgery for Anorexia Nervosa

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Anorexia nervosa (AN) is one of several neuropsychiatric disorders that are increasingly tackled experimentally using stereotactic neurosurgery (deep brain stimulation and ablative procedures). We analyze all 27 such cases published between 1990 and 2014. The majority of the patients benefitted significantly from neurosurgical treatments, in terms of both weight restoration and psychiatric morbidity. A remission of AN was reported in 61% of patients treated with DBS and 100% of patients treated with ablative surgery. Unfortunately, information on side effects is insufficient, and after DBS, severe side effects occurred in some cases. Altogether, the risk–benefit evaluation is positive, particularly for ablative stereotactic procedures. However, fundamental ethical issues are raised. We discuss whether neurosurgery can be justified for treating psychiatric disorders of the will that are seemingly self-inflicted, such as addiction or AN, and where cultural factors contribute significantly to their development. We suggest that although psychosocial factors determine the onset of AN, this is not a legitimate argument for banning neurosurgical treatments, since in AN, a vicious circle develops that deeply affects the brain, undermines the will, and prevents ceasing the self-destructive behavior. Three confounding issues provide ethical challenges for research in neurosurgery for AN: first, a scarce information base regarding risks and benefits of the intervention; second, doubtful capabilities for autonomous decision making; and third, the minor age of many patients. We recommend protective measures to ensure that stereotactic neurosurgery research can proceed with respect for the patients' autonomy and orientation to the beneficence principle.

Keywords: neuroethics, psychiatric neurosurgery, psychosurgery, anorexia nervosa, deep brain stimulation

Currently, we experience a renaissance of neurosurgical interventions for treating psychiatric disorders, including anorexia nervosa (AN). This is remarkable, as in the 1970s, psychosurgery had become discredited and had been nearly completely abandoned after its frequent serious complications became public. Since 2000, different neuromodulation techniques have been examined: repetitive transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation, and particularly deep brain stimulation (DBS; McClelland et al. 2013). In the course of this development, ablative neurosurgical procedures are investigated, too, since they have become much safer, particularly if performed by radiosurgery (e.g., Gamma Knife). (For an extensive review of the state of the art of psychiatric DBS, microsurgery, and radiosurgery see Lévèque [2014] and Sun and De Salles [2015].) This reflects a therapeutic paradigm shift in psychiatry from a predominating psychosocial to a brain-based paradigm, and within the latter, from global interventions (e.g., via psychotropic drugs) to localized interventions.

Nevertheless, the use of surgical brain interventions to treat AN raises additional ethical concerns compared to other neurosurgical interventions for treating psychiatric disorders because of the nature of the disorder and the young age of most patients. Many physicians and psychologists understand AN as a developmental problem that emerges in the course of puberty or as a symptom of the Western obsession with slimness. Therefore, the idea to perform brain interventions in adolescents refusing nutrition might appear fundamentally wrong. However, it has to be kept in mind that AN is a serious condition with the highest mortality of all psychiatric disorders (Smink, van Hoeken, and Hoek 2013).

In this article, we review the published cases of neurosurgically treated AN patients. Based on this and on a discussion of its limitations, we analyze the ethical justification of the use of stereotactic neurosurgery for AN. In particular, we investigate the doubtable therapy resistance of the patients that have been treated neurosurgically so far; the unclear benefit–risk relationship due to

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underreported side effects and a selective publication practice; the nosological uncertainty of AN that is reflected in the exploration of targets; challenges to informed consent; and coercive interventions in the brains of adolescents.

ANOREXIA NERVOSA AND STEREOTACTIC NEUROSURGERY

Anorexia Nervosa

Definition and diagnostic criteria. Anorexia nervosa (AN) is characterized by intentionally induced underweight, an intense fear of gaining weight, a distorted body image, and frequently psychiatric comorbidity. The restricting type primarily loses weight by reducing caloric intake and/or excessive exercising. The binge/purging type additionally engages regularly in binge eating or purging behavior. Many AN patients deny being underweight and show resistance to treatment, partly due to the ego-syntonic nature of the disorder (Kaye 2008).

In the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV: American Psychiatric Association [APA] 2000), AN was characterized by (A) refusal to maintain body weight at or above a minimally normal weight for age and height (i.e., below 85% of the normal weight for age and height, or BMI $\leq$ 17.5 kg/m^2); (B) an intense fear of gaining weight or becoming fat, even though underweight; (C) a disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight; and (D) amenorrhea in the case of postmenarcheal females. In *DSM-5* (APA 2013), criteria A and B have been weakened and criterion D has been eliminated. This reduces the threshold for diagnosing anorexia nervosa so that the lifetime prevalence according to *DSM-5* might be almost twice as high as according to *DSM-IV* criteria (Smink, van Hoeken, and Hoek 2013).

Prevalence. AN develops mostly in adolescence or early adulthood; its peak of onset is between 15 and 19 years of age (Wu et al. 2013). According to more recent reviews, the female/male ratio is 2.2:1 (Qian et al. 2013), which attenuates earlier findings wherein AN is predominately a disease that affects women (Hoek and van Hoeken 2003). Furthermore, prevalence data of AN differ eminently across time and countries due to cultural factors and the evolution of diagnostic criteria. The lifetime prevalence of AN in Western countries is 0.32% (Qian et al. 2013); in non-Western countries, it is only 0.002–0.09% (Aigner et al. 2011).

Psychiatric comorbidity. Most AN patients have psychiatric comorbidities: major depressive disorder (15–60%), obsessive–compulsive disorder (OCD; about 40%), and anxiety disorders (20–60%) (Herpertz-Dahlmann 2008). Furthermore, AN and body dysmorphic disorder are highly comorbid (Hartmann, Greenberg, and Wilhelm 2013). Many AN patients have characteristic personality traits, particularly perfectionism, obsessive–compulsiveness, dysphoric mood, high levels of anxiety, asceticism, neuroticism, harm avoidance, overcontrol, and a perservative and rigid style. It is not yet sure whether these personality traits are a cause or consequence of malnutrition (Kaye 2008).

Medical risks. AN patients are at risk for serious medical and metabolic complications; electrolyte disorders, osteoporosis, or renal insufficiency can become life-threatening (Wang et al. 2013). Further long-term effects are cardiovascular disturbances, thyroid disorders, gastrointestinal disorders, and fertility and pregnancy problems. AN has the highest mortality of all psychiatric disorders (Smink, van Hoeken, and Hoek 2013). The crude mortality rate for AN is 5.1 deaths per 1,000 person-years; the overall standardized mortality ratio of AN is 5.9. Twenty percent of all AN patients who died have committed suicide (Arcelsus et al. 2011).

Therapies. The main goals of AN therapy are weight restoration, prevention of relapse, a change in eating behavior and body image, and reduction of psychiatric comorbidities and starvation-associated conditions (Aigner et al. 2011; Hartmann, Greenberg, and Wilhelm 2013). Psychotherapy is the treatment of choice, although outcome research is scarce. At least, there is some support for the efficacy of cognitive behavioral therapy, which includes motivational aspects, psychoeducation, mirror retraining, weight restoration, and the management of the overvaluation of body shape and weight. For adolescents, family-based therapy is the gold standard (Hartmann, Greenberg, and Wilhelm 2013).

Pharmacotherapy is often used in the treatment of AN, but evidence for benefits is weak for most therapies. According to the World Federation of Societies of Biological Psychiatry guidelines, there is no clear evidence for the general use of antidepressants in AN. For the atypical antipsychotic olanzapine, there is category grade B evidence (limited positive evidence from controlled studies) for weight gain. For zinc supplementation, there is grade B evidence for weight gain, and reduction of depression and anxiety (Aigner et al. 2011).

In severe cases, it can be necessary to hospitalize patients for medically stabilizing or refeeding them (potentially with nasogastric or percutaneous endoscopic gastronomy-based tubes; Hartmann, Greenberg, and Wilhelm 2013) or for treating cardiac problems (Lipsman et al. 2013a).

The recovery rate at 6-year follow-up is 52% (Smink, van Hoeken, and Hoek 2013). In 20.8% of the surviving AN patients the disorder becomes chronic (Steinhausen 2002).

Between 1950 and 1973, 17 AN patients were treated with leucotomy that resulted in most cases in weight restoration and improvements in psychiatric disorders, but in several patients psychiatric problems remained, and one patient committed suicide (Lipsman et al. 2013b; Sun et al. 2015). Stereotactic neurosurgery restarted in 1993 in two

AN patients (Zamboni et al. 1993), and in 2010, the first AN patient was treated with DBS (Israël et al. 2010).

Pathogenesis. Several very different pathogenesis models for AN have been proposed. Psychoanalytical models explain AN as the avoidance of maturation into womanhood and of the development of sexuality. According to the psychosomatic family model, AN is caused by an overprotective and conflict-avoiding parent–child interaction. A recent theory based on the analysis of phenomenological descriptions of AN and on Théodule Ribot's theory of passions understands AN as a passion, that is, as a complex affective syndrome that has parallels with addictions. Passions are relatively stable; they organize thoughts, feelings, and emotions around a fixed idea, and determine how the person evaluates experiences and forms beliefs. Although fixed ideas are not necessarily obsessive or delusional, passions can turn into mental disorders; indeed, the link between passion and psychopathology is intimate (Charland et al. 2013; Charland 2013). AN is very similar to alcohol dependence; it can be considered as an "auto-addiction" to starvation, perhaps as the result of brain changes caused by dieting (Szmukler 2013).

Although biological factors have gained in appreciation, sociocultural aspects play an important role in the development of AN. In fact, dieting is the most important predictor of developing an eating disorder. According to a large, randomized study, female teenagers who dieted at a severe level were 18 times more likely to develop a new eating disorder within 6 months than those who did not diet (Patton et al. 1999).

The second biggest predictive factor for eating disorders is psychiatric morbidity. Individuals with the highest psychiatric morbidity had an almost sevenfold higher risk of developing an eating disorder (Patton et al. 1999).

Twin and family studies have documented the heritability of AN (relative risk 11.3 in first-degree relatives of AN probands); heritablity has been estimated to be 56% (Sullivan et al. 2012). Thus far, neither candidate gene nor genome-wide studies have identified truly validated genes for eating disorders. Also, the most recent genome-wide association study, comprising 5551 AN cases and 21,080 controls in the meta-analysis, did not report genome-wide significant findings (Boraska et al. 2014), which, however, is not surprising as the number of cases with a relatively low heritability (compared to, say, schizophrenia) is still to low for a sufficiently powered genome-wide association study (GWAS).

In summary, current research suggests that the disorder is multifactorial, including genetic, hormonal, neuropsychological, sociocultural, and starvation-induced factors.

Neuronal correlates of AN. Several neuroimaging studies suggest an abnormal activity of the serotonin system in individuals with AN, which might be trait-related. This abnormal activity contributes to appetite dysregulation, anxious and obsessional behaviors, and extremes of impulse control (Kaye 2008; Sun et al. 2015). When people discover that caloric restriction results in a brief relief from dysphoric mood, this may become reinforcing; this produces a vicious circle that contributes to the chronicity of AN (Kaye 2008). Additionally, striatal dopamine function and levels are changed in individuals with AN. This might account for altered reward and affect, decision making, executive control, and stereotypic motor activity, and decreased food ingestion (Kaye 2008; Zhang et al. 2013; Wu et al. 2013; Sun et al. 2015). The reward system of individuals with AN seems to be differently activated by underweight-related cues; this supports an interpretation of AN as "starvation dependence" (Fladung et al. 2010).

According to the insula hypothesis of AN, a dysfunction or disconnection of the insular cortex is a crucial risk factor for developing AN. The insula's main role is to orchestrate the balance between those parts of the brain responsible for the adaptation to the external environment and those responsible for internal homeostasis. Among the insula's functions are the regulation of the autonomous nervous system, appetite, eating, taste, and visceral memory; monitoring of the body state; integration of thoughts and feelings; regulation of the experience of pain; and interoceptive processing, and particularly the experience of disgust (Nunn et al. 2011). A disturbed insula function is considered to cause AN symptoms like distorted body image, lack of recognition of malnutrition, and elevated pain thresholds (Kaye 2008). The insula might be crucial for behaviors whose bodily effects are initially aversive but become pleasurable through learning. This hypothesis is supported by the observation that smokers with insula lesions are more likely to disrupt smoking addiction immediately, easily, and without relapse (Naqvi et al. 2007). If AN is an addiction for hunger and exercise, it becomes understandable why the insula is also involved in AN.

Drug addiction and AN have in common the phenomenon of allostasis, which occurs when "an organism must vary all of the parameters of its internal milieu and match them appropriately to perceived and anticipated environmental demands in order to maintain stability" (Koob and Le Moal 1997, 55). Both drug addicts and individuals with AN engage in repetitive dysfunctional behaviors without sufficient concern for the negative consequences (Halmi 2009).

Stereotactic Neurosurgery for Psychiatric Disorders

Current indications of DBS in psychiatry include OCD, major depressive disorder, dementia, Tourette's syndrome, drug addiction, and AN (Luigjes et al. 2013). The main advantages of DBS in comparison to ablative procedures are its reversibility (in principle) and adjustability. The targeting of the electrodes is to a great extent based on literature about ablative psychosurgery. Additional targets have been selected on grounds of tractography and functional neuroimaging studies. For example, five different targets are addressed for treating OCD (Blomstedt et al. 2013). Notably, the same targets are used to treat different

Table 1. Neurosurgical studies with anorexia nervosa patients

Study	Aim of the study	Number of patients	Age at surgery (years)	Target	Therapy effect	Adverse effects
DBS						
Israël et al. 2010	Treatment of refractory MDD	1	56	Subgenual cingulate area (SGCA) bilaterally	3-year follow-up: remission of AN; improvement in depression	Not reported
McLaughlin et al. 2013	Treatment of OCD	1	48	VC/VS bilaterally	Remission of AN	Relapse after reprogramming an electrode; reversible
Lipsman et al. 2013a	Treatment of AN	6	Mean: 38, range: 24–57	SCC	9 months post op: 33% of patients: normal BMI; 67%: improvement in depression; 50%: improvement in OCD and quality of life	Pancreatitis and hypokalemia (1 patient), refeeding delirium and hypophosphatemia (1), worsening mood (1), QT prolongation and seizure (1), pain (3); nausea (1); intraoperative panic attack (1); increased lead impedance (1), cardiac air embolus (1)
Wang et al. 2013	Treatment of AN	2	Mean: 23 (18 and 28)	NAcc bilaterally	1 year post op: remission of AN + anxiety; reduction of depression and OCD; improved intelligence, memory, quality of life and social functioning; restoration of menstruation cycle	headache and in some patients centric fever (3–5 days post op)

(Continued on next page)

Table 1. Neurosurgical studies with anorexia nervosa patients *(Continued)*

Study	Aim of the study	Number of patients	Age at surgery (years)	Target	Therapy effect	Adverse effects
Wu et al. 2013	Treatment of AN	4	mean: 16.5 (range: 16–17)	NAcc bilaterally	9–50 months post op: 100% of patients: remission of AN (average BMI: 19.6, range: 18,4–22,1); remission of anxiety and OCD ; restoration of menstruation cycle	Not reported
Zhang et al. 2013	Treatment of AN and metabolic imaging of AN with and without DBS (18F-FDG PET/CT study)	4	Range: 16–18	NAcc	Stopping the intake of SSRIs and neuroleptics after DBS; 1 month post op: mean BMI of 15,65 (preoperatively: 12.12)	Not reported
Stereotactic Ablation						
Zamboni et al. 1993	Treatment of AN and OCD (and schizophrenic psychosis)	2	17 and 21	Dorsomedial thalamotomy	Major improvement in AN, OCD, depression, anxiety and behavior	Not reported
Barbier et al. 2011	Treatment of AN and OCD	1	38	Bilateral anterior capsulotomy (thermocoa-gulation)	Remission of AN and OCD, stop of medication	Transient bradycardia; mild disorientation in place and time, moderate somnolence, loss of concentration, apathy, emotional emptiness and mild loss of decorum
Wang et al. 2013	Treatment of AN	6	Mean: 20.3, range: 18–25	NAcc radiofrequency ablation	1 year post op: remission of AN, depression, anxiety, and OCD; improved intelligence, memory, quality of life and social functioning; restoration of menstruation cycle	Headache and in some patients centric fever (3–5 days post op)

symptoms, and different targets to treat the same symptoms (Blomstedt et al. 2013). This indicates the still experimental state of psychiatric DBS.

In spite of the advent of DBS, ablative procedures have been affirmed by international expert panels as important alternatives for appropriately selected patients (Bronstein et al. 2011; Nuttin et al. 2014). Modern psychiatric neurosurgery is safer and more effective than historical psychosurgery. The improvements are based on the refinement of surgical techniques, the usage of neuroimaging technologies and stereotactic methods for the accurate placement of lesions, and the introduction of radiosurgery (e.g., Gamma Knife). The main advantages of ablative procedures are their relative low costs, and exclusion criteria or practical limitations of DBS. Examples are patients who would not tolerate implanted devices, patients with pronounced infection risks, and patients who would not comply with the long-term follow-up after DBS. Particularly, radiosurgery offers a unique advantage: Since it does not require a craniotomy, the risks of anesthesia, hemorrhage, and infection do not exist. Recently, the first double-blind placebo-controlled trial with Gamma Knife capsulotomy for OCD has demonstrated an efficacy comparable to DBS for OCD (Lopes et al. 2014).

REVIEW OF STUDIES ON STEREOTACTIC NEUROSURGERY FOR ANOREXIA NERVOSA

Methods

We performed two searches in two databases (PubMed, National Library of Medicine, Washington; Web of Science Core collection; Thomson Reuters, New York, NY) on June 26, 2014. The Boolean search string for DBS studies was "("deep brain stimulation" OR DBS) AND (anorexia OR "eating disorder*")"; the search string for ablative studies was "(stereotactic* OR ablat* OR "functional neurosurg*" OR capsulotomy OR cingulotomy) AND (anorexia OR "eating disorder*")." The search was limited to publication dates between 1990 and 2014.

The initial search yielded 76 papers for ablative studies and 45 for DBS. We excluded papers on cancer-related anorexia, animal studies, reviews, comments, editorials, and bioethical papers. For DBS, four studies and two case reports with a total number of 18 patients have been identified; for ablation, there were one study and two case reports with a total number of 9 patients.

Additionally we searched for current books on psychiatric neurosurgery. One book (Sun and De Salles 2015) that was in press when we revised this article contains a chapter on surgical treatments of AN (Sun et al. 2015). The authors report that they treated 150 AN patients with capsulotomy and 15 patients with NAcc-DBS. However, only four of these patients have been described in work published in a journal (Wu et al. 2013); they are included in our review. Since detailed data on these patients is not available, we could not include these patients in the current review. However, we refer to them in the discussion.

Results of the Review

Information on the studies and case reports is presented in Table 1, and data on individual patients in Table 2.

Aims of the Studies

DBS. Two case reports (Israël et al. 2010; McLaughlin et al. 2013) describe AN as comorbidity of MDD or OCD, whereas four studies (Lipsman et al. 2013a; Wang et al. 2013; Wu et al. 2013; Zhang et al. 2013) aimed explicitly at treating AN. Zhang et al. (2013) also investigated the change in brain glucose metabolism after DBS.

Stereotactic ablation. Two case reports (Zamboni et al. 1993; Barbier et al. 2011) report three patients treated for AN with severe psychiatric comorbidities. The main goal of the study of Wang et al. (2013) was to treat AN.

Patients

DBS. All 18 patients were female and suffered from AN and associated psychiatric disorders such as major depressive disorder (MDD), OCD, or anxiety disorder. Their age range was 16–57 years, whereby 7 patients were minors. The range of disease duration was 1–39 years. The patients' body mass index (BMI) before DBS ranged from 10.0 to 18.5 kg/m^2.

Stereotactic ablation. Eight out of nine patients were female; all suffered from AN and associated psychiatric disorders such as MDD, OCD, and anxiety disorder. The only male patient had a chronic schizophrenic psychosis with prominent OCD features. The patients' preoperative BMI ranged from 9.1 to 14.4 kg/m^2. All but one patient were of full age (17–38 years). The range of disease duration was 2–24 years (Table 2).

Targets

DBS. Three groups have chosen the nucleus accumbens (NAcc) as target (Wang et al. 2013; Wu et al. 2013; Zhang et al. 2013), two groups the subcallosal cingulum (Israël et al. 2010; Lipsman et al. 2013a), and one group the ventral capsula/ventral striatum (VC/VS) (McLaughlin et al. 2013).

Stereotactic ablation. Each group has chosen different targets and ablation methods: dorsomedial thalamotomy (Zamboni et al. 1993), bilateral anterior capsulotomy through thermocoagulation (Barbier et al. 2011), and nucleus accumbens (NAcc) radiofrequency ablation (Wang et al. 2013).

Therapy Success

DBS. After DBS, 14 out of 18 patients had higher BMI values than preoperatively, but in 2 patients (Lipsman et al. 2013a) the increase was very small; 4 patients had lower BMI values postoperatively (Lipsman et al. 2013a). Eleven out of 18 patients (61%) had a remission

Table 2. Individual patients with anorexia nervosa treated neurosurgically

Number	Study	Diagnosis	Therapies	Age at AN onset (years)	Age at surgery (years)	BMI (historical low)	BMI before surgery	BMI after surgery	Target	Therapy effects	Adverse effects and relapses
				DBS							
1	Israël et al. 2010	Refractory MDD and AN	Multiple pharmacological interventions, several courses of electroconvulsive therapy	17	56	14.4	18.2	19.1 (average over 2 years post op)	SGCA, bilaterally	3 year post op.: lasting remission of AN (BMI 19,1; EAT-26 score of 1); improvement of depression (pharmacological treatment continued)	2 moderate depressive relapses
2	McLaughlin et al. 2013a	Childhood-onset, refractory OCD; MDD (3 suicide attempts), generalized anxiety disorder, ADHD, and AN	Behavioral therapy, aggressive pharmacological treatment	—	48	17.4	18.5	18.9–19.6	VC/VS bilaterally	remission of AN; normalization of eating behavior; less distress about weight	Relapse after reprogramming an electrode (deterioration of anxiety, mood, OCD, and weight); remission after turning off the responsible electrode contact
3	Lipsman et al. 2013a	AN, MDD, OCD	Selective serotonin reuptake inhibitors (SSRI) + antipsychotics	11	24	11.0	16.0	21.0 (9 months post op)	SCC	AN: remission (BMI 21.0 after 9 months); depression: response; increased QoL	temporary weight loss, pain, nausea
4	Lipsman et al. 2013a	AN, MDD, OCD, substance us disorder (SUD), posttraumatic stress disorder (PTSD)	SSRI + antipsychotics	16	39	11.9	16.3	16.0 (9 months post op)	SCC	BMI higher than at baseline (16.0 vs 14.2); depression: response; OCD: response; slightly increased QoL	temporary weight loss, pancreatitis, hypokalaemia, pain, intraoperative panic attack
5	Lipsman et al. 2013a	AN, OCD	SSRI	17	35	12.4	14.6	14.3 (9 months post op)	SCC	no significant change in BMI (as compared to baseline)	temporary weight loss, refeeding delirium, hypophosphataemia, increased lead impedance
6	Lipsman et al. 2013a	AN, MDD	SSRI + antipsychotics	36	40	13.1	18.4	14.0 (9 months post op)	SCC	no significant change in BMI (as compared to baseline)	temporary weight loss, depression: worsening (HAM-D increased from 22 to 25), pain at battery side
7	Lipsman et al. 2013a	AN, MDD, OCD, PTSD	SSRI + antipsychotics	20	35	13.5	16.9	20.0 (9 months post op)	SCC	AN: remission (BMI 20.0 after 9 months); depression: remission; OCD: response; increased QoL	temporary weight loss, QT prolongation, seizure during electrode programming
8	Lipsman et al. 2013a	AN, OCD	—	20	57	13.0	14.2	14.1 (9 months post op)	SCC	no significant change in BMI (compared to baseline); OCD: response (from 25 to 15)	intraoperative cardiac air embolus (resolved within 5 min); temporary weight loss
9	Wang et al. 2013a	AN, OCD, depression, anxiety	Nutritional support treatment, psychotherapy	26	28	—	13.3	18.0 (12 months post op)	NAcc, bilaterally	AN + anxiety: remission; OCD: reduction; depression: response; reduction of psychoticism, neuroticism, tendency to lie; improvements in intelligence, memory, quality of life and social functioning; restoration of menstruation cycle	headache (3–4 days post op)
10	Wang et al. 2013	AN, OCD, depression, anxiety	Nutritional support treatment, psychotherapy	15	18	—	12.9	20.8 (12 months post op)	NAcc, bilaterally	AN + anxiety: remission; OCD + depression: response; reduction of psychoticism, neuroticism, tendency to lie; improvements in intelligence, memory, quality of life and social functioning; restoration of menstruation cycle	headache (3–4 days post OP)

11	Wu et al. 2013	AN, OCD	SSRI + antipsychotics	14	16	—	12.2	22.1 (48 months post op)	NAcc, bilaterally	AN and OCD: remission; restoration of menstruation cycle	feeling of heat in the upper body and a rise in blood pressure and pulse during electrode implantation
12	Wu et al. 2013	AN, generalized anxiety disorder	SSRI + antipsychotics	15	17	—	13.3	18 (48 months post op)	NAcc, bilaterally	AN and generalized anxiety disorder: remission; restoration of menstruation cycle	feeling of heat in the upper body and a rise in blood pressure and pulse during electrode implantation
13	Wu et al. 2013	AN, OCD	SSRI + antipsychotics	16	17	—	12.0	18.4 (48 months post op)	NAcc, bilaterally	AN and OCD: remission; restoration of menstruation cycle	feeling of heat in the upper body and a rise in blood pressure and pulse during electrode implantation
14	Wu et al. 2013	AN, OCD	SSRI	15	16	—	10.0	19 (48 months post op)	NAcc, bilaterally	AN and OCD: remission; restoration of menstruation cycle	feeling of heat in the upper body and a rise in blood pressure and pulse during electrode implantation
15	Zhang et al. 2013	AN	SSRI	17	18	—	11.8	17.9 (1 month post op)	NAcc	weight gain; intake of SSRIs stopped	not reported
16	Zhang et al. 2013	AN	SSRI + antipsychotics	14	16–17	—	11.2	13.1 (1 month post op)	NAcc	weight gain; intake of SSRIs and neuroleptics stopped	not reported
17	Zhang et al. 2013	AN	SSRI + antipsychotics	15	16–17	—	13.3	14.5 (1 month post op)	NAcc	weight gain; intake of SSRIs and neuroleptics stopped	not reported
18	Zhang et al. 2013	AN	SSRI	13	16–17	—	12.2	17.1 (1 month post op)	NAcc	weight gain; intake of SSRIs stopped	not reported
						Stereotactic ablation					
19	Zamboni et al. 1993	AN, schizophrenic psychosis, OCD	Not reported	—	17	6.1	9.1	19.4 (54 months post op)	dorsomedial thalatomy (dorsomedial nuclei bilaterally + lamella medialis unilateral)	improvement of AN, OCD and depression, remission of anxiety	not reported
20	Zamboni et al. 1993	AN, occasional psychotropic drug abuse, occasional robbery, several suicide attempts	Not reported	16	21	9.7	12.5	17.8 (23 months post op)	dorsomedial thalatomy (dorsomedial nuclei bilaterally + lamella medialis unilateral)	remission of AN, depression and anxiety; improvement of IQ; cessation of deviant behavior	not reported
21	Barbier et al. 2011	AN, OCD	SSRI, antipsychotics, lithium, benzodiazepines, dialectic behavioral therapy	14	38	9.1	13.1	23.0 (3 months post op)	bilateral anterior capsulotomy (thermocoagulation)	remission of AN and OCD, stop of all medications	14 days post op.: transient bradycardia; mild disorientation in place and time, moderate somnolence, loss of concentration, apathy, emotional emptiness and mild loss of decorum
22	Wang et al. 2013	AN, OCD, depression, anxiety	Nutritional support treatment, psychotherapy	16	19	—	13.6	20.5 (12 months post op)	NAcc radiofrequency ablation	AN + OCD + depression + anxiety: remission; reduction of psychoticism, neuroticism, tendency to lie; improvements in intelligence, memory, QoL and social functioning; restoration of menstruation cycle	headache and perhaps centric fever (3–5 days post OP.)

(*Continued on next page*)

Table 2. Individual patients with anorexia nervosa treated neurosurgically *(Continued)*

Number	Study	Diagnosis	Therapies	Age at AN onset (years)	Age at surgery (years)	BMI (historical low)	BMI before surgery	BMI after surgery	Target	Therapy effects	Adverse effects and relapses
23	Wang et al. 2013	AN, OCD, depression, anxiety	Nutritional support treatment, psychotherapy	22	25	—	12.9	20.1 (12 months post op)	NAcc radiofrequency ablation	AN + OCD + depression + anxiety: remission; reduction of psychoticism, neuroticism, tendency to lie; improvements in intelligence, memory, QoL and social functioning; restoration of menstruation cycle	headache and perhaps centric fever (3–5 days post op.)
24	Wang et al. 2013	AN, OCD, depression, anxiety	Nutritional support treatment, psychotherapy	16	20	—	12.8	21.2 (12 months post op)	NAcc radiofrequency ablation	AN + OCD + depression + anxiety: remission; reduction of psychoticism, neuroticism, tendency to lie; improvements in intelligence, memory, QoL and social functioning; restoration of menstruation cycle	headache and perhaps centric fever (3–5 days post OP)
25	Wang et al. 2013	AN, depression, anxiety	Nutritional support treatment, psychotherapy	16	18	—	14.4	22.2 (12 months post op)	NAcc radiofrequency ablation	AN + depression + anxiety: remission; reduction of psychoticism, neuroticism, tendency to lie; improvements in intelligence, memory, QoL and social functioning; restoration of menstruation cycle	headache and perhaps centric fever (3–5 days post OP.)
26	Wang et al. 2013	AN, depression, anxiety	Nutritional support treatment, psychotherapy	16	19	—	13.5	18.5 (12 months post op)	NAcc radiofrequency ablation	AN + depression + anxiety: remission; reduction of psychoticism, neuroticism, tendency to lie; improvements in intelligence, memory, QoL and social functioning; restoration of menstruation cycle	headache and perhaps centric fever (3–5 days post OP.)
27	Wang et al. 2013	AN, OCD, depression, anxiety	Nutritional support treatment, psychotherapy	18	21	—	13.1	19.8 (12 months post op)	NAcc radiofrequency ablation	AN + OCD + depression + anxiety: remission; reduction of psychoticism, neuroticism, tendency to lie; improvements in intelligence, memory, QoL and social functioning; restoration of menstruation cycle	headache and perhaps centric fever (3–5 days postop.)

Note. AN: anorexia nervosa. MDD: major depressive disorder. OCD: obsessive-compulsive disorder. EAT-26: Eating Attitudes Test-26. SUD: Substance use disorder. PTSD: Post-traumatic stress disorder. HAM-D: Hamilton depression rating scale 17. Y-BOCS: Yale-Brown Obsessive-Compulsive Scale (score range: 0–40). Depression: response: >50% reduction in HAMD score; remission: HAMD <7. OCD: Response: >35% reduction in Y-BOCS score; remission: Y-BOCS ≤ 7. QoL: quality of life. SSRI: Selective serotonine reuptake inhibitors. SGCA: subgenual cingulate area. SCC: subcallosal cingulate.

of underweight (BMI > 17.5 kg/m^2). The pre- and postoperative BMI difference ranged from minus 4.4 kg/m^2 to plus 9.9 kg/m^2. Postoperative BMI values ranged from 13.1 to 22.1 kg/m^2, that is, from very severe underweight (BMI < 15.0 kg/m^2) to normal weight (18.5 kg/m^2 $\leq$ BMI $\leq$ 25.0 kg/m^2). In 16 patients, psychiatric comorbidities improved, in most cases markedly. Five out of eight patients had a considerably improved quality of life and social functioning after DBS (Lipsman et al. 2013a; Wang et al. 2013); for the other 10 patients, quality of life (QoL) data are missing. Two patients displayed improvements in intelligence and memory, and decreased psychoticism, neuroticism, and tendency to lie (Wang et al. 2013). Weight restoration and remission of psychiatric comorbidities were considerably higher in patients with NAcc DBS than with SCC DBS.

Stereotactic ablation. All nine patients had higher BMI values postoperatively (from +2.3 kg/m^2 to +10.3 kg/m^2). They reached BMI values from 17.8 to 23.0 kg/m^2. Postoperatively, one patient had moderate underweight (17.0 kg/m^2 $\leq$ BMI < 18.5 kg/m^2); 8 patients had normal weight (18.5 kg/m^2 $\leq$ BMI $\leq$ 25.0 kg/m^2). In all patients, psychiatric comorbidities improved, mostly even remitted. (Unfortunately, scores of depression, OCD, and anxiety are missing for 6 patients [Israël et al. 2010; Zhang et al. 2013; McLaughlin et al. 2013].) Six patients had a considerably improved QoL and social functioning, improvements in intelligence and memory, and decreased psychoticism, neuroticism, and tendency to lie (Wang et al. 2013).

Side Effects and Complications

DBS. Several severe complications were reported: an intraoperative panic attack that caused an interruption of the surgery, a cardiac air embolus, and an epileptic seizure during electrode programming (Lipsman et al. 2013a). One patient had two depressive relapses (Israël et al. 2010); another patient had a relapse after reprogramming an electrode (McLaughlin et al. 2013). Further adverse events were pancreatitis, hypophosphatemia (probably because of further weight loss), hypokalemia (indicating binge eating and purging behavior), a refeeding delirium, increased lead impedance, QT prolongation, and worsening of mood (Lipsman et al. 2013a; comment: De Zwaan and Schlaepfer 2013).

Stereotactic ablation. Only transient adverse effects were reported: bradycardia, mild disorientation in place and time, moderate somnolence, loss of concentration, apathy, emotional emptiness and mild loss of decorum (Barbier et al. 2011), and headache and centric fever (Wang et al. 2013).

ETHICAL DISCUSSION

Ethical Justification of Neurosurgery for Treating Anorexia Nervosa

Most authors from bioethics and medicine do not consider psychiatric DBS as a continuation of the discredited historical psychosurgery. Although they reflect the historical background of DBS, they highlight the important differences between old-fashioned psychosurgery and DBS with regard to invasiveness, reversibility, adjustability, and orientation to the principles of beneficence and patient's autonomy. Astonishingly, stereotactic ablative procedures for psychiatric disorders are rarely discussed in neuroethics. Since some of the highlighted differences, namely, reversibility and adjustability, do not apply to stereotactic ablative procedures, they might be considered as being more similar to the discredited historical psychosurgery and thus as less ethically justifiable. We do not support this viewpoint, since, as explained earlier, for some patients ablative procedures are preferable for medical or practical reasons. Furthermore, we propose to counteract the adjustability argument by staged radiosurgical procedures: that is, in the first step, a unilateral lesion is created, and if necessary, in another step complemented by a contralateral lesion. Since radiosurgery does not imply risks of craniotomy and anesthesia, the lack of reversibility and adjustability is partly compensated by its minimal invasiveness.

With regard to disorders that are seemingly self-inflicted, namely, addictions and eating disorders, there might be less consent for approving neurosurgical interventions of any kind than for other psychiatric disorders. For example, Ford and Kubu (2007) are concerned about treating drug addiction with DBS because of the disagreement over the classification of addiction as either "a neuropsychiatric illness or a behavioral disorder with moral shortcomings."

Drug addiction and anorexia nervosa indeed differ from most other psychiatric disorders in several aspects: First, in most cases, they are self-inflicted insofar as a voluntary behavior is at their onset, namely, drug consumption or diet, respectively. Second, they are associated with certain cultural or social settings. Third, they represent certain lifestyles, albeit in an extreme form. Both drug addiction and anorexia nervosa develop gradually from habits, which are (relatively) normal in the individual's (sub)culture and become more and more excessive, until a loss of control occurs so that the behavior cannot be ceased in spite of negative consequences.

Fundamental skepticism against neurosurgical treatments of AN may ground in a primarily sociocultural understanding of the disorder. A common fallacy is to transfer the responsibility for the onset to the responsibility for ceasing the disorder. In the case of drug addiction and eating disorders, the individuals might be largely responsible for the onset of the disorder, but hardly able and therefore hardly responsible for ceasing it. Skepticism about expensive high-tech interventions in the brain for treating seemingly self-inflicted disorders might be based on the false assumption that the patients are responsible for having the disorder and could therefore overcome it with some willpower. But although diet plays the major role for the onset of AN, a vicious circle develops that deeply affects the brain, undermines the will, and prevents ceasing the self-destructive behavior. Therefore, the conclusion that psychotherapy is necessarily the best therapy option, and that neurosurgery must not be performed to treat AN, is a fallacy. Anorexia nervosa is a paradigmatic case against the brain–culture dichotomy.

Doubtable Therapy-Resistance

In the studies reviewed, only 10 patients received the antipsychotic olanzapine, the sole drug with category grade B evidence for weight gain in AN; no patient received zinc supplementation, which has grade B evidence for weight gain and reduction of depression and anxiety (Aigner et al. 2011). Ten patients had psychotherapy, eight patients nutritional support treatment, and one patient had electroconvulsive therapy. Detailed data about the type and duration of psychotherapies and pharmacological treatments is missing. Furthermore, the disease duration of 8 patients was only 1 or 2 years. Therefore, we doubt whether all patients had been treated according to current guidelines and were really therapy-refractory; thus, it is questionable whether neurosurgery was really performed as an *ultima ratio* treatment (see also De Zwaan and Schlaepfer 2013). We consider this practice as ethically problematic with regard to the beneficence and nonmaleficence principle since experimental high-risk interventions should not be performed unless guideline-approved therapies with lesser risks have failed. This general strategy is particularly important for neurosurgical treatments of AN patients because of their unclear benefit and their considerable risks of mortality and morbidity.

Evaluation of Benefits and Risks

According to our review, most patients benefitted considerably from stereotactic neurosurgery. Eleven out of 18 patients treated with DBS (61%) and all 9 patients treated with ablative procedures (100%) had postoperative BMI values outside of the pathological range ($\geq$17.5 kg/m^2). In 93% of the patients (25/27), the anorexia-associated psychiatric disorders were improved, in most cases considerably. According to the data of Sun et al. (2015) (not included in our review), the beneficial effects of neurosurgical treatments of AN are not that pronounced. Nevertheless, 85% out of 150 patients treated with capsulotomy experienced an improvement in symptoms, whereas only 20% of the DBS patients (3/15) were treated successfully; 80% underwent a second surgery (anterior capsulotomy), which improved eating behavior and psychiatric symptoms in all patients. These data indicate that stereotactic neurosurgery for AN is not only a method to increase the body weight; rather, it is a therapy with effect on psychiatric symptoms as well. This is highly relevant, as a weight gain achieved by neurosurgery without a synchronistic change in self-perception and mood would rather be considered as a "psychological hell" (Wu et al. 2013) than a benefit. Interestingly, quality of life increased only in those patients with major BMI increases (Lipsman et al. 2013a; Wang et al. 2013).

Information on side effects and complications is insufficient: Five papers do not mention this issue at all (Zamboni et al. 1993; Israël et al. 2010; McLaughlin et al. 2013; Wu et al. 2013; Zhang et al. 2013). Mainly mild, transient side effects are reported with the exception of the study of Lipsman et al. (2013a), which reports severe side effects after DBS of the subcallosal cingulum, for example, seizure, cardiac air embolus, pancreatitis, refeeding delirium, hypophosphatemia, and hypokalemia.

An evaluation of risks and benefits of stereotactic neurosurgery for AN has to consider also the general literature on psychiatric stereotactic neurosurgery. The reported experiences demonstrate that substantial benefits for patients with different, severe, treatment-resistant psychiatric disorders are possible: For DBS in OCD patients, the responder rate of bilateral DBS ranges between 33% and 100%, and for MDD between 54% and 64% (Luigjes et al. 2013). For currently practiced stereotactic ablative procedures, the efficacy is supported by level II evidence in treatment-refractory MDD and OCD (Nuttin et al. 2014). A recent review found response rates of 55% to 70% in patients with different diagnoses treated with Gamma Knife anterior capsulotomy (Lévèque, Carron, and Régis 2013).

Regarding risks and complications, the mortality rates in patients treated with DBS for movement disorders range from 0% to 7.7%. Intracranial hemorrhage occurs in up to 10% of the patients, infections in up to 15%, and device problems in up to 19%. Persistent neurologic deficits remain in up to 6% of patients (Boviatsis et al. 2010; Bronstein et al. 2011). Also, severe adverse mental effects have occurred in the case of DBS for psychiatric disorder: Following ventral capsule/ventral striatum (VC/VS) or NAcc stimulation, hypomania, a mixed-bipolar state, or increased depression, partly with suicidality, occurred in nearly half of the cases (Malone et al. 2009). In ablative surgery, the incidence of general risks such as coma, hemorrhage in the brain, paralysis, seizures, and infections is very small; nevertheless, they have to be taken seriously (Sun and Liu 2013). Possible short-term complications of bilateral capsulotomy include incontinence, disorientation, sleep disorders, and refeeding syndrome; long-term effects (in less than 5% of the patients) include memory loss, fatigue, excessive weight gain, and personality changes (Sun et al. 2015). Adverse effects of cingulotomy are less frequent and include headache, confusion, and urinary incontinence (Sun et al. 2015).

With regard to neurosurgical risks, for AN patients, special precaution is necessary: For most AN patients, surgery or anesthesia is contraindicated due to their unstable physical condition; their risk of hematomas is elevated; and the burr hole procedure needs specific caution, since their skull is usually very thin (Sun et al. 2015). Since many of them suffer from an imbalance of electrolytes, bradycardia, hypothermia, and so on, they have a high risk for developing a multi-organ dysfunction. If they lose further weight postoperatively, they might become cases of emergency. Indeed, the patients of Lipsman et al. (2013a) lost two BMI points on average after surgery; one patient developed hypokalemia and pancreatitis, and another patient hypophosphatemia and refeeding delirium. Furthermore, comorbid psychiatric disorders might complicate DBS surgery. Indeed, one patient suffered from a panic attack during the implantation (Lipsman et al. 2013a). The risk of wound infections is higher after DBS than after lesioning procedures (Sun et al. 2015). The special risks of craniotomy and anesthesia for AN patients are an argument for treating them radiosurgically.

The evaluation of risks and benefits of the different procedures remains preliminary, since only a minority of cases are reported in English journals. Our systematic literature search yielded only 27 cases, whereas we heard on conferences and personal communication with neurosurgeons that many more patients have been treated with ablative neurosurgery. Websites of private clinics in Europe as well as in China offer ablative surgery for a broad spectrum of psychiatric disorders as part of clinical routine instead of clinical studies. The already-mentioned book of Sun and De Salles has published the results of several studies with ablative neurosurgery for different psychiatric disorders. We assume that psychiatric neurosurgery has a severe publication bias.

Major Nosological Uncertainty Underlying the Exploration of the Different Targets

Currently, it is not possible to decide whether one of the targets is superior in terms of efficacy. The different targets of DBS and ablation can be subdivided in three groups, which correspond each to a different understanding of AN:

1. *AN as depression—The target subcallosal cingulum.* Lipsman et al. (2013a) held the view that AN is a symptom of depression; therefore, they use their DBS target for MDD, namely, the subcallosal cingulum (SCC), for treating AN (Lipsman et al. 2013a). The SCC is a subcomponent of the anterior cingulate cortex (ACC), which is involved in arousal and emotional processing, and plays a key role in depression, OCD, and presumably AN (Van Kuyck et al. 2009). The high comorbidity of AN and depression, and the hypermetabolism in the subcallosal gyrus of both MDD and AN patients, comprise the rationale for choosing the SCC as the stimulation target for AN (Lipsman et al. 2013b). Also the idea of treating AN with either dorsomedial thalamotomy or anterior capsulotomy is based on the classification of AN to the spectrum of anxiety disorders and OCD. Indeed, the meta-analysis of Leiphart and Valone (2010) revealed that these disorders had the greatest improvements from anterior capsulotomy.

2. *AN as obsessive compulsion and addiction—The targets ventral capsule/ventral striatum and nucleus accumbens.* Understanding AN as a symptom of OCD or as a kind of addiction supports DBS or ablation of targets within the reward system, particularly the VC/VS, including the NAcc. The striatum, which contains the NAcc and is divided by the internal capsule (IC), is supposed to be involved in the pathophysiology of OCD. The IC has been the target of both capsulotomies and DBS for OCD. The areas used for bilateral DBS of the NAcc or the IC are so close that they might be considered as a single target, which is nowadays called VC/VC (Blomstedt et al. 2013).

The targets of groups 1 and 2 have in common an understanding of anorexia nervosa as a primary emotional disorder in spite of the life-threatening physical symptoms. Furthermore, they are based on the idea that pathological behaviors are driven by dysfunctional loops that connect the cortex to subcortical structures and back to the cortex (Lipsman et al. 2013b).

3. *AN as a starvation-induced disorder—The targets nucleus subthalamicus (STN) and ventromedial hypothalamus.* On grounds of an alternative understanding of anorexia nervosa, namely, as a starvation-induced disorder of appetite and hunger, the ablation or stimulation of brain areas involved in the homeostatic regulation of appetite could be expected to be successful. However, these targets have not yet been investigated in AN patients. First, STN DBS could be appropriate, since it causes weight gain and/or overeating in many Parkinsonian patients (McClelland et al. 2013), and reduces obsessive compulsion in Parkinsonian (Blomstedt et al. 2013) and OCD patients (Mallet et al. 2008). Second, the anterior hypothalamus is a supposable target, since it controls feeding behavior and metabolism of food. It contains two antagonistic structures, the ventromedial and the lateral hypothalamus, which produce opposite effects when stimulated or ablated (Benabid and Torres 2012; Sun and Liu 2013; McClelland et al. 2013). DBS of the ventromedial hypothalamus has been proposed for treating AN (Benabid and Torres 2012). However, interventions in the hypothalamus bear the risk of affecting sexual behavior. Stereotactic lesions of the ventromedial hypothalamic nucleus of 10 homosexual men reduced or abolished the sex drive of all patients (Roeder, Orthner, and Müller 1972). Therefore, we do not consider the hypothalamus an appropriate target.

According to the hypothesis that AN is a symptom of depression or OCD, DBS of the aforementioned targets should be effective only in AN patients with such a comorbidity. The current data do not allow for any conclusion, since all AN patients treated with stereotactic neurosurgery had a considerable comorbidity of depression, OCD, and/or anxiety. However, the data offer some support for this hypothesis: All patients who had a higher BMI postoperatively than preoperatively also had an improvement or even remission of depression, anxiety disorder, and/or OCD. Therefore, it might be that stimulation or ablation of the subcallosal cingulum or the VC/VS is essentially a therapy of depression or OCD, not of AN itself. Thus, we suspect that these targets would be ineffective in patients whose AN is merely starvation induced.

We believe that the current exploration of the "optimal target" points to major nosological challenges of psychiatric diseases. This becomes apparent as each target used for treating AN has been used for treating other psychiatric disorders. Thus, the question emerges of how far nosological entities in psychiatry actually correspond to biological entities with respect to characteristic structural and functional patterns.

Challenges to Informed Consent

Informed consent is a necessary condition for respecting the patient's autonomy, but in case of neurosurgery for AN, this requirement is difficult to fulfill for several reasons:

1. Information deficits: Since information about the effects of psychiatric neurosurgery, particularly about possible changes in personality, affectivity, and feeling of identity, is scarce, it is not possible to supply all relevant information to the patients.
2. Doubtful capability of decision-making in spite of legal capacity to consent: Although most adult AN patients are legally competent and score well on tests such as the MacArthur Competence Assessment Tool for Treatment (MacCAT-T), their decision-making capability can be diminished by the disease, first due to difficulties with thought processing, and second due to changes in values (Tan et al. 2006). Since AN patients are subjected to an internal coercion that forces them to repeat dysfunctional behaviors even if they understand the behavior's self-destructive character and they try hard to stop it, their capability to decide about accepting an AN therapy can be doubtable. Disease-related factors, such as missing insight into illness, a disturbed body image, and cognitive or affective deficits in decision making, can compromise the capacity to consent. We think that the question of capacity to consent cannot be assessed appropriately by cognitive measures alone, since not only cognitive deficits but also internal coercions and affective disturbances can corrupt it (Breden and Vollmann 2006; Tan et al. 2006; Charland 2013).

However, these arguments refer mainly to patients who refuse treatments and whose refusal is at least partly caused by disorder-related problems of thinking and valuating. These arguments are relevant in the ethical justification of forced treatment. But we are arguing about patients who want to be treated, and even consider experimental brain surgery. We do not discuss the question of compulsory psychiatric neurosurgery, which is forbidden for adult patients in Germany, Switzerland, the United States, and many other countries. We assume that most AN patients who consider brain surgery have the capacity to consent, even if no mere cognitive criteria are applied. However, their capacity to consent might be challenged by despair, false hopes, or a therapeutic misconception. All these issues should be carefully evaluated by independent psychiatrists without conflicts of interest in order to guard patients against consenting to an experimental and perhaps overhasty brain surgery.

Coercive Interventions in the Brains of Adolescents

Since AN begins mostly in minors, the question is raised of how to respect the developing autonomy of adolescents with regard to a brain intervention that might change their personality or threaten their sense of identity. Teenagers should neither be regarded as incompetent persons, nor as fully competent persons. Their (developing) autonomy has to be respected adequately, whereas limitations of their capability for autonomy also have to be taken into account in order to protect them from negative consequences of only seemingly autonomous decisions. Limitations in adolescents' decision-making capacity may be due to a lack of both medical knowledge and experience of life, due to their extreme persuasibility by both parents and peers, and due to pubertal defiance against suggestions brought forward by parents or other persons of authority. In anorectic adolescents, several of these autonomy-related factors might be aggravated.

Neurosurgery for certain psychiatric disorders sometimes aims at changing certain traits that can be considered as part of one's personality. This is valid particularly for anorexia nervosa, since certain personality traits are considered as constitutive for the disorder. Whether AN patients will consent to a personality-changing neurosurgical interventions is questionable, since many have built up an "anorectic identity," which is strongly defended and causes resistance against treatments that endanger this identity. Although many AN patients oscillate ambiguously between the view that anorexia is a part of their true self, and that it has completely taken over their self (Charland 2013), we expect that they will regard an intervention in the brain as a much greater threat to the anorectic identity than psychotherapy or forced nutrition, which might be annulled by counterstrategies. Since this fear is not irrational, but an apprehension of a real threat, we are convinced that psychiatric neurosurgery should not be performed against the patients' will, independently of their age and state of starvation.

Furthermore, it can be questioned whether the patients' parents are optimal surrogate decision makers. Because of desperation about their child's life-threatening behavior, and because of courtesy stigma, they are particularly vulnerable themselves. Therefore, they might be tempted by the promise of a neurosurgical fix of the problem and might consent to any great and desperate cure.

Furthermore, the use of DBS in minors is discussed controversially, particularly because of the lack of knowledge on its long-term effects on the developing brain and on the personality. An expert panel has stated that DBS should not be performed in children for psychiatric indications, among others since children are particularly vulnerable to their parents' perception of disease severity (Rabins et al. 2009). However, an early neurosurgical intervention might prevent long-term damages and could thus be particularly beneficial for adolescents. We are convinced that psychiatric neurosurgery in minors can be justified in some cases, but warrants extra attention to decision-making capacities and an extra careful risk–benefit evaluation.

Particularly, we are convinced that psychiatric neurosurgery must not be performed against the will of an adolescent for two reasons: First, legal minors should not have fewer rights than people with mental disabilities, and for the latter, compulsive psychiatric neurosurgery is forbidden in most Western countries. Second, the harm of a coercive intervention in an adolescent's brain with the aim to "correct" her personality and behavior, which threatens her sense of identity, and disregards her autonomy, might cause a long-term traumatization and mistrust against physicians, parents, and adults, which cannot be compensated by possible benefits.

RECOMMENDATIONS

The high mortality rate in anorexia nervosa, its chronicity, and its severe impact on mental and physical health justify research for new therapeutic options. Because of evidence for disturbed neural circuits in AN patients, interventions in the brain might in general be justified. However, because of their risks (particularly in extremely underweight patients), investigational neurosurgical treatments require the highest ethical and scientific standards. In order to promote an ethically responsible and effective research on stereotactic neurosurgery for AN, we recommend the following:

Testable hypotheses on dysfunctional circuits in AN have to be developed and tested in rigorous studies. Future studies should use similar inclusion and exclusion criteria and assessment instruments in order to make them comparable (De Zwaan and Schlaepfer 2013). Since in psychiatric neurosurgery many targets are tested for many different psychiatric disorders, their efficacy and safety have to be compared. Furthermore, ablative neurosurgery and DBS should be evaluated in comparative studies.

Individual treatment attempts should not be performed; rather, patients should be transferred to centers that conduct clinical studies (optimally integrated in multicenter studies) that are approved by an ethics committee.

We recommend case registries that have to register all clinical studies and individual treatment attempts, in order to avoid a publication bias and its negative consequences, namely, faulty evaluations of therapies, flawed therapy recommendations, unpromising treatment attempts, and unneeded clinical studies.

For each patient, the therapy resistance has to be demonstrated. Particularly, a therapy according to evidence-based guidelines has to be performed before therapy resistance is determined. Because of the special risks for minors, neurosurgery for AN should be applied only as a last-resort therapy in life-threatening conditions.

Neurosurgery for anorexia nervosa should be performed only on patients who have supplied valid informed consent. It should not be used as a compulsory treatment (in Germany, this would be illegal for adults). Particularly, for interventions in the brain with a risk of mortality, morbidity, and severe long-lasting disability, we are convinced that coercive treatments of the brains of adolescents (even if demanded by their legal guardians) should be forbidden. This demand is in accordance with the recommendations on psychosurgery of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1977) and the consensus paper on stereotactic neurosurgery for psychiatric disorders (Nuttin et al. 2014).

The minor's ability to consent has to be assessed individually by pediatrists or child psychiatrists who are not involved in the research project. Unfortunately, the studies do not report how the adolescents' capability to consent had been assessed, and whether they had been convinced or persuaded.

In the studies included in our reviews, both minors and their legal guardians had given informed consent, whereas Sun et al. (2015) report that patients (at least 14 years old) or their representatives had given informed consent.

The long-term efficacy and safety of neurosurgical treatments of AN should be investigated carefully, whereby not only BMI values should be recorded, but also information on adverse effects, psychiatric comorbidities, quality of life, attitudes toward nutrition and weight, and psychosocial consequences of the treatments.

Finally, we recommend investigating whether DBS must be applied chronically or only for a limited period. If AN is more a trait-related condition, then it might be necessary to stimulate the patients forever, which may favor an ablative procedure. But if AN is a development-related, starvation-induced disorder that develops under given sociocultural circumstances in biologically vulnerable individuals, then it might be cured by DBS. If DBS not only suppresses certain symptoms of AN, but provides a real cure, then the stimulation could be stopped when body weight and eating behavior are stabilized and psychiatric comorbidities are remitted. And if the patients do not relapse after a longer period without stimulation, the whole DBS system might be removed, which would also be advantageous for medical, psychological, and financial reasons. But if the majority of patients relapse after stopping the stimulation, this would be an indirect argument for ablative procedures that cause permanent effects in the brain. According to Sun et al. (2015), the young AN patients reported by Wu et al. (2013) were in remission after the DBS system was explanted. Their age at surgery was 16 or 17 years; their disease duration was 1–2 years. In this, we suspect that in these patients, AN was development-related and not therapy-resistant, so that a temporary DBS treatment might have been a permanent cure. However, Sun et al. (2015) report that 12 patients with the binging–purging subtype of AN did not profit from NAcc DBS, and received a subsequent anterior capsulotomy that had considerable improvements in eating behavior and psychiatric symptoms. According to Sun et al. (2015), AN patients with the binging–purging subtype and patients suffering more than 10 years from AN do not benefit from DBS, but possibly from capsulotomy or cingulotomy. Undoubtedly, more research is necessary for finding out which neurosurgical method is best for different types of AN patients.

CONCLUSION

Because of the high mortality rate in anorexia nervosa, its frequent therapy-resistance, and the severe psychiatric and somatic morbidity associated with AN, and because of the accumulating evidence for the effectiveness of neurosurgical therapies for AN, we think that further research in this area is generally justified. However, this does not justify therapeutic adventurism. The current research practice in this area does not fulfill the highest ethical and scientific standards in all cases. Therefore, we have recommended several protective measures to ensure that neurosurgery research can proceed with regard to ethical principles.

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