Life on a scale

Deep brain stimulation in anorexia nervosa

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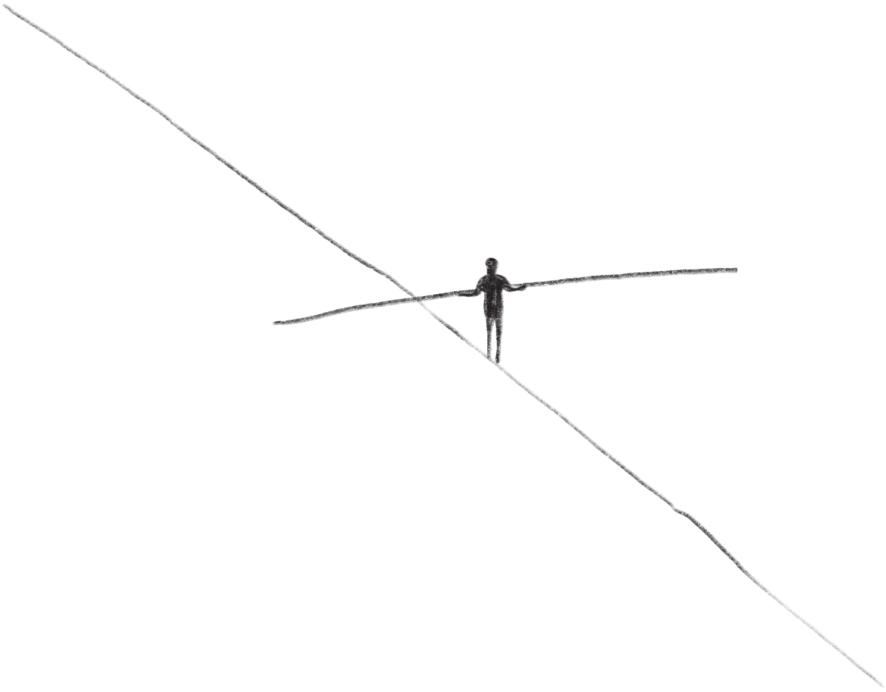

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Colophon

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Al te vaak gewogen en te licht bevonden

J.v.G.

Contents

PART I

General introduction I

Since my first days in Medical School, I have been fascinated by the relationship between body and mind. During my residency in psychiatry, I got aware of the gap between psychiatric and medical care, both in terms of physical healthcare facilities and in terms of treatment approaches. This gap leads to inadequate care or even dangerous situations and increased mortality for patients with both psychiatric and medical problems. Fortunately, the need for more integrated care was recognized in the healthcare community, leading to the emergence of medical-psychiatric units (MPUs). I was lucky to have been given the opportunity to start an MPU at the Amsterdam UMC, location AMC and have been working there as a hospital psychiatrist ever since.

Though fascinated and intellectually stimulated by the diagnostics and treatment of a broad range of intertwined psychiatric and somatic conditions, there is one disorder that stands out for me because of its intriguing clinical picture, the pervasiveness of the condition, the severity of comorbidities and its potential devastating outcome, and that is anorexia nervosa (AN).

ANOREXIA NERVOSA

AN is a severe mental health condition characterized by an intense fear of gaining weight and a distorted body image that leads to restricted food intake and other behaviors leading to a failure to maintain a minimally normal body weight. Patients often are in a state of denial with regard to their own low body weight and its adverse impact on their health (1). The condition can have devastating effects on multiple organ systems, leading to severe medical complications such as cardiac complications, electrolyte imbalances, osteoporosis, and even death. Beyond the physical consequences, AN also has significant psychological and emotional impact, affecting relationships, academic or work performance, and overall quality of life (2). AN has one of the highest mortality rates (crude mortality rate (CMR) 5.1 deaths per 1000 person-years (95% CI 4.0–6.1), standardized mortality rate (SMR) 5.9 (95% CI 4.2–8.3) among psychiatric conditions (3). The risk of death is significantly increased through both physical complications and an elevated risk of suicide.
Treatment options for AN consist of psychological treatments such as cognitive behavioral therapy for eating disorders (CBT-E), family-based therapy (FBT) and nutritional rehabilitation.

Psychopharmacological agents can be used to treat underlying mood and thought disorders, but are generally considered less effective than psychological treatment (4). Specialized eating disorder units and eating disorders expert health care professionals are often limited, there are long waiting lists, and require a stabilized medical condition. Medical units often lack the psychiatric expertise to provide and establish nutritional habilitation. The integrated care for severely compromised patients with AN can be provided at some MPUs. However, overall, the severity of AN cannot be overstated. Its complex, multi-systemic impact, the high mortality and the scarcity

of effective, accessible treatments make it a critical issue in both medical and mental health settings. Investigating novel, effective treatment options for AN is crucial. The life of AN patients is literally on a scale.

AN has multifactorial origins that include psychological, biological, and environmental factors. While the complete pathophysiology is not yet fully understood, a variety of mechanisms have been proposed to explain its development and persistence.

The neurobiology of AN is a complex and still-emerging field of study. A variety of factors, including genetics, neurotransmitter activity, brain structure and function, as well as environmental influences, contribute to the onset and persistence of the disorder (5). Studies on the neurobiology of AN show that the brain reward system in particular, largely mediated by the neurotransmitter dopamine and implicated in motivation, pleasure and reinforcement learning, is involved in the pathophysiology of AN (6).
In the search for novel, effective treatment options for AN, treatment modalities that could influence the neurobiological mechanisms involved in AN, and specifically the dysfunctionality of the reward system are of special interest.

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is an integrative treatment that involves the implantation of electrodes into specific brain regions to modulate neural activity. While initially developed and approved for the treatment of movement disorders such as Parkinson's disease, the application of DBS for psychiatric disorders has become an area of active research and clinical interest. DBS involves the placement of thin, electrode-tipped wires into brain regions identified as focal points for pathological neural activity. These electrodes are connected to a pulse generator, typically implanted in the chest, which delivers electrical pulses to the target brain regions.

Among psychiatric disorders, the most robust evidence for the effectiveness of DBS exists for severe, treatment-resistant OCD. Multiple clinical trials have demonstrated significant symptom reduction and improvement of quality of life (7). In psychiatric disorders like OCD DBS is effectively targeted at the brain reward system. The mechanism through which DBS works is complex and not entirely understood, but it is thought to modulate the activity of neural circuits, effectively overriding pathological network activity allowing for reinstating psychological activity to alleviate symptoms (8). The 20-year experience of the departments of psychiatry and neurosurgery of the Amsterdam UMC, location AMC, with DBS in OCD-patients showed strong and long-lasting effects of targeting the ventral anterior limb of internal capsule (vALIC), part of the reward-circuitry (9).

DEEP BRAIN STIMULATION IN ANOREXIA NERVOSA

Clinically, there are many similarities between OCD and AN. AN is characterized by obsessions and compulsions regarding body image, weight, food intake and energy expenditure. Furthermore, there are substantial rates of comorbidity between AN and OCD. There is also considerable pathophysiological overlap between AN and OCD. Both conditions have been associated with dysfunction in the cortico-striato-thalamo-cortical circuitry (also known as the aforementioned reward circuitry), altered dopamine signaling, and altered reward processing (10).

Therefore, we hypothesized that targeting the vALIC may exert comparable beneficial effects in treatment-refractory AN. Moreover, our DBS methodology has distinctive characteristics, including an extensive optimization period during which DBS-settings are optimized with thorough phenotyping. This may provide new insight in the psychological, somatic and functional effects of (vALIC) DBS in AN. We thus developed the first research protocol in The Netherlands to study the efficacy, safety and tolerability of DBS in patients with severe, chronic, treatment-refractory AN.

SCOPE AND OUTLINE OF THIS THESIS

Part I – Introduction

Part II - Deep brain stimulation in anorexia nervosa: hypothesis-formation

In the second part of this thesis, we will outline the formation of our hypothesis, stating that deep brain stimulation (DBS) will serve as an effective treatment for patients suffering from chronic, treatment-refractory Anorexia Nervosa (AN). We will argue that DBS will not only facilitate weight restoration but will also yield significant and sustained improvements in the core symptoms of AN, along with associated comorbidities and complications. Additionally, we will propose potential targets within the brain that could be most effective for DBS application in treating AN.

Moreover, inspired by a case study that reported smoking cessation and substantial weight loss following DBS treatment for Obsessive-Compulsive Disorder (OCD) in an obese patient, we will investigate the impact of DBS on body weight across a larger cohort of patients diagnosed with obsessive-compulsive disorder and depression.

Part III – Deep brain stimulation in anorexia nervosa: clinical effects

In the third part of this thesis, we will present the primary findings of our pilot study, titled 'Deep Brain Stimulation of the Ventral Anterior Limb of the Capsula Interna in Patients with Treatment-Refractory Anorexia Nervosa.' For this challenging study, we have included a small sample

size (n=4) of patients suffering from exceptionally severe AN. The severity of both the disorder and the medical conditions of these patients has made the study's execution highly challenging. Nevertheless, these participants represent the prototypical patients who may qualify for DBS as a last-resort treatment option. We note that the results were published as a letter-to-the-editor in Brain Stimulation in December 2021, and in this thesis, we will incorporate the full manuscript along with supplementary material.

During the final few years, a few other groundbreaking studies on DBS in AN, as well as several case reports, have been published. Consequently, we will present the first meta-analysis assessing the efficacy and safety of DBS in AN treatment. This analysis encompasses four studies, including our own. We will describe the outcomes of this meta-analysis in the fourth chapter of this thesis.

Part IV – Deep brain stimulation in anorexia nervosa: functional effects

Part IV of this thesis will present the results of our sub-studies focusing on the functional effects of Deep Brain Stimulation (DBS) in Anorexia Nervosa (AN).

In Chapter 5, we will disclose the findings from our task-based fMRI study, which utilized a monetary reward task and a food picture viewing task. Our objective is to enhance the understanding of both the operational mechanisms of DBS and the pathophysiological mechanisms underlying AN.
Chapter 6 will detail our investigation into the time-dependent electrophysiological changes induced by DBS in patients with AN. Our aim here is to contribute to a more comprehensive understanding of the electrophysiological effects of DBS. Such insights may enable us to personalize and optimize the intervention, thereby increasing its effectiveness in treating AN.

Lastly, in Chapter 7, which is the final chapter devoted to the functional effects of DBS in AN, we will explore endocrine and metabolic alterations post-DBS, with a particular emphasis on neuroendocrine parameters that influence food reward and satiety. We will conduct repeated endocrine and metabolic measurements during the follow-up period. Our hypothesis will suggest that these parameters, which are associated with AN, will undergo changes over time due to DBS treatment and/or weight gain in the course of the DBS intervention.

Part V - Anorexia nervosa: conceptual hypotheses

During the course of our study, we have intensively monitored the clinical status of the subjects. As stated before, executing the study posed several challenges, which we will elaborate on in the discussion section of this thesis. One observation stood out markedly: clinically, subjects reported a subjective decrease in the rewarding properties of their eating-disorder related behaviors. Concurrently, we observed an increase in self-destructive behavior in our subjects. This lead to questions about the link between AN and self-destructive behavior: whether they share a

common pathogenesis, and why such a potential shared pathogenesis leads to varying clinical expressions.

We will explore this connection between the two constructs, which are both conceptually and structurally distinct, in a narrative review focused on AN and Non-Suicidal Self-Injurious Behavior (NSSI). Furthermore, we will propose several hypothetical models to delineate the relationship between AN and NSSI, integrating both psychopathology and neurobiology. Our aim will be to better understand and characterize their relationship, thereby laying the groundwork for future research. This will be covered in Chapter 8 of the thesis.

Part VI – General discussion

Part VI will provide an overall summary and discussion of the findings presented in this thesis, in the line of related work by others and by us. We will elaborate on neurobiological, psychological, philosophical, ethical and sociological aspects of DBS in AN. Finally, we will share our thoughts on future research.

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PART II

Deep brain stimulation in anorexia nervosa: hypothesis-formation

1

Is deep brain stimulation a treatment option for anorexia nervosa?

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ABSTRACT

Anorexia nervosa (AN) is a severe psychiatric disorder with high rates of morbidity, comorbidity and mortality, which in a subset of patients (21%) takes on a chronic course. Since an evidence based treatment for AN is scarce, it is crucial to investigate new treatment options, preferably focused on influencing the underlying neurobiological mechanisms of AN.

The objective of the present paper was to review the evidence for possible neurobiological correlates of AN, and to hypothesize about potential targets for Deep brain stimulation (DBS) as a treatment for chronic, therapy-refractory AN. One avenue for exploring new treatment options based on the neurobiological correlates of AN, is the search for symptomatologic and neurobiologic parallels between AN and other compulsivity- or reward-related disorders. As in other compulsive disorders, the fronto-striatal circuitry, in particular the insula, the ventral striatum (VS) and the prefrontal, orbitofrontal, temporal, parietal and anterior cingulate cortices, are likely to be implicated in the neuropathogenesis of AN.

In this paper we will review the few available cases in which DBS has been performed in patients with AN (either as primary diagnosis or as comorbid condition). Given the overlap in symptomatology and neurocircuitry between reward-related disorders such as obsessive compulsive disorder (OCD) and AN, and the established efficacy of accumbal DBS in OCD, we hypothesize that DBS of the nucleus accumbens (NAc) and other areas associated with reward, e.g. the anterior cingulated cortex (ACC), might be an effective treatment for patients with chronic, treatment refractory AN, providing not only weight restoration, but also significant and sustained improvement in AN core symptoms and associated comorbidities and complications. Possible targets for DBS in AN are the ACC, the ventral anterior limb of the capsula interna (vALIC) and the VS. We suggest conducting larger efficacy studies that also explore the functional effects of DBS in AN.

INTRODUCTION

Anorexia Nervosa (AN) is a severe psychiatric disorder characterized by an intense fear of gaining weight com- bined with a failure to maintain a minimally normal body weight (85% of the expected standard for age and height/ ideal body weight). Patients with AN have a disturbed body image, are obsessed with weight and body shape, and are in a state of a denial with regard to their low body weight and its adverse impact on health (1). In a subgroup of patients AN is associated with characteristic compulsive behaviors such as dieting, exercise, and/or purging with or without binge eating. Amenorrhea is often present in female patients but no longer required for the diagnosis (2) . With a narrow age of onset, a stereotypic presentation of symptoms and course, and a relative gender specificity AN is possibly the most homogenous of all psychiatric disorders. The average point prevalence rate of AN is 0.3% in young females (3, 4) and the lifetime prevalence is 2.2% among females (5). The condition largely affects young adolescent females, with a female–male ratio between 10:1 and 4:1 (3, 6).

Medical complications

AN is often associated with medical complications resulting from starvation, purging and/or over exercising. Common signs and symptoms include cardiovascular complications such as brady-cardia, prolonged QTc and orthostatic hypotension, loss of subcutaneous fat tissue, impaired menstrual function, hair loss, and hypothermia (7). With improved nutritional status or with remittance of abnormal eating and purging behaviours, most pathophysiological complications are reversible. Nevertheless, some physical consequences of AN can be life-threatening, such as electrolyte imbalances, severe bradycardia, and hypotension. Moreover, nutritional deficiencies may increase the risk of cardiac arrhythmias and intercurrent infection. Some medical conse-quences of eating disorders may be irreversible or have later serious consequences on health, especially osteoporosis, growth retardation, malfunctioning of the reproductive system and neurobiological changes of the brain caused by malnutrition (8, 9).

Mortality, course and comorbidity

AN is associated with the highest rate of mortality among all mental disorders, with a crude mortality rate of 5,9% and a mortality rate of 5,6% per decade (10, 11). Other studies found mortality rates in the same range (12-17). Steinhausen found a mean crude mortality rate of 5,0% (13). Causes of death ranged from eating disorder complications to suicide. The majority of individuals with eating disorders reported suicidal thoughts and about 22% attempt to commit suicide (18, 19).

In an extensive literature review Steinhausen showed that less than half (46,9%) of the surviving patients recover on average from AN, one-third (33,5%) improve partially, and in 20,8% (0-79%) the disease takes on a chronic course (13). It had to be noted that the criteria used to define recovery

and chronicity are very divergent. The studies reviewed, vary considerably in duration of follow-up (1–29 years), whereas outcome is influenced significantly by the duration of follow-up, with a higher mortality but also a tendency towards recovery with increasing duration of follow-up in surviving patients (13). On the other hand, chronicity is associated with poor outcome, indicating that some cases of AN are indeed treatment refractory (20). For the purpose of this article, we chose to define chronicity as an illness duration of five years or more.

Patients with AN have elevated rates of lifetime diagnoses of anxiety disorders, depressive disorders, obsessive-compulsive disorder (OCD), personality disorders and substance abuse disorders (8, 9, 20). Comorbidity in eating disorders is substantial and contributes to a less favorable outcome of AN.

Treatment options

The therapeutic options for AN consist of different treatment-approaches that focus on weight restoration, changes in behaviour and reducing the psychological features of AN. However, evidence-based treatment for AN is very limited. There is no category A evidence and only family interventions meet category B criteria according to the NICE-guidelines (21-24).

Psychotherapeutic interventions include cognitive behavioural therapy (CBT) and family therapy. A number of studies have reported that CBT after weight restoration could be effective in reducing the risk of relapse in adults with AN, but it is unknown what the efficacy is in underweight patients (see (25) for review). Variants of family therapy show a modest level of evidence with regard to efficacy in adolescents but not in adults.

SSRIs are ineffective in reducing AN symptoms or restoring weight and the American Psychiatric Association does not support the use of SSRIs in the management of underweight patients with AN (25) (Treatment of patients with eating disorders, APA 2006). There is some, however weak, evidence that the use of SSRIs may help in preventing relapse in weight restored patients (26, 27). Tricyclic antidepressants seem ineffective on weight gain or improvement of AN symptoms (28, 29). For atypical antipsychotics, there are only limited data available (30). Bissada et al. conducted a double-blind, placebo-controlled trial in 34 patients with AN. Olanzapine treatment resulted in more rapid weight gain and improvement in obsessive symptoms (31). Two other randomized, controlled trials with olanzapine showed similar results (32, 33). Another study, conducted in an inpatient setting, failed to show any benefit for olanzapine on weight and psychological symptoms (34). These results indicate that olanzapine may be helpful in increasing weight and decreasing obsessive symptoms in chronic severe AN in outpatient (35), but practice guidelines do not recommend its routine use (36, 37) (American Psychiatric Association 2006).

Unfortunately, there is no agreement on the definition of treatment-refractoriness in AN (38). Refractory AN is a term used in clinical psychiatry to describe cases of AN not responding to typical modes of treatment, such as psychotherapy and psychopharmacology. Strober et al. (1997) and Herzog et al. (1999) found that the possibility of recovery in AN patients with an illness duration longer than 10 years is very low (39, 40).

REVIEW

ETIOPATHOLOGY OF AN

The pathophysiology of AN remains unknown. It is unclear whether there is a primary disturbance of appetite, or whether the disturbed appetite is secondary to other phenomena, such as body image disturbance, or anxiety (41). The aetiology of eating disorders is considered multifactorial, with involvement of genetic factors (42-47), neurobiological factors, and temperamental vulnerabilities such as negative emotionality, poor intraceptive awareness, perfectionism and obsessive-compulsive personality traits (43, 48-50), that may interact with environmental factors resulting in an increased risk (41, 51). The neurobiology and neurocircuitries involved in AN are a main focus in today's AN research. Of particular interest are the brain areas involved in registering the reward value and modulation of reward of food and the motivation to eat, considered to be located within the mesolimbic cortex and striatum (52, 53). Moreover, the brain areas involved in the cognitive control of eating and appetite, located in the dorsolateral prefrontal and parietal cortices may be involved in AN (41, 51).

Neurotransmitters

Results from positron-emission tomography (PET) studies indicate differences between subjects recovered from AN and healthy subjects in serotonin and dopamine receptor activity, indicating dysregulation of these systems involved in mood, anxiety, appetite and impulse control (41, 54).
Several studies showed alterations in the serotonergic (5-HT)-system in AN. For example, Kaye et al. (2009) reported elevated 5-HT metabolite levels, as well as elevated binding potential for postsynaptic 5-HT1a receptors and diminished binding potential for 5-HT2a receptors in recovered AN patients (55-57). In contrast, ill AN patients were shown to have reduced amounts of the major 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA) (41). Finally, it has been found that a dietary-induced reduction of tryptophan, the precursor of serotonin, is associated with decreased anxiety in AN patients (58). Starvation may help AN patients to briefly reduce 5-HT activity and thus give symptom relief. These alterations in 5-HT function may be related to AN symptoms regarding inhibition of appetite, generalized inhibition, anxiety and obsessions through stimulation of 5-HT1a receptors.
Several studies showed that ill and recovered AN patients also have altered striatal dopamine (DA) function. Kaye et al. (1999) found reduced levels of DA metabolites in the cerebrospinal fluid in ill and recovered AN patients (59). Frank et al. (2005) found that patients recovered from AN had increased D2/D3 receptor binding potential in the ventral striatum (VS), indicating either increased D2/D3 receptor density or decreased extracellular DA, or both (60). In addition, functional DA D2 receptor gene polymorphisms have been associated with AN (61) and subjects with AN have impaired visual discrimination learning, indicating altered DA neurotransmission

in AN (62). Disturbances in the DA-system may contribute to an altered response to reward and alterations in decision-making and executive control found in patients with AN.
Similar alterations of 5-HT and DA function are also found in other reward-related disorders like OCD, although the exact mechanisms and the interactions between these and other neurotransmitter systems are not clarified yet (63).

Neuroimaging

Imaging studies showed that in the acute phase of AN, patients have a reduced brain volume and enlargement of the cortical sulci and the ventricles (64-66). Alterations in activity in the insula and the prefrontal, orbitofrontal, temporal, parietal and anterior cingulate cortices and the VS at rest and during symptom provocation were found (67-73). These alterations may however be contributed to malnourishment and are mostly reversible with weight restoration.
However, functional imaging studies conducted in patients recovered from AN possibly reflect trait-related rather than state-related changes which could be an indication of the possible underlying neurobiological mechanisms in AN (74-76). Several studies reported hypoperfusion of temporal, parietal, occipital and frontal regions in AN patients not correlated to their BMI (77-79). It has also been reported that remitted as well as non-remitted AN patients have increased activations in brain regions implicated in the reward system (the medial prefrontal cortex and anterior cingulated cortex (ACC)) in response to food stimuli (80). In a study of Wagner et al. (2007) no difference was found in ventral striatal response discriminating between positive and negative feedback in recovered AN patients, suggesting an impairment to identify the emotional significance of stimuli and the involvement of the brain reward system. Recovered AN patients also showed exaggerated activation of the caudate-dorsal striatum region and the dorsolateral prefrontal and parietal cortex, regions concerned with planning and consequences (81). Zastrow et al. (2009) showed that impaired behavioral set shifting in AN is associated with hypoactivation in the ventral anterior cingulate-striato-thalamic loop and with hyperactivation of frontoparietal networks (82). Another study by Wagner et al. (2008) showed a reduced BOLD signal response to sucrose in the anterior insula, the ACC and the striatum, indicating an altered incentive processing in the anterior insula (83). All these studies implicate the involvement of the fronto-striatal circuitry in the neuropathogenesis of AN.
The insula is thought to be implicated in taste and its incentive value, interoceptive awareness and fear (51). The ACC is associated with emotional processing, body image, self-monitoring, conflict resolution, and reward-based decision making (74, 80, 84). The parietal lobe is functionally associated with disturbed body image and the low or absent insight in their condition, two of the core features of AN (69, 74). It is hypothesized that disturbances in interoceptive awareness, impairments of the ventral striatal pathways and an enhanced cognitive control (either inhibiting the reward system or compensating for primary deficits in limbic function) are involved in the pathogenesis of AN (41).

Because of the involvement of the reward-related neurocircuitries described above, the areas communicating between the limbic and the cortical systems , such as the nucleus accumbens (NAc) and the cingulate and insular cortices (41, 85) may be of particular interest as possible target areas for future neurosurgical interventions.

DEEP BRAIN STIMULATION

Deep brain stimulation (DBS) is an innovative and promising approach for the treatment of patients with treatment-refractory reward-related psychiatric disorders (86-89). DBS is a reversible and adjustable neurosurgical treatment involving the implantation of electrodes that send electrical impulses to specific locations in the brain, selected according to the type of symptoms to be addressed and its putative neuroanatomical correlates (90, 91).

Our center has experience with DBS in OCD, addiction, and major depressive disorder. In all these disorders, DBS targets reward related brain areas such as the NAc and the ventral capsule/ventral striatum (VC/VS). Target selection has evolved based on clinical results from earlier ablative procedures and DBS-studies, neuroimaging studies and theoretical considerations regarding the implicated neurocircuitries involved in these disorders (86, 88, 89, 92). The current working hypothesis is that DBS inhibits or functionally overrides pathological network hyperactivity in several treatment-resistant psychiatric disorders. Our research group showed efficacy for DBS in OCD targeted at the NAc normalizing NAc activity, reducing excessive connectivity between the NAc and prefrontal cortex, and decreasing frontal low-frequency oscillations during symptom provocation in patients with OCD. These findings taken together suggest that DBS is able to reduce maladaptive activity and connectivity of the stimulated region and to restore disease-related brain networks to a healthy state (93).

To consider a psychiatric disorder as a possible new indication for DBS and a particular patient as candidate Denys (2008) suggested the following criteria (94):

Disorder-related criteria:

(a) A general agreement on the neuropsychiatric nature of the disorder.
(b) A proven relationship with a dysfunctional brain circuitry.
(c) Objectively measurable symptoms.

Patient-related criteria:

(a) Presence of very severe symptoms and considerable suffering.
(b) Absence of available effective treatments.
(c) Potential to regain reasonable functioning and integration in society.

DBS IN AN

Considering 1) the clear neurobiological correlates of the disorder, 2) the homogeneity of the disorder, 3) the severity of AN, its complications and high mortality rates, 4) the fact that AN takes on a chronic course in a considerable percentage of patients and the fact that, up to date, evidence based treatment for AN is very limited, it is crucial to investigate new treatment options for AN that focus on influencing the underlying neurobiological mechanisms of the disease rather than focus on weight restoration alone. In this review article we want to propose DBS as a possible new treatment option for patients with chronic, treatment-resistant AN.

For a long time, neurosurgery targeted at various brain areas (mostly leucotomy) has been considered a last resort treatment for AN. While reviewing the literature on neurosurgical procedures in AN, we found most articles reported weight gain and sometimes other symptomatic improvements. However, there was much heterogeneity as well as missing data on patient selection, follow-up and outcome measurements. Therefore, clinical outcome appears at least to us, somewhat inconclusive (95-103). In a case-report of Barbier et al. (2011) a successful anterior capsulotomy in comorbid AN and OCD is described, resulting in normalization of eating pattern and weight and a significant decrease of food-related obsessive compulsive symptoms after three months (104).

To date, there are very limited data on the effect of DBS in the treatment of AN. There are two case reports, a case series of four patients and a pilot study published on DBS in AN (see Table 1). Israël et al. (2010) described a patient treated with DBS in the subgenual cingulate cortex, part of the ACC, for severe refractory depression, whose co-morbid eating disorder showed lasting remission, consisting of a normalisation of BMI (19,1 kg/m^2) and Eating Attitudes Test-26 at 2-year follow-up. It must be noted that pre-surgery this patient also had periods of (partial) recovery from her eating disorder, and that her BMI pre-surgery was 20,9 kg/m^2 (105). A more recent case report by McLaughlin (2012) described improvements in AN symptoms following DBS of the VC/VS for intractable OCD (106). The first study (case series) on DBS in AN was conducted by Sun et al. from the Shanghai group. Preliminary results reported an average of 65% increase in body weight at 38-month follow-up in four adolescent patients with AN treated with DBS of the NAc, showing that DBS might be a valuable option for weight-restoration in AN (107). Very recently, Lipsman et al. (2013) published the results of a phase-1 pilot trial of subcallosal cingulate (ACC) DBS in six adult patients with treatment-refractory AN. They found that DBS was relatively safe in this population and found to result in improvements of mood, anxiety, affective regulation and anorexia-related obsessions and compulsions in four patients. Furthermore, at a 9 month follow up period improved BMI's compared to the estimated historical baseline BMI's in three patients were found (103, 108).

Table 1. DBS in AN

Study	*n*	*DBS target*	*Result*
Israel (2010)	1	Subgenual cingulate cortex	DBS for treatment resistant major depression. Co morbid eating disorder-NOS in lasting remission (normalisation of scores on the Eating Attitudes Test-26 and Eating Disorders Examination; normalisation of weight (BMI 19,1 kg/m2) at 2 and 3 year follow-up)
McLaughlin (2012)	1	Ventral capsule/ ventral striatum	DBS for treatment resistant OCD. Improvements in AN symptoms consisting of less distress about caloric intake and weight (assessment tools and length of follow-up not mentioned; BMI pre-surgery 18,5 kg/m2, post-surgery 19,6 kg/m2)
Sun et al. in Wu et al. (2012)	4	Nucleus accumbens	Average of 65% increase in body weight at 38-month follow-up (average baseline BMI: 11,9 kg.m2; average BMI at follow-up: 19,6 kg/2); restoration of the menstrual cycle (n = 4); regaining school functioning (n = 3); remission of AN according to the DSM-IV (n = 4)
Lipsman et al. (2013)	6	Subcallosal cingulate	Relatively safe (1 serious adverse event), improvement of BMI compared to historical baseline (n = 3) at 9 month follow-up (average baseline BMI: 13,7 kg/m2; average BMI pre-surgery: 16,1 kg/m2; average BMI at 9 month follow-up: 16,6 kg/m2). Improvements in mood, anxiety, affective regulation and anorexia-related obsessions and compulsions (the latter assessed with the Yale-Brown-Cornell eating disorder scale) at 6 month follow-up; Improvements in quality of life (n = 3)

Possible DBS targets for AN

As stated before, many parallels can be drawn with regard to symptoms of AN and OCD (109). Moreover, there is a considerable overlap between the neurocircuits implicated in OCD and eating disorders, suggesting a possible etiological relationship between the two disorders. Both disorders consist of repetitive thoughts and preoccupations about a feared stimulus, followed by a negative emotion, than followed by compensatory behaviours. Like OCD, AN can be considered a compulsivity disorder. Compulsivity encompasses the repetitive, irresistible urge to perform a behavior, the experience of loss of voluntary control over this intense urge, the diminished ability to delay or inhibit thoughts or behaviors, and the tendency to perform repetitive acts in a habitual or stereotyped manner (110). Research showed that AN is associated with impairments in set shifting and behavioural response shifting (82, 111). Furthermore, there is a high rate of comorbidity between eating disorders and anxiety disorders (112-114). Kaye et al. reported that 41% of AN patients have a lifetime diagnosis of OCD (113). Alterations in the activity of corti-co-thalamo-striatal circuits similar to those found in OCD and other compulsivity disorders have commonly been found in AN, as described above (41, 74, 115-117).

Given the similarities in symptomatology and associated neurocircuits between OCD and AN, the established efficacy of DBS in OCD (89), and the neurobiological correlates of AN as described above, we hypothesize that DBS of the NAc and other areas associated with reward, e.g. the ACC, might be effective in patients with chronic, treatment refractory AN, providing not only weight restoration,

but also significant and sustained improvement in AN core symptoms and associated comorbidities and complications. Possible targets for DBS in AN are the ACC, the ventral anterior limb of the capsula interna (vALIC) and the VS (consisting of the ventral caudate nucleus and the NAc).

Suggestions for in- and exclusion criteria

As DBS in AN is an experimental treatment whose efficacy still needs to be established, it would be logical to initially include only patients with a chronic course who are treatment-resistant and have a poor prognosis. As stated before, there has thus far been no agreement on the definitions of recovery and treatment-refractoriness in AN (37). We suggest to define treatment-refractoriness as a lack of response to two or more typical modes of treatment, including one hospital admission or inpatient treatment in a clinic specialized in the treatment of eating disorders, and an illness duration of five years or more. We suggest inclusion and exclusion criteria for studies investigating the efficacy of DBS in AN similar to those suggested by Wu et al. (2012) and Lipsman et al. (2013) (107, 108):

Inclusion criteria

- Primary diagnosis: Anorexia Nervosa (restricting or purging type) according to the DSM-IV criteria based on a psychiatric interview.
- Chronicity, defined by an illness duration > 5 years.
- Disabling severity with substantial functional impairment according to the DSM-IV criterion C and a Global Assessment of Function (GAF) score of 45 or less for at least two years.
- Treatment refractoriness, defined as lack of response to two or more typical modes of treatment, including one hospital admission or inpatient treatment in a specialized clinic.
- Weight <85% of ideal body weight (and/or BMI < 17,5).
- Age: 21–65 years old.
- Able to fully understand the consequences of the procedure capable to make his or her own choice without coercion and able to give written informed consent.

Exclusion criteria

- Unstable physical condition (severe electrolyte disturbances, cardiac failure, other physical contraindications for surgery/anesthesia).
- A treatable underlying cause of anorexia/underweight.
- An active neurological disease like Parkinson's disease, dementia, tic disorder or epilepsy.
- Schizophrenia/history of psychosis, bipolar disorder.
- Alcohol or substance abuse (including benzodiazepines) during the last 6 months.
- Antisocial personality disorder.
- Standard MRI scan exclusion criteria (pregnancy, pacemaker and metals contraindicated for MRI except for the DBS implantation and stimulator itself).

Safety considerations

In general, potential risks involved in DBS include the risks associated with the surgical procedures, including the small risk (< 1%) of intracranial haemorrhage or infection and the associated neurological consequences (118). In addition, some patients may show some temporary neurological symptoms (e.g. eye movement abnormalities) that generally disappear spontaneously or after some fine-tuning of the stimulator.

Patients with AN are predisposed to significant risk of multi-organ dysfunction related to starvation and purging. This can have implications on mortality and morbidity associated with anesthetic complications during DBS implantation (119). Therefore, a thorough pre-operative anaesthetic assessment and evaluation is required to assist the planning of safe peri-operative care. Patients should be rehydrated adequately and any deranged electrolyte levels should be corrected pre-operatively. There is an increased risk of intra-operative hypothermia. Therefore measures should be taken to keep the patient warm during surgery. Doses of most (anaesthetic) drugs should be adjusted for weight. Patients are particularly susceptible to nerve palsies due to their cachexia and loss of cushioning subcutaneous tissue. Therefore they must be placed carefully on the operating table. During the operation, ECG-changes and potassium levels should be monitored carefully to minimize the risk of arrhytmias. To minimize the overall increased risks associated with anaesthesia the weight and somatic condition will be maximally optimized prior to surgery.

Lipsman et al. (2013) reported several adverse events in their pilot study on DBS in AN, with one serious DBS-related adverse event (seizure during programming) and the other serious adverse events being related to the underlying illness. One patient in this study developed hypophosphataemia and a refeeding delirium (108). It is expected that weight increase following treatment with DBS will be gradual rather than sudden and excessive. Other DBS studies, for example in OCD and depression, showed that improvement of symptoms takes several months (87-89, 108). However, in case of rapid weight gain following successful treatment with DBS, there is a risk of development of a refeeding syndrome (120). Therefore, AN patients treated with DBS should be advised to increase their food intake gradually and under supervision of a dietary consultant. The somatic condition and the potential development of a refeeding syndrome should be closely monitored by a physician.

CONCLUSIONS

AN is a serious psychiatric disorder with high rates of morbidity, comorbidity and mortality, that takes on a chronic course in a considerable percentage of patients. Since evidence-based treatments are scarce, it is crucial to investigate treatment options based on underlying neurobiological mechanisms of the disease.

The fronto-striatal circuitry, in particular the insula, the VS and the prefrontal, orbitofrontal, temporal, parietal and anterior cingulate cortices, appear to be implicated in the etiopathogenesis of AN. Thus, the areas communicating between the limbic and the cortical systems, such as the NAc and the cingulate and insular cortices may be of interest as target areas for future neurosurgical interventions.

DBS had the advantage over ablative neurosurgery in being reversible and adjustable and studies show that DBS is able to reduce maladaptive activity and connectivity of the stimulated region and to restore disease-related brain networks to a healthy state. Given the overlap in symptomatology and associated neurocircuits between reward-related disorders like OCD and AN, and the established efficacy of accumbal DBS in OCD, we hypothesize that DBS of the NAc and other areas associated with reward, e.g. the ACC, might be an effective treatment for patients with chronic, treatment refractory AN, providing not only weight restoration, but also significant and sustained improvement in AN core symptoms and associated comorbidities and complications. Possible targets for DBS in AN are the ACC, the vALIC and the VS (consisting of the ventral caudate nucleus and the NAc).

Larger studies with primary outcome aimed at sustained core symptom reduction and weight restoration are necessary. Preferably, studies should be conducted with a double blind cross-over design with active and sham stimulation. Furthermore, functional effects of DBS in AN should be explored by evaluating neuropsychological parameters and by using neuroimaging techniques.

In our opinion, the seriousness of the disorder and the clear neurobiological substrates of AN justify considering an invasive procedure like DBS as a treatment-option for chronic, treatment-refractory AN. When carefully selecting the stimulation target, using clear in- and exclusion criteria and closely monitoring the safety aspects of DBS in this population, and in the meanwhile thoroughly investigating the clinical and functional effects, DBS could be promising in attacking the core symptoms of AN and contribute to the knowledge of the intriguing pathophysiological mechanisms of AN .

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2

Body weight changes after deep brain stimulation for obsessive compulsive disorder or major mood disorder

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ABSTRACT

Background

In 2010, we published an often-cited case report describing smoking cessation and substantial weight loss after deep brain stimulation (DBS) for obsessive-compulsive disorder (OCD) in an obese patient. To test whether this single observation was also observed in the treated population at large, the weight changes of a larger cohort of patients who underwent DBS for OCD or major depressive disorder (MDD) were studied.

Results

Data were available for 46 patients (30 OCD and 16 MDD patients; mean age 46.2 years, SD 10.9) with an average baseline body mass index (BMI) of 28.0 (SD 7.3), 26 of whom (57%) were overweight (n = 11), obese (n = 12), or morbidly obese (n = 3). Mean follow-up was 3.8 years (range 10 months to 8.7 years, SD 2.3), after which the average BMI was 28.1 (SD 7.0), not significantly different from baseline. The average BMI of the 15 patients with (morbid) obesity at baseline decreased from 36.8 to 34.6 (ns), while the average BMI of the 31 normal or "only" overweight patients at baseline increased from 23.8 to 25.0 (ns).

Conclusion

There was no significant change in body weight on group level after DBS for either OCD or MDD.

INTRODUCTION

In 2010, we published a case report on substantial weight loss in an obese patient with intractable obsessive-compulsive disorder (OCD) treated by deep brain stimulation (DBS) (1). This patient was amongst the first that we treated with DBS for OCD, and had a very good response reflected by an improvement of >90% on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Interestingly, after the OCD symptoms had disappeared, she quit smoking effortlessly, and, with the help of a dietician, started a program to lose weight. Her body mass index (BMI) went rapidly from 37 to 25, starting 10 months after surgery, with a further reduction to 21 which was retained during 7 years of follow-up.

Case reports can spark new ideas or shed light on a particular aspect of a disorder or treatment. Conversely, selective publication of single effects can lead to a distortion of the available evidence for treatment application or lead to duplication of research efforts (2). Therefore, after our initial observation, we analyzed the changes in body weight over time in our entire sample of patients treated with DBS in the ventral part of the anterior limb of the internal capsule (vALIC) (3) for either OCD or major depressive disorder (MDD).

METHODS

The records of all patients undergoing DBS surgery between April 2005 and June 2014 for OCD and MDD were evaluated. For baseline weight and BMI data, we used values measured at the department of anesthesiology before the initial electrode implantation. For follow-up data, we used the most recently available value for the BMI measured by anesthesiology before subsequent operations for stimulator replacements, or measured at the department of psychiatry during follow-up visits.

In order to study the relation between possible changes in BMI and the effect of therapy, patients were categorized as responders or nonresponders at the time of this follow-up for BMI. A responder was defined as having an improvement of >35% on the Y-BOCS for OCD, or >50% on the Hamilton Depression Rating Scale (HDRS) for MDD, in comparison to the preoperative baseline score. IBM SPSS Statistics for Windows, v20 was used for statistical analysis and the paired Student *t* test was carried out to assess the average change in BMI over time. ANOVA was performed for the comparison of BMI changes for different body weight groups (morbidly obese, obese, and nonobese) and the treatment response.

RESULTS

In the stipulated time period, 68 patients underwent DBS for either OCD (n = 43) or MDD (n = 25). Sufficient details for this analysis were available for 46 patients (30 OCD and 16 MDD patients; 29 females and 17 males, mean age 46.2 years, SD 10.9). All patients received DBS treatment with active electrode contacts in the vALIC and there were no patients with active contacts in the nucleus accumbens (NAc). In 22 patients, there was no reliable recording of a postoperative measurement of body weight.

The average baseline BMI in our sample of 46 patients was 28.0 (SD 7.3), with 26 (57%) being overweight (BMI 25–30, n = 11), obese (BMI 30–40, n = 12), or morbidly obese (BMI ≥40, n = 3). There were no significant differences in baseline BMI between males and females or between the diagnostic groups.

Follow-up time ranged from 10 months to 8.7 years (mean 3.8 years, SD 2.3). In the OCD group, 17 were classified as responders and 13 as nonresponders, using the criterium of >35% improvement on the Y-BOCS. In the MDD group, 6 were responders and 10 were nonresponders, using the criterium of >50% improvement on the HDRS. Figure 1 shows the individual BMI values at baseline and at the last follow-up (the patient from our earlier published case report is identifiable as the outlier at the bottom right on the graph).

There were considerable changes in BMI in one-fifth of the sample; it increased by >5.0 in 3 patients and decreased by >5.0 in 6 patients. The average BMI at the last follow-up was 28.1 (SD 7.0), which was not significantly different from baseline (paired t test, ns). However, a subanalysis showed a two-way interaction for obesity as a small-effect modifier on BMI over time. The average BMI of the 15 patients with (morbid) obesity at baseline decreased slightly from 36.8 to 34.6 (ns), while the average BMI of the 31 normal or "only" overweight patients at baseline increased slightly from 23.8 to 25.0 (ns).

There was no significant difference in changes in BMI between the responders and nonresponders to DBS for either OCD or MDD in the open-label evaluations of symptoms. There was also no correlation between changes in body weight and the absolute values of Y-BOCS or HDRS score at baseline or score changes at the time of follow-up.

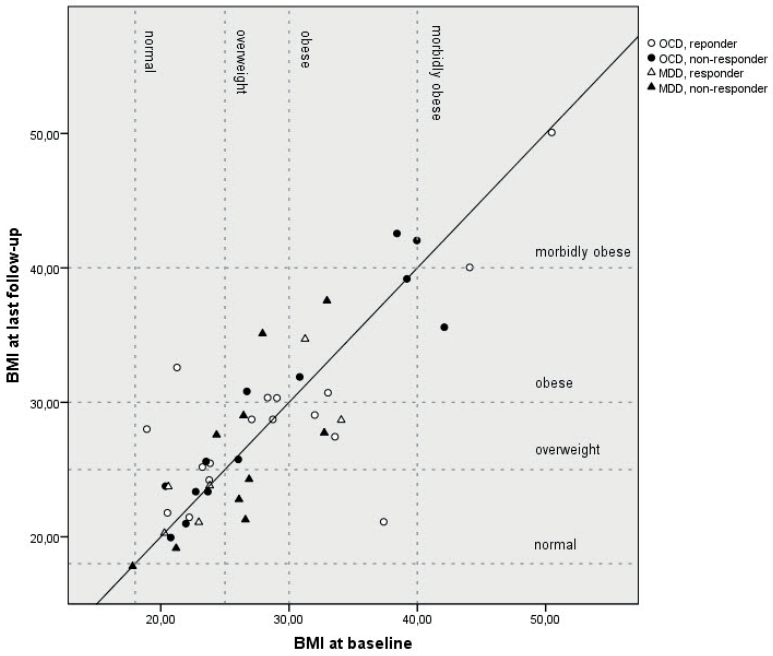

Figure 1. Scatterplot of BMI at baseline (*x* axis) and at last follow-up (*y* axis) for all patients. The vertical distance to the diagonal represents the change in BMI. Dashed lines indicate the various BMI categories, so that a change in category after surgery can be seen for each subject. Patients below the diagonal had a decrease in BMI and those above the diagonal had an increase in BMI. In both OCD and MDD, there were no significant differences in the changes in BMI between the diagnostic groups, or between responders and nonresponders to DBS.

DISCUSSION

There was no significant change in body weight on the group-level after vALIC DBS for either OCD or MDD. The potential of this therapy to change reward-related behavior did not result in significant weight loss in these patients, who were overweight on average at baseline. We did find a trend towards a decline in BMI in the subgroup of patients with (morbid) obesity, but we did not see a replication of the substantial weight loss previously described (1). The vALIC is currently being explored as a potential target for DBS in obesity for its assumed role in reward-related behavior (4-6). Evidence for the involvement of the NAc/vALIC in compulsive eating and obesity is limited to preclinical studies that show low D2-binding in the striatum in obese individuals after food-related sensory stimuli, and in animal studies that show reduced caloric intake and weight loss associated with an upregulation of the D2 receptor. There were increased DA levels in diet-induced obese rats treated with NAc shell DBS (7), whilst mice treated with NAc shell DBS were found to have a decrease in binge-eating and an increase in immediate D2 gene expression in the NAc shell. In diet-induced obese mice, chronic NAc shell DBS reduced caloric intake and led to weight loss (8).

In this study, weight loss or normalization of body weight was not a primary treatment target and the patients did not receive any motivational therapy targeted at losing weight. It is possible that if they had been coached specifically to lose weight in addition to combating the primary symptoms of OCD or MDD, this could have been effective with the reward system being under the influence of DBS. It is thus possible that we underestimated the possible effect of DBS on changes in BMI in morbidly obese patients. The patient in our previous study focused on losing weight out of intrinsic motivation without external prompting (1).

A severe limitation of this report is the amount of missing data on BMI during the follow-up of all patients treated with DBS, due to the fact that body weight was not routinely measured at fixed postoperative intervals. We cannot show that body weight did not fluctuate over time, with an initial significant weight loss followed by secondary weight gain, which is common with all weight loss methods available. However, from our frequent contact with these patients, we could ascertain that there were no such cases of strong fluctuations in BMI in our sample.

Further research is necessary to provide more insight into the possible effects of the modulation of the brain reward circuitry on food intake, energy balance, and body weight, and the possibility of a selective normalizing effect of vALIC DBS on body weight in eating disorders. Our findings may be of relevance for research groups working on DBS in eating disorders.

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PART III

Deep brain stimulation in anorexia nervosa: clinical effects

3

Deep Brain Stimulation of the Ventral Anterior Limb of the Capsula Interna in Patients with Chronic Treatment-Refractory Anorexia Nervosa

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(full manuscript)

ABSTRACT

Background

Pilot studies showed mixed but promising effects of deep brain stimulation (DBS) as a last-resort treatment option for life-threatening treatment-refractory anorexia nervosa (AN). The ventral anterior limb of the capsula interna (vALIC) is an effective DBS target in related psychiatric disorders. This is the first DBS study targeting the vALIC in AN.

Objective

To investigate the efficacy, feasibility and safety of vALIC DBS in chronic, treatment-refractory AN.

Methods

Four female patients with AN received DBS of the vALIC between November 2016 and June 2020. Primary effectiveness was assessed using physical (Body Mass Index, BMI), psychological (Yale-Brown-Cornell Eating Disorder Scale, YBC-EDS), Eating Disorder Quality of Life (ED-QOL) and safety outcomes up to 22-months follow-up.

Results

Following stimulation, average BMI increased 5.32 kg/m^2 (+42.8%, P=.017), with two patients achieving a normal BMI. The YBC-EDS improved 23.9% (P=.024), and the ED-QOL improved 50% on physical health (P=.005). The Hamilton Rating Scale for Depression (HAM-D) improved 37% and the Hamilton Anxiety Rating Scale (HAM-A) nearly 50%. Overall, the procedure was relatively well tolerated. Side effects were on average mild, but adverse events possibly related to the intervention were (hypo) mania, impulsiveness, self-destructive behavior, migraine, seizures, and pain at battery site.

Conclusion

This first study of vALIC DBS in AN supports its effectiveness and feasibility as a last-resort treatment in chronic, treatment-refractory patients. Although the procedure was well tolerated and relatively safe, the severely compromised somatic and psychiatric condition of the patients made the study challenging, also touching on several ethical dilemmas.

INTRODUCTION

Anorexia nervosa (AN) has a lifetime prevalence of 4.2% (1) and a crude mortality rate of 5.6% per decade, due to suicide and other medical complications (2, 3). Even with the best available treatments, 21% of AN-patients will become chronic and treatment-refractory (4).

In search of novel treatments for these patients, pioneering studies have investigated deep brain stimulation (DBS) (5-14). DBS is a treatment involving implantation of electrodes, which send electrical impulses to alter activity in specific neurocircuits. Past research has investigated the subgenual cingulate cortex (SCC), ventral striatum (VS), nucleus accumbens (NAc), medial fore brain (MFB)/post hypothalamic area (PHA), and the bed nucleus of the stria terminalis (BNST) as stereotactic target in AN-patients, although AN was not always the primary disease for which DBS was implanted.

Cumulatively, the literature described 56 AN patients treated with DBS worldwide. Studies were usually small, consisting of cases/case series, with varying in- and exclusion criteria and outcome measures. Results are mixed, with some studies showing promise, while others showed limited effectiveness. As a result of this small number of heterogeneous studies, the evidence of the efficacy, feasibility and safety of DBS for chronic, treatment-refractory AN, remains unclear.

Our 15 year experience with DBS in OCD-patients showed strong and long-lasting effects of targeting the ventral anterior limb of internal capsule (vALIC), part of the reward-circuitry (15). Interestingly, AN and OCD show several clinical similarities, including anorectic obsessions and compulsive food-related behavior. Therefore, we hypothesized that targeting the vALIC may exert comparable beneficial effects in treatment-refractory AN. Moreover, our DBS methodology has distinctive characteristics, including an extensive optimization period during which DBS-settings are optimized with thorough phenotyping. This may provide new insight in the psychological, somatic and functional effects of (vALIC) DBS in AN.

In the present study, we targeted DBS in AN for the first time to vALIC. We included a highly selective sample of patients with exceptionally severe and enduring AN, with an a priori low expected response to treatment. Although challenging, they reflect the prototypical patients that may be eligible for DBS as a last resort treatment option in AN (16).

METHODS

Study Design and Patients

In this first open-label pilot study, we report on the efficacy, feasibility and safety of bilateral vALIC DBS in chronic, treatment-refractory AN. The Medical Ethical Committee (MEC) of the Amsterdam University Medical Centers, location AMC (AUMC-AMC) approved this study, which we preregistered in the Netherlands Trial Register under trial number NL3322. A data safety monitoring board (DSMB) was installed.

Inclusion Criteria for DBS

We recruited patients from major adult specialized eating disorder treatment centers in the Netherlands. Inclusion criteria included clear primary diagnosis of AN (restricting or purging subtype) based on the Diagnostic and Statistical Manual for Mental Disorders version 4 (DSM-IV) (17), confirmed by psychiatric interview and review by an independent psychiatrist. In order to include patients eligible for DBS as a last-resort treatment, we included patients with an illness duration of ≥10 years and a lack of response to ≥2 typical modes of treatment including ≥1 hospital admission and/or inpatient treatment in an eating disorder center. Furthermore, there had to be substantial functional impairment according to the DSM-IV criterion C and the Global Assessment of Function (GAF-score) of 45 or less for ≥2 years. The patients BMI had to be <15, classifying as extremely severe according to the DSM-5 (18).

Exclusion Criteria

Absolute contraindications for DBS were the inability to stop the use of anticoagulants, active neurological disease (like Parkinson's disease, dementia, epilepsy), schizophrenia/history of psychosis, bipolar disorder, alcohol or substance abuse (including benzodiazepines) during the last 6 months, current tic disorder, antisocial personality disorder, presence of unstable physical condition (severe electrolyte disturbances, cardiac failure, other physical contraindications for surgery/anesthesia), treatable underlying cause of anorexia/underweight and standard MRI scan exclusion criteria (e.g. pacemaker and metals contraindicated for MRI).

Surgical procedure

We conducted bilateral stereotactic implantation of quadripolar DBS electrodes (model 3389, Medtronic, Minneapolis), contact points being 1.5 mm long and separated from adjacent contacts by 0.5 mm, and an implantable neurostimulator under general anesthesia. Electrodes were implanted in the anterior limb of the internal capsule with an anterior angle of approximately 75° to the intercommissural line, using stereotactic frame-based 1.5 Tesla magnetic resonance imaging (MRI) coregistered to pre-operative 3T MRI with 1-mm slices for target determination. The upper three contact points of the electrode were placed in the vALIC, the lowest contact point was placed in the nucleus accumbens, ±3 mm anterior to the anterior commissure according to Mai et al., 2015.

The electrodes were connected via a subcutaneous extension cable to a neurostimulator (Activa Primary Cell/Rechargeable Cell, Medtronic, Minneapolis), implanted under the pectoral muscle in the infraclavicular region. Postoperative computed tomography (CT) was performed and coregistered to pre-operative MRI to confirm accurate position of the electrodes.

Treatment procedure

In accordance with our earlier DBS studies (15) the complete study comprised four sequential phases: preoperative, surgery, optimization and maintenance phase (figure 1).

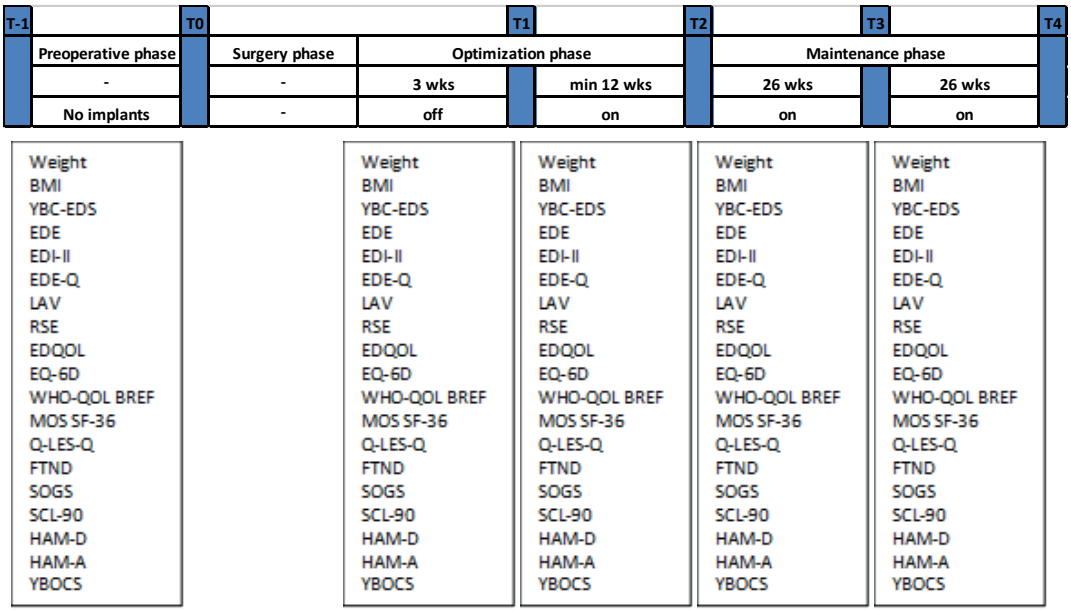

Figure 1. Treatment protocol (wks = weeks; min = minimal)

In the preoperative phase (T-1) we conducted baseline measurements. Standard somatic and psychiatric care was available to all patients throughout this period, including hospitalization.
Once patients were considered fit for surgery (T0), the electrodes and stimulator were implanted. The patients were discharged from the department of neurosurgery one or several days after the procedure, depending on the physical condition of the patient.

The optimization phase lasted between three and nine months. In brief, immediately after recovery from surgery, the neurostimulator stayed in off mode during three weeks in order to prevent interference with the effects from surgery that might have complicated the fine-tuning of the stimulation parameters (electrode contact selection, frequency, voltage). After these three weeks, we switched the neurostimulator on (T1) and performed fine-tuning/optimization of

the neurostimulation during three to six months. During this phase, we determined the stimulation parameter settings that provided the best clinical improvement (16). If, thereafter, we still expected clinical improvement with additional changes in neurostimulator settings, a continuation of the fine-tuning phase was possible for three more months (optimization was performed during three to nine months), with assessments of improvement every week until a plateau of effectiveness was reached.

Patients entered the maintenance phase of the study after the optimization period was completed (T2). The maintenance phase consisted of a 12 months period with the stimulator on, to assess the long-term effect of DBS on BMI, comorbidity, and eating behavior. Measuring points during the maintenance phase were at 6 months (T3) and at 12 months (T4, end of the study).

Outcome Measures

Outcome measures can be categorized in physical, psychological, quality of life and safety. Primary physical outcome measure was the change in BMI. Primary psychological outcome measure was the YBC-EDS (19), scores ranging from 0 to 40; higher scores indicating more severe symptoms. The YBC-EDS assesses the nature and severity of preoccupations and rituals related to the subjects eating disorder comparable to the Yale Brown Obsessive-Compulsive Scale (YBOCS) for obsessive-compulsive disorder. Clinically relevant improvement was defined as a reduction of ≥35% on the YBC-EDS. Primary quality of life outcome measure was the ED-QOL (20), scores ranging from 0 to 100; higher scores indicating lower quality of life.

Secondary psychological outcome measures included the Eating Disorder Inventory (EDI-II)(21), the Eating Disorder Examination Questionnaire (EDE-Q) (22), and the Eating Disorder Examination (EDE) (22). Secondary quality of life outcome measures included the Euroqol 6 Dimension (EQ-6D) (23), World Health Organization-Quality of Life (WHO-QOL-BREF) (24), the Medical Outcome Study Short Form (MOS-SF-36) (25), Sheenan Disability Scale (SDS) (26) and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) (27).

We established side effects and safety through frequent and intensive monitoring by a psychiatrist, including routine checks of vital parameters, standard clinical laboratory assessments and ECG. Additionally, at the main time-points of the study, we assessed all patients using (self-report) questionnaires: the South Oaks Gambling Screen (SOGS) (28) Symptom Check List (SCL-90) (29), Yale Brown Obsessive Compulsive Scale (YBOCS) (30), Fagerstrom Test for Nicotine Dependence (FTND) (31), Body Attitude Questionnaire (BAQ) (32), Rosenberg Self-esteem Scale (RSES) (33), Hamilton Depression Rating Scale (HAM-D) (34) and Hamilton Anxiety Rating Scale (HAM-A) (35). Furthermore, we took a six-question AN-symptom checklist comprising method of purging (laxatives, diuretics or self-induced vomiting), excessive exercise, binge-eating and amenorrhea. Answers were dichotomous (yes/no). Finally, a visual analog scale assessed emotions comprising

anxiety, restlessness, mood, obsessiveness, compulsiveness, avoidance, euphoria, impulsiveness and self-esteem.

Statistical Analyses

We analyzed data using Statistical Package for the Social Sciences (SPSS), version 26; IBM, Armonk, NY. We tabulated demographic and clinical characteristics using means and standard deviations for continuous variables. Linear mixed models analyzed changes between baseline and the 12-month follow-up, with repeated measurements being nested within patients. This study estimated a linear mixed model as the criterion and fixed effects of time (in phases) (on vs off) on subject specific slopes. We selected the covariance matrix using the corrected Akaike information criterion.

Power analyses

Given that this is the first study on vALIC DBS in AN, no formal a priori power calculations were conducted. The original target n was 6, in line with previous DBS studies (9, 10). During the course of the study, after the inclusion of 4 subjects, the new Medical Device Regulations (MDR) was implemented. Because the MDR was expected to cause delays in inclusion, in consultation with the DSMB and MEC, data of the 4 included subjects were deemed sufficient to answer the research questions and therefore further inclusion was considered redundant, thereby preventing any delays in the communication of these novel findings.

RESULTS

Patients' demographics

Four female patients with treatment-refractory anorexia nervosa were enrolled and underwent DBS of the vALIC between November 2016 and June 2020. Patients had a mean age of 39 years (SD=10) and average illness duration of 21 years (SD=3). Average baseline (T-1) BMI was 12.5 (SD=1.0) kg/m^2, indicating extremely severe AN. All patients had a long and serious clinical history of treatment non-response, which included multiple hospital admissions for acute medical stabilization, medical treatment, in- and outpatient psychiatric treatment in specialized eating disorder centers and outpatient follow-up in the community. All patients suffered psychiatric comorbidities, including e.g. affective, obsessive-compulsive and personality disorders (table 1). Although the preoperative condition of the subjects was poor (low BMI and compromised physical status), no physical stabilization like refeeding was conducted. In three cases pre-operative supplementation of electrolytes was advised and given to minimize perioperative complications.

Table 1. Patient's Demographics.

	Sex	*Age at onset (years)*	*Age at surgery (years)*	*Illness duration (years)*	*Anorexia Subtype*	*BMI (screening)*	*BMI (Historic low)*	*Psychiatric comorbidities*	*Psychiatric medication at surgery*
Patient 1	f	15	32	18	Purging	12.4	9.5	GAD, Depression, Personality Disorder NOS	Aripiprazole, Quetiapine, Oxazepam
Patient 2	f	15	39	24	Purging	11.2	10.2	SUD*, Personality Disorder NOS	Aripiprazole, Quetiapine, Oxazepam
Patient 3	f	14	33	19	Purging**	13.4	10.6	Depression, OCD, BPD	Venlafaxine, Clorazepate, Oxazepam, Temazepam
Patient 4	f	27	53	24	Purging	13.1	9.7	Personality Disorder NOS	Citalopram, Alprazolam, Zolpidem
Mean (SD)		18 (6)	39 (10)	21 (3)		12.5 (1.0)	10.0 (0.5)		

(BMI= Body Mass Index, f= female, GAD= Generalized Anxiety Disorder, OCD=Obsessive-Compulsive-Disorder, NOS= Not Otherwise Specified, SUD= Substance use disorder and BPD=Borderline Personality disorder) *The substance in question was alcohol, at the screening this was in remission. ** Important to note that for purging this patient used ± 50 Bisacodyl.

DBS-settings

Monopolar DBS at the middle two contacts was switched on at T1 (pulse width 90 µs, frequency 130 ms) at a mean voltage of 3,0 V (2,5-3,5 V). The mean voltages at T2, T3 and T4 were respectively 3,8 V (3,0-5,0 V), 3,8 V (3,0-4,5 V) and 3,8 V (2,7-4,8 V). Pulse width and frequency remained unchanged during the study.

Clinical Outcomes (table 2)

Physical: The primary physical outcome BMI showed a substantial and significant increase at the end of follow-up (5.32 kg/m^2; +42.8%; P=.017) (figure 2). This effect was supported by significant linear improvements over time in the vital parameters systolic blood pressure (*SBP),* diastolic blood pressure (*DBP)* and body temperature (*T)* (P=.005, P=.007 and P=.018, respectively). At the end of follow-up, *SBP, DBP* and *T* showed a 27.75 mmHg (26.6%), 20.16 mmHg (31.0%) and 1.12 °C (3.3%) increase compared to T-1, respectively. Two patients reached a BMI in the normal range, two remained in the underweight BMI range.

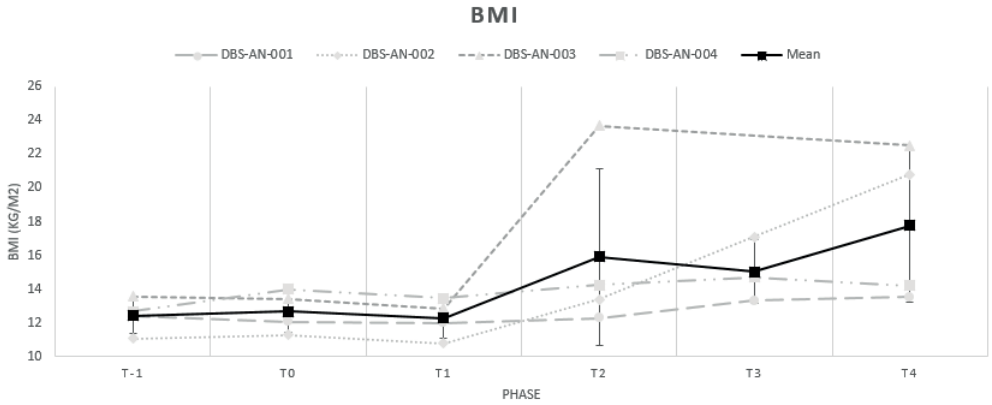

Figure 2. Time course of DBS-induced BMI (fixed effects ± SE).

Linear mixed model analyses showed a significant linear effect of time on BMI (43.16±15.96, CI 95% 9.07-77.25, t=2.704, P=.017).

Psychological: The primary psychological outcome YBC-EDS showed a significant improvement over time (-23.9%; P=.012). This effect was driven by significant decreases in both the *Preoccupation* and *Rituals* subscales (-16.2%; P=.026, and -31.1%; P=.001, respectively). This effect corresponded with the secondary outcome EDE-Q, which showed significant improvements over time on the subscales *Restraint* and *Eating Concern* (P=.039 and P=.024, respectively). The HAM-D and HAM-A showed additional significant improvements over time (-36.7% and -47.9%, respectively). The additional VAS questionnaire showed an increase in Impulsiveness (P<.001).

Quality of Life: The primary outcome ED-QOL showed a significant improvement over time on the subscale *Physical Health* (P=.005). This effect was supported by secondary outcome MOS-SF-36, which showed a significant effect on the subscale *Physical Function* (P=.027). The SDS showed a significant effect on the subscale *Responsibilities* (P=.042).
In the clinical interviews all four subjects stated that in their subjective experience, their overall quality of life had improved considerably. All four subjects indicated that they would choose DBS if they had to do it all over again, even though their eating disorder did not reach remission with DBS.

Table 2. DBS-induced changes in different parameters over time.

	T-1	*T0*	*T1*	*T2*	*T3*	*T4*	*Baseline vs. End of follow-up*	*t-value*	*p-value*
Weight (kg)	34.03(±4.35)	34.48(±4.35)	33.38(±4.35)	43.18(±4.35)	45.91(±4.61)	**47.88(±4.35)(P=.028)**	**40.70%**	**2.742**	**0.016***
BMI (kg/m2)	12.44(±1.71)	12.70(±1.71)	12.28(±1.71)	15.91(±1.71)	17.01(±1.80)	**17.76(±1.71)(P=.028)**	**42.80%**	**2.704**	**0.017***
Systolic BP (mmHg)	104.25(±5,13)	-	94,50 (±5,13)	102.00(±5,13)	109.50(±7.26)	**132.00(±7.26)(P=.010)**	**26.62%**	**3.548**	**0.005****
Diastolic BP (mmHg)	66.75(±6.38)	-	61.00(±6.38)	72.50(±6.38)	73.91(±7.64)	**87.41(±7.64)(P=.015)**	**30.95%**	**3.488**	**0.007****
Body Temperature (^{0}C)	35.63(±0.23)	-	35.90(±0.23)	36.23(±0.23)	36.05(±0.33)	**36.80(±0.33)(P=.014)-**	**30.32%**	**2.787**	**0.018***
YBC-EDS									
Preoccupations	17.00(±1.07)	-	17.00(±1.07)	15.50(±1.07)	**13.25(±1.07)(P=.017)**	14.25(±1.07)	**-16.20%**	**-2.509**	**0.026***
Rituals	18.50(±0.99)	-	18.25(±0.99)	15.75(±0.99)	**13.00(±0.99)(P=.003)**	**12.75(±0.99)(P=.002)**	**-31.10%**	**-4.483**	**0.001****
Total	35.50(±1.96)	-	35.25(±1.96)	31.25(±1.96)	**26.25(±1.96)(P=.028)**	**27.00(±1.96)(P=.006)**	**-23.90%**	**-3.567**	**0.012***
EDQOL									
Psychological	3.00(±0.20)	-	3.33(±0.16)	2.53(±0.68)	3.20(±0.25)	2.88(±0.36)	-4.00%	-0.553	0.614
Physical/Cognitive	2.30(±0.31)	-	2.45(±0.31)	1.58(±0.31)	1.48(±0.31)	**1.15(±0.31)(P=.020)**	**-50.00%**	**-3.321**	**0.005****
Financial	1.25(±0.31)	-	1.45(±0.31)	1.65(±0.31)	0.55(±0.31)	1.00(±0.31)	-20.00%	-1.414	0.178
Work/School	2.85(±0.76)	-	1.60(±0.76)	0.98(±0.76)	1.00(±0.76)	0.85(±0.76)	-70.20%	-1.750	0.104
Total	2.40(±0.32)	-	2.63(±0.32)	2.38(±0.32)	2.30(±0.32)	1.83(±0.32)	-23.80%	-1.388	0.188
HAM-D	27.25(±2.09)	-	**18.25(±2.09)(P=.018)**	**19.00(±2.09)(P=.028)**	**15.25(±2.09)(P=.003)**	**17.25(±2.09)(P=.011)**	**-36.70%**	**-3.114**	**0.009****
HAM-A	29.25(±2.17)	-	**17.25(±2.17)(P=.001)**	**16.75(±2.17)(P=.001)**	**16.50(±2.17)(P=.001)**	**15.25(±2.17)(P=.000)**	**-47.90%**	**-4.194**	**0.001****

Linear mixed model analyses showed a significant linear effect of time on Weight (113.34±41.33, CI 95% 24.88-201.81, t=2.742, P=.016), BMI (43.16±15.96, CI 95% 9.07-77.25, t=2.704, P=.017), YBC-EDS Preoccupations (-9.25±3.69, CI 95% -17.22 - -1.28, t=-2.509, P=.026), YBC-EDS Rituals (-16.75±3.74, CI 95% -25.08 - -8.42, t=-4.483, P=.001), YBC-EDS Total (-26.00±7.29, CI 95% -43.84 - -8.16, t=-3.567, P=.012), ED-QOL Physical/Cognitive (-3.28±0.99, CI 95% -5.38 - -1.17, t=-3.321, P=.005), HAM-D (-23.00±7.39, CI 95% -39.09 - -6.91, t=-3.114, P=.009) and HAM-A (-28.70±6.86, CI 95% -43.36 - -14.14, t=-4.194, P=.001)

Tolerability and Adverse Events

There were no intraoperative adverse events in any of the four patients. However, 28 SAE's occurred during this study, with two being probably and nine possibly related to the intervention (table 3). In addition 73 AE's occurred, with three being probably and 34 possibly related to the intervention (supplement 1). All five probably related events (SAE's and AE's) were (hypo)manic symptoms. Possibly related events mostly consisted of self-destructive behavior (41) (autointoxication, auto-mutilation and aggression), other possibly related events were seizures (2), migraine (4) and pain at battery site (1). Severely compromised somatic condition related to severe malnutrition (hypokalemia; hypoglycemia; hypothermia; hyponatremia; low consciousness; edema), characteristic for malnourished AN-patients, presented itself 39 times in this study (table 3 and supplement 1).

Table 3. Serious adverse events and their relation to the intervention.

Related to DBS	*Event*	*Times Reported*	*n*	*DBS-AN-001*	*DBS-AN-002*	*DBS-AN-003*	*DBS-AN-004*
Probable (2)	Hypomanic/manic symptoms (admission)	2	1			2	
Possible (9)	Auto-intoxication	6	3	4	1	1	
	Seizure	2	1	2			
	Severe auto mutilation	1	1		1		
Unlikely (17)	Severely compromised somatic condition related to severe malnutrition (hypokalemia; hypoglycemia; hypothermia; hyponatremia)[1]	11	2	2	7		
	Low consciousness	2	1		2		
	Edema	1	1		1		
	Appendicitis acuta	1	1			1	
	Conversion	1	1		1		
	Fracture of cervical vertebrae after collapse	1	1		1		
Total number SAE's		**28**		**8**	**14**	**4**	**0**

This number of (S)AE's reflects the challenging nature of the study, with severely affected patients undergoing a last-resort intervention. The hypomanic symptoms and impulsive character of some (S)AE's may reflect the adverse effects of DBS. Nevertheless, all patients, the DSMB and the research team deemed it safe to continue the study. DBS did not need to be paused or stopped in any of the patients.

Patient reported outcome

It proved challenging to adequately measure 'outcome' in this chronically ill patient group, with symptoms and consequences of their long history of anorexia nervosa and compromised

somatic state. However, when asked, all patients report a *subjective* improvement of their overall psychological state and quality of life. One patient successfully started schema therapy after her participation in the study, grasping on subjects that were not accessible for her before. Another subject achieved to become an experience expert conducting training sessions for other patients through professional organizations.

The majority of the patients report a decrease in the satisfactory aspects of the eating disorder behavior, meaning that this behavior, although sustained, lost its rewarding properties, leaving the more room for other, healthier behavior. All subjects state that they would undergo the whole process again if needed, because of the overall positive effects on their mood and life.

DISCUSSION

To the best of our knowledge, this is the first study of vALIC DBS in AN. By applying an extensive optimization period with throughout phenotyping, we provide detailed insight in the psychological, somatic and functional effects. We demonstrated that vALIC DBS can be an effective and relatively safe new target for chronic, treatment-refractory AN.

The mean baseline BMI of our patents was extremely low (categorized as 'very severe' in the DSM-5), which on average improved at one year postoperatively to the DSM-5 category 'mild'. As can be seen in figure 2, the increase in BMI was primarily seen in two of four patients. The other two subjects showed only a mild increase in BMI. The response rate is comparable to other major studies in this field; Liu et al., 2020 (14) and Lipsman et al., 2017 (12), reported a 61% and 57% response rate respectively. Other clinically important physical improvements (SBP, DBP and T) likely reflect a direct consequence of the weight restoration (36, 37). The improvement was also seen clinically, in a decrease in eating-related behavior like purging and caloric and body checking. One of the patients, who was using laxatives in extremely high amounts (bisacodyl 10 mg, 100-150 tablets per day) before DBS, succeeded in completely quitting the use of laxatives.

The improvement in our patients was also seen in the psychological outcomes. The YBC-EDS showed an overall improvement compared to baseline. Two out of four patients could be formally categorized as responders (≥35% decrease). All patients reported a decrease in preoccupations and rituals, because they experienced them as less rewarding. Similar response was reported in Lipsman et al., 2017 (12). The other questionnaires supported the improvements, with a substantial and significant decrease in mean depression and anxiety symptoms. This corresponds to effects of vALIC DBS in other disorders. Also given the high comorbidity rates, these outcomes are of great clinical importance in AN (38).

In the QoL domain we found improvements on the ED-QOL (physical health), MOS-SF-36 (physical function) and SDS (responsibilities). Other QoL subscales did not show improvement, suggesting that despite the clinical improvements made, this exceptionally severely and chronically affected patient group still suffers from psychopathology of AN and comorbid disorders. Nevertheless, in clinical assessments all patients reported an improvement, despite their pathology still being significant, no requests to switch off or remove the DBS have been made.

Safety & Feasibility Given the precarious health of the patients with chronic, treatment-refractory AN, the safety of DBS was a prominent interest and related directly to the feasibility of this study. Overall, the surgery was well tolerated by all patients, despite their low baseline BMI and compromised physical health. Because of the vulnerable cutaneous and hypotrophic subcutaneous layers, we implanted the neurostimulator under the pectoral muscle. During the study, no infection, hemorrhage, intraoperative adverse events or even death occurred.

SAE's were generally related to the severity of the underlying AN and its somatic complications rather than the intervention. Transient symptoms, known to appear with DBS were reported ((hypo) manic symptoms, pain at battery site and seizures).

The self-reported VAS showed an increase in impulsiveness. On closer inspection a significant increase in impulsiveness can be found between DBS-On vs Off at T1, which remains throughout the remainder of the study. This effect has not been explicitly reported in any of the previous DBS in AN studies, but has been extensively documented in OCD-patients (39). However, impulsiveness due to DBS in OCD is usually transient, while our study indicates a sustained increased impulsiveness. A possible explanation is that vALIC DBS downregulates the involvement of the reward and emotion regulation circuitry (16, 40). The experienced positive reinforcement of the ritualistic behavior normally exerted by AN-patients is negated by vALIC DBS. This decreased reinforcement may make the ritualistic behavior less usable as a coping strategy, which may lead to the surfacing of underlying problems in emotion regulation. The need for alternative coping strategies, in combination with pre-existent emotion regulation problems and increased impulsiveness due to DBS, may lead to the development of new (inadequate) coping involving self-destructive behavior, which may explain some of our (S)AE's.

On the one hand, this can be interpreted as a negative effect of DBS, and it made the study challenging. On the other hand, one might also argue that the surfacing of underlying emotion regulation problems and inadequate coping, that were previously masked by eating disorder symptomatology, provides a new entry for treatment targeted at these core problems. In response to the surfacing of these emotion regulation problems induced by DBS, three out of four subjects in our study became eligible for additional psychotherapy aimed at coping and emotion regulation and showed clinical improvement on these domains. Before DBS, treatment aimed at

PTSD, substance use disorders, personality disorders or emotion dysregulation did not help due to the dominating consequences of AN. Because this is the first study of vALIC DBS in AN, we did not include additional outcome measures specifically regarding emotion regulation or self-destructive behavior. Based on our findings, future vALIC DBS studies can focus on these aspects in order to provide further insight in these interesting novel perspectives on the underlying pathophysiological mechanisms in chronic treatment-refractory AN.

Based on this pilot-study, DBS for severely and chronically ill, treatment-refractory AN patient seems to be a relatively safe and feasible last-resort option. Ethics dictate that DBS should only be considered in a population with grim perspective in treatment options and mortality, and our population qualifies as such.

Limitations As DBS was provided open-label, results might be influenced by placebo or other non-specific effects. For example, the increase in contact or the participation in this study might have caused an increase in the patient-involvement and with it a more positive outcome. We minimized these limitations by providing a one-year follow-up period, providing the possibility to investigate sustained effects.

The type of patients in our study warrants some attention. Our subjects were extremely ill patients with chronic, treatment-refractory AN for whom pharmacological and psychotherapeutic treatments had failed for decades and who were completely functionally impaired in almost all aspects of life. Preoperatively their physical condition was very poor, all patients were severely underweight and suffered acute and long-term complications of severe and enduring malnutrition. The average illness duration was 21 years, classifying as chronic (38). The findings of our study can therefore be extrapolated to this specific, severely affected patient group, not to AN in general.

The small sample size of this first vALIC DBS study limits the power. However, this sample size is similar to several DBS pilot trials for other novel indications, and -in consultation with the DSMB and MEC- sufficient to answer the research questions. The moral debate of applying an experimental and invasive procedure in a physically severely compromised patient group justifies the lack of a control group.

CONCLUSION AND FUTURE PERSPECTIVES

Results of this first study indicate that vALIC DBS seems a valid last-resort intervention in chronic, treatment-refractory AN. Our findings pave the way for a follow-up study with a larger sample size, to establish DBS as a standardized last resort treatment in this challenging patient group.

Supplement 1. Adverse events and their relation to the intervention.

Related to DBS	*Event*	*Times reported*	*n*	*DBS-AN-001*	*DBS-AN-002*	*DBS-AN-003*	*DBS-AN-004*
Probable (3)	Hypomanic symptoms	3	3		1	1	1
Possible (34)	Auto-intoxication	19	3	10	3	6	
	Self-destructive behavior	6	2	3	3		
	Aggressive behavior	1	1			1	
	Alcohol consumption	1	1		1		
	Water intoxication	2	2	1	1		
	Migraine	4	1	4			
	Pain at battery site	1	1				1
Unlikely (36)	Compromised somatic condition related to malnutrition (hypokalemia; hypoglycemia; hypothermia; hyponatremia)[2]	18	2	11	7		
	Low consciousness	2	1		2		
	Edema	3	2		2	1	
	Low vitamin D	2	2	1		1	
	Urinary tract infection	1	1			1	
	Pneumonia	2	1	2			
	High anti-TPO	1	1			1	
	Shoplifting	3	2	2		1	
	Pain lower legs	1	1	1			
	Ear infection	1	1	1			
	Pain legs/back	1	1	1			
	Cannabis usage	1	1		1		
Total number AE's		**73**		**37**	**21**	**13**	**2**

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3

Deep Brain Stimulation of the Ventral Anterior Limb of the Capsula Interna in Patients with Treatment-Refractory Anorexia Nervosa

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Dear editor,

Anorexia nervosa (AN) is a severe and often chronic psychiatric disorder with high morbidity and mortality (1). Pilot studies and cases showed mixed but promising effects of deep brain stimulation (DBS) as a last-resort treatment option for life-threatening treatment-refractory AN (2, 3).

The present study (N=4) is the first to target DBS in AN at the ventral anterior limb of the capsula interna (vALIC), part of the reward circuitry. vALIC-DBS showed strong and long-lasting effects in obsessive-compulsive disorder (OCD). We hypothesized that, due to the clinical and neurobiological similarities between AN and OCD, vALIC-DBS may exert comparable effects in treatment-refractory AN. We included a sample of patients with exceptionally severe AN. Although challenging, they reflect the prototypical patients that may be eligible for DBS as a last resort treatment option (4).

Inclusion criteria included primary diagnosis of AN, a Body Mass Index (BMI) <15, a Global Assessment of Function score (GAF-score) of 45 or less for ≥2 years (5), an illness duration of ≥10 years and a lack of response to ≥2 typical modes of treatment including ≥1 inpatient treatment of hospitalization.

We conducted bilateral stereotactic implantation of DBS electrodes in the vALIC. In accordance with our DBS studies (6) the study comprised four sequential phases: preoperative (T-1), surgery (T0), optimization (3-9 months; T1-T2) and maintenance phase (12 months; T2-T4) (**Supplement 1**, methods and statistical analysis). During the study the patients received standard medical and psychiatric care, comprised of regular visits with a nurse-practitioner and a psychiatrist. No major psychopharmacological adjustments were made.

Primary outcome measures were 1) change in body mass index (BMI), 2) change in Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS)-score (7) and 3) change in Eating Disorder Quality of Life (ED-QOL)-score (8). We established side effects and safety through frequent and intensive monitoring by a psychiatrist, including checks of vital parameters, standard laboratory assessments and ECG. All patients were assessed using (self-report) questionnaires.

Four female patients were enrolled between 2016 and 2020. Patients had a mean age of 39 years (SD=10) and illness duration of 21 years (SD=3). Average baseline BMI was 12.5 (SD=1.0) kg/m^2, indicating extremely severe AN.

Monopolar DBS at the middle two contacts was switched on at T1 (pulse width 90 μs, frequency 130 ms) at a mean voltage of 3.0 V (2.5-3.5 V). The mean voltages at T2, T3 and T4 were respectively 3.8 V (3.0-5.0 V), 3.8 V (3.0-4.5 V) and 3.8 V (2.7-4.8 V). Adjustment of the stimulation intensity occurred in steps of 0,5 V, later fine-tuning in steps of 0,1 V. Pulse width and frequency remained unchanged during the study.

BMI increased substantially and significantly at the end of follow-up (5.32 kg/m^2; +42.8%; P=.017) (**figure 1**).

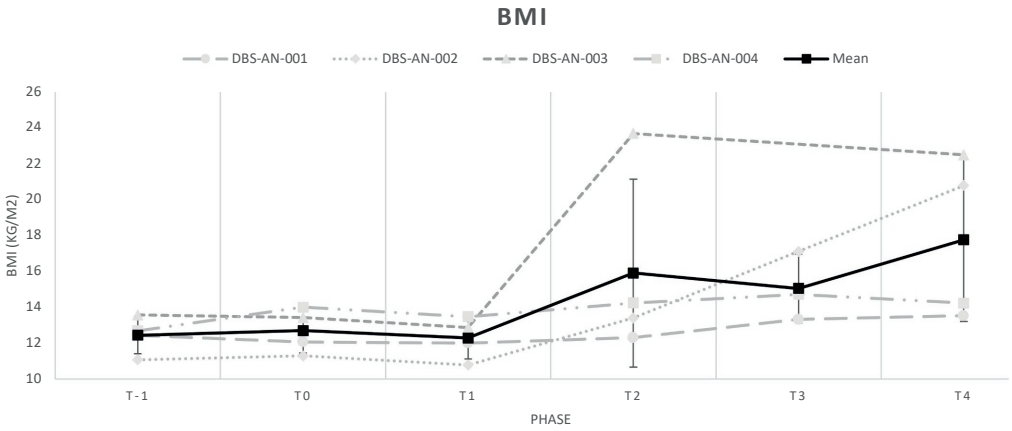

Figure 1. Time course of DBS-induced BMI (fixed effects ± SE).

Linear mixed model analyses showed a significant linear effect of time on BMI (43.16±15.96, CI 95% 9.07-77.25, t=2.704, P=.017).

The score on the YBC-EDS showed a significant improvement over time (-23.9%; P=.012). This effect was driven by significant decreases in the *Preoccupation* and *Rituals* subscales (-16.2%; P=.026, and -31.1%; P=.001, respectively). This corresponded with the secondary outcome EDE-Q, which showed significant improvements on the subscales *Restraint* and *Eating Concern* (P=.039 and P=.024, respectively). The HAM-D and HAM-A showed additional significant improvements (-36.7% and -47.9%, respectively).

The ED-QOL showed a significant improvement over time on the subscale *Physical Health* (P=.005) (**Supplement 2**, results).

Evidently, there are points of discussion. The mean baseline BMI of our patients was extremely low (categorized as 'very severe' in the DSM-5), which on average improved at one year postoperatively to the DSM-5 category 'mild'. The increase in BMI was primarily seen in two of four patients. The other two subjects showed only a mild increase in BMI. This response rate of 50% is comparable to other studies (2, 3).

Improvement was also observed in psychological outcomes. Two out of four patients were categorized as responders (≥35% decrease on the YBC-EDS). All patients reported a decrease in preoccupations and rituals, experiencing them as less rewarding. There was a decrease in eating-related behavior like purging and caloric and body checking, and significant decrease in depression and anxiety symptoms, which have great clinical importance for AN-patients (9).

All patients reported a *subjective* improvement of their psychological state and quality of life. The majority of patients reported that eating disorder behavior and rituals have lost their rewarding properties, leaving the more room for healthier behavior. All patients confirmed that they still would prefer DBS, even though their eating disorder did not reach complete remission.

There were no intraoperative adverse events in any of four patients. Nevertheless, 28 severe adverse events (SAE's) occurred, with two being probably and nine possibly related to the intervention. Probable related SAE's were (hypo)manic symptoms. Possible related SAE's consisted of self-destructive behavior (autointoxication, auto-mutilation and aggression). SAE's were mostly related to the severity of AN and its somatic complications rather than DBS (n=11).

The number of SAE's reflects the challenging nature of this study. Transient hypomanic and impulsive symptoms may be caused by downregulation of reward and emotion regulation circuitries due to DBS (4, 10). We hypothesize that vALIC-DBS inhibits positive reinforcement of ritualistic AN behavior making them useless as a coping strategy. Patients develop alternative coping strategies such as self-destructive behavior, explaining some of our (S)AE's. Three out of four patients showed improvement on coping and emotion regulation following psychotherapy.

DBS was provided open-label, therefore results might be influenced by placebo or other non-specific effects. These were however minimized due to the one-year follow-up period. Though the small sample size of this vALIC DBS study limits its power, it is deemed sufficient to answer basic research questions.

To the best of our knowledge, this is the first study of vALIC-DBS in AN. The results indicate that vALIC-DBS is a valid, safe and feasible last-resort intervention in treatment-refractory AN. Our findings pave the way for a follow-up study with a larger sample size.

SUPPLEMENT 1. METHODS AND STATISTICAL ANALYSIS

Methods

Study Design and Patients

In this first open-label pilot study, we report on the efficacy, feasibility and safety of bilateral vALIC DBS in chronic, treatment-refractory AN. The Medical Ethical Committee (MEC) of the Amsterdam University Medical Centers, location AMC (AUMC-AMC) approved this study, which we preregistered in the Netherlands Trial Register under trial number NL3322. A data safety monitoring board (DSMB) was installed.

Inclusion Criteria

- Clear primary diagnosis of AN (restricting or purging subtype) based on the Diagnostic and Statistical Manual for Mental Disorders version 4 (DSM-IV) (11), confirmed by psychiatric interview and review by an independent psychiatrist.
- BMI < 15
- Illness duration of ≥10 years
- Lack of response to ≥2 typical modes of treatment including ≥1 hospital admission and/or inpatient treatment in an eating disorder center.
- Substantial functional impairment according to the DSM-IV criterion C and the Global Assessment of Function (GAF-score) of 45 or less for ≥2 years.

Exclusion Criteria

- Presence of unstable physical condition (severe electrolyte disturbances, cardiac failure, other physical contraindications for surgery/anesthesia)
- Treatable underlying cause of anorexia/underweight
- Inability to stop the use of anticoagulants, active neurological disease (like Parkinson's disease, dementia, epilepsy)
- Schizophrenia/history of psychosis
- Bipolar disorder
- Alcohol or substance abuse (including benzodiazepines) during the last 6 months
- Current tic disorder
- Antisocial personality disorder
- Standard MRI scan exclusion criteria (e.g. pacemaker and metals contraindicated for MRI)

Surgical procedure

We conducted bilateral stereotactic implantation of quadripolar DBS electrodes (model 3389, Medtronic, Minneapolis), contact points being 1.5 mm long and separated from adjacent contacts by 0.5 mm, and an implantable neurostimulator under general anesthesia. Electrodes were

implanted in the anterior limb of the internal capsule with an anterior angle of approximately 75° to the intercommissural line, using stereotactic frame-based 1.5 Tesla magnetic resonance imaging (MRI) coregistered to pre-operative 3T MRI with 1-mm slices for target determination. The upper three contact points of the electrode were placed in the vALIC, the lowest contact point was placed in the nucleus accumbens, ±3 mm anterior to the anterior commissure according to Mai et al., 2015.

The electrodes were connected via a subcutaneous extension cable to a neurostimulator (Activa Primary Cell/Rechargeable Cell, Medtronic, Minneapolis), implanted under the pectoral muscle in the infraclavicular region. Postoperative computed tomography (CT) was performed and coregistered to pre-operative MRI to confirm accurate position of the electrodes.

Treatment procedure

In accordance with our earlier DBS studies (6) the complete study comprised four sequential phases: preoperative, surgery, optimization and maintenance phase.

In the preoperative phase (T-1) we conducted baseline measurements. Standard somatic and psychiatric care was available to all patients throughout this period, including hospitalization. Once patients were considered fit for surgery (T0), the electrodes and stimulator were implanted. The patients were discharged from the department of neurosurgery one or several days after the procedure, depending on the physical condition of the patient. The optimization phase lasted between three and nine months. In brief, immediately after recovery from surgery, the neurostimulator stayed in off mode during three weeks in order to prevent interference with the effects from surgery that might have complicated the fine-tuning of the stimulation parameters (electrode contact selection, frequency, voltage).

After these three weeks, we switched the neurostimulator on (T1) and performed fine-tuning/optimization of the neurostimulation during three to six months. We optimized the stimulation intensity with initial steps of 0,5 V, fine-tuning occurred by adjusting the voltage with steps of 0,1 V. During this phase, we determined the stimulation parameter settings that provided the best clinical improvement (4). If, thereafter, we still expected clinical improvement with additional changes in neurostimulator settings, a continuation of the fine-tuning phase was possible for three more months (optimization was performed during three to nine months), with assessments of improvement every week until a plateau of effectiveness was reached. In one patient the contact points were changed during the optimization period in order to use the two contact points that were closest to the medial forebrain bundle (MFB).

Patients entered the maintenance phase of the study after the optimization period was completed (T2). The maintenance phase consisted of a 12 months period with the stimulator on, to assess the long-term effect of DBS on BMI, comorbidity, and eating behavior. Measuring points during the maintenance phase were at 6 months (T3) and at 12 months (T4, end of the study).

Table 1. DBS-induced changes in different parameters over time.

	T-1	*T0*	*T1*	*T2*	*T3*	*T4*	*Baseline vs. End of follow-up*	*t-value*	*p-value*
Weight (kg)	34.03(±4.35)	34.48(±4.35)	33.38(±4.35)	43.18(±4.35)	45.91(±4.61)	**47.88(±4.35)(P=.028)**	**40.70%**	**2.742**	**0.016***
BMI (kg/m2)	12.44(±1.71)	12.70(±1.71)	12.28(±1.71)	15.91(±1.71)	17.01(±1.80)	**17.76(±1.71)(P=.028)**	**42.80%**	**2.704**	**0.017***
Systolic BP (mmHg)	104.25(±5,13)	-	94,50 (±5,13)	102.00(±5,13)	109.50(±7.26)	**132.00(±7.26)(P=.010)**	**26.62%**	**3.548**	**0.005****
Diastolic BP (mmHg)	66.75(±6.38)	-	61.00(±6.38)	72.50(±6.38)	73.91(±7.64)	**87.41(±7.64)(P=.015)**	**30.95%**	**3.488**	**0.007****
Body Temperature (^{0}C)	35.63(±0.23)	-	35.90(±0.23)	36.23(±0.23)	36.05(±0.33)	**36.80(±0.33)(P=.014)-**	**30.32%**	**2.787**	**0.018***
YBC-EDS									
Preoccupations	17.00(±1.07)	-	17.00(±1.07)	15.50(±1.07)	**13.25(±1.07)(P=.017)**	14.25(±1.07)	**-16.20%**	**-2.509**	**0.026***
Rituals	18.50(±0.99)	-	18.25(±0.99)	15.75(±0.99)	**13.00(±0.99)(P=.003)**	**12.75(±0.99)(P=.002)**	**-31.10%**	**-4.483**	**0.001****
Total	35.50(±1.96)	-	35.25(±1.96)	31.25(±1.96)	**26.25(±1.96)(P=.028)**	**27.00(±1.96)(P=.006)**	**-23.90%**	**-3.567**	**0.012***
EDQOL									
Psychological	3.00(±0.20)	-	3.33(±0.16)	2.53(±0.68)	3.20(±0.25)	2.88(±0.36)	-4.00%	-0.553	0.614
Physical/Cognitive	2.30(±0.31)	-	2.45(±0.31)	1.58(±0.31)	1.48(±0.31)	**1.15(±0.31)(P=.020)**	**-50.00%**	**-3.321**	**0.005****
Financial	1.25(±0.31)	-	1.45(±0.31)	1.65(±0.31)	0.55(±0.31)	1.00(±0.31)	-20.00%	-1.414	0.178
Work/School	2.85(±0.76)	-	1.60(±0.76)	0.98(±0.76)	1.00(±0.76)	0.85(±0.76)	-70.20%	-1.750	0.104
Total	2.40(±0.32)	-	2.63(±0.32)	2.38(±0.32)	2.30(±0.32)	1.83(±0.32)	-23.80%	-1.388	0.188
HAM-D	27.25(±2.09)	-	**18.25(±2.09)(P=.018)**	**19.00(±2.09)(P=.028)**	**15.25(±2.09)(P=.003)**	**17.25(±2.09)(P=.011)**	**-36.70%**	**-3.114**	**0.009****
HAM-A	29.25(±2.17)	-	**17.25(±2.17)(P=.001)**	**16.75(±2.17)(P=.001)**	**16.50(±2.17)(P=.001)**	**15.25(±2.17)(P=.000)**	**-47.90%**	**-4.194**	**0.001****

Linear mixed model analyses showed a significant linear effect of time on Weight (113.34±41.33, CI 95% 24.88-201.81, t=2.742, P=.016), BMI (43.16±15.96, CI 95% 9.07-77.25, t=2.704, P=.017), YBC-EDS Preoccupations (-9.25±3.69, CI 95% -17.22 - -1.28, t=-2.509, P=.026), YBC-EDS Rituals (-16.75±3.74, CI 95% -25.08 - -8.42, t=-4.483, P=.001), YBC-EDS Total (-26.00±7.29, CI 95% -43.84 - -8.16, t=-3.567, P=.012), ED-QOL Physical/Cognitive (-3.28±0.99, CI 95% -5.38 - -1.17, t=-3.321, P=.005), HAM-D (-23.00±7.39, CI 95% -39.09 - -6.91, t=-3.114, P=.009) and HAM-A (-28.70±6.86, CI 95% -43.36 - -14.14, t=-4.194, P=.001)

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4

Efficacy and safety of deep brain stimulation for treatment-refractory anorexia nervosa: a systematic review and meta-analysis

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ABSTRACT

Background

Several pioneering studies investigated deep brain stimulation (DBS) in treatment-refractory anorexia nervosa (AN) patients, but overall effects remain yet unclear. Aim of this study was to obtain estimates of efficacy of DBS in AN-patients using meta-analysis.

Methods

We searched three electronic databases until 1st of November 2021, using terms related to DBS and AN. We included trials that investigated the clinical effects of DBS in AN-patients. We obtained data including psychiatric comorbidities, medication use, DBS target, and study duration. Primary outcome was Body Mass Index (BMI), secondary outcome was quality of life, and the severity of psychiatric symptoms, including eating disorder, obsessive-compulsive, depressive, and anxiety symptoms. We assessed the risk of bias using the ROBINS-I tool.

Results

Four studies were included for meta-analysis, with a total of 56 patients with treatment-refractory AN. Follow-up ranged from 6-24 months. Random effects meta-analysis showed a significant increase in BMI following DBS, with a large effect size (Hedges's g = 1 · 13; 95% CI = 0 · 80 to 1 · 46; Z-value = 6 · 75; P < 0 · 001), without heterogeneity (I^2 = 0 · 00, P = 0 · 901). Random effects meta-analysis also showed a significant increase in quality of life (Hedges's g = 0 · 86; 95% CI = 0 · 44 to 1 · 28; Z-value = 4 · 01, P < 0 · 001). Furthermore, DBS decreased the severity of psychiatric symptoms (Hedges's g = 0 · 89; 95% CI = 0 · 57 to 1 · 21; Z-value = 5 · 47; P < 0 · 001, I^2 = 4 · 29, P = 0 · 371).

Discussion

In this first meta-analysis, DBS showed statistically large beneficial effects on weight restoration, quality of life, and reduction of psychiatric symptoms in patients with treatment-refractory AN. These outcomes call for more extensive naturalistic studies to determine the clinical relevance for functional recovery. This study is preregistered in PROSPERO,CRD42022295712.

INTRODUCTION

Anorexia nervosa (AN) has an alarming mortality rate (1-3). About 20% of AN patients remain treatment-refractory to psychotherapy and pharmacological treatment aimed at weight restoration (4). To ameliorate this grim perspective, there is an urgent need for novel treatment options.

One promising new treatment is deep brain stimulation (DBS). DBS is neuromodulation therapy involving implantation of electrodes at targeted brain areas, which conduct electrical impulses to the brain tissue. These electrical impulses are controlled by a neurostimulator, a device similar to a pacemaker (5). DBS is already established as an effective treatment for Parkinson's disease (PD), essential tremor, idiopathic dystonia, epilepsy, and obsessive-compulsive disorder (OCD) (6, 7).

The idea of treating AN with DBS came from serendipitous positive effects that were noted in earlier DBS studies for other indications. In these case reports, patients were being treated with DBS for major depressive disorder (MDD) (8, 9) or OCD (10, 11), while they simultaneously suffered from comorbid AN. Follow-up showed not only a decrease of the MDD or OCD symptoms, but also an improvement of the AN symptoms, including cognitive and emotional symptoms. Patients presented significant improvement in BMI and decreased anxiety and distress in relation to weight gain (8-11).

DBS also holds promise for understanding AN from a pathophysiological perspective. The reward system has been proposed as a key brain circuit in AN (12). This system regulates motivation and hedonic experience of food intake and provides feedback on the value of a specific food. Several lines of evidence show disturbances in the reward system in AN-patients, including failure to connect appropriate responses to stimuli (13), and limited awareness of intero- and exteroceptive homoeostatic triggers (14, 15). Moreover, these disturbances in the reward system are linked to formation of habits (16), reflected in repetitive anorectic behaviours and associated altered activation of striatal brain areas (13, 17). DBS has been shown to directly influence the reward and habit brain circuits, normalizing the aberrant activity associated with psychiatric disorders (18).

Based on these serendipitous clinical observations and pathophysiological insights, pioneering studies tested the effects of DBS in patients with AN. In 2013, Lipsman et al. hypothesized the subcallosal cingulate cortex (SCC) and the nucleus accumbens (NAcc) to be effective DBS targets for AN because they met the following criteria; (1) prominent afferent and efferent connection with the anterior insula, (2) involved in reward-processing, (3) involved in AN-related provocation and imaging studies, and (4) involved in anxiety and dysphoric mood (14). Indeed, studies observed positive effects of both NAcc and SCC DBS on AN symptoms (6, 9). Moreover, based on effectiveness in psychiatric disorders phenomenologically related to AN, including treatment-refractory OCD and depression, other targets such as the ventral anterior limb of the internal capsule (vALIC) have been successfully tested in AN (15, 19, 20).

Despite promising trial results, to our knowledge, a meta-analysis on the effects of DBS in AN had yet to be performed. In order to provide an estimate on the overall effect of DBS in AN, we

performed such a meta-analysis, combining all available evidence from treatment trials. Based on previous case reports, we hypothesized a beneficial effect of DBS on weight restoration, quality of life, and reduction of psychiatric symptoms in AN patients. Results of this meta-analysis may justify further clinical application in future and more extensive naturalistic research.

METHODS AND MATERIALS

Following PRISMA guidelines (21), the systematic review and meta-analysis protocol was registered in PROSPERO (22).

Search strategy

A literature search was performed on MEDLINE, Embase, and PsycInfo, in the period between the last week of August 2020 and up to the 1st of November 2021 (**Appendix 1**). Publication date was not a restriction.

Selection process

Two independent reviewers (DMK, PC) screened titles and abstracts of found studies. We included clinical studies investigating the effects of DBS in patients with AN. Duplicates, case reports, and reviews were excluded. Articles were excluded if they did not cover AN and/or DBS, were based on animals, or contained <four participants. We did not exclude studies based on the availability of a control group, studies comparing outcomes before and after DBS will also be included. Inconsistencies were solved by means of discussion, if necessary, with a third and fourth reviewer (MSO, RJTM). **Appendix 2** shows a list of studies that were excluded at the full-text screening stage.

Critical appraisal and quality assessment

Critical appraisal of all included studies was performed independently in duplicate (DK, PC) by using the ROBINS-I tool (Risk Of Bias In Non-randomised Studies—of Interventions) (23). Furthermore, we used GRADE (24) for assessing the overall quality of evidence. Inconsistencies were solved by means of discussion.

Data extraction and outcome data

The extracted data consisted of the following study characteristics: number of participants, number of time points, participants' characteristics, study duration, and study outcome data. BMI change after DBS was considered our primary outcome. One study used the mean BMI achieved either in the year or in the 3-month prior to surgery, chosen depending on the characteristics of every patient (25). The combined effect on psychiatric symptoms at the last observation was considered our secondary outcome. In this meta-analysis no other eating disorder related symptoms than BMI could be used as primary outcome data, because of inconsistencies

in outcome assessment selection between the included studies. The secondary outcome data was represented using several scales: Yale-Brown-Cornell Eating Disorder Scale (26), Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (27), Hamilton Anxiety Rating Scale (HAM-A) (28), and Hamilton Depression Rating Scale (HAM-D) (29). Quality of life was assessed using the Quality of Life Scale (30), SF36 (31), and Eating Disorder Quality of Life (32). Next to effectiveness data, we also extracted safety data including adverse effects and complications.

Statistical analyses

Main analyses

We used random effect models with Comprehensive Meta-Analysis V3 for our quantitative data synthesis. We used Hedges' *g* for continuous results, with a 95% confidence interval and two-tailed *p*-values. Sensitivity analyses were performed using pre-operative BMI measures of Villalba et al. instead of the calculated reference BMI value (25). Forest plots with I^2 statistics were used to examine any study heterogeneity.

Publication bias

A funnel plot was plotted to assess publication bias. The classic and Orwin's fail-safe N, Begg and Mazumdar rank correlation, and Egger's regression intercept were calculated. Should it be deemed necessary Duval and Tweedie's trim-and-fill method was used to report adjusted values.

RESULTS

Study selection

The literature search provided a set of 290 articles. 276 articles were excluded based on title and abstract (**Figure 1**). The full text of the fourteen remaining articles was reviewed. Duplicates and articles that turned out to be protocols were removed from analysis. Four of these fourteen articles were included for meta-analysis. **Figure 1** shows the process of study selection.

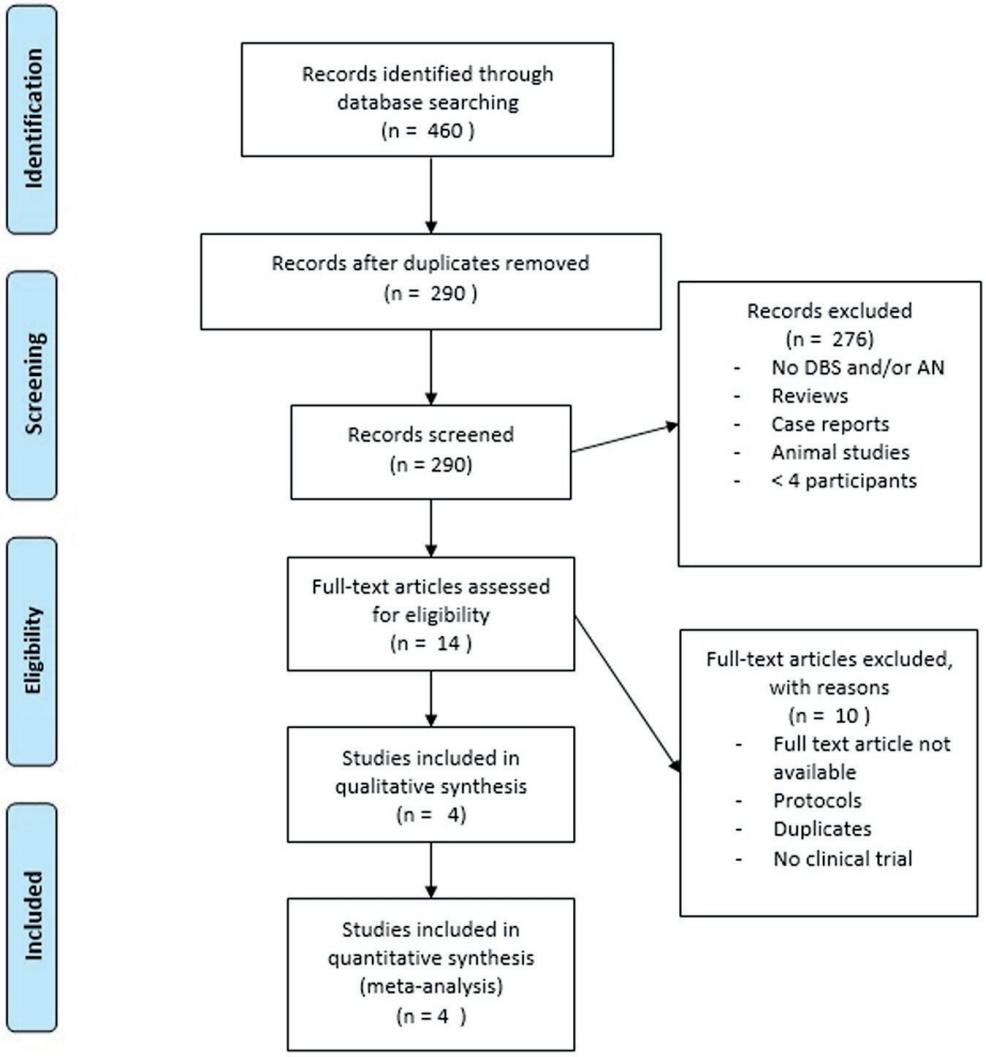


Figure 1. Prisma flow diagram for included studies.

Study characteristics

Four included non-randomized non-controlled clinical trials contained a total of 56 participants. The follow-up period was either 6 (25), 12 (15, 33) or 24 months (4). The average age of the participants over all studies was 29·8 years, with a range of 18–57 years. The mean illness duration over the four included studies was 12·8 years. All but one of the participants were female. All patients were diagnosed with AN, with either the restrictive ($n = 28$) or the (binge-) purging subtype ($n = 28$). All participants were defined as treatment-refractory, which for instance included numerous hospital admissions and extensive psychiatric treatment. Most patients suffered from

psychiatric comorbidities ($n = 54$). These comorbidities were diagnosed as: MDD ($n = 33$), OCD ($n = 19$), anxiety/generalised anxiety disorder (GAD) ($n = 11$), post-traumatic stress disorder (PTSD) ($n = 10$), panic disorder ($n = 3$), borderline personality disorder (BPD) ($n = 3$), personality disorder not otherwise specified (PD-NOS) ($n = 2$), and substance use disorder ($n = 2$). **Supplementary table 1** shows all study and patients characteristics.
At time of surgery, eight participants were not taking medication, six used one drug and 42 used two drugs or more. The types of drugs consisted of SSRIs (selective and non-selective), benzodiazepine agonists, atypical antipsychotics, antiepileptics, and tetracyclic antidepressants. No major psychopharmacological adjustments were made during the follow-up.

32 out of 56 participants received DBS to the NAcc, 20 patients received DBS to the SCC, and 4 to the vALIC. Three of the studies (4, 15, 33) used either the SCC, NAcc, or the vALIC as the DBS target, while the fourth study (25) used either the SCC or NAcc for their patients, based on their primary comorbidity. 4 out of 8 participants received DBS to the SCC, and 4 to the NAcc in the last mentioned study. Overall, 3 out of 56 participants had their electrodes explanted before the end of follow-up (4, 33, 34).

Main analyses: effects on BMI

Random effects meta-analysis showed a significant increasing effect of DBS on primary outcome BMI change after DBS, with a large effect size (Hedges's $g = 1 \cdot 13$; 95% CI = 0 · 80 to 1 · 46; *Z*-value = 6 · 75; $P < 0 \cdot 001$, **figure 2**), without heterogeneity ($I^2 = 0 \cdot 00$, $P = 0 \cdot 901$) (**Figure 2**).

Secondary analysis: effects on psychiatric symptom domains

DBS also had a beneficial effect on secondary outcome combined psychiatric symptom severity at last observation (Hedges's g = 0 · 89; 95% CI = 0 · 57 to 1 · 21; Z-value = 5 · 47; P < 0 · 001, I2 = 4 · 29, P = 0 · 371, Supplementary Fig. 2).

Eating disorder symptoms

Three non-randomized non-controlled clinical trials (15, 25, 33) assessed eating disorder symptoms. Random effects analyses showed a beneficial main effect of 0 · 98 (Hedges's g; 95% CI = 0 · 28 to 1 · 68; Z-value = 2 · 74; P = 0 · 006; **Supplementary figure 3**).

Symptoms of depression

All studies assessed symptoms related to depression. Random effects analyses showed a beneficial main effect of 0 · 98 (Hedges's g; 95% CI = 0 · 54 to 1 · 41; Z-value = 4 · 43; P = 0 · 00; **Supplementary figure 4**).

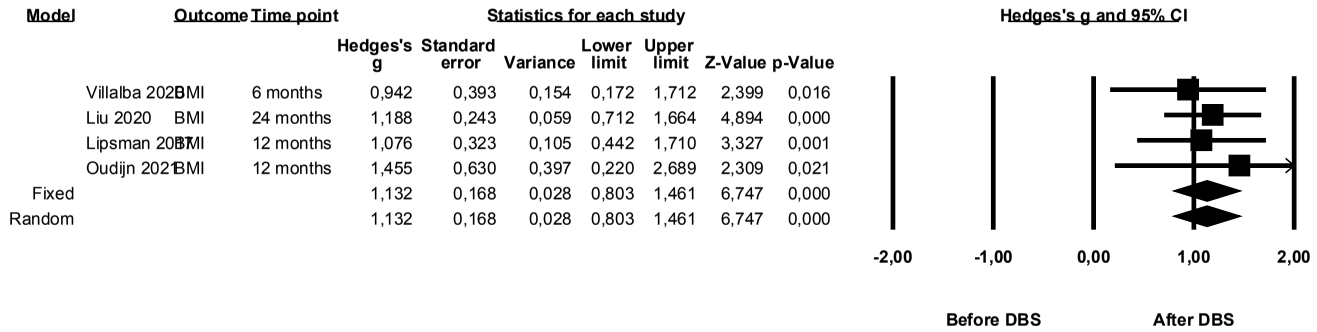


Figure 2. Forrest plot showing meta-analysis effects of DBS on primary outcome BMI.

Obsessive-compulsive symptoms

All studies assessed obsessive-compulsive symptoms. Random effects analyses showed a beneficial main effect of 0·72 (Hedges's g; 95% CI = 0·39 to 1·06; Z-value = 4·19; P = 0·00; **Supplementary figure 5**).

Symptoms of anxiety

Three non-randomized non-controlled clinical trials [4, 15, 25] assessed symptoms of anxiety. Random effects analyses showed a beneficial main effect of 0·85 (Hedges's g; 95% CI = 0·38 to 1·31; Z-value = 3·55; P = 0·00; **Supplementary figure 6**).

Secondary analysis: quality of life

Three non-randomized non-controlled clinical trials (15, 25, 33) assessed eating disorder symptoms. Random effects analyses showed a beneficial main effect of 0·86 (Hedges's *g*; 95% CI = 0·44 to 1·28; *Z*-value = 4·01; *P* = 0·00; **Supplementary figure 7**).

Adverse events

The most frequently occurring adverse events in the four studies were related to surgery or procedure; pain at incision site within <4 days ($n = 22$), pain at incision site after >4 days ($n = 5$), cutaneous complications ($n = 4$), and to stimulation procedure; hypomanic symptoms ($n = 3$), seizure ($n = 3$), and auto-intoxication ($n = 3$). **Supplementary table 2** lists all reported adverse events, including those possibly but not probably related to the intervention (15). Other reported adverse events were either defined as unrelated to the intervention and attributed to underlying illness, or had no cause specified. Short-term side-effects like flush and sweating were observed during the programming of the DBS device, but were relieved with adjustment of the parameters.

Risk of bias and quality of evidence

Risk of bias summary is shown in **Supplementary figure 1**. The risk of bias of the objective (BMI) and subjective (psychological outcomes) measurements of the included studies are respectively shown in **Supplementary figure 1a, b**. Overall, the risk of bias was moderate for objective outcome measurements and serious for subjective outcome measurements. This was mainly caused by the lack of a control group in the included studies, potentially leading to biases. Furthermore, the studies did not report blinding of both the participants and the researchers, or assessment of the subjective outcomes by an independent party, leading to serious risk of potential bias in measurement of subjective psychological outcomes. No other clear evidence for biases was found.

Supplementary table 3 shows details of the assessment of quality of the resulting evidence using GRADE. For the more objective outcome BMI, the quality of evidence that deep brain stimulation improves BMI in refractory-treatment AN-patients is considered moderate, whereas for subjective outcomes psychiatric symptoms and quality of life the quality of evidence is deemed low.

Publication bias

The classic fail-safe *N* was 40, Orwin's fail-safe *N* was 42 with criterion for a 'trivial' standardized difference in means as 0·1. This suggested that at least 40 studies without any effect must be reported to decrease the overall effect to a trivial effect. Concerning the Begg and Mazumbar rank correlation test, Kendall's tau's with as well as without continuity correction was 0·00 (P2-sided = 1·00), suggesting no publication bias. Egger's regression intercept was 0·23 (95% confidence interval: −3·47 to 3·94; P2-sided = 0·81), also indicating no publication bias.

Duval and Tweedie's trim-and-fill method used the random-effects model looking for missing studies to the left of the mean, meaning a less favourable effect of deep brain stimulation, showed one study that needed to be trimmed. This resulted in an effect size of 0·91 (*Q*-value; 95% CI = 0·79 to 1·43). **Figure 3** shows the values of the Duval and Tweedie's trim-and-fill method. Using a fixed effect model, the resulting point estimate did not change.

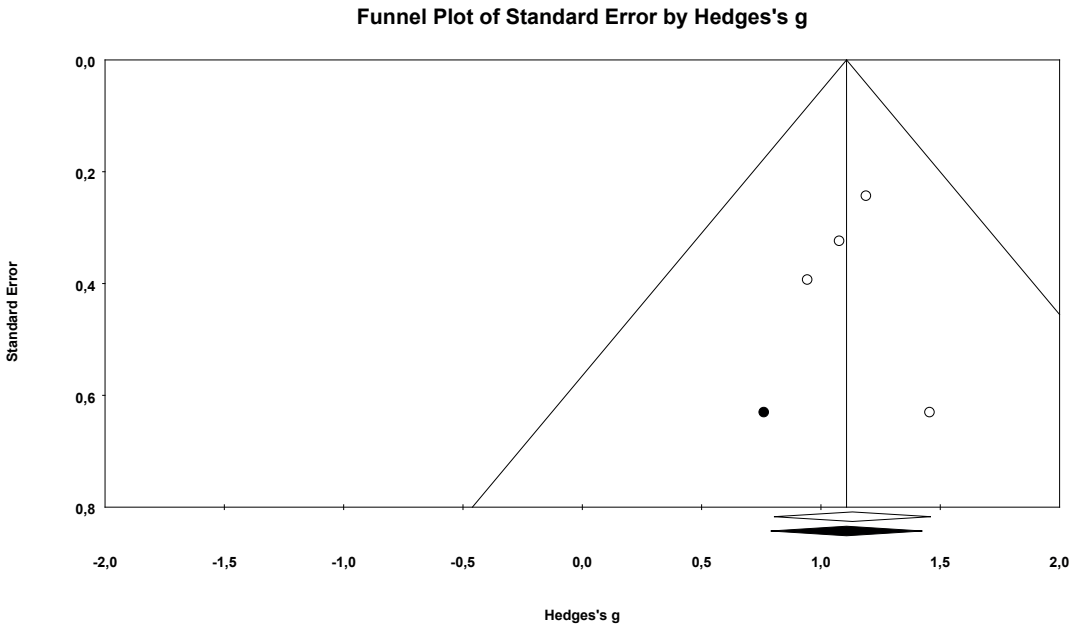


Figure 3. Funnel plot of precision of standard error by Hedges's g for publication bias.

Sensitivity analyses

Using the pre-operative BMI instead of the reference BMI for the study of Villalba et al. resulted in a comparable overall effect of DBS on primary outcome BMI change after DBS, with a large effect size (Hedges's $g = 0 \cdot 90$; 95% CI = $0 \cdot 58$ to $1 \cdot 21$; Z-value = $5 \cdot 60$; $P < 0 \cdot 001$).

DISCUSSION

This first meta-analysis combined all available trials on the effect of DBS in AN. Four non-randomized non-controlled studies provided a total of 56 participants. Random effects meta-analysis showed an improvement in primary outcome BMI, with a large effect size of $1 \cdot 13$ and no heterogeneity. Moreover, meta-analysis showed a beneficial effect on overall psychiatric symptom severity, with a comparable large effect size of $0 \cdot 89$. All four symptom domains showed a large effect: depressive symptoms (Hedges's $g = 0 \cdot 98$), obsessive-compulsive symptoms (Hedges's $g = 0 \cdot 72$), symptoms of anxiety (Hedges's $g = 0 \cdot 85$), and eating disorder symptoms (Hedges's $g = 0 \cdot 98$). Furthermore, DBS also improved the quality of life, with a large effect size (Hedges's $g = 0 \cdot 86$). There was limited evidence for publication bias. The quality of evidence was considered moderate for the more objective primary outcome BMI, and low for the subjective secondary psychological outcome measurements. All in all, results suggest that DBS has statistically large beneficial effects in severe and life-threatening treatment-refractory AN.

Although no statistical heterogeneity was found between included studies, some differences are worth mentioning. It is important to note that the study of Villalba et al. had a relatively short period of follow-up of 6 months. This is particularly noteworthy in comparison to the study of Oudijn et al., where an optimization period was included prior to the maintenance phase leading to a maximal post-operative follow-up of 91 weeks. This shorter follow-up may explain the relatively low post-intervention BMI in Villalba et al., although this did not result in statistical heterogeneity between studies. However, the studies used different targets for DBS, possibly resulting in clinical heterogeneity. Another important difference is that only one study reported psychiatric adverse events related to DBS (15). Other studies either experienced no psychological adverse events or did not report them systematically.

The risk of bias was considered moderate for objective outcome measurements (BMI) and serious for subjective secondary outcome measurements. This was caused by the lack of a control group, which ethically speaking would be difficult to implement in such a treatment-refractory patient group. A placebo effect could therefore not be excluded. Independent outcome assessors blinded for treatment status could theoretically ameliorate this bias. Nevertheless, we did not find any clear evidence for other biases.

The present meta-analysis showed statistically large effects of DBS in treatment-refractory AN for weight gain, whereas effect sizes otherwise found in literature for pharmacological and psychological treatment seem to be respectively moderate (35, 36) and low (37). The effects of DBS in AN are in line with effects of DBS in other psychiatric disorders including depression and OCD (38).

The beneficial clinical effects of DBS in this meta-analyses may also improve insight in the pathophysiology of AN. It is hypothesised that DBS creates a reversible lesion to the stimulated area (6, 39). However, recent evidence suggests that DBS modulates widespread brain network activity, e.g. normalizing neuronal firing in reward circuitry. Due to the uncertainties in the pathophysiology of AN and the working mechanisms of DBS, included trials used diverse stimulation sites, including the NAcc, SCC, and vALIC. However, the effects of the studies were comparable with low heterogeneity. This shows that DBS may be effective at diverse targets, potentially suggesting diverse inroads to normalize aberrant activity in comparable brain circuits. This is in line with the concept of connectomic DBS, where different implementation targets all relate to similar pathophysiologically relevant white matter tracts (40). Moreover, these effects may be shared with other psychiatric disorders, where similar targets resulted in transdiagnostic beneficial effects (34, 41).

Literature on the biological effects of DBS in AN is sparse. Zhang et al. used FDG-PET to image glucose metabolism in the brain after DBS to the NAcc to identify which brain regions would be affected by DBS in AN (42), and noted a reduction of (hyper)metabolism in the lentiform nucleus, hippocampus, and frontal lobe. Further evidence comes from research other disorders. DBS to the NAcc in treatment-resistant depression showed metabolic decreases in prefrontal subregions, subgenual cingulate region, posterior cingulate cortex, thalamus and caudate nucleus. DBS of the anterior limb of the internal capsule in patients suffering from OCD, resulted in long-term changes in metabolic activity (43). A decrease of frontal metabolism is a fundamental component of NAcc-DBS mechanism (44). Moreover, Fridgeirsson et al. found an association in OCD between improvement in mood and anxiety with decreased functional connectivity between the amygdala and insula due to DBS (45). These circuitries are also involved in AN, presumably, though the precise mechanisms of action of DBS remains to be determined.

Limitations and strengths

The main limitation of this study was the inability to rule out the presence of a placebo effect. The nature of DBS and particularly AN make it difficult to apply a double-blind study design. Nevertheless, effects, including on the objective outcome BMI, in this severe and extremely treatment-refractory population maintained over a study follow-up of up to 24 months, which argues for consistency and durability.

Another limitation is the variation in stimulation targets between the studies. Nevertheless, heterogeneity was low, suggesting that the different stimulation sites have comparable effects. Furthermore, the overall risk of bias of the included studies was moderate to serious. This could be improved by adding an independent assessor to the study. Also the quality of evidence was considered moderate for the more objective primary outcome, and low for the subjective outcome measurements.

The pooled results showed statistically large effects suggesting clinical relevance, however more parameters should be taken into account to allow the conclusion of relevant clinical functional improvement. It is important to note that our meta-analysis showed a large beneficial effect of DBS on BMI, however not all patients reached BMI in a normal range at the end of the follow-up. Also, three included studies reported only somatic adverse events related to surgery or stimulation. Only one study reported psychiatric adverse events related to DBS (15).

Finally, no international consensus has been reached on the definition of response to treatment or remission in anorexia nervosa in general, and of response to DBS in AN in particular. The included studies used heterogeneous definitions of response to DBS, therefore responder rates could not be determined. This study again emphasizes the need for such a consensus, as this would allow clinicians to assess the efficacy of this procedure.

A major strength of this study was that it is the first meta-analysis of the effect of DBS in treatment-refractory AN. Thereby, we provide an overall estimate of the size of the effect and the strength and quality of the evidence for the efficacy of DBS in treatment-refractory AN.

Research implications

Results from this meta-analyse provide several new inroads for future research. A first point of focus are the differences and similarities of the diverse DBS targets that have been applied. Studies might focus on clinical and biological differences in effects, e.g. by applying advanced clinical phenotyping and diverse biological assessments including advanced (connectomic) neuroimaging.

A second issue is prediction of response to improve patient selection. It would be helpful to identify factors that may predict response to DBS treatment in AN, and test whether the predictive value is strong enough for clinical implementation (46).

A third aspect is the combination with psychotherapy. DBS studies in psychiatry for other indications suggested that DBS may improve the response to psychotherapeutic interventions. It would be worthwhile to test whether this is also the case for AN-patients, and whether psychotherapy may increase the effectiveness of DBS.

An international database, including up-to-date naturalistic data from all AN-patients that are treated with DBS worldwide, may substantially increase power to test for subgroup effects.

Clinical implications

It is striking to note that deep brain stimulation, being effective in several psychiatric disorders, is relatively understudied in anorexia nervosa, being the world's most lethal psychiatric disorder. However, it needs to be noted that, as of yet, both the mechanism of action of DBS and the pathophysiology of AN are not fully understood. To be able to understand and treat AN, more insight is needed in the complex dynamics in which this psychiatric disorder comes to expression. Using DBS targeting different brain areas gets us closer to this understanding or even finding the root of this complex disorder.
Of note, other forms of neuromodulation (i.e. electro-convulsive therapy) also show promising results in anorexia nervosa, particularly on symptoms of depression (47).

Our results suggest that DBS can be an effective last-resort treatment option in severe treatment-refractory AN. Despite the invasive nature of the procedure and the risk of side-effects, we suggest that there is a clinical indication for DBS in selected cases of AN, under strict monitoring and scientific evaluation of effects. Target selection should be based on the available experience of the involved neurosurgeon and psychiatric treatment team. After DBS, the potential effect of concomitant psychological and/or pharmacological therapy should be re-evaluated.

CONCLUSION

This meta-analysis demonstrated a statistically large beneficial effect of DBS on weight restoration, quality of life, and psychiatric symptoms severity in patients with treatment-refractory AN. Adverse effects were related to surgery and stimulation. The size of the beneficial effects suggest potential clinical relevance as a last-resort treatment option in severe and life-threatening AN. Future, more extensive, naturalistic research could strengthen conclusions regarding clinical relevance and incorporation in guidelines, also in relation to other forms of neuromodulation. These promising outcomes form new inspiration for future research, and may provide a more hopeful perspective for patients that did not yet respond sufficiently to other forms of therapy.

Registration and protocol

The systematic review and meta-analysis protocol was preregistered in PROSPERO under study's registration number: CRD42022295712.

SUPPLEMENTARY MATERIAL

Supplementary table 1. Study characteristics of included studies

	Villalba et al. (N=8)	***Liu et al. (N=28)***	***Lipsman et al. (N=16)***	***Oudijn et al. (N=4)***	***Total / Mean (N=56)***
Mean age in years (range)	41 (SD = 16)	23 (SD = 4)	34 (SD = 8)	39 (SD = 10)	***30 (18-57)***
Follow-up period	6 months	24 months	12 months	12 months*	
Mean illness duration in years	25 (SD = 11)	5 (3 – 10)	18 (SD = 6)	21 (SD = 3)	***13 (SD = 9)***
Percentage female patients	87·5%	100%	100%	100%	***98·2%***
Restrictive subtype	6	13	9	0	***28 (50%)***
(Binge-)purging subtype	2	15	7	4	***28 (50%)***
Suffering from psychiatric comorbidities (percentage)	8 (100%)	28 (100%)	14 (87·5%)	4 (100%)	***54 (96·4%)***
MDD	7 (87·5%)	12 (42·9%)	12 (75%)	2 (50%)	***33 (58·9%)***
OCD	3 (37·5%)	9 (32·1%)	6 (37·5%)	1 (25%)	***19 (33·9%)***
GAD / severe anxiety	0	7 (25%)	3 (18·8%)	1 (25%)	***11 (19·6%)***
PTSD	0	0	10 (62·5%)	0	***10 (17·9%)***
Panic disorder	3 (37·5%)	0	0	0	***3 (5·4%)***
BPD	0	0	2 (12·5%)	1 (25%)	***3 (5·4%)***
PD-NOS	0	0	0	3 (75%)	***3 (5·4%)***
SUD	0	0	1 (6·3%)	1 (25%)	***2 (3·6%)***
No medication use	1 (12·5%)	0	7 (43·8%)	0	***8 (14·3%)***
1 drug	4 (50%)	1 (3·6%)	1 (6·3%)	0	***6 (10·7%)***
2 or 2> drugs	3 (37·5%)	27 (96·4%)	8 (50%)	4 (100%)	***42 (75%)***
DBS Target	NAcc (n=4) or SCC (n=4)	NAcc	SCC	vALIC	-
BMI (kg/m3); average baseline	12·67 (SD = 1·64)	13·01 (SD = 1·86)	13·83 (SD = 1·49)	12·44 (SD = 0·52)	***12·99 (0·61)***
BMI (kg.m3); post intervention**	13·98 (SD = 2·05)	17·73 (SD = 3·54)	17·34 (SD = 3·40)	17·76 (SD = 2·27)	***16·70 (1·83)***
Y-BOCS; at baseline	16·50 (SD = 7·69)	20·46 (SD = 8·86)	27·88 (SD = 8·57)	-	***21·61 (5·78)***
Y-BOCS; post intervention **	12·75(SD = 11·76)	13·04 (SD = 9·61)	19·71 (SD = 10·31)	-	***15·17 (3·94)***
HAM-A; at baseline	13·63 (SD = 6·30)	21·39 (SD = 8·54)	-	29·25 (SD = 2·46)	***21·42 (7·81)***
HAM-A; post intervention**	10·94 (SD = 11·84)	12·63 (SD = 9·18)	-	15·25 (SD = 1·11)	***12·94 (2·17)***
HAM-D; at baseline	15·38 (SD = 5·52)	26·93 (SD = 11·97)	19·40 (SD = 6·76)	27·25 (SD = 2·02)	***22·24 (5·84)***
HAM-D; post intervention**	10·50 (SD = 9·87)	15·93 (SD = 12·33)	8·79 (SD = 7·64)	17·25 (SD = 1·67)	***13·12 (4·11)***
Analyses	PP	PP	PP	PP	-

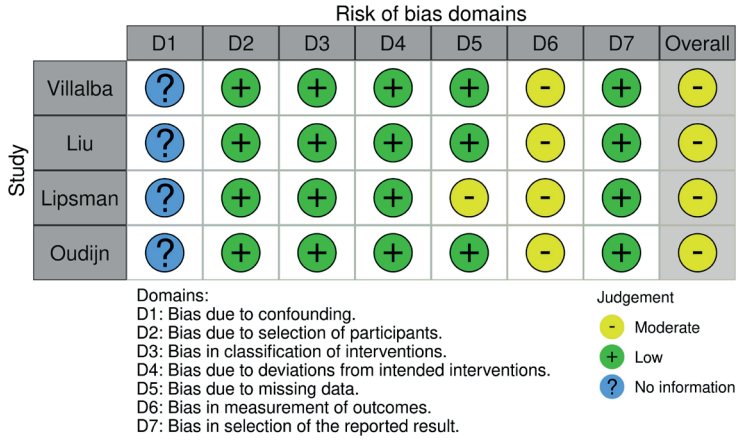
Abbreviations: N: number of subjects; AN: Anorexia Nervosa; DBS: Deep brain stimulation; MDD: Major depressive disorder; OCD: Obsessive-compulsive disorder; GAD: Generalized anxiety disorder; PTSD: Post-traumatic stress disorder; BPD: Borderline personality disorder; PD-NOS: Personality disorder not otherwise specified; SUD: Substance use disorder; NAcc: Nucleus accumbens; SCC: Subcallosal cingulate cortex; vALIC: Ventral anterior limb of the internal capsule; YBOCS: Yale-Brown Obsessive-Compulsive Scale; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; PP: per protocol. * After surgery DBS parameters were optimized for 3 weeks with DBS-off and a minimum of 12 weeks with DBS-ON. After optimization phase, the 12 months long maintenance phase followed after. ** The elapsed time for the variables measured after the intervention (BMI, Y-BOCS, HAM-A, HAM-D) is the same as the follow-up period.

Supplementary table 2. Number of patients experiencing adverse events probably or possibly related to DBS as reported in the studies

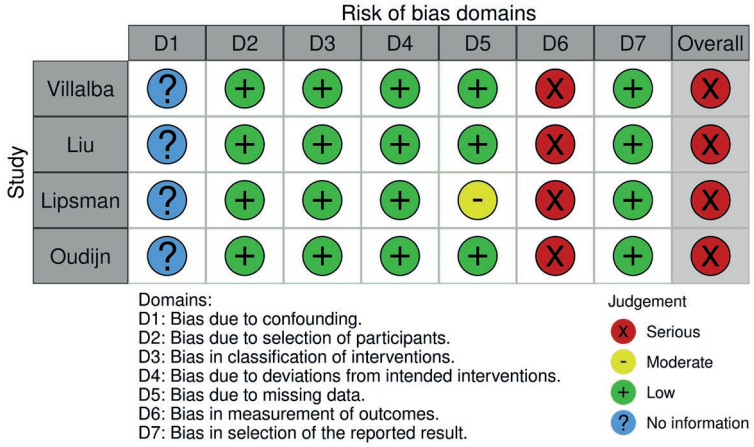
	Villalba et al (N=8)	*Liu et al (N=28)*	*Lipsman et al (N=16)*	*Oudijn et al (N=4)*	*Total / Mean (N=56)*
No adverse events	5 (62·5%)	6 (21·4%)	5 (31·3%)	0 (0%)	16 (28·6%)
Cutaneous complications	3 (5·4%)	-	1 (1·8%)	-	4 (7·1%)
Pain at incision site (<4d)	-	22 (39·3%)	-	-	22 (39·3%)
Pain at incision site (>4d)	-	-	5 (8·9%)	-	5 (8·9%)
Intra-operative panic attack	-	-	1 (1·8%)	-	1 (1·8%)
Hypomanic/manic symptoms	-	-	-	3 (5·4%)	3 (5·4%)
Hypophosphatemia	-	-	1 (1·8%)	-	1 (1·8%)
Nausea	-	-	1 (1·8%)	-	1 (1·8%)
QT prolongation	-	-	1 (1·8%)	-	1 (1·8%)
Seroquel overdose	-	-	1 (1·8%)	-	1 (1·8%)
Increased lead impedance	-	-	1 (1·8%)	-	1 (1·8%)
Worsening mood	-	-	1 (1·8%)	-	1 (1·8%)
Refeeding delirium	-	-	1 (1·8%)	-	1 (1·8%)
Pancreatitis	-	-	1 (1·8%)	-	1 (1·8%)
Seizure	-	-	2 (3·6%)	1*(1·8%)	3 (5·4%)
*Auto-intoxication	-	-	-	3 (5·4%)	3 (5·4%)
*Self-destructive behavior	-	-	-	2 (3·6%)	2 (3·6%)
*Aggressive behavior	-	-	-	1 (1·8%)	1 (1·8%)
*Alcohol consumption	-	-	-	1 (1·8%)	1 (1·8%)
*Water intoxication	-	-	-	2 (3·6%)	2 (3·6%)
*Migraine	-	-	-	1 (1·8%)	1 (1·8%)
*Pain at battery site	-	-	-	1 (1·8%)	1 (1·8%)
*Severe auto mutilation	-	-	-	1 (1·8%)	1 (1·8%)
**Hyponatraemia	-	-	1 (1·8%)	-	1 (1·8%)
**Hypokalaemia	-	-	1 (1·8%)	-	1 (1·8%)

Supplementary table 3. Quality of the evidence of analyses on the effect of DBS on refractory-treatment AN patients

Analysis	*Study design*	*Risk of bias*	*Inconsistency*	*Indirectness*	*Imprecision*	*Publication bias*	*Effect size*	*Final GRADE score*
BMI	+3, non-RCTs	-1	0, no heterogeneity	0	0	0, undetected	+1	⊕⊕⊕⊖ moderate
Psychiatric symptoms	+3, non-RCTs	-2	0, no heterogeneity	0	0	0, undetected	+1	⊕⊕⊖⊖ low



Supplementary figure 1a. Risk of bias of objective measurements of included studies (BMI)



Supplementary figure 1b. Risk of bias of subjective measurements of included studies (psychiatric symptom severity)

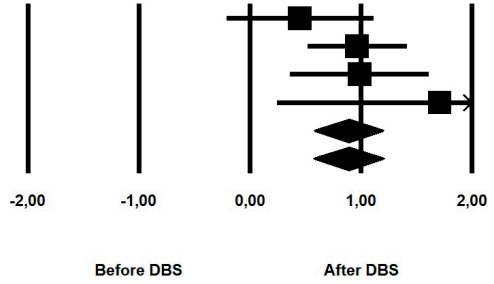
Appendix 1. Search (MEDLINE, Embase, PsycINFO)

1	exp anorexia nervosa/	47913
2	anorexi*.ti,ab,id.	105216
3	exp deep brain stimulation/	59871
4	DBS.ab,ti.	35426
5	(stimul* adj3 (brain or deep)).ab,ti.	72708
6	1 or 2	113152
7	3 or 4 or 5	107874
8	6 and 7	460
9	remove duplicates from 8	290

Appendix 2. List of studies excluded at full-text screening stage

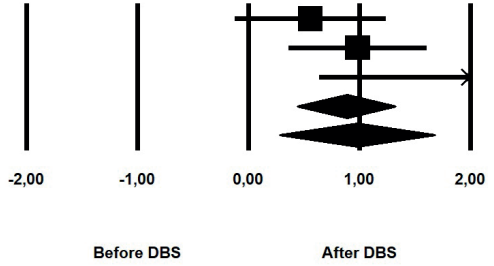
Study	***Reason of exclusion***
A randomized trial of deep brain stimulation to the subcallosal cingulate and nucleus accumbens in patients with treatment-refractory, chronic, and severe anorexia nervosa: Initial results at 6 months of follow up. Martinez G.V., Justicia A., Salgado P., Gines J.M., Guardiola R., Cedron C., Polo M., Delgado-Martinez I., Medrano S., Manero R.M., Conesa G., Faus G., Grau A., Elices M., Perez V.	Same study as Villalba et al.
Nucleus accumbens deep brain stimulation for treatment-refractory anorexia nervosa: A two-year follow-up study. Hu K., Sun B.	Conference abstract, same study as Liu et al.
Study protocol: Using deep-brain stimulation, multimodal neuroimaging and neuroethics to understand and treat severe enduring Anorexia Nervosa. Park R.J., Scaife J.C., Aziz T.Z.	Study protocol
Subcallosal cingulate deep brain stimulation for treatment-refractory anorexia nervosa: A phase 1 pilot trial. Lipsman N., Woodside D.B., Giacobbe P., Hamani C., Carter J.C., Norwood S.J., Sutandar K., Staab R., Elias G., Lyman C.H., Smith G.S., Lozano A.M.	Phase I of included study in meta-analysis, duplicate
Metabolic imaging of deep brain stimulation in anorexia nervosa: A 18F-FDG PET/CT study. Zhang H.-W., Li D.-Y., Zhao J., Guan Y.-H., Sun B.-M., Zuo C.-T.	Metabolic imaging as outcome measure
Six women pilot deep brain stimulation for intractable anorexia nervosa. Anonymous	Anonymous authors, note not an article, same patients as in Lipsman et al.
Deep brain stimulation of the subcallosal cingulate area for treatment-refractory anorexia nervosa: Phase I pilot trial. Lipsman N., Woodside B., Giacobbe P., Hamani C., Lozano A.M.	Phase I of included study in meta-analysis, duplicate
Metabolic imaging of deep brain stimulation in anorexia nervosa: An 18F-FDG PET/CT study. Zhang H.	Metabolic imaging as outcome measure, duplicate
Phase I trial of deep brain stimulation of the subcallosal cingulum for treatment-refractory anorexia nervosa. Lipsman N., Woodside B., Giacobbe P., Hamani C., Lozano A.M.	Duplicate, phase I
Deep brain stimulation for anorexia nervosa - authors' reply. Lipsman N; Woodside DB; Lozano AM.	Authors reply, comment

Model	Time point	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Villalba 2020	Combined 6 months	0,450	0,335	0,112	-0,206	1,107	1,345	0,179
Liu 2020	Combined 24 months	0,965	0,225	0,050	0,524	1,405	4,294	0,000
Lipsman 2017	Combined 12 months	0,985	0,316	0,100	0,365	1,605	3,115	0,002
Oudijn 2021	Combined 12 months	1,709	0,745	0,555	0,249	3,169	2,294	0,022
Fixed		0,890	0,157	0,025	0,582	1,197	5,664	0,000
Random		0,889	0,163	0,026	0,570	1,208	5,467	0,000



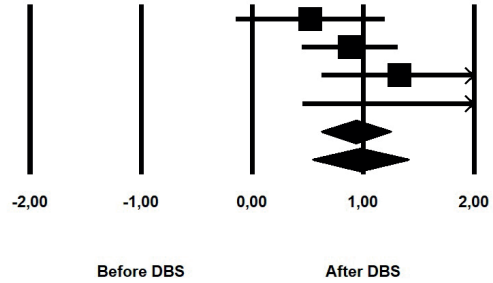
Supplementary figure 2. Forrest plot showing meta-analysis effects of DBS on secondary outcome combined psychiatric symptom severity

Model	Outcome	Time point	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Villalba 2020	YBOCS-EDS	6 months	0,556	0,344	0,118	-0,117	1,230	1,619	0,105
Lipsman 2017	Combined	12 months	0,983	0,313	0,098	0,370	1,596	3,142	0,002
Oudijn 2021	YBOCS-EDS	12 months	2,543	0,970	0,941	0,642	4,445	2,622	0,009
Fixed			0,884	0,225	0,051	0,443	1,325	3,929	0,000
Random			0,978	0,357	0,127	0,278	1,677	2,740	0,006



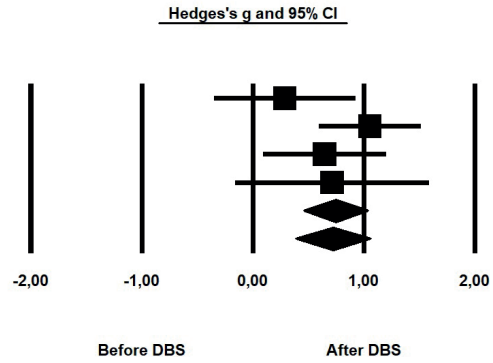
Supplementary figure 3. Forrest plot showing meta-analysis effects of DBS on eating disorder symptoms

Model	Outcome	Time point	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Villalba 2020	HAMD	6 months	0,523	0,340	0,116	-0,144	1,190	1,537	0,124
Liu 2020	HAMD	24 months	0,880	0,218	0,048	0,452	1,307	4,034	0,000
Lipsman 2017	HAMD	12 months	1,327	0,355	0,126	0,631	2,023	3,736	0,000
Oudijn 2021	HAMD	12 months	2,053	0,812	0,659	0,462	3,644	2,529	0,011
Fixed			0,937	0,160	0,026	0,624	1,251	5,860	0,000
Random			0,976	0,220	0,048	0,544	1,407	4,432	0,000



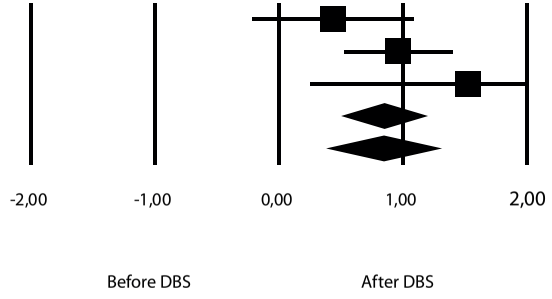
Supplementary figure 4. Forrest plot showing meta-analysis effects of DBS on symptoms of depression

Model	Outcome	Time point	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Villalba 2020	YBOCS	6 months	0,288	0,322	0,104	-0,344	0,920	0,893	0,372
Liu 2020	YBOCS	24 months	1,055	0,232	0,054	0,601	1,508	4,555	0,000
Lipsman 2017	YBOCS	12 months	0,648	0,280	0,078	0,100	1,196	2,317	0,021
Oudijn 2021	YBOCS	12 months	0,714	0,443	0,196	-0,153	1,582	1,613	0,107
Fixed			0,745	0,147	0,022	0,456	1,033	5,059	0,000
Random			0,724	0,173	0,030	0,385	1,062	4,192	0,000



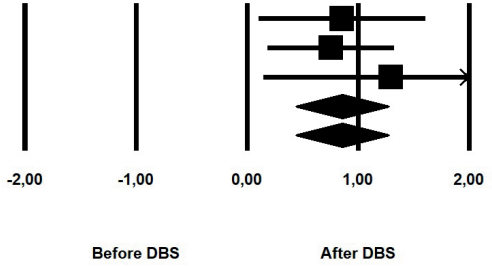
Supplementary figure 5. Forrest plot showing meta-analysis effects of DBS on obsessive-compulsive symptoms

Model	Study name	Outcome	Time point	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Villalba 2020	HAMA	6 months	0,434	0,332	0,111	-0,218	1,085	1,305	0,192
	Liu 2020	HAMA	24 months	0,959	0,224	0,050	0,520	1,398	4,282	0,000
	Oudijn 2021	HAMA	12 months	1,525	0,650	0,423	0,250	2,800	2,345	0,019
Fixed				0,850	0,179	0,032	0,500	1,200	4,760	0,000
Random				0,846	0,239	0,057	0,379	1,314	3,547	0,000



Supplementary figure 6. Forrest plot showing meta-analysis effects of DBS on symptoms of anxiety

Model	Outcome	Time point	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Villalba 2020	SF-36	6 months	0,853	0,380	0,144	0,109	1,598	2,246	0,025
	Lipsman 2017	QOLS	12 months	0,753	0,289	0,084	0,187	1,320	2,606	0,009
	Oudijn 2021	EDQOL	12 months	1,295	0,585	0,342	0,149	2,442	2,215	0,027
Fixed				0,858	0,214	0,046	0,438	1,277	4,006	0,000
Random				0,858	0,214	0,046	0,438	1,277	4,006	0,000



Supplementary figure 7. Forrest plot showing meta-analysis effects of DBS on quality of life

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PART IV

Deep brain stimulation in anorexia nervosa: functional effects

5

Neural effects of deep brain stimulation on reward and loss anticipation and food viewing in anorexia nervosa: a pilot study

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ABSTRACT

Background

Anorexia nervosa (AN) is a severe and life-threatening psychiatric disorder. Initial studies on deep brain stimulation (DBS) in severe, treatment-refractory AN have shown clinical effects. However, the working mechanisms of DBS in AN remain largely unknown. Here, we used a task-based functional MRI approach to understand the pathophysiology of AN.

Methods

We performed functional MRI on four AN patients that participated in a pilot study on the efficacy, safety, and functional effects of DBS targeted at the ventral limb of the capsula interna (vALIC). The patients and six gender-matched healthy controls (HC) were investigated at three different time points. We used an adapted version of the monetary incentive delay task to probe generic reward processing in patients and controls, and a food-specific task in patients only.

Results

At baseline, no significant differences for *reward anticipation* were found between AN and HC. Significant group (AN and HC) by time (pre- and post-DBS) interactions were found in the right precuneus, right putamen, right ventral and medial orbitofrontal cortex (mOFC). No significant interactions were found in the food viewing task, neither between the conditions high-calorie and low-calorie food images nor between the different time points. This could possibly be due to the small sample size and the lack of a control group.

Conclusion

The results showed a difference in the response of reward-related brain areas post-DBS. This supports the hypotheses that the reward circuitry is involved in the pathogenesis of AN and that DBS affects responsivity of reward-related brain areas.

INTRODUCTION

Anorexia nervosa (AN) is a severe and life-threatening psychiatric disorder. Deep brain stimulation (DBS) has been proposed as a promising last-resort treatment option for severe therapy refractory AN-patients (1). A recent meta-analysis showed overall beneficial effects of DBS on weight, eating disorder, depression and anxiety symptoms, as well as quality of life (2). A better understanding of the working mechanisms of DBS in AN would improve our understanding of the pathophysiology AN and enhance DBS therapy by optimizing patient and target selection.

Studies on DBS in AN have explored diverse targets including the subcallosal cingulate cortex (SCC), nucleus accumbens (NAcc) and ventral anterior limb of the internal capsule (vALIC) (1, 3-6). Interestingly, different targets have shown comparable clinical effects, suggesting that DBS is effective at different targets and normalizes wider aberrant network activity in the brain. This aligns with the concept of connectomic DBS, where different DBS targets relate to similar pathophysiologically relevant white matter tracts (7).

One important circuit that may play a role in the clinical effects of DBS in AN is the reward system which has been proposed as a key brain circuit in the pathophysiology of AN (8-17). The reward circuit encompasses multiple brain regions including the ventral striatum, insula and prefrontal cortex. In AN, the reward system processes the *motivation* for eating, the *hedonic* experience of food, and the *value* of specific food items. Neuroimaging studies have demonstrated dysfunctional activation in structures associated with salience and reward networks related to emotional and reward processing, as well as in a cortical cognitive circuit related to selective attention and planning, in both individuals with AN and those who have recovered from the disorder (17). These brain regions are part of the cortico-striatal-limbic neurocircuit, which is also implicated in other reward related psychiatric disorders such as obsessive-compulsive disorder (OCD) (18, 19).

Reward-based neurobiological models suggest that AN is characterized by deficient reward processing and enhanced punishment processing. AN symptoms are thought to be maintained by reward-based learning, where abnormal eating- and weight-related cognitions alter reward processing. One hypothesis is that AN patients have a diminished sense of reward towards food and a decreased motivation for food consumption, (20-22). Additionally, studies have found an exaggerated response to losses in executive and striatal regions using a monetary guessing task (14), as well as increased activation in the insula and cingulate during loss anticipation in a monetary incentive delay task, indicating hypersensitivity to punishment in general (23). It is hypothesized that in AN, cues compatible with the illness (such as weight-loss behaviors, thinness and excessive exercising) become positively associated with reward while healthy cues (such as seeing, tasting and smelling food and foraging behavior) lose their primary rewarding properties,

and instead become aversive (9, 24, 25). These findings are accompanied by studies that have found altered activation in areas associated with cognitive control and rigidity (26).

Despite the importance of the reward circuit in AN and impact of DBS, the effects of DBS on the reward circuit in AN remain unknown. One study demonstrated that DBS reduces maladaptive activity and connectivity of the stimulated regions in OCD patients (27). Previous studies on DBS in AN have used positron emission tomography (PET) to investigate effects of DBS on resting glucose metabolism (4, 28, 29). One study found significant reduced activity of the subcallosal and anterior cingulate and significant hyperactivity of parietal structures including the supramarginal gyrus and cuneus, following treatment with DBS using PET. This suggests that a focal intervention can have a broad effect on neural structures downstream, albeit slightly different, but relevant to key illness-related structures structures (4, 28). An F-FDG PET study in patients with AN showed that the pre-DBS found hypermetabolism in frontal lobe, hippocampus, lentiform nucleus, left insula and left subcallosal gyrus decreased after NAcc-DBS (29). A study using diffusion magnetic resonance imaging (dMRI) and deterministic multi-tensor tractography in patients with AN undergoing DBS identified widely-distributed differences in subcallosal white matter (SCC) connectivity, consistent with heterogenous clinical disruptions (30).
In this study we utilized task-based functional MRI to investigate changes in activity in the cortico-striatal-limbic circuit during an adapted version of the monetary incentive delay (MID) task, employing monetary reward and loss as motivational rewarding stimuli (31). Additionally, we employed a food viewing task, where subjects were presented with high- and low-calorie food pictures and neutral pictures. The MID task was chosen to explore non-food related changes in the reward response, while the food viewing task aimed to examine responses to disease-specific stimuli.

Our hypotheses were twofold:
Patients with AN would exhibit heightened activation in reward-related brain areas in monetary tasks before DBS compared to healthy controls, particularly with regard to losses (indicative of the heightened sensitivity to punishment). We expected this heightened activation to normalize following DBS.
We anticipated increased activation in reward-related areas during the food viewing tasks before DBS, especially in response to high-calorie food pictures compared to low-calorie or neutral pictures. This might indicate a heightened response to aversive cues (high-calorie food pictures) in AN. Additionally, we expected low-calorie pictures to elicit higher activation in the cortico-striatal circuit, as these cues are thought to be rewarding in AN patients. Furthermore, we hypothesized a possible hyperactivation of areas associated with cognitive control in AN before DBS (17, 32). We speculated that aberrant reward-response to high-calorie and low-calorie food pictures would normalize after DBS.

METHODS

Study design

We conducted this study at the Department of Psychiatry and the Department of Neurosurgery of the Amsterdam UMC (Amsterdam University Medical Centers), location AMC (1). The Medical Ethical Committee (MEC) of the Amsterdam UMC, location AMC, approved the study (MEC number: 2012_169). We used an open label intervention clinical trial design. For the monetary reward task, we used a control group, whereas the food viewing task followed a within-subject design.

Participants

Patients were recruited from major clinics specialized in adult eating disorders in the Netherlands. We applied the following inclusion criteria: a clear primary diagnosis of AN (restricting or purging subtype) based on the DSM-IV, confirmed by a psychiatric interview conducted by an independent physician; illness duration of ≥10 years; and BMI <15. Additionally, patients must have shown no response to ≥2 typical modes of treatment, including one hospital admission or inpatient treatment in an eating disorder specialized clinic. They should also have exhibited substantial functional impairment according to the DSM-IV criterion C and a Global Assessment of Function-score (GAF-score) of ≤45 for ≥2 years. The exclusion criteria are described previously (1). This resulted in four female AN-patients who were enrolled from 2016 to 2020. Additionally, data from six healthy control subjects were included from previous (neuroimaging) projects of our department. The control subjects and their first-degree relatives had to have negative lifetime histories of psychiatric illness, as evaluated by SCID I and SCID II interviews. The controls were matched for sex (all female), but not for age (M=54; SD=4.7). The control subjects had no DBS-electrodes implanted and but were scanned at three different time-points.

Procedure

We conducted bilateral stereotactic implantation of DBS electrodes in the ventral anterior limb of the capsula interna (vALIC). Following our earlier DBS studies, we distinguished four sequential study phases: preoperative (T-1), surgery (T0), optimization (3–9 months; T1-T2) and maintenance (12 months; T2-T4). After screening at T-1, bilateral DBS electrodes were implanted in the vALIC at T0. We turned on and optimized DBS settings from T1 to T2, and followed patients up to T4. During the study, patients received standard medical and psychiatric care, which included regular visits with a nurse-practitioner and a psychiatrist. No major psychopharmacological adjustments were made.

Measurements

We conducted fMRI scans at three time-points: 1) pre-operatively at T-1 as a baseline measurement, 2) at the end of the optimization period (T2, to investigate short-term effects of stimulation), and 3) at 12 months after ending the optimization period (T4, at the end of the maintenance phase) (See **figure 1**). For controls, fMRI was conducted at three time-points as well, matching the time intervals of the AN group, however they did not receive DBS treatment. In addition to neurophysiological measures, we closely monitored patients clinically and psychologically during follow-up by means of BMI and psychiatric symptom questionnaires (1) .

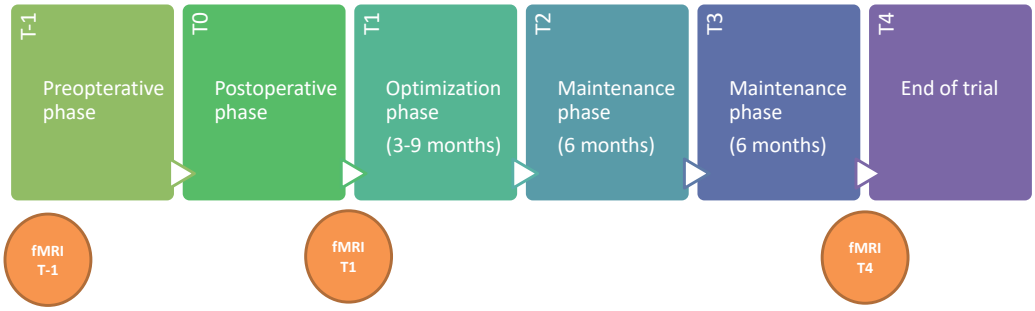


Figure 1. The temporal phases of the DBS treatment with the fMRI time-points at T-1, T2 and T4

Tasks

The monetary reward task used motivational rewarding stimuli (31) in the form of cues predicting a rewarding, neutral or loss outcome. Each condition consisted of three different levels regarding the magnitude of the outcome to motivate participants and enhance reward uncertainty. The presentation of the cues, which constituted the reward anticipation phase, was followed by a target to which participants had to respond as fast as possible. After responding, participants received feedback on their final monetary rewarding, neutral or loss outcome. In case of a positive monetary rewarding outcome, the actual amount of money was provided. Time to respond was limited by individual reaction times collected before the experiment to create equal performance across participants. Trial conditions were counterbalanced at random order (36 trials per condition) and trial durations were randomly varied (6-10s per trial). The total duration of the task was 14 minutes.

During the food viewing task, subjects were presented with images of non-food, high-calorie food and low-calorie food using a paradigm similar to previous studies conducted on both healthy subjects and anorexia patients (21, 33). We used standardized food and neutral pictures from the database developed by Charbonnier e.a. (34). The images were presented over six blocks with a duration of 30s per block. The blocks were pseudorandomized and alternately consisted of

10 images from one condition (non-food, high-calorie or low-calorie). Between blocks, subjects received questions about their desire to eat and level of anxiousness. The total duration of the task was 12 minutes.

Data acquisition

The data were collected using the 1.5 Tesla Siemens Avanto scanner at the Amsterdam UMC (location AMC, department of radiology). To minimize exposure of DBS electrodes to the pulsed radiofrequency field, a transmit and receive head coil was used. DBS was turned off before patients entered the scanner, and the specific absorption rate was limited to 0.1 W/kg. During task performance, the blood oxygen level dependent (BOLD) MRI signal was acquired using a functional T2*-weighted two-dimensional echo-planar imaging sequence (TR = 2000ms, echo time = 30ms, flip angle = 90°, field of view = 230 × 230 mm, matrix = 64 × 64, 25 slices, slice thickness = 4mm, slice gap = 0.4mm).

Data analysis

The MRI data were analyzed using SPM12 (version 6685, Wellcome Trust Centre for Neuroimaging, London, UK) and MATLAB (version R2014a, The MathWorks Inc., Natick, MA, USA). fMRI data preprocessing consisted of realignment, slice-time correction, normalization to Montreal Neurological Institute (MNI) space, resampling to 2 x 2 x 2 mm^3 and spatial smoothing with a Gaussian-kernel of 8 mm full width at half maximum (FWHM). A high pass filter of 1/128 Hz was applied to the data and serial correlations were accounted for using the autoregressive AR(1) modelling. A general linear model (GLM) was used to model the conditions of interest (see below), convolved with a hemodynamic response function (HRF) using 3 regressors related for either the reward task (neutral, reward, loss) or the food task (non-food, high-calorie and low-calorie food), and 6 additional regressors to account for head motion parameters.

For the reward task, the conditions of interest (reward > neutral; loss > neutral) were specified in first-level modelling, including the onset and duration of anticipation cues. A second-level full factorial design was created, combining time (T-1, T2, T4), group (AN, controls) and condition (reward > neutral, loss > neutral). The interaction effects between group and time were investigated for both reward and loss anticipation separately.

For the food task, the non-food, high-calorie food and low-calorie food conditions were modeled as box-car regressors at first-level, and a second-level repeated measures ANOVA design was created,combining time (T-1, T2, T4), and condition (high-calorie food > non-food, low-calorie food > non-food). The interaction effects for time and condition were investigated within subjects. The results for both tasks were masked to exclude voxels with DBS-related signal dropout in the normalized EPI scans.

First, an assessment was made of significant differences between the two post-operative sessions. As we did not observe significant group by time interactions when comparing the two post-DBS timepoints (T2, T4), we created a contrast in which both post-DBS time points were equally

weighed against the pre-DBS time point (T-1) to improve statistical power.

A region of interest (ROI) analysis was performed for the ventral striatum (VS) and the medial orbitofrontal cortex (mOFC). These regions were chosen *a-priori* based on their strong relation to reward processing (13), their role in AN pathology and their previous use in AN-fMRI-studies (14-16). Furthermore, the VS was also the target of DBS. The VS was based on peak-coordinates from a previous study using a similar monetary reward task (17). The mOFC was based on the IBASPM 71 atlas in the WFU Pickatlas toolbox in SPM12. Voxel-wise statistical tests were family-wise error (FWE) rate corrected for multiple comparisons ($p<0.05$) across the whole-brain at the cluster level using a height-threshold of $p<0.001$ or for ROIs at the voxel level using a small volume correction (SVC) (35).

RESULTS

Sample characteristics

Four patients with treatment-refractory AN were included in this study and underwent DBS of the vALIC, during 12 months follow-up. Mean age was 39 (SD=10) and illness duration 21 years (SD=3). All patients were female and suffered from binge-purging subtype of AN. Average BMI at baseline was 12.5 (SD=1.0) kg/m^2, indicating extremely severe AN. All patients suffered from psychiatric comorbidities. Two patients were diagnosed with personality disorder not otherwise specified (PD-NOS), one patient was diagnosed with major depressive disorder (MDD) and one patient was diagnosed with both PD-NOS and MDD. All demographic characteristics are shown in **table 1**.

Table 1. Patient's demographics.

	Sex	*Age at onset (years)*	*Age at surgery (years)*	*Illness duration (years)*	*Anorexia Subtype*	*BMI (screening)*	*BMI (Historic low)*	*Psychiatric comorbidities*	*Psychiatric medication at surgery*
Patient 1	f	15	32	18	Purging	12.4	9.5	GAD, Depression, Personality Disorder NOS	Aripiprazole, Quetiapine, Oxazepam
Patient 2	f	15	39	24	Purging	11.2	10.2	SUD*, Personality Disorder NOS	Aripiprazole, Quetiapine, Oxazepam
Patient 3	f	14	33	19	Purging**	13.4	10.6	Depression, OCD, BPD	Venlafaxine, Clorazepate, Oxazepam, Temazepam
Patient 4	f	27	53	24	Purging	13.1	9.7	Personality Disorder NOS	Citalopram, Alprazolam, Zolpidem
Mean (SD)		18 (6)	39 (10)	21 (3)		12.5 (1.0)	10.0 (0.5)		

(BMI= Body Mass Index, f= female, GAD= Generalized Anxiety Disorder, OCD=Obsessive Compulsive Disorder, NOS= Not Otherwise Specified, SUD= Substance use disorder and BPD=Borderline Personality disorder) *The substance in question was alcohol, at screening this was in remission. ** Important to note that for purging this patient used ± 50 Bisacodyl.

At time-point T1 for the AN-patients, monopolar DBS at the middle two contacts was switched on, with a pulse width of 90µsa and a frequency of 130ms, at a mean voltage of 3.0V (2.5–3.5V). The mean voltages at T2, T3 and T4 were 3.8V (3.0–5.0V), 3.8V (3.0–4.5V) and 3.8V (2.7–4.8V) respectively. Adjustment of the stimulation intensity occurred in steps of 0.5V, with later fine-tuning in steps of 0.1V. Pulse width and frequency remained unchanged during the study.

We previously published the primary outcomes of this study(1). In our findings, we observed a significant increase in BMI at the end of the follow-up period (5.32 kg/m^2; +42.8%; P=.017). This increase in BMI was primarily seen in two out of the four patients (subject 2 and subject 3) (see **figure 2**). Additionally, we found significant decreases in psychiatric symptom questionnaire scores, which measured eating disorder symptoms, depression and anxiety.
During the intraoperative period, no adverse events were observed. However, we recorded 28 severe adverse events (SAEs), with two being probably related((hypo)manic symptoms) and nine being possibly related (self-destructive behavior)to the intervention. It is worth noting that most of the SAEs were related to the (somatic) severity of AN rather than DBS (n=11).

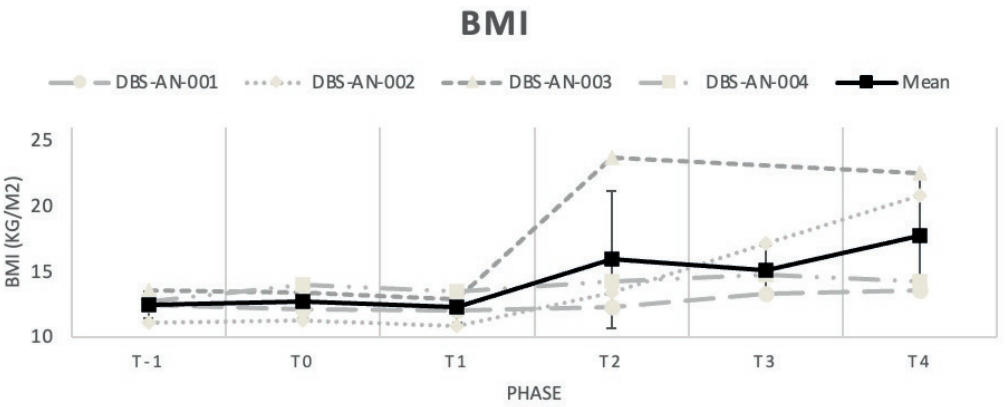


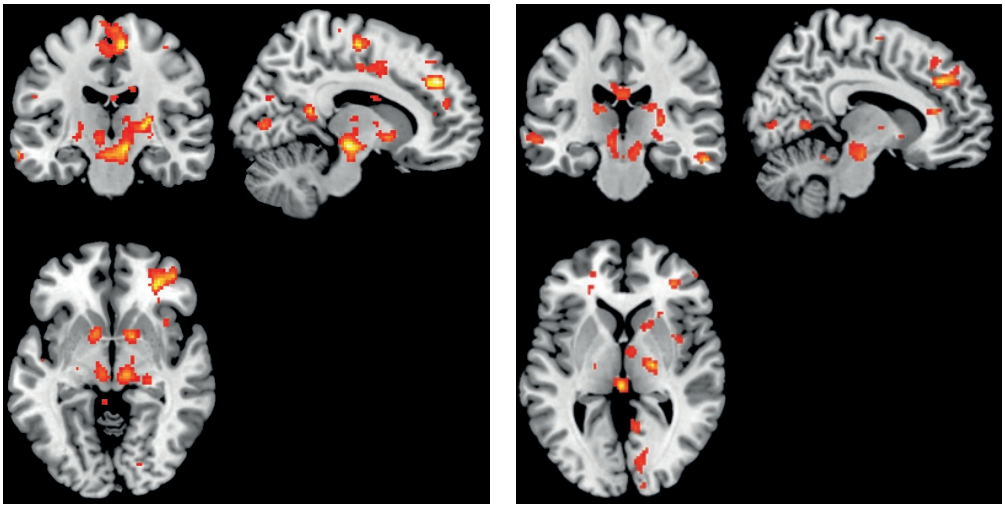
Figure 2. Time course of DBS-induced BMI (fixed effects ± SE).

Linear mixed model analyses showed a significant linear effect of time on BMI (43.16±15.96, CI 95% 9.07-77.25, t=2.704, P=.017).

This figure was originally published in Oudijn MS et al. Deep brain stimulation of the ventral anterior limb of the capsula interna in patients with treatment-refractory anorexia nervosa. Brain Stimul. 2021;14(6):1528-30

Neuroimaging results

Monetary incentive delay task - The MID task revealed a main effect of reward anticipation, showing higher activation n the bilateral thalamus, ventral striatum, insula, medial prefrontal cortex and brain stem during the anticipation of reward compared to neutral cues (See **figure 3a**). The threshold of p<0.01 uncorrected for visualization purposes was used. Similarly, the main effect of loss anticipation also showed activation in the same regions (See **figure 3b**).

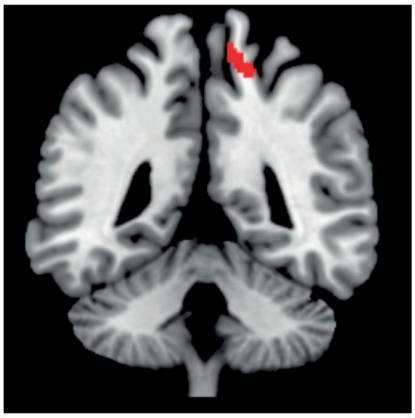


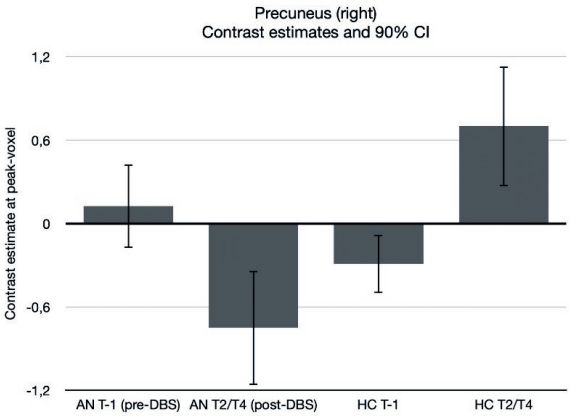
a. Main effects reward anticipation

b. Main effects loss anticipation

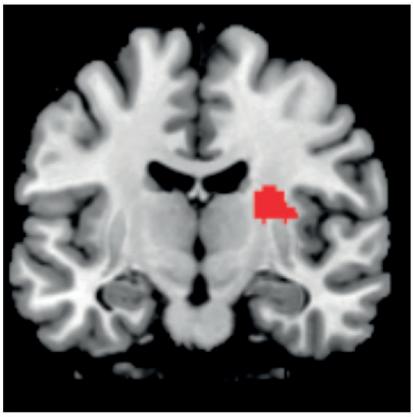
Figure 3. Main effects of task illustrated for AN and HC combined at all timepoints, using a threshold of p<0.01 uncorrected for visualization purpose.

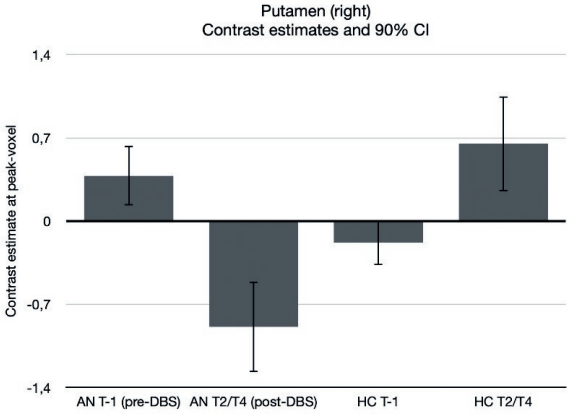
At baseline (pre-DBS, T-1), no significant differences in *reward anticipation* were found between AN and HC. However, significant group (AN and HC) by time (pre- and post-DBS) interactions were found in the right precuneus (xyz=16,-44,60; Z=3.99; p-FWE=0.035; cluster size=132), right dorsal putamen (xyz=26,-10,16; Z=4.69; p-FWE=0.025; cluster size=169), right ventral striatum (xyz=8,0,-6; Z=3.64; p-SVC=0.030), and mOFC (xyz =-2,32,-22; Z=3.55; p-SVC=0.043) (See **figure 4** and **table 2**). Follow-up testing revealed that the interaction effects in the precuneus, putamen and VS could be explained by lower activation for AN post-DBS compared to pre-DBS, whereas in HC, there was higher activation (right precuneus (xyz=12,-42,64; Z=3.97; p-FWE=0.058; cluster size=135), right putamen (xyz=26,-10,16; Z=4.08; p-FWE=0.020; cluster size=85) and right VS (xyz=8,0,-6; Z=3.50; p-SVC=0.041). The interaction effect in the mOFC could be explained by higher activation for AN post-DBS compared to pre-DBS, while in HC, activation was lower (xyz =-2,32,-22; Z=3.55; p-SVC=0.043).



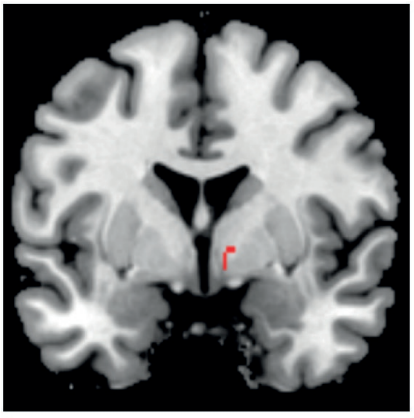


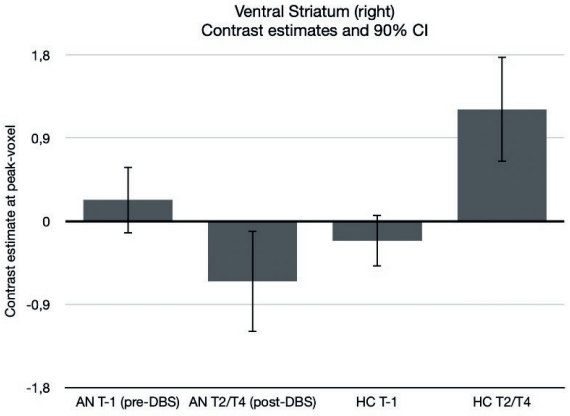
a. Right precuneus



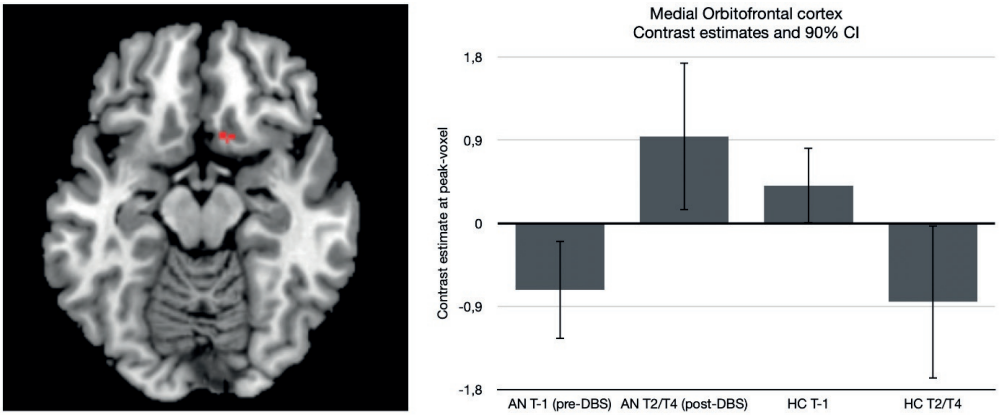


b. Right putamen





c. Right ventral striatum



d. Medial orbitofrontal cortex

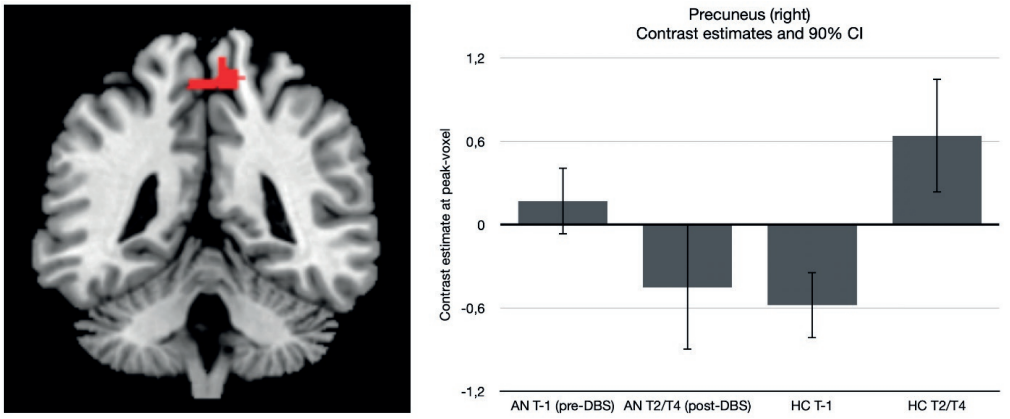
Figure 4. Significant interaction effects for reward anticipation for each anatomical region displayed at p<0.001, uncorrected (left) and corresponding bar plots displaying the contrast estimates for the interactions at the peak voxels (right).

Table 2. Significant interaction effects for reward anticipation, pre- and post-DBS are compared for AN versus HC. The direction of the effect is illustrated by an increase or decrease for the AN group post-DBS.

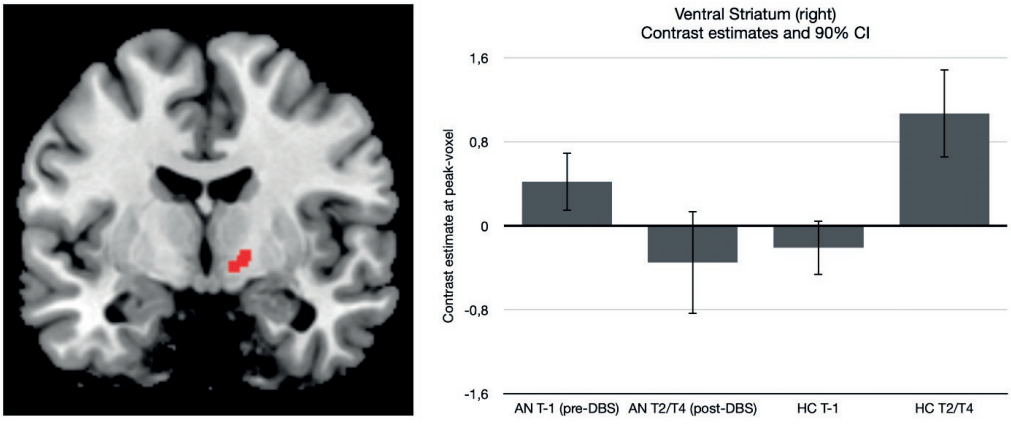
Anatomical region	*Time point*	*Effect ↑ increase ↓ decrease*	*Cluster size*	*MNI-coordinates*			*Statistics*	
				x	*y*	*z*	*Z-score*	*p-value*
Precuneus R.	Post-DBS	AN ↓	132	16	-44	60	3.99	0.035
Putamen R.	Post-DBS	AN ↓	169	26	-10	16	4.69	0.025
VS R.	Post-DBS	AN ↓	N/A	8	0	-6	3.64	0.030*
mOFC	Post-DBS	AN ↑	N/A	-2	32	-22	3.55	0.043*

* p-value after small volume correction (SVC)

At baseline (pre-DBS), no significant differences for *loss anticipation* were found between AN and HC. However, significant group (AN and HC) by time (pre- and post-DBS) interactions were observed in the right precuneus (xyz = 10,-44,64; Z = 4.15; p-FWE = 0.007 ; cluster size = 222) and the right VS (xyz=12,-4,-4; Z=3.75; p-SVC=0.021) (See **figure 5** and **table 3**). These interactions could both be explained by significantly lower activation for AN post-DBS compared to pre-DBS, while activations were higher in the HCs, especially in the right precuneus (xyz = 10,-44,64; Z = 4.15; p-FWE = 0.007 ; cluster size = 222) and right VS (xyz=12,-4,-4; Z=3.89; p-SVC=0.012).



a. Right precuneus



b. Right ventral striatum

Figure 5. Significant interaction effects for loss anticipation for each anatomical region displayed at p<0.001, uncorrected (left) and corresponding bar plots displaying the contrast estimates for the interactions at the peak voxels (right).

Table 3. Significant interaction effects for loss anticipation, pre- and post-DBS are compared for AN versus HC. The direction of the effect is illustrated by an increase or decrease for the AN group post-DBS.

Anatomical region	*Time point*	*Effect ↑ increase ↓ decrease*	*Cluster size*	*MNI-coordinates*			*Statistics*	
				x	*y*	*z*	*Z-score*	*p-value*
Precuneus R.	Post-DBS	AN ↓	222	10	-44	64	4.15	0.007
VS R.	Post-DBS	AN ↓	91	12	-4	-4	3.89	0.012*

* p-value after small volume correction (SVC)

Figure S1 (supplementary material) illustrates that the ROI in the ventral striatum is located outside the regions that are affected by signal dropout from the DBS electrode.

Food viewing task - No significant interactions were found between the conditions of high-calorie and low-calorie food images. Therefore, both conditions were combined as one food condition for further comparisons. Additionally, no significant interactions were found between the different time points, indicating that we did not find evidence for altered responses for food viewing between the pre- and post-DBS time points.

DISCUSSION

The present study investigated the neurobiological effects of vALIC DBS in AN patients using two tasks: the monetary incentive delay task and a food viewing task. The monetary incentive delay task was usedto study non-illness-specific food related reward-processing, while the food viewing task focused on more illness-specific reward processing. We hypothesized that AN-patients would show higher activation than HCs in reward-related brain areas during the monetary tasks pre-DBS, especially with losses -indicative of the heightened sensitivity to punishment in AN- and that this activation would normalize following DBS. We expected to find similar effects in the illness-specific task.

In contrast to other studies (21, 22), we did not observe differences between AN patients and controls at baseline. However, we did find changes in the frontostriatal circuit during reward and loss anticipation in AN patients, with a decrease in right precuneus, right putamen and right VS activation, and an increase in mOFC activation following DBS. Conversely, increases in activation were seen in the HC group over time. These findings indicate a difference in response in het AN group after treatment with DBS.

The VS mediates reward, reinforcement and motivational salience. In response to both monetary and visual food cues, AN patients show hypoactivity of the striatum (36). Our hypothesis was that in AN, there would be hyperactivity of the reward system in response to illness-compatible cues (including punishment) and less increased activity of the reward system in response to immediate rewards. The decreased activation of the right VS following DBS suggests a normalization of aberrant hyperactivity of the VS to reward and punishment, possibly indicating restoration of goal-directed rather than illness-compatible behavior.
The mOFC, a subregion of the ventromedial prefrontal cortex, is linked to cognitive flexibility and context-specific responding, encoding emotional and reward value in decision-making. The fact that we found an increase in mOFC activation following DBS seems contradictory to the hypothesis that excessive cognitive control would decrease after treatment. One possibility is

that the mOFC activity increases after DBS due to changes in other parts of the reward circuitry, leading to increased contingencies. Another explanation for the increase in mOFC activation following DBS could be that patients have improved in valuating outcome relative to context.
The above findings are in line with a study on DBS and OCD that showed that DBS targeted at the nucleus accumbens (NAc; part of the VS) normalized NAc activity and restored pathological network activity (27).
The precuneus is implicated in self-processing and agency. Decreased activity of the precuneus after DBS might indicate an increase in non-self-referential goal-directed behavior and a restoration of the brain default network.

Despite our hypothesis of increased activation in reward-related areas in the food viewing tasks with explicit rating, especially with high-calorie food pictures compared to low-calorie pictures, the results did not show any significant pre- and post DBS differences in activation in response to all pictures. This could be possibly due to the small sample size and the lack of a control group.
Both the literature and our study support the hypothesis regarding the involvement of the reward circuitry in the pathogenesis of anorexia nervosa. However, reward processing is heterogeneous and is influenced by emotions such as fear and body image perception. Furthermore, it remains unclear whether aberrant activation in specific areas is related to reward or punishment, which should be examined in future research. Nevertheless, the correspondence of our results for reward and punishment anticipation suggests that the effects of DBS may be generic for motivational behavior.

In healthy controls, hunger enhances sensitivity to and motivation for reward. However, remitted AN patients do not show the same increased activation in reward salience circuitry during the processing of immediate reward when hungry, nor do they show increased activation in the cognitive control circuitry when satiated, as observed in healthy controls (22). We conducted the fMRI scans in a non-fasted state. However, it is difficult to assess whether a non-fasted state in AN patients equates to being sated, and vice versa. We did assess hunger with a visual analogue scale in the AN group, but all patients rated their hunger as low to absent, regardless of previous food intake or fasting. As a result, we could not determine whether hunger, as an enhancer of motivational drive, influenced the outcomes this study.

The differences in outcomes in our study compared to other imaging studies (4, 29), which found reduced activity of the subcallosal and anterior cingulate, and hyperactivity of parietal structures, as well as decreased activity in the frontal lobe, hippocampus, lentiform nucleus, left insula, and left subcallosal gyrus after DBS, could be explained by the fact that those studies used resting-state PET instead of task-based fMRI. The differences in results could, therefore, be attributed to investigating tonic activity (PET) versus phasic activity (fMRI), which may occur at the same time.

Limitations of our study include the small sample size, which is a result of the highly specific setting and population of the study (an experimental intervention study in physically compromised patients), leading to very low power. Moreover, the food viewing task was even more underpowered due to the lack of a control group, which precluded testing for group x time interactions. Due to the small sample we were unable to link changes in activation patterns to clinical effect, symptoms and/or behavior.

Future directions

To gain more insight into the involvement of the reward circuitry in the etiopathogenesis and treatment of AN, larger neuroimaging studies should be conducted. It is also of great importance to develop ways to link neuroimaging data to clinical/behavioral data. Future studies on DBS in AN should include (functional) neuroimaging using more disease-specific tasks to better understand the differences in reward response to clinical features of AN. This could contribute to the knowledge of the etiopathological mechanisms in AN and the functional effects of DBS. Forming an international collaboration to conduct fMRI on a larger group of AN patients treated with DBS or a transdiagnostic approach comparing DBS in AN with DBS in OCD or MDD would be valuable for investigating possible individualized DBS-targeting.

Conclusion

The aim of our fMRI study was to investigate the effects of reward-circuitry targeted DBS in AN patients. We conducted functional MRI scans pre and post DBS and found differences in the response of reward-related brain areas post DBS. This supports the hypothesis that the reward circuitry is involved in the pathogenesis of anorexia nervosa and that DBS influences aberrant network activity. Further neuroimaging studies on DBS in AN with larger sample sizes, a more disease-specific paradigm, and a sham control condition should be considered.

SUPPLEMENT 1

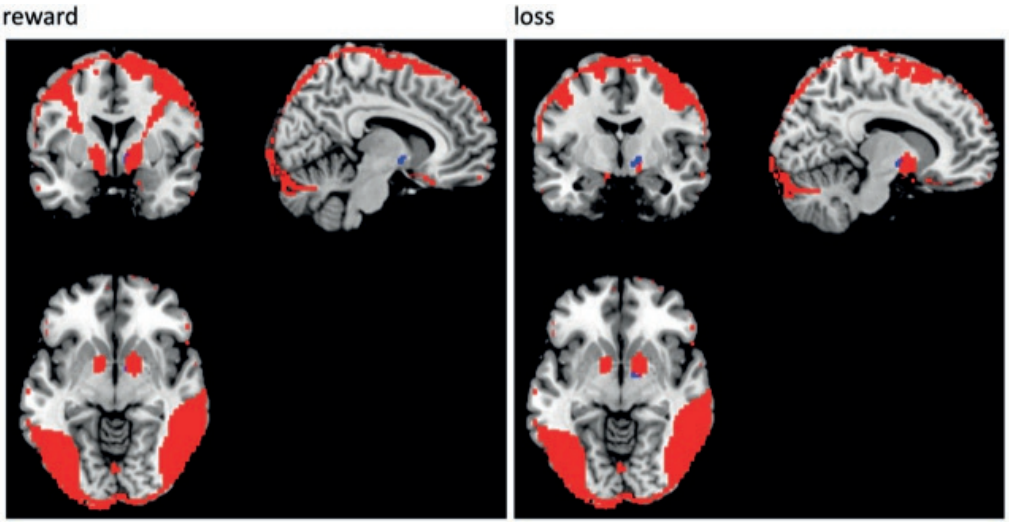


Figure S1. This figure illustrates that the ROI in the ventral striatum (blue) is located outside the regions that are affected by signal dropout form the DBS electrodes (red).

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6

Electrophysiological effects of deep brain stimulation in anorexia nervosa

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In submission

ABSTRACT

Objective

To study deep brain stimulation (DBS)-induced electrophysiological changes over time in patients with anorexia nervosa (AN).

Methods

We performed EEG recordings on 4 AN patients treated with DBS at 3 time points, and on 8 age-matched controls. We extracted oscillatory power in the alpha and beta bands, connectivity and global network organization parameters based on graph theory.

Results

We found strong significant within-subject changes in alpha and beta power over time. Nominally significant effects were observed for posterior L alpha (p=0.034) and anterior/posterior L scalp areas (p=0.034 and p=0.013, respectively), however, multiple testing indicated that the effects are heterogeneous across subjects. We found V-shaped curves over time for average functional connectivity. This was largely re-established at the final time-point. The graph-theoretical measures showed similar V-shaped effects consistent with an initially disordered network state.

Conclusion

Within-subject effects of stimulation were large, widespread over frequencies, and visible across wide brain areas and networks. Prolonged stimulation seemed to reinstate organization in the functional brain networks. Our results support the observations that effects of DBS are not merely local, but influence widespread pathological network activity and that, after an initial period of disorganisation, the brain adapts to the stimulation.

Significance

A better understanding of the electrophysiological effects of DBS may allow us to personalize and optimize the intervention and thereby further improve effectiveness in AN.

INTRODUCTION

Anorexia nervosa (AN) is a severe and potentially life-threatening psychiatric disorder. Deep brain stimulation has been performed as last resort treatment option for severe therapy refractory AN-patients (1). A recent meta-analysis in AN showed beneficial overall effects of DBS on weight, quality of life, and eating disorder, depression and anxiety symptoms (2). The studies on DBS in AN used diverse targets including the subcallosal cingulate (SC), nucleus accumbens (NAc), and the ventral part of the anterior limb of the internal capsule (vALIC) (1, 3, 4). These targets differ in nature and known function. The SC and NAc both consist of grey matter and are part of the limbic and reward network, respectively. The vALIC however consists of white matter fibres with widespread cortico-striatal projections. All different targets showed comparable clinically relevant average effects. The working mechanisms of DBS in AN via stimulation of the various target areas remain largely unknown, but it is hypothesized that DBS in obsessive compulsive disorder (OCD) resets the neural output of the stimulated area by overriding disruptive oscillatory communication between network nodes (5).

Although overall DBS treatment in AN was considered promising, not all individual patients included in the DBS studies showed a response. This may be because the DBS target and stimulation paradigm were sub optimally tailored to the brain network disruptions present in each individual patient (6). A better understanding of the underlying effects of DBS may allow us to personalize and optimize the intervention and thereby further improve effectiveness. This requires a basic understanding of the effects of DBS in the functioning brain. Our aim is to investigate this using electrophysiological recordings that capture the oscillatory activity that drives long distance communication in the brain (7, 8).

Earlier studies that investigated the electrophysiological effects of DBS did so in psychiatric disorders other than AN (9). For example, electroencephalography (EEG) changes - including increased frontal theta concordance- after DBS of the vALIC target in major depression disorder (MDD) patients predicted later clinical outcome (10). In OCD reduction of frontal low-frequency oscillations was associated with symptom improvement (11). Establishing similarly predictive EEG changes may be particularly useful in AN, because clinical effects such as weight gain and symptom improvement cannot always be observed immediately and may require more prolonged therapeutic periods (1).

To the best of our knowledge, there are no existing EEG studies following DBS in AN yet. There are some indications about the differences in electrophysiological changes in resting brain activity in AN compared to healthy controls (HC). For example, AN patients show evidence of a decreased alpha/increased beta complex as well as elevated theta power, in addition to an altered processing of stimuli related to food and body image (12-15). Geisler et al. showed

altered global brain network architecture in AN characterized by increases in path length (longer routes between nodes) and assortativity (more nodes with a similar connectedness link together) indicating wide-scale disturbance in information flow across brain networks. Furthermore, this study found locally decreased connectivity strength and increased path lenghts (16). It remains undecided to what extent these findings can be explained by indirect effects (e.g., metabolic changes induced by malnutrition, or sleep disturbances), or direct effects (i.e., as a biomarker of the psychopathology itself). It is also unknown whether these electrophysiological biomarkers are affected by DBS treatment. One neuroimaging study by Zhang et al. used PET/CT to study brain glucose metabolism in six AN patients treated with NAc DBS. After DBS, hypermetabolism in the frontal lobe, hippocampus, and lentiform nucleus decreased (15). Another, by Lipsman et al., investigated the effect of SC DBS on cerebral glucose metabolism with PET and found significant reduced activity of the subcallosal and anterior cingulate and significant hyperactivity of parietal structures including the supramarginal gyrus and cuneus, showing that a focal intervention like DBS can have a broad effect on neural structures downstream from the stimulation site in key illness-relevant structures (3, 17). Recently a pioneering magnetoencephalographic study on the effects of DBS in AN preliminary showed an increase in alpha power, as well as evoked power at latencies typically associated with visual processing, working memory, and contextual integration in DBS ON compared to OFF. Furthermore, an increase in evoked power at P600-like latencies as well as an increase in γ-band phase-locking over anterior-to-posterior regions were observed for high- compared to low-calorie food image only in ON sessions. These findings indicate that DBS modulates neuronal process in regions far outside the stimulation target site and at latencies possibly reflecting task specific processing (18).
The precise electrophysiological correlates of the observed coarser metabolic effects remain unclear and it is unknown how local stimulation of the vALIC with DBS affects the global network structure away from the pathological state (19).

Our aim was to investigate how vALIC DBS affected local and global cortical activity and network organization. In our study, we compared four patients with severe treatment-refractory AN to eight matched healthy controls at baseline. In addition, we investigated the long term effects of DBS by following the patients for over up to two years during the course of DBS treatment, measuring their resting-state brain activity before DBS, after the optimization period, and after 12 months. From these recordings we derived the main oscillatory parameter of EEG power, which reflects the level of synchronicity of the dendritic post-synaptic potentials on a mesoscale of neuronal clusters in the cortex and their spread along the apical dendrite that result in current sinks and sources, that we expect to be affected by longer term DBS (20). In addition, we assessed how DBS affects brain communication by extracting properties that reflect global network organization, based on connectivity and graph theoretical measures (21). Describing the brain with network parameters has shown that there are non-random properties to how distant brain areas are organized, with a system of highly connected hubs of (multimodal) association cortical areas

that form a so-called robust rich-club (22, 23). Network measures further reflect optimality of the network organization, specifically the level of organization (inversely related to disorganisation and randomness of the network) and integration (reflecting the level of information exchange in the brain network). We expect that DBS affects the communication between brain and therefore network organization.

The combined data allowed for both between-subject comparisons and within-patient change in brain network organization. We hypothesized that DBS causes changes in electrophysiological power spectra over time, and influences global graph parameters that describe optimization of communication within in the functional brain network.

METHODS

Study design

As described previously (1) we conducted this study at the departments of psychiatry and neurosurgery of the Amsterdam University Medical Centers (Amsterdam UMC) location Academic Medical Center (AMC). The Medical Ethical Committee (MEC) of the Amsterdam UMC approved the study (METC AMC: 2012_169). We used an open label intervention clinical trial design, with the additional comparison of baseline pre-DBS values of patients to a matched control group in a patient-control design.

Participants

We recruited patients from the major clinics specialized in adult eating disorders in the Netherlands. We applied the following inclusion criteria: clear primary diagnosis of AN (restricting or purging subtype) based on the DSM-IV, confirmed by a psychiatric interview by an independent physician; illness duration ≥10 years; lack of response to ≥2 typical modes of treatment including one hospital admission or inpatient treatment in an eating disorder specialized clinic; substantial functional impairment according to the DSM-IV criterion C and Global Assessment of Function (GAF-score) ≤45 for ≥2 years; and BMI <15. Other in- and exclusion criteria are described previously (1).
In addition, we recruited eight healthy control subjects from previous (neuroimaging) projects of our department and by advertisements. The control subjects were matched in age and gender, were right-handed and had to have a BMI between 18.5 and 25. The control subjects and their first-degree relatives had to have negative lifetime histories of psychiatric illness.

Procedure

Following our earlier DBS studies on OCD and MDD (24, 25), we distinguished four sequential study phases: preoperative (T-1), surgery (T0), optimization (3–9 months; T1-T2) and maintenance (12

months; T3-T4). After screening (T-1) we stereotactically implanted bilateral DBS electrodes model 3389, connected to an infraclavicular Activa PC neurostimulator (Medtronic, Minneapolis, USA), in the vALIC as visible on 3D reconstructed anatomical MRI-scans, 3-4 mm anterior to the anterior commissure, with a slight anterior angulation (T0). We turned on and optimized DBS settings from T1 to T2, and followed patients up to T4. During the study patients received standard medical and psychiatric care, comprising of regular visits with a nurse-practitioner and a psychiatrist. No major psychopharmacological adjustments were made.

We obtained EEG recordings in patients at T1 (unstimulated but post-operative so as to remove confounding from surgery), at the end of the optimization period (T2, to investigate short term effects of stimulation), and at 12 months after ending the optimization period (T4, at the end of the maintenance phase) (See figure 1). For controls, we obtained EEG recordings once.

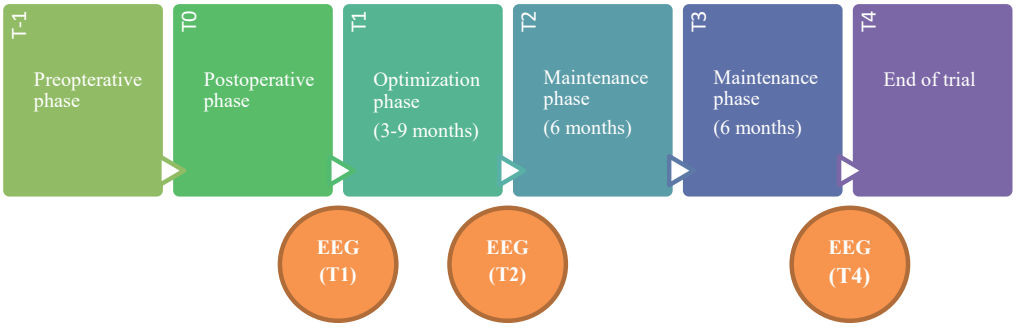

Figure 1. The temporal phases of the DBS treatment with the timepoints of EEG at T1, T2 and T4

We closely monitored patients clinically and psychologically during the study. Primary and secondary outcomes and adverse events were published by Oudijn et al. (1).

EEG recording and pre-processing

Resting-state EEG recordings were obtained while patients were comfortably seated. All participants were instructed to keep their eyes open for 3 minutes and closed for a consecutive 3 minutes. For patients, resting-state EEG was obtained in two states, namely, with DBS on and DBS turned off consecutively. Only the data for DBS off are used in the current protocol.

EEG was recorded using an ANT Eego system (ANT Neuro, The Netherlands) with 64 Ag/AgCl electrodes in a 10/10 montage, which included 62 EEG cannels plus two mastoid electrodes. Fpz served as ground electrode. Faulty channels (disconnected) were removed as well as highly noisy channels based on near-zero and extreme standard deviations of the detrended signals. Next, recordings were offline rereferenced against an imputed unipolar infinite reference via

reference electrode standardization technique (REST) following Yao (2001) (26) and Yao e.a. (2019) (27). Recordings were cleaned in EEGLAB and selected plugins using the following steps. First data were filtered, then subjected to an initial independent components analysis (28). IClabel (29) was used to identify eye components and removed. Next, data were cleaned using the artefact subspace reconstruction (ASR) (30). Next, a full ICA was performed and remaining artefactual components identified with ICLabel, removing Eye, Heart, line noise, and muscle artefacts identified with 50% certainty or above. Finally, missing or deleted channels were back-imputed using spherical interpolation.

EEG processing

Power spectra were obtained using fast Fourier transform (FFT). From these, individual alpha and beta power were derived as average power from 8 to 13 Hz and 14 to 20 Hz respectively. This was done for segments of EEG data of 1s epoch to obtain multiple measures for each individual.

Connectivity was established using coherence and weighted PLI (31) between all possible pairs of signals for the same frequency bands (alpha, beta). Global graph metrics -average connectivity, average path length, diameter, rich-club metric, and assortativity- were extracted from the resulting 62 x 62 connectivity matrices based on alpha and beta oscillations using the MITGraph-Toolbox (32). For a full overview of what these metrics represent we refer to Stam (2014) (21). We use the nondirected weighted network versions of all metrics. Average connectivity reflects the average level of alpha or beta band synchronicity seen between all possible pairs of electrode signals, and may measure the average amount of integration between the distant brain areas. Path length is the graph metric that is inversely related to the level of functional integration of the network (19) and thus the optimality of communication between brain areas for information transfer (21). Diameter is also a related concept, but reflects the maximal distance in the graph. The rich-club metric detects whether there is a community of nodes that preferentially connect to each other, while remaining nodes are precluded from forming a similar club. Rich-club networks are well connected (highly integrated) while maintaining a substantial level of robustness to attacks (i.e. less-of-function when specific brain areas are lost) (22, 33). Assortativity reflects the tendency for nodes to connect to nodes of similar degree. Biological networks often show disassortativity, where high degree nodes preferentially link to low degree ones. Combined, all metrics vary across particular network topologies, specifically, disorganized random networks, rich-club networks, and hierarchically organized scale-free networks.

Statistical analyses

The data were analysed with statistical techniques accommodating the nature of the data (multiple measures per person for EEG power; single measure per person for network and graph measures) and the different comparisons (within-subject / repeated measures over time / between subjects). Within-subject comparisons were performed only for the power data in 1s

epochs across time (i.e. with multiple observations per person). Repeated-measures comparisons were used to test effects over time, which was performed in two ways. First, we used repeated measures model to compare change of power (alpha and beta bands) over time within the patient group. When power was first averaged across channels in four regions (anterior L and R, posterior L and R), the results were Bejamini-Hochberg False Discovery Rate (FDR) corrected for the eight band x region combinations. The second method for repeated effects compared difference scores of T2-T1 and T4-T1 (which were FDR corrected with across channels for multi-channel comparisons). These were tested against an alpha level of 0.05/2 to correct for the two comparisons across time. Between-subject analysis was performed to test for significant effects of AN against HC. For graph parameters (single observation per person) simple t-tests were used to compare cases versus controls. Comparing band power (alpha, beta) between AN (at T1) and HC was performed on the power averaged across channels within four regions, using simple t-tests and corrected for the eight band x region combinations. Finally, power spectra were also compared between cases and controls for alpha peak frequency differences by averaging the spectra over the regions (see above) and tested with simple t-tests using FDR corrected for the eight band x region combinations.

RESULTS

Sample characteristics

From 2016 to 2020, four female AN patients were enrolled. Mean age was 39 (SD=10) and illness duration 21 years (SD=3). Average baseline BMI was 12.5 (SD=1.0) kg/m^2, indicating extremely severe AN. Eight control subjects were matched for age. The controls had a BMI between 18.5 and 25 kg/m^2, were right-handed, and had no history of mental illness.

As reported earlier, in the patient group, at T1, monopolar DBS using the middle two contacts was switched on (pulse width 90µs, frequency 130ms) at a mean voltage of 3.0V (2.5–3.5V). The mean voltages at T2, T3 and T4 were respectively 3.8V (3.0–5.0V), 3.8V (3.0–4.5V) and 3.8V (2.7–4.8V). Adjustment of the stimulation intensity occurred in steps of 0.5V, later fine-tuning in steps of 0.1V. Stimulated contacts, pulse width and frequency remained unchanged during the study.

Significant clinical improvements were seen during the study, including increases in BMI and decreases in psychiatric symptom questionnaire scores, as described previously (1). This was mainly attributable to two responders, although all patients reported subjective improvements. No intraoperative adverse events were observed. However, 28 severe adverse events (SAE's) occurred, with two being probably ((hypo)manic symptoms) and nine possibly (self-destructive behaviour) related to the intervention. Most SAE's were related to (somatic) AN severity rather than DBS (n=11) (1).

Effects of DBS on power spectra

Figure 2 shows the power spectra for patients at the three time points and the healthy controls. On average, clear changes in regional alpha and beta power were seen.

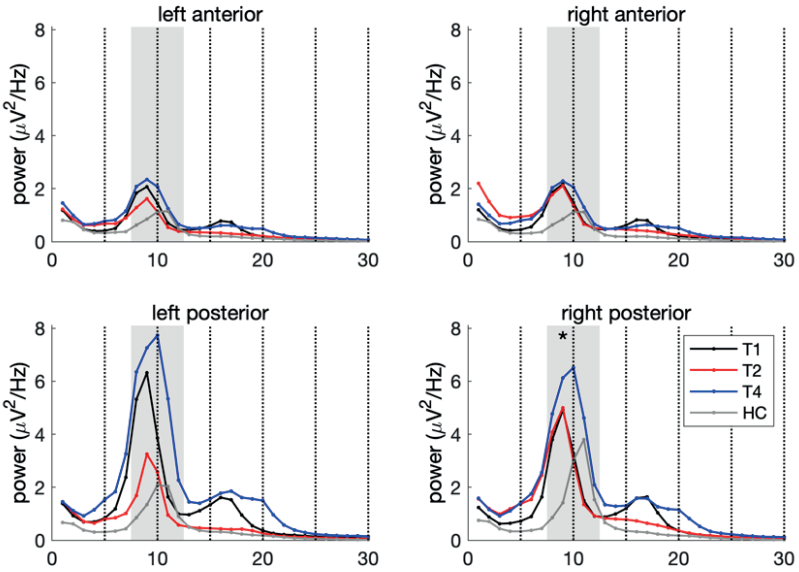

Figure 2. Power spectra of the patients across three timepoints (T1, T2, T4) and healthy controls (HC; grey). The spectra reveal clear peaks in power in the alpha (8-13 Hz) and beta (14-20 Hz) bands.

Figure 3 shows the significance of the within-subject ANOVA on the alpha and beta power values with time (T1, T2, T4) as fixed factor, p-values FDR corrected across the 62 channels. All subjects showed significant change in alpha and beta power over time during DBS treatment for either many channels (patient 1) or nearly all channels (patients 2, 3, 4).

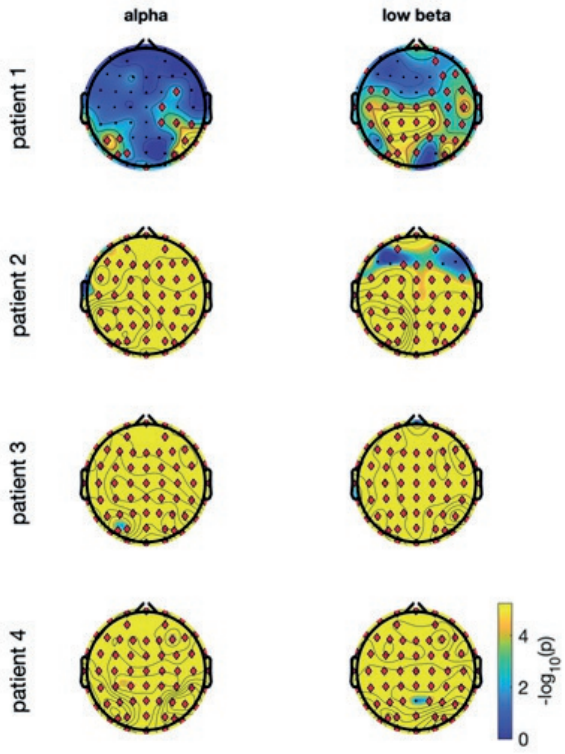

Figure 3. Within-subject changes in EEG alpha and beta power were highly significant in all patients. In patients 2-4 almost all channels showed significant effects. For patient 1, the FDR-adjusted p-values are shown converted to a positive scale (stronger effects are higher values) with $-\log_{10}(p)$. Significance is reached at approximately $-\log_{10}(0.05)=1.3$.

Figure 4 shows the change over time for the individual patients for the four regions anterior left (L) and right (R) and posterior left (L) and right (R). The general pattern that emerged was that most patients showed an initial reduction in alpha and beta power at T2 compared to baseline T1 and a subsequent increase at T4. To test whether these alpha and beta power changes over time were systematic across subjects we used the repeated-measures design. Nominally significant effects were observed for posterior L alpha (p=0.034) and anterior / posterior L beta (p=0.034 and p=0.013, respectively), however, multiple testing correction resulted in no significant effect across subjects for any region/frequency combination being found, indicating that the effects are still quantitatively heterogeneous across subjects.

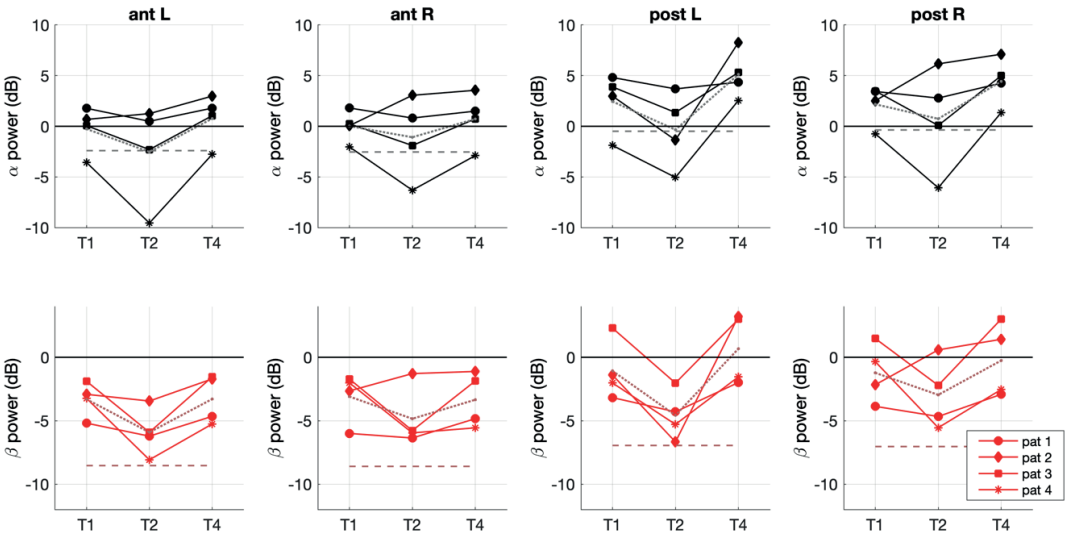

Figure 4. Alpha and beta power averaged over the four regions showed a general pattern of lowering at T2, which reached nominal significance for posterior L alpha (p=0.034) and anterior / posterior L (p=0.034 and p=0.013, respectively). Dotted line: average over patients. Dashed line: average of HC. The comparison of AN at T1 to HC revealed significant differences for beta power all four regions (FDR-p=0.043).

Power differences of AN versus HC

No significant effects were observed for alpha power when comparing the four regions in a simple t-test (p>0.18). Beta power showed significant effects (uncorrected-p between 0.012 and 0.022; FDR-p=0.043 in all regions). To specify in more detail which channel by frequency combination may have been responsible for these significant effect, we calculated a linear effect comparing the 4 AN patients to the 8 HC for each of the 62 channels and each of the 1 Hz frequency bins from 1 to 30 Hz. Supplementary Figures S1-3 show the topographic distribution of power and significant electrodes after FDR correction.

Supplementary figure S1 compared T1 against HC, figure S2 T2 against HC, and figure S3 T4 against HC. All times showed some significant differences compared to HC. For T1, the main differences were observed at lower (15 to 18 Hz) and upper (23 to 30 Hz) beta frequencies. These effects were localized at fronto-central electrodes. Alpha power did not show any significant change, except for a small right-central cluster at 9 Hz. T2 showed only few channels with significant increases (FDR q=0.05), consistent with the observed reduced power observed at T2 in the spectrum. T4 showed more widespread differences with strong increases in power compared to HC and many channel by frequency combinations, reaching corrected significance at FDR q=0.01. Interestingly, here, too, upper alpha power did not show significant differences. This may indicate that the observed power increases in the alpha band are confounded with the lower alpha peak

frequency: lower alpha peak frequency counteracts any power increase in the upper alpha band while increasing the effect in the lower alpha band/theta band.

Effect of DBS on connectivity measures

To characterize changes in spatial structure across time (within AN) and between subjects (AN vs HC), we calculated coherence and the weighted phase lag index (wPLI) as measures of connectivity between all possible pairs of electrodes. Figure 5 (top row) shows the connectivity for coherence in the four regions, while figure 5 (bottom row) shows connectivity estimated with wPLI. For each region, the cross-spectra of all electrodes within that region with all other electrodes were averaged (ignoring connections closer than 4 cm in a standard spherical head model of 8.5 cm radius to reduce spurious connectivity due to volume conduction effects (34)). All spectra showed clear peaks in the alpha band. Many spectra also showed beta band peaks in connectivity, although these were more prominent in the T1 and T4 periods. This suggests that the alpha and lower beta bands are important oscillation frequencies for default-mode communication.

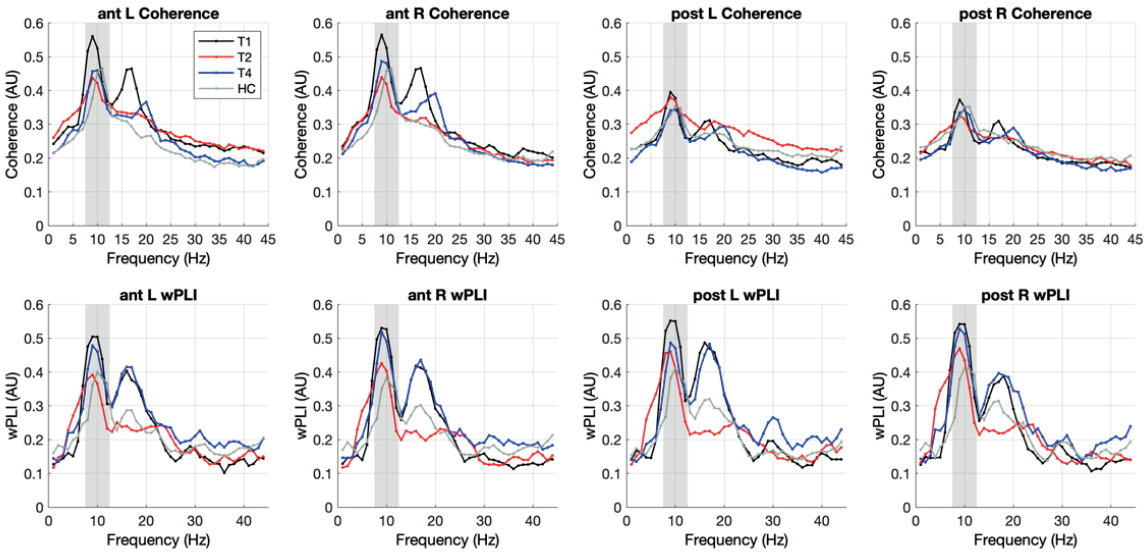

Figure 5. Connectivity spectra averaged over channels within a region. (Top row) Coherence spectra of AN showed clear peaks at T1 in the alpha and beta bands. T2 reduced peak size and increased resemblance to HC (grey). T4 showed re-emergence of the alpha and beta peaks in all four regions, albeit with slightly increased frequency. Posterior areas showed reduced connectivity in all groups. **(Bottom row)** weighted Phase Lag Index (wPLI) spectra showed a similar pattern to coherence spectra for connectivity between left temporal-parietal to right frontal areas. No clear regional differences were observed.

Although at face value time seemed to substantially affect the regional coherence spectra due to the large spectral differences between T1-T2-T4, none of the repeated measures models reached significance for the changes in beta and alpha connectivity ($p>0.06$). Similarly, no effect of time was found for wPLI alpha and beta band connectivity ($p>0.08$). Figures 6 and 7 show the coherence and wPLI scalp topography for AN at the 3 time points as well as the HC in the alpha and beta frequency range. For coherence, no large changes in the topography can be seen, despite a change in overall connectivity.

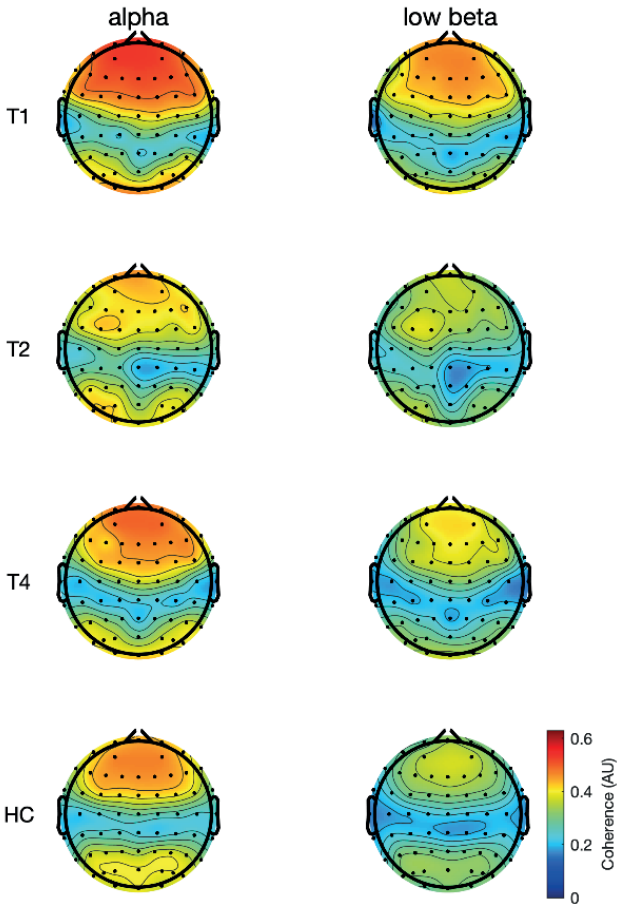

Figure 6. Topography of Coherence. For each electrode, the connectivity in the alpha (left) and beta (right) bands are shown, averaged over each electrode's connectivity with all other electrodes. Top three rows are for the three timepoints T1, T2, T4. Bottom row is for HC.

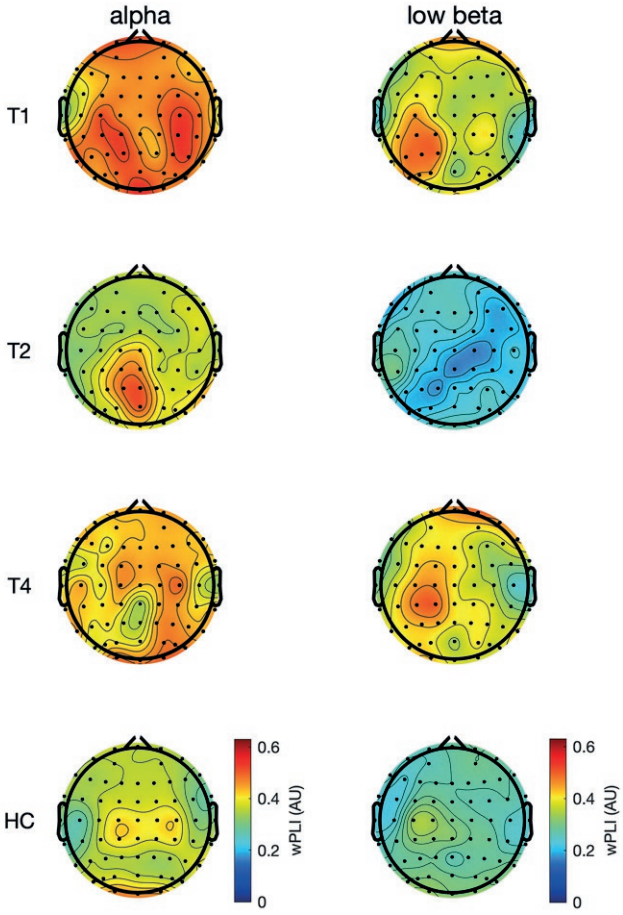

Figure 7. Topography of wPLI connectivity. For each electrode, the connectivity in the alpha (left) and beta (right) bands are shown, averaged over each electrode's connectivity with all other electrodes. Top three rows are for the three timepoints T1, T2, T4. Bottom row is for HC.

Differences in connectivity between AN and HC

Figure 5 also shows the connectivity spectra for HC (grey lines) averaged over the four regions. Most spectra showed clear peaks in the alpha band, and very often also in the (lower) beta band. For the alpha band, both coherence and wPLI showed increased alpha band connectivity comparing AN at T1 to HC. In the beta band, this effect (AN_{T1}>HC) seemed stronger for wPLI (both posterior and anterior).

Averaging over the frequency bands, coherence and wPLI in the alpha band were substantially increased for AN at T1 compared to HC. These did not reach significance for coherence, but reached significance for right-anterior channels (p= 0.0304). Beta showed small peaks in the coherence and wPLI spectra at T1, which was absent in HC. This reached nominal significance

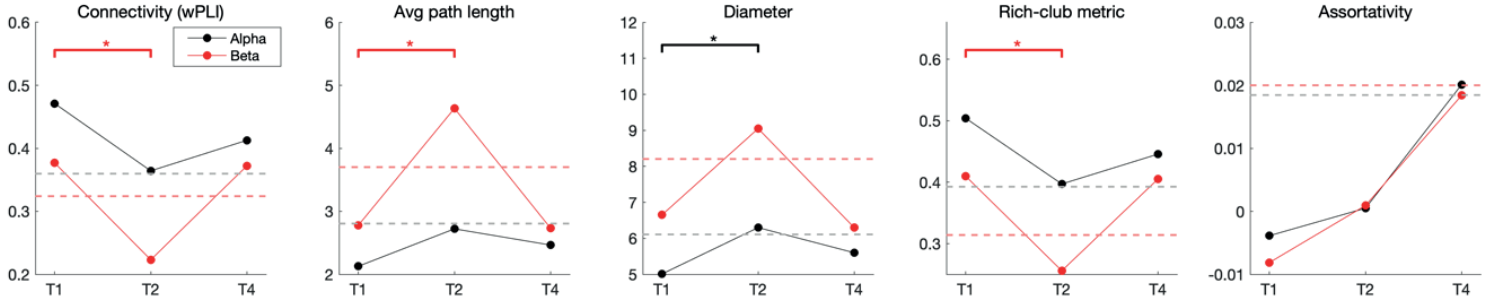

Figure 8. Development over time of global network measures (connectivity and graph parameters). Dashed lines indicate the graph parameter level for HC, black for alpha and red for beta. Connectivity based on wPLI showed a decrease from T1 to T2, which reached significance for beta (path length, rich-club metric) and alpha oscillations (diameter). T4 did not significantly differ from T1 or T2, but generally was near the same level as T1**.** Assortativity showed a continuous increase and normalized towards HC values (dashed lines) as time progressed. This effect was not significant. *p<0.05 corrected.

for coherence in right and left anterior channels ($p<0.038$) and left-posterior channels for wPLI ($p=0.028$). None of these differences survived correction for multiple testing.

Whole-brain connectivity and graph measures

Graph measures describe the organization of the brain connectivity as a property of the whole network. For this, we only used the wPLI-based connectivity matrices, as this algorithm is designed to suffer less from spurious connectivity due to volume conduction effects. The effects for the graph measures are shown in figure 8. The level for HC is indicated with the dashed line. Graph measures showed no significant differences with HC after multiple testing correction. Average connectivity, path length, diameter, rich-club metric showed a U curve (inverted for path length and rich-club). FDR-corrected p-values showed significant change at T2 compared to T1 for beta band average connectivity, path length, and the rich-club metric. Diameter showed a significant change at T2 compared to T1 for the alpha band ($p=0.032$ for all). Assortativity did not significantly change over time.

DISCUSSION

We hypothesized that DBS causes changes in electrophysiology of the brain of AN patients beyond the local influence of DBS at the stimulation target. We found evidence for such a widespread effect: strong and significant within-subject changes in oscillatory power were observed for all patients. These power changes indicated that DBS affected EEG across the scalp (patients 2-4), and for both frequency bands. In patient 1 significant changes were also found, albeit less widespread. The effects of DBS on brain activity were specific for individual patients: Patients 1, 3, and 4 showed a decrease in both alpha and beta power after the first DBS period (T2), and a subsequent increase at T4. Patient 2, however, showed an increase in power in many regions of the brain, mainly over the right hemisphere. Overall, network activity showed a V-shaped curve, with initial disorganization and later reorganization. Averaging individual data resulted in heterogeneity, suggesting that the effects of DBS on network activity in AN are strong and widespread yet highly personalized. Our results are in line with the findings of the recent MEG-study on DBS in AN that indicate that DBS modulates neuronal process in regions far outside the stimulation target site and at latencies possibly reflecting task specific processing (18).

We observed a V-shaped curve over time for average connectivity. In particular, beta connectivity showed significant changes from T1 to T2. At T4, beta connectivity appears to increase again and shows no significant difference with baseline. A possible explanation for this curve is that at T1, there is a relatively highly structured but pathological network organisation. This could be consistent with the findings of a study that showed an altered global network architecture with local degradations in patients with AN (16). It could be hypothesized that DBS disrupts this high

level of organisation, causing a temporary network disorganisation, which later reorganises into a stronger signal at T4. This may indicate that the brain adapts to DBS treatment.

The changes in graph parameters showed a similar V (or corresponding inverted-V) shape, and are therefore likely to reflect a uniform effect. Lower connectivity indicates that effective communication is reduced. The interesting observation is that DBS at the target area does not change the activity in the subcortical area directly, but indirectly affects communication between cortical areas. Decreased connectivity and rich-club metric, in combination with increased Path Length are typical for a less communicative, more segregated, and less integrated network. Although the effect was not significant, assortativity monotonically increased over time (i.e., not in a V-shape). If these results hold in future studies, it may indicate that the network changes *qualitatively* from T1 to T4: a linear increase of greater assortativity combined with V-shaped development of graph metrics that reflect integration. Future investigations may establish whether the combined network parameter assortativity is a useful biomarker of DBS induced brain network changes in AN.

At the initial measurement T1 AN patients showed evidence of abnormalities in their EEG spectra compared to healthy controls. The power spectra showed clear peaks in the lower beta range where HC did not. Although the averaging into regional beta and alpha power did not reveal significant effects, more detailed inspection revealed that significant differences were found. AN patients showed increased lower and upper beta power in a wide central region. Although we have no source-localized data, the central location may suggest involvement of somatosensory or motor cortices. The prominent role of beta in sensorimotor cortices could explain associations with sensory and motor processing deficits in AN (35-37). Interestingly, after the initial stimulation, beta power normalized to levels close to HC, after which they showed an increase back to approximately baseline (T1) levels. Whether or not this is correlated with treatment success (e.g. BMI increases, reduction of eating disorder psychopathology) remains to be investigated. It is also unclear whether these initial differences are a cause or consequence of the disease state. However, these first observations suggest that central beta oscillations may be used to track the progression of DBS.

In addition, alpha peak frequency showed evidence for slowing in AN. Nominal significance was observed for right parietal peak alpha frequency that was lower at T1 than in healthy controls. Although alpha peak slowing has mostly been related to aging and dementias, it also seems to be a general psychiatric phenomenon and useful for tracking treatment response in depression (38-40). However, these changes must be verified in follow-up studies, for example, controlling for medication use (40).

Limitations

Limitations of this study are the very small sample size due to the highly specific setting and population of the study (an experimental high risk intervention study in a physically severely compromised patient group). When combined, average effects did not always reach significance, however, nominal significance was observed that might result in significant overall effects when more patients are investigated for the effect of DBS on brain function in the future. Possible suboptimal band power selection and the large number of channels could have contributed to the fact that we did not find significance in summarized power. The current results suggest that some level of idiosyncratic response to DBS in AN is to be expected. The parameters that affect this differential response (electrode placement, stimulation duration and response, other confounding variables) are beyond the scope of the current investigation.

We did find changes in functional connectivity. However, the direction of these changes and whether this indeed reflects a form of disorganisation of pathological connectivity which is later restored to normalized connectivity is of course highly speculative. A larger sample size, EEG-measurements during symptom-provoking tests and the establishment of a correlation with clinical symptom improvement in future studies could ameliorate these limitations.

Conclusion

To our knowledge this is the first study on DBS in AN examining the effect that DBS has on brain function as revealed in EEG signals. Within-subject effects of stimulation were large, widespread over frequencies, and visible across wide brain areas and networks, even with DBS turned off. Prolonged stimulation (>one year) seemed to reinstate organization in the functional brain networks. Our results support the observations that effects of DBS are not merely local, but influence widespread pathological network activity and that, after an initial period of disorganisation, the brain seems to adapt to the stimulation with reorganization in a potentially more healthy state. The functional relevance of these findings must be established in future studies. Future studies may extend our findings by increasing sample size, evaluation of the parameters that best predict treatment outcome, and the influence of DBS on source localized EEG activity.

SUPPLEMENTARY MATERIAL

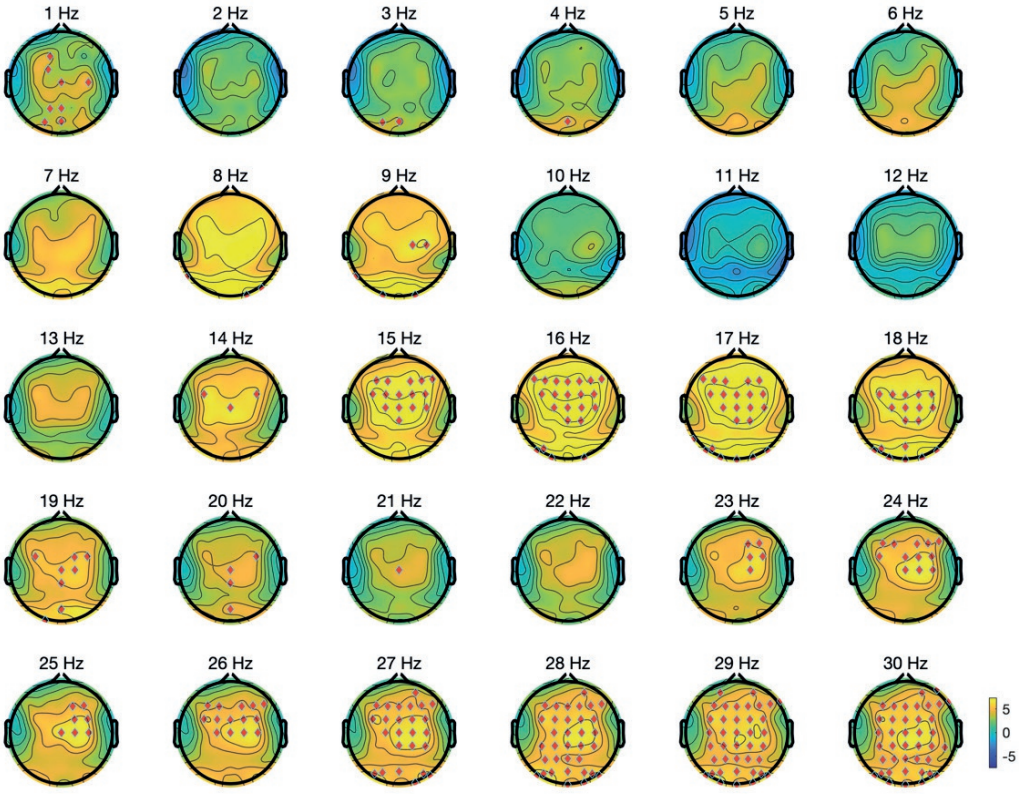

Figure S1. The detailed electrode-by-frequency bin comparison of EEG power between AN at T1 compared to HC. Headplots are colored by the difference in oscillation power. FDR-corrected significance (corrected for the 62 x 30 comparisons) are marked with red diamonds (q=0.05) and purple dots (q=0.01).

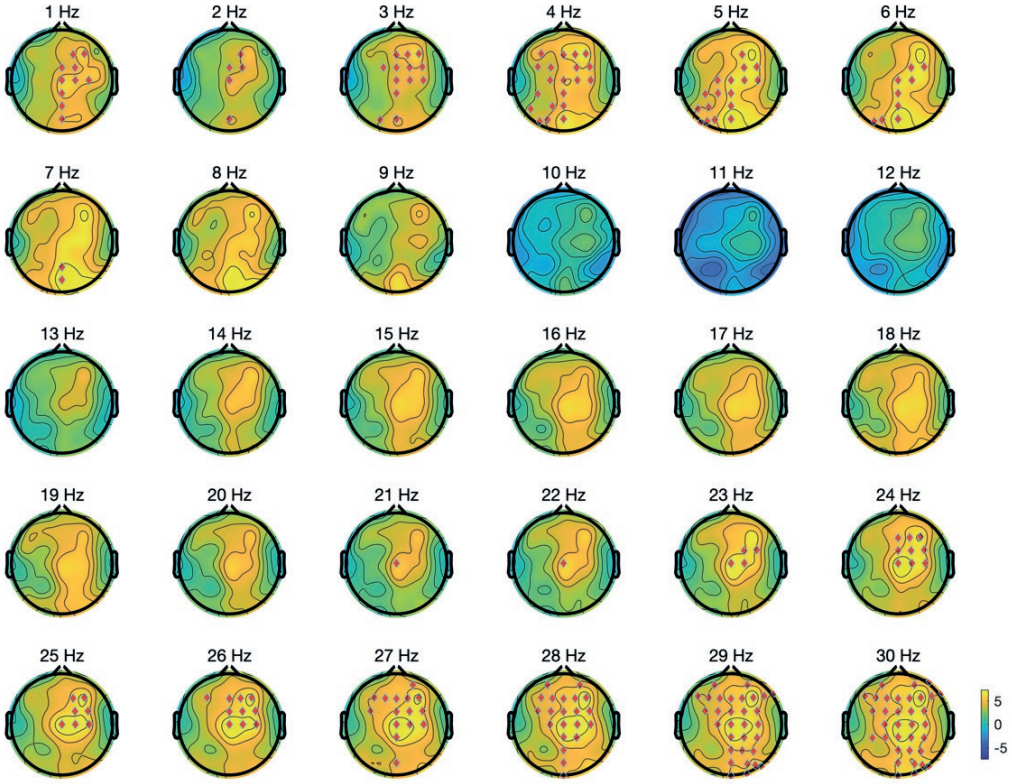

Figure S2. The detailed electrode-by-frequency bin comparison of EEG power between AN at **T2** compared to HC. Headplots are colored by the difference in oscillation power. FDR-corrected significance (corrected for the 62 x 30 comparisons) are marked with red diamonds (q=0.05) and purple dots (q=0.01).

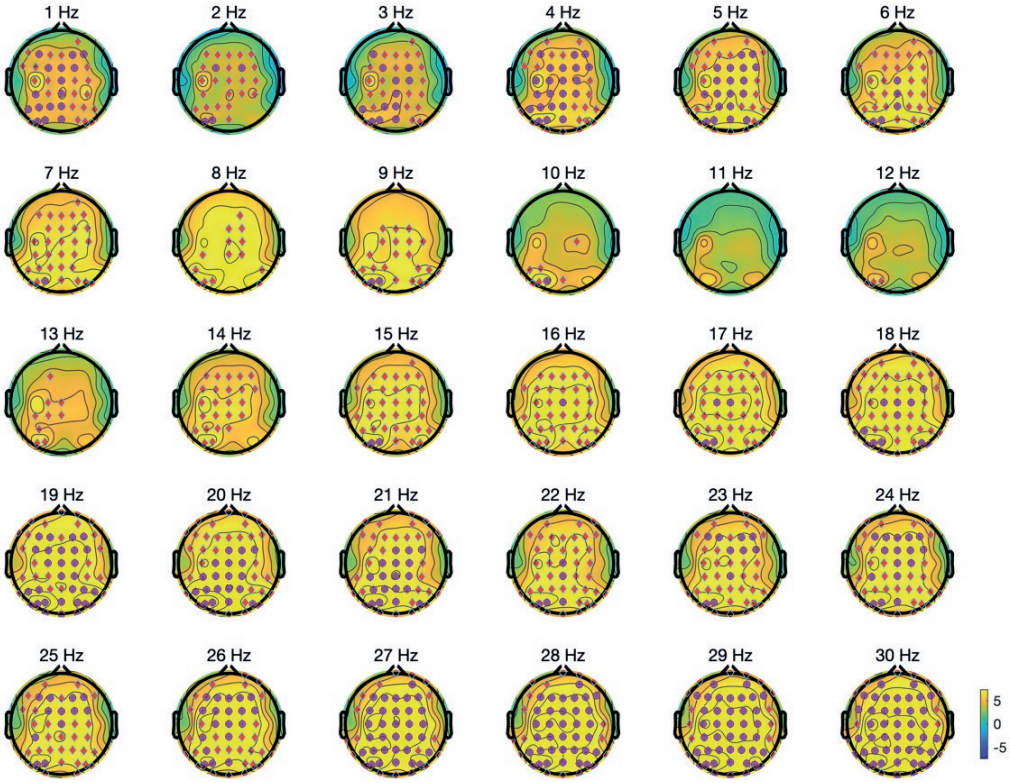

Figure S3. The detailed electrode-by-frequency bin comparison of EEG power between AN at **T4** compared to HC. Headplots are colored by the difference in oscillation power. FDR-corrected significance (corrected for the 62 x 30 comparisons) are marked with red diamonds (q=0.05) and purple dots (q=0.01).

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7

Endocrine and Metabolic Alterations following Deep Brain Stimulation in Anorexia Nervosa

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In submission

ABSTRACT

Introduction

Deep brain stimulation (DBS) targeted at the brain reward system is a promising last resort treatment option for therapy refractory anorexia nervosa (AN)-patients. As part of our pilot study on the efficacy, safety and feasibility of ventral anterior limb of the internal capsule (vALIC) DBS in AN we conducted repeated endocrine and metabolic measurements. We hypothesized that these AN-associated parameters would normalize over time with DBS treatment.

Methods

Four female patients with AN received DBS of the vALIC. We conducted repeated endocrine and metabolic measurements on the hypothalamic-pituitary gonadal, adrenal and thyroid axis, and measured growth hormone, insulin-like growth factor-1, appetite regulating hormones, adipokines, posterior pituitary hormones and renal and noradrenergic function before DBS (pre- and post surgery), after DBS-optimization and after a 1-year follow-up period.

Results

We found a significant decrease in the levels of testosterone (21.47%; 0.18 ± 0.10 nmol/L, CI 95% -0.06 – 0.41, t = 1.705, P = .034) and cortisol (47.39%; 360.25 ± 125.17 nmol/L, CI 95% 27.29 – 693.21, t = 2.88, P = 0.025) over time during treatment with DBS. Furthermore, we found decreases in progesterone, ACTH, GH, adiponectin, ADH, adrenalin and noradrenalin levels, and increases in T3, IGF-1, and leptin, although not significant. The decrease in cortisol and the increase in leptin seem more prominent in the weight-responders than in the non-responders.

Conclusion

This first study on endocrine and metabolic changes during DBS treatment of AN showed significant decrease of plasma cortisol and testosterone over time. Other changes did not reach significance, possibly due to the small sample size and high variability. However, some of the results we found, like the over time and the non-significant increase in leptin in the subjects that responded to DBS with weight gain, suggest an effect of DBS or DBS-modulated weight changes on endocrine and metabolic parameters. These findings stimulate further research on the complex interaction between physiology, disordered eating and neuromodulation.

INTRODUCTION

Anorexia nervosa (AN) is a challenging psychiatric disorder with the highest mortality rate of all psychiatric disorders (1, 2). AN is characterized by severe food restriction, an inability to maintain a normal body weight, and body image disturbances (DSM-5) (3). Even with the best available treatments, 21% of AN-patients will become chronic and treatment-refractory (4).

Deep brain stimulation (DBS) targeted at the ventral anterior limb of the capsula interna (vALIC), part of the brain reward circuit, is being investigated as a last resort treatment option for therapy refractory AN-patients (5). A recent meta-analysis showed statistically large beneficial overall effects of DBS on weight, quality of life and symptoms of eating disorders, depression and anxiety (6).

The limited research on the working mechanisms of DBS in AN focused so far on neuroimaging parameters, showing changes in the reward circuitry. However, AN and the accompanying severe weight loss is also associated with endocrine and metabolic alterations including alterations in hypothalamic-pituitary axis function (7-11).

On the hypothalamic-pituitary-gonadal axis the chronic state of malnutrition in AN often results in disturbed luteinizing hormone (LH) pulsatility manifesting as hypothalamic amenorrhea. Gonadotropin releasing hormone (GnRH) levels are reduced, leading to reduced gonadotropin secretion and low androgen levels (10). The hypothalamic-pituitary-adrenal (HPA) axis is in a continuous overstimulated state with corticotrophin releasing hormone (CRH) hyperstimulation and elevated adrenocorticotropic hormone (ACTH) and cortisol levels , and the degree of hypercortisolaemia correlates inversely with BMI (9, 11). Moreover, severe malnutrition/underweight is characterized by nonthyroidal illness syndrome, with low levels of total T3, and low to normal free T4 and thyroid stimulating hormone (TSH) levels (10). In AN there is a state of acquired growth hormone (GH) resistance due to chronic nutritional deprivation, with increased GH secretion and decreased insulin-like growth factor 1 (IGF 1) (12).

Alterations in adipokine and appetite-regulating hormones are also found in AN. Leptin, an anorexigenic adipokine, plays a role in satiety and thus appetite regulation. In AN, basal and pulsatile secretion of leptin is reduced in association with reduction of fat mass (10, 11). Most studies in AN found increased levels of adiponectin, but its role is unclear (13).

Preclinical studies show a relationship between the noradrenergic system and binge-like behavior, some evidence suggests a noradrenergic-mediated genetic risk to develop AN (14). Clinical studies show conflicting alterations in plasma noradrenaline in patients with AN (14). Dopamine, with its direct involvement in the brain reward system, is the most studied neurotransmitter in AN. Studies show that dopamine neurotransmission is altered in AN (15), with increased dopaminergic neurotransmission.

In conclusion, AN is associated with adaptive, reactive and/or etiologic endocrine and metabolic alterations in levels of neuroendocrine factors that are involved in food reward valuation, satiety and learning via their interactions with the mesolimbic dopamine system (15-17).

To the best of our knowledge, the endocrine and metabolic effects of DBS in AN have not been studied before. Cortisol has been studied in DBS in OCD patients (18, 19) showing increased urinary excretion of free cortisol when stimulation was turned off. This finding was correlated strongly with OCD symptom increase. Understanding the (neuro) endocrine and metabolic changes accompanying the observed clinical effects of DBS in AN could provide unique insight in the pathophysiology of AN, open up new therapeutic targets and further personalize DBS therapy.

The present study aimed at testing endocrine and metabolic alterations following DBS in AN, with a focus on neuroendocrine parameters involved in food reward and satiety (16). As part of our pilot study on the efficacy, safety and feasibility of ventral anterior limb of the internal capsule (vALIC) DBS in AN (5) we conducted repeated endocrine and metabolic measurements on the hypothalamic-pituitary gonadal, adrenal, thyroidal and growth-hormone axis, appetite regulating hormones, adipokines, posterior pituitary hormones, renal and noradrenergic function and fatty-acid metabolism during follow-up. We hypothesized that such parameters associated with AN, would alter over time with DBS treatment and/or weight gain in the course of DBS treatment. We expected normalization of endocrine and metabolic parameters following weight restoration, possibly in part mediated by a normalizing effect of DBS on the reward system.

MATERIAL AND METHODS

Study design

This is an analysis of laboratory measurements as part of an open label experimental pilot study conducted at the department of Psychiatry and Neurosurgery of the Amsterdam University Medical Centers (Amsterdam UMC), location Academic Medical Center (AMC) (5). The Medical Ethical Committee (MEC) of the Amsterdam UMC approved the study. Both assessors and researchers were not blinded. No control group was included. Four patients were included undergoing DBS as an experimental treatment for their treatment-refractory AN.

Subjects

We recruited patients from the major clinics specialized in adult eating disorders in the Netherlands. We applied the following inclusion criteria: clear primary diagnosis of AN (restricting or purging subtype) based on the DSM-IV, confirmed by a psychiatric interview by an independent physician; illness duration ≥10 years; lack of response to ≥2 typical modes of treatment including

one hospital admission or inpatient treatment in an eating disorder specialized clinic; substantial functional impairment according to the DSM-IV criterion C and Global Assessment of Function (GAF-score) ≤45.

Procedure

We conducted bilateral stereotactic implantation of DBS electrodes in the anterior limb of the internal capsule (vALIC). Following our earlier DBS studies, we distinguished four sequential phases: preoperative (T-1), surgery (T0), optimization (3–9 months; T1-T2) and maintenance (12 months; T2-T4). After screening at T-1, bilateral DBS electrodes were implanted in the vALIC at T0. We turned on and optimized DBS settings from T1 to T2, and followed patients up to T4. During the study patients received standard medical and psychiatric care, comprised of regular visits with a nurse-practitioner and a psychiatrist. No major psychopharmacological adjustments were made. For an extended overview of the methods see Oudijn e.a. 2021 (5).

Data acquisition and analysis

We took fasting blood and urine samples for laboratory analysis at T-1, T1, T2 and T4 (see **figure 1**). All samples were taken at the same time of day (9 a.m.). As one subject was postmenopausal, and the other three where amenorrhoeic, the phase of the menstrual cycle at the time of blood collection was not known. Samples were analysed by the Central Diagnostic Laboratory (CDL), the Laboratory for Endocrinology (ENDO), the Laboratory of Genetic Metabolic diseases (GMZ) in the Amsterdam UMC, location AMC, Amsterdam and by the Radboud Medical Center (Nijmegen). **Supplement 1** shows type of tests and samples used, detection limits, reference ranges, and the inter-assay coefficients of variation.

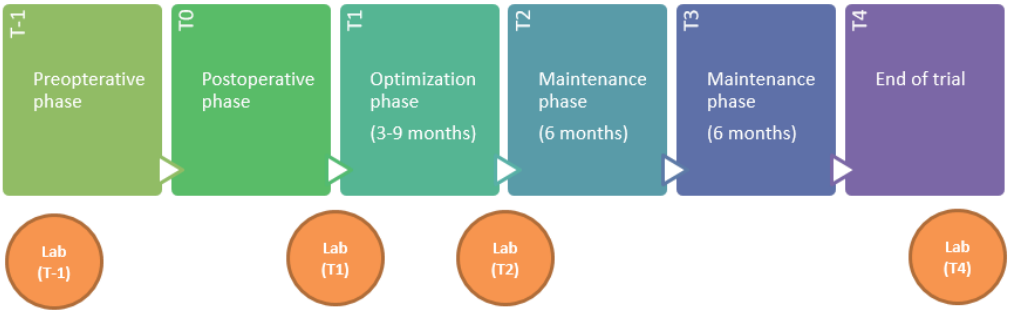

Figure 1. The temporal phases of the DBS treatment with the timepoints of laboratory analyses at T-1, T1, T2, and T4.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 26. Due to low sample size (n=4) we did not conduct tests for normality of the data. For

continuous outcomes we reported fixed effects means and standard error (SE). Analysis was performed using linear mixed models. P-values of less than 0·05 were considered significant. We present data for individual patients, also to observe possible relations with weight change.

We applied imputation for non-detectable concentrations (4.65%) using the detection limit divided by √2 (20). Missing values (0.35%) were mostly due to insufficient sample volume at a certain time point for laboratory analyses. Possibly, low BMI contributed to low sample volumes drawn from patients. In line with previous research, to limit the number of tests needed to investigate fatty acid metabolism, we calculated the fatty acid chain length, unsaturation and peroxidability indices (20).

RESULTS

Patient demographics

Four patients with treatment-refractory AN who underwent DBS of the vALIC, during 12 months follow-up, were included in this study. The mean age was 39 years, with a range of 32 to 53 years. The mean illness duration was 21 years (SD=3). All patients were female and suffered from binge-purging subtype of AN. Average BMI at baseline was 12.5 (SD=1.0) kg/m^2, indicating extremely severe AN. All patients suffered from psychiatric comorbidities. Two patients were diagnosed with personality disorder not otherwise specified (PD-NOS), one patient was diagnosed with major depressive disorder (MDD) and one patient was diagnosed with both PD-NOS and MDD. All demographic characteristics are shown in **table 1**.

Table 1. Patient's demographics. (BMI= Body Mass Index, f= female, GAD= Generalized Anxiety Disorder, OCD=Obsessive Compulsive Disorder, NOS= Not Otherwise Specified, SUD= Substance use disorder and BPD=Borderline Personality disorder) *The substance in question was alcohol, at screening this was in remission. ** Important to note that for purging this patient used ± 50 Bisacodyl.

	Sex	*Age at onset (years)*	*Age at surgery (years)*	*Illness duration (years)*	*Anorexia Subtype*	*BMI (screening)*	*BMI (Historic low)*	*Psychiatric comorbidities*	*Psychiatric medication at surgery*
S1	f	15	32	18	Purging	12.4	9.5	GAD, Depression, Personality Disorder NOS	Aripiprazole, Quetiapine, Oxazepam
S2	f	15	39	24	Purging	11.2	10.2	SUD*, Personality Disorder NOS	Aripiprazole, Quetiapine, Oxazepam
S3	f	14	33	19	Purging**	13.4	10.6	Depression, OCD, BPD	Venlafaxine, Clorazepate, Oxazepam, Temazepam
S4	f	27	53	24	Purging	13.1	9.7	Personality Disorder NOS	Citalopram, Alprazolam, Zolpidem
Mean (SD)		18 (6)	39 (10)	21 (3)		12.5 (1.0)	10.0 (0.5)		

Primary outcomes of this study were published previously (5). A significant increase in BMI was found at the end of follow-up (5.32 kg/m^2; +42.8%; P=.017). The increase in BMI was primarily seen in two of four patients (subject 2 and subject 3) (see **figure 2**).

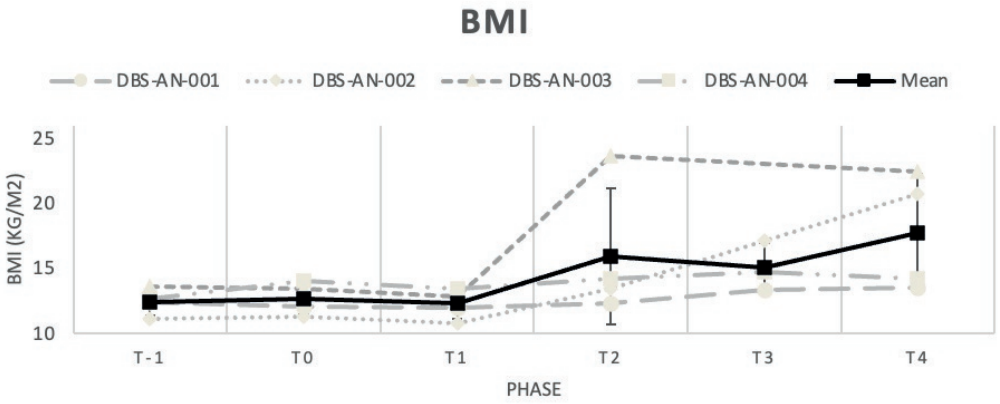

Figure 2. Time course of DBS-induced BMI (fixed effects ± SE).

Linear mixed model analyses showed a significant linear effect of time on BMI (43.16±15.96, CI 95% 9.07-77.25, t=2.704, P=.017).

This figure was originally published in Oudijn MS et al. Deep brain stimulation of the ventral anterior limb of the capsula interna in patients with treatment-refractory anorexia nervosa. Brain Stimul. 2021;14(6):1528-30

Endocrine and metabolic results

The changes in endocrine and metabolic parameters over time and the mean changes at T4 compared to baseline are shown in **table 2**. The individual changes in each parameter are shown in **supplement 2**. We found a significant decrease in testosterone (21.47%; 0.18 ± 0.10 nmol/L, CI 95% -0.06 – 0.41, t = 1.705, P = .034) and cortisol (47.39%; 360.25 ± 125.17 nmol/L, CI 95% 27.29 – 693.21, t = 2.88, P = 0.025) over time. When analyzing the individual changes in each parameter (see **supplement 2 and figure 2**) the decrease in mean testosterone seems unrelated to the individual weight change. The decrease in cortisol seems more prominent in the weight-responders (subject 2 and 3) than in the non-responders.

Table 2. Endocrine and metabolic markers in AN patients at four time points during follow-up.

Axes		*T-1 (Screening)*	*T2*	*T3*	*T4*	*F-value*	*P-value*	*Reference range*
Hypothalamic-pituitary								
Hypothalamic-pituitary-gonadal	LH (mIU/mL)	6·64 ± 6·16	6·64 ± 5·69	6·04 ± 4·99	6·95 ± 5·34	2·235	0·218	Depends on phase of menstruation cycle
	FSH (mIU/mL)	15·69 ± 12·13	15·89 ± 11·53	14·51 ± 10·20	15·32 ± 10·75	0·216	0·881	Females 30-35 years 0.14 -13 µg/L Females 35-40 years < 11 µg/L Females >45 years < 0.48 µg/L
	*Testosteron (nmol/L)	0·82 ± 0·13	0·83 ± 0·13	0·50 ± 0·13	0·64 ± 0·13	4·519	0·034*	Females 0.3 – 1.6 nmol/L
	Estradiol (pmol/L)	23·86 ± 8·08	67·18 ± 26·94	42·86 ± 19·97	69·11 ± 48·03	0·910	0·522	Depends on stimulation schedule
	Progesteron (nmol/L)	1·13 ± 0·42	0·83 ± 0·08	0·71 ± 0·07	0·71 ± 0·07	1·530	0·329	<3.3 nmol/L
	Prolactin (U/L)	0·27 ± 0·15	0·31 ± 0·20	0·22 ± 0·11	0·16 ± 0·06	0·623	0·634	<0.6 U/L premenopausal <0.4 U/L postmenopausal
	DHEAS (µmol/L)	2·30 ± 0·83	1·41 ± 0·28	1·53 ± 0·33	1·19 ± 0·23	1·052	0·451	Females 1 - 12 µmol/L
Hypothalamic-pituitary-adrenal	ACTH (pmol/L)	5.41 ± 1.03	4.16 ± 0.20	6.15 ± 3.26	3.15 ± 0.43	2.238	0.307	<9pmol/L
	*Cortisol in plasma (nmol/L)	760·25 ± 167·27	615·50 ± 51·40	469·25 ± 50·09	400·00 ± 105·09	7·50	0·025*	250 - 650 nmol/L
Hypothalamic-pituitary-thyroid	TSH (mE/L)	2·53 ± 1·10	2·01 ± 0·77	2·83 ± 0·98	1·99 ± 0·83	3·577	0·140	0.3 – 4.2 mE/L
	Free FT4 (pmol/L)	14·08 ± 1·56	13·78 ± 1·56	13·38 ± 1·56	16·48 ± 1·56	1·729	0·230	12.0 – 22.0 pmol/L
	T3 (nmol/L)	0·96 ± 0·25	1·08 ± 0·21	1·10 ± 0·12	1·31 ± 0·06	6·51	0·069	1.1 – 2.2 nmol/L
Growth hormone-insuline-like-growth-factor-1	GH (mU/L)	15·58 ± 3·31	8·94 ± 3·31	9·12 ± 3·31	8·72 ± 3·31	1·014	0·421	Pulses to 20 mU/L (in females)
	IGF-1 (nmol/L)	11·09 ± 2·92	12·78 ± 2·92	18·86 ± 2·92	15·65 ± 2·92	1·363	0·301	Depends on age and gender
	Insulin (pmol/L)	24·88 ± 10·71	101·83 ± 75·06	34·65 ± 17·16	29·08 ± 8·89	1·736	0·315	12 - 96 pmol/L

Table 2. Continued

Axes		*T-1 (Screening)*	*T2*	*T3*	*T4*	*F-value*	*P-value*	*Reference range*
Appetite regulating hormones/gut peptides and adipokines	Leptin (ng/mL)	3·75 ± 0.73	16.00 ± 12.45	16.00 ± 10.91	13.00 ± 6.72	1·635	0·309	2.2 – 27.9 for females with BMI 20-25
	Adiponectin (µg/mL)	17·13 ± 3·82	15·55 ± 3·82	11·28 ± 3·82	10·17 ± 3·82	1·523	0·355	
Posterior pituitary hormones and renal function	ADH (pmol/L)	20·72 ± 16·30	12·62 ± 2·35	8·57 ± 3·40	9·62 ± 4·83	2·049	0·241	< 14 pmol/L
	Urine osmolality (mOsm./kg)	299·50 ± 149·81	454·50± 149·81	485·25 ± 149·81	552·50 ± 149·81	2·087	0·172	300 - 900 mOsm/kg H2O
	Urine sodium (mmol/L)	23·75 ± 15·13	103·00 ± 61·46	44·00 ± 14·34	57·00 ± 24·92	1·917	0·274	40 - 220 mmol/24 hours
Noradrenergic	Adrenaline (nmol/L)	0·12 ± 0·03	0·12 ± 0·03	0·10 ± 0·03	0·09 ± 0·03	0·321	0·810	
	Noradrenaline (nmol/L)	8·98 ± 2·45	4·79 ± 1·05	3·61 ± 1·17	3·19 ± 0·10	2·666	0·219	
	Dopamine (nmol/L)	0·36 ± 0·13	0·18 ± 0·04	0·13 ± 0·01	0·12 ± 0·03	1·776	0·313	

Furthermore, we saw a non-significant mean decrease of progesterone (37.43%), ACTH (41.72%), GH (44.07%), adiponectin (40.63%) and ADH (53.60%). Adrenaline (26.02%) and noradrenaline (64.49%) levels showed a non-significant decrease as well. At baseline, leptin in our patients was low (3.75±0.73 ng/mL), as would be expected in AN patients. We found a mean increase of leptin (247.67%) at the other time points, but this was not significant due to a large variability (67.4-345.7%), with the most increase in weight-responders. IGF-1 (41.16%), urine osmolality (84.47%) and urine sodium (140.00%) also showed an increase after DBS, although these findings were not significant.

Although our patients were all severely underweight at baseline and the mean T3 at baseline was below the reference value (0.96 ±0.25 nmol/L), there was no significant change in T3, free T4 and TSH levels over time. Also we did not find significant changes in GH, IGF 1, insulin and adiponectin levels over time. Catecholamines did not show any significant changes over time either, although in the individual charts there seems to be a downward trend in dopamine as well as noradrenaline (see **supplement 2)** over time.

We found no significant changes in the three fatty acids indices, arachidonic acid (AA)/ eicosapentaenoic acid (EPA) ratio, or docosahexaenoic acid (DHA) as shown in **table 3**.

Table 3. Fatty acids in AN patients at four time points during follow-up.

		T-1 (Screening)	*T2*	*T3*	*T4*	*F-value*	*P-value*	*Reference range*
Fatty acids	Free fatty acids (mmol/L)	0·50 ± 0·13	0·41 ± 0·13	0·44 ± 0·13	0·57 ± 0·13	0·532	0·672	0.14 – 0.44 mmol/L
	Chain-length index	17·73 ± 0·04	17·56 ± 0·17	18·83 ± 1·16	17·74 ± 0·03	0·646	0·630	
	Unsaturation index	1·19 ± 0·03	1·22 ± 0·03	1·20 ± 0·02	1·23 ± 0·04	0·221	0·878	
	Peroxidation index	0·65 ± 0·05	0·69 ± 0·05	0·66 ± 0·05	0·71 ± 0·05	3·022	0·087	
	AA/EPA ratio	15·40 ± 5·09	18·67 ± 5·09	17·99 ± 5·09	21·20 ± 5·09	0·402	0·755	
	DHA	104·60 ± 46·51	102·85 ± 36·50	91·53 ± 24·60	122·18 ± 45·67	0·905	0·513	

DISCUSSION

As part of a pilot study on the efficacy of vALIC DBS in AN, we found a significant decrease in the levels of testosterone and cortisol over time during treatment and non-significant changes on other axes. In AN, many endocrine and metabolic parameters are altered, either associated with the acute and chronic state of malnutrition, or the etiopathophysiology of AN, or both. In the following paragraphs we will discuss the changes we found after DBS per hormonal axis.

Hypothalamic-pituitary-gonadal axis

In our study we did not find significant changes in LH and FSH levels. Though a correlation between weight gain and changes in endocrine parameters was not possible in this small sample size, literature shows that amenorrhea persists in up to 15% of women despite weight recovery (21). It remains unclear whether this is due to persistent eating disorder pathology, atrophy of gonadotrophic cells or other factors like persisting low levels of leptine (22) . We did not find significant changes in estradiol levels over time. However, when looking at the individual changes in estradiol levels over time, we see a remarkable increase in estradiol levels (189.62%) at the end of the study in subject 2 (see **supplement 2**). This subject showed a significant increase in BMI after DBS, potentially suggesting a normalization of the HPG axis with weight restoration. It has to be notes that the follicular phase of the subjects at the measurementpoint was not known due to their postmenopausal and amenorrhoeic state.

The observed significant decrease of testosterone levels over time seems contradictory to the fact that androgen concentrations in AN tend to be low. This decrease seemed irrespective of weight change. Low androgen levels may be a consequence of hypothalamic dysfunction and depletion of fat mass in AN. Miller e.a. (2009) found that low androgen levels in AN might contribute to anxiety, depression and eating disordered thinking and behavior in AN (23). Another

study describes an interaction between gonadal hormones and the dopaminergic reward system. Testosterone replacement therapy is considered in AN and might influence the reward dysfunction found in AN (16).

Hypothalamic-pituitary-adrenal axis

In our study we found elevated plasma cortisol levels at baseline (T-1) and a significant decrease of plasma cortisol over time, suggesting an attenuation of the hypercortisolaemia. We found no significant decrease of ACTH over time.

Hypercortisolaemia is associated with stress, depression, anxiety (24) and sometimes plays a role in maintaining euglycemia in patients with AN (9). It is also suggested that cortisol plays a role in the pathophysiology of AN, in particular in the hypoactivation of the food-motivation circuitry (25).

Our results are in line with this findings of de Koning e.a. (2012), who conclude that DBS for obsessive-compulsive disorder at the same target as our study, the vALIC, is associated with cortisol changes (19). Our results also support the hypothesis that DBS might normalize aberrant HPA-axis functioning and reward dysfunctioning in AN, resulting in normalization of increased plasma cortisol.

Hypothalamic-pituitary-thyroid axis

Although we found no significant change in T3, T4 and TSH levels over time, on an individual level two of our subjects (one weight-responder and one weight-non-responder) had low levels of T3 at baseline, which normalized over time (see **supplement 2**), indicating that on an individual level, thyroid function might normalize with DBS, apparently irrespective of weight change.

Growth hormone, insulin-like growth factor 1 and insulin

In our study we did not find significant changes in GH, IGF 1 and insulin levels over time. This is contrary to expectations given that insulin levels are low in a state of undernutrition, have a role in GH resistance and are associated with the reward circuitry and endogenous dopamine (DA). (26). The lack of significant findings is possibly due to the small sample size and the chronic malnourished state of our AN patients.

Posterior pituitary hormones and renal function

In accordance with the literature we did find mean elevated plasma levels of ADH at baseline and a normalization at T4, but the change over time was not significant and looking at the individual results, the mean elevation of ADH at baseline is mainly caused by one subject. Urine osmolality and urine sodium fell in the normal range throughout the study. Due to these inconsistencies and the small sample size it is not possible to draw any conclusions with regard to the effect of DBS on ADH levels.

Appetite regulating hormones, gut peptides and adipokines

At baseline, leptin in our patients was low (3.75±0.73 ng/mL), as would be expected in AN patients (10, 11). We found a mean increase of leptin at the other time points, but this was not significant due to a large variability. On an individual level, a numerical increase in leptin was seen in the two subjects that also responded to DBS with significant weight increase (see supplement 2). An increase in leptin levels would be in line with the hypothesis that leptin levels are associated with appetite regulation and fat mass and thus normalize after treatment and weight gain (22).

In our study we found no significant changes in adiponectin levels over time. In human (non-AN) studies administration of adiponectin seems to reduce body weight by various mechanisms, and/or by reducing food intake, increasing energy expenditure and enhancing fatty acid oxidation (27). It could be hypothesized that this hyperadiponectinaemia could contribute to the pathogenesis of AN (28). However, the role of adiponectin in AN remains unclear and our results were insufficient to support any hypothesis.

Catecholamines and dopamine

We assessed plasma levels of dopamine, noradrenaline and adrenaline, but did not find any significant changes over time, although in the individual charts there seems to be a downward trend in dopamine as well as noradrenaline (see **supplement 2)** over time. These decreases seem most prominent in our weight-responders which is supportive of our hypothesis that improvement of eating disorder pathology, in this case weight gain, is associated to normalization of epinephrines and dopamine.

Fatty acids

Fatty acid changes during DBS treatment did not reach significance. Given the widespread potential significance of lipids in brain structure/function and inflammatory regulation (29-38), this may be because of power issues. Of interest was the numerical increase in lipid peroxidation index, apparently mostly in weight-responders, which deserves follow-up in larger studies in AN.

Limitations

A major limitation of this study is of course the small sample size. Therefore it was not possible to statistically correlate endocrine and metabolic parameters to weight change or severity of symptoms. As stated in the introduction, AN is characterized by a wide variety of endocrine and metabolic alterations, and the causality of these alterations is hard to establish. Furthermore, this study consisted of a specific subgroup of AN patients, which all were extremely and chronically ill, with major acute and long-term complications of severe and enduring malnutrition. Furthermore, the population we studied was heterogeneous due to a variety of comorbid conditions. Many endocrine parameters do have a diurnal rhythm and the levels of gonadotrophins are highly dependable on the pase of the menstrual cycle. Therefore, we are cautious in interpreting

observed alterations, but do not negate their interest. It is difficult to extrapolate our finding to either AN or DBS.
Finally we did not find any changes within fatty acid levels. Brain lipid peroxidation is not able to be directly assessed in living subjects. The calculated peroxidation index can approximate lipid peroxidation, however more direct measures of lipid peroxidation are needed to determine lipid peroxidation in the brain more specifically (29).
Nevertheless, this is a first investigation of major endocrine and metabolic parameters to establish possible changes over time during DBS treatment. Data - including strong changes over time - provide new insights in DBS working mechanisms and AN pathophysiology.

Conclusion

In this first pilot study on the endocrine and metabolic effects of DBS in AN we hypothesized that endocrine and metabolic parameters associated with AN would show changes over time with DBS treatment and associated weight gain. We found a significant decrease in testosterone (21.47%) and cortisol (47.39%) levels over time. Furthermore, we found decreases in progesterone, ACTH, GH, adiponectin, ADH, adrenalin and noradrenalin levels, and increases in T3, IGF-1, and leptin, although not significant, possibly due to the small sample size and the high variability of individual levels. However, some of the results we found, like the significant decrease of plasma cortisol over time, suggesting an attenuation of the hypercortisolaemia, and the non-significant increase in leptin in the subjects that responded to DBS with weight gain, suggest an effect of DBS or DBS-modulated weight changes on endocrine and metabolic parameters. These findings stimulate further research on the complex interaction between physiology, disordered eating and neuromodulation.

Future perspectives

Larger studies on the effects of DBS on endocrine and metabolic parameters in AN are needed. It would also be interesting to conduct measurements in DBS-ON and DBS-OFF state to study the direct influences of DBS on the endocrine and metabolic system.

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PART V

Anorexia nervosa: conceptual hypotheses

8

Psychopathological and neurobiological overlap between anorexia nervosa and self-injurious behavior: a narrative review and conceptual hypotheses

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ABSTRACT

Empirical evidence and clinical observations suggest a strong -yet under acknowledged- link between anorexia nervosa (AN) and non-suicidal self-injurious behavior (NSSI).

By reviewing the literature on the psychopathology and neurobiology of AN and NSSI, we shed light on their relationship. Both AN and NSSI are characterized by disturbances in affect regulation, dysregulation of the reward circuitry and the opioid system.

By formulating a reward-centered hypothesis, we explain the overlap between AN and NSSI. We propose three approaches understanding the relationship between AN and NSSI, which integrate psychopathology and neurobiology from the perspective of self-destructiveness: (1) a nosographical approach, (2) a research domain (RDoC) approach and (3) a network analysis approach. These approaches will enhance our knowledge of the underlying neurobiological substrates and may provide groundwork for the development of new treatment options for disorders of self-destructiveness, like AN and NSSI.

In conclusion, we hypothesize that self-destructiveness is a new, DSM-5-transcending concept or psychopathological entity that is reward-driven, and that both AN and NSSI could be conceptualized as disorders of self-destructiveness.

INTRODUCTION

Empirical evidence and clinical observation suggest a strong link between eating disorders (EDs) and non-suicidal self-injurious behavior (NSSI). Up to 72% of patients with EDs also engage in NSSI, and 25-54% of patients that engage in NSSI report comorbid disordered eating (1).

In addition, NSSI and EDs share clinical risk factors and there is overlap in motivational and behavioral aspects of both disorders (2), suggesting shared underlying (neurobiological) mechanisms.

In our recent study on deep brain stimulation (DBS) as a potential new treatment option for anorexia nervosa (AN) we saw an increase in self-destructive behavior when the eating-disorder symptoms lost their rewarding properties (3) This rose the question how AN and self-destructive behavior are linked, whether there is a shared pathogenesis, and why this potential shared pathogenesis leads to different clinical expressions. On a more fundamental level, we wondered whether the self-starvation of AN-patients, which seems to be an ultimate form of self-destruction, could be considered primarily self-destructive. In this review self-destructive or self-injurious behavior is narrowed down to NSSI and suicidal intent is excluded.

As is common in psychiatric practice, therapeutic options often aim at either eating disorder pathology or self-injurious behavior (4, 5). If NSSI and EDs share etiopathogenetic mechanisms, acknowledging them may improve understanding, diagnosis and treatment efficacy. However, research is scarce and there is currently no overview on the neurobiological association between EDs and NSSI.

Although all EDs evidently show pathological eating behaviors with related cognitions and emotions, suggesting a common root, there are also significant clinical and etiopathogenic differences between EDs. Since the clinical overlap between self-destructive behavior and one particular eating disorder, namely anorexia nervosa, seems to be the most striking, and most neurobiological evidence is available for AN, we will focus this review on AN.

With this narrative review we summarize the literature on the psychopathology and neurobiology of anorexia nervosa (AN) and NSSI and shed new light on their links (6).
We propose a new conceptualization of the overlap between AN and NSSI and suggest new approaches to better characterize their relation. Thereby we aim at providing a groundwork for future research and the development of new biological treatment options for AN and NSSI, especially if they are occurring simultaneously.

METHODS AND OUTLINE

We conducted this narrative review according to the steps described by Demiris e.a. (6). To answer the above questions we first summarize the literature on the psychopathology (clinical picture and psychological theories on the etiopathogenesis) and the neurobiology of AN and NSSI separately. For this search we used various combinations of search terms regarding 'Anorexia nervosa' 'Self-destructive behaviour','NSSI' AND/OR 'psychopathology' AND/OR 'neurobiology'. We chose relevant articles that focus on the combination of and/or overlap between the two. Because this search did not reveal many relevant hits we expanded the search with 'Eating disorders' AND 'Self-destructive behavior' for topics on which there was no literature specific to AN. We scanned reference lists of included articles for additional relevant literature.

First, we summarize the psychopathology and neurobiology of AN and NSSI separately. In chapter 3 we discuss the commonality between AN and NSSI on a psychopathological and neurobiological level, leading to a reward centered hypothesis on this overlap. We made the somewhat artificial distinction between psychopathology in general and neurobiology in specific for reasons of clarification from a research perspective. Finally we propose three conceptual hypotheses explaining the relationship between AN and NSSI, integrating psychopathology and neurobiology.

RESULTS: PSYCHOPATHOLOGY AND NEUROBIOLOGY OF AN AND NSSI RESPECTIVELY

Anorexia nervosa

Psychopathology of AN

Anorexia nervosa (AN) is an eating disorder characterized by (1) an intense fear of gaining weight or becoming fat; (2) persistent behavior that interferes with weight gain, potentially leading to self-starvation and severe somatic complications; (3) and a misperception of one's body weight or shape (and often also the seriousness of the malnutritive state of the body). There are two subtypes of AN: the restrictive subtype (AN-R), characterized by restrictive eating; and the binge eating/purging subtype (AN-BP), characterized by restrictive energy intake but also binging and/or purging (self-induced vomiting, misuse of laxatives and/or diuretics) (7).

AN typically has its onset in adolescence (8) and the female-male ratio is 4:1 (9). AN has a prevalence of 1-4% and (9, 10). With a mortality rate of 5.6% per decade (resulting from medical complications and suicide), AN has the highest mortality rate of all psychiatric disorders (9, 11).

Psychiatric comorbidity is high: comorbid psychiatric disorders are reported in over 70% of AN-patients and include affective disorders, obsessive compulsive disorder, personality disorders, and

impulse control disorders (9)/. Studies found correlations between AN and childhood trauma and between AN and specific personality traits (like perfectionism, negative emotionality and bodily dissatisfaction (12). Despite increased knowledge of neurobiological, psychological and environmental factors that contribute to the development and maintenance of the (9, 13, 14), effective treatment options are limited, and AN takes on a chronic course in a considerable number of patients (20%) (15).

Neurobiology of AN

Several neurobiological factors have been investigated in AN, including neurotransmitter systems and brain network functioning (16). Changes in serotonin (5-HT) and dopamine (DA) have been most often examined.

Several studies show alterations in 5-HT-metabolites, -receptor binding potential and -activity, suggesting involvement of 5-HT function in AN (17, 18). Dopamine (DA) is related to motivation and reward, and to eating and the reinforcing value of food (19). Studies on DA metabolites and receptor density in AN suggest an altered DA functioning and disturbed reward processing in AN (19-22). Bailer e.a. (2017) (23) found a positive association between DA release and anxiety in the dorsal caudate in AN patients, possibly explaining why food-related DA-release produces anxiety in AN but is considered pleasurable in healthy individuals.

Brain areas involved in eating and eating disorders can be classified in circuits that are interconnected and mutually interact with each other. Although difficult to compare, functional magnetic resonance imaging (fMRI) studies in AN show consistently altered activation in emotional, reward and cognitive brain networks as well as networks implied in interoception. In **Supplementary Table 1**, we summarize fMRI studies in ill and recovered AN patients according to Frank e.a. (2019) and O'Hara e.a. (2015) (24, 25).

In summary, the structures showing dysfunctional activation in ill and recovered AN patients are part of 1) salience and reward networks related to emotional processing and reward processing, and 2) a cortical cognitive circuit related to selective attention and planning. Together they form the cortico-striatal-limbic neurocircuit, which is implicated also in other reward related psychiatric disorders such as obsessive compulsive disorder (OCD) (26).

Several models refer to a dysfunctional reward circuit in AN (e.g. the bottom-up top-down model by Kaye e.a. 2009, (27)). Frank e.a. (2019) (24) suggest that there is a conflict between the conscious motivation to restrict food in AN and a body-homeostasis driven motivation to approach food. There seems to be a reinforcing mechanism between AN behavior and anxiety. Some AN behavioral symptoms provide short time relief of anxiety and stress and are rewarding.

Based on these findings, O'Hara e.a. (2015) (25) formulated a reward-based model of AN. In this model the etiopathophysiology of AN is described as an increased reward responsiveness for and habit formation of anorectic behavior. AN is thought to originate in striatal reward dysfunction, reflected by reward-based learning of stimulus-driven bottom-up processes. Illness-compatible cues become positively associated with reward, while food-related healthy cues lose their rewarding properties, and instead become punishing, a process the authors call 'reward contamination'.

Non-suicidal self-injurious behavior

Psychopathology of NSSI

As opposed to AN, non-suicidal self-injurious behavior (NSSI) is no disorder or disease category. NSSI is defined as 'any socially unaccepted behavior involving deliberate and direct destruction of bodily tissue without suicidal intent' (28-30). Examples of NSSI are skin-cutting, self-hitting, self-burning and scratching. In the DSM-III, NSSI was described as a symptom of emotional and developmental disorders like borderline personality disorder (BPD) and impulse control disorder (31). The DSM-5 has included NSSI in the category 'Conditions for Further Study' (7), which, according to Cipriano e.a. (2017) (32), is a first step towards recognizing NSSI as a separate disorder. One of the criteria of NSSI in the DMS-5 is that the behavior attempts to diminish inter- as well as intrapersonal psychological discomfort.

Since self-injurious behavior is often studied simultaneously with suicidal behavior, it is difficult to separate findings for NSSI from suicidality. Moreover, self-injurious behavior has been studied under various acronyms (e.g. (non-suicidal) self-injury, self-mutilation, self-harm, deliberate self-harm, parasuicidal behavior) with varying in- and exclusion criteria (with the most prominent variation being the in- or exclusion of suicidal intent), which complicates interpretation of the literature. In this review self-injurious behavior is narrowed down to NSSI and suicidal intent is excluded.

NSSI has an onset in early adolescence (12-14 years) and a higher prevalence in women than in men (29, 32). According to a recent systematic review by Cipriano e.a. (2017) (32), NSSI has a prevalence of 4-23% in adults and 7.5-46.5% in adolescents, with wide ranges due to differences in samples and methods. The prevalence rates of NSSI in psychiatric populations are higher: 20% in adult psychiatric populations and 40-80% in adolescent psychiatric populations (29, 33). Because of the association of NSSI with psychiatric conditions (borderline personality disorder, depressive disorder, anxiety disorders, post-traumatic stress disorder, substance abuse and eating disorders) individuals engaging in NSSI are part of a diagnostically heterogeneous population.

Accordingly, the described etiopathogenesis of NSSI is diverse. Several studies found environmental or social risk factors for NSSI, like childhood trauma, attachment problems and dysfunctional interpersonal relationships, as well as individual risk factors like emotion regulation problems (32, 34). Paivio and McCulloch (2004) (35) showed that difficulties to identify and express emotional experience appropriately (i.e. alexithymia) mediated the relation between childhood trauma (except sexual abuse) and NSSI .

Most studies on NSSI describe emotion regulation problems as the primary source. Typically, an increase in negative emotionality is observed before engaging in NSSI, which is reduced after NSSI, resulting in a positive rewarding experience (32). Ammerman e.a. (2018) (36) reviewed experimental studies using physical aversive (painful) stimuli like heat, electric shocks or cutting to induce NSSI related responses and found that when NSSI functioned as self-punishment, NSSI individuals had a less intense pain response to painful stimuli than controls (36).

There are several models of NSSI. Favaro & Santonastaso (2000) (37) distinguish two forms of NSSI: 1) impulsive NSSI, described as an impulsive act functioning as an episodic relief after increasingly build up tension (e.g. skin cutting, burning), and 2) compulsive NSSI, described as a compulsive act expressed as a habitual, repetitive, non-functional motor behavior (e.g. hair pulling, skin picking) .

Others (38) have proposed a four-factor model, which states that NSSI can be reinforced by either intrapersonal of interpersonal motives, and can be either positively reinforcing (by generating a positive feeling) or negatively reinforcing (by reducing a negative feeling). This model is supported by empirical evidence and is widely used for categorizing functionality of NSSI (29, 33). Klonsky & Muehlenkamp (2007) (29) have extended this model to seven groups of functions or motivations of NSSI: 1) affect regulation, 2) self-punishment, 3) interpersonal influence, 4) anti-dissociation, 5) anti-suicide, 6) sensation seeking, 7) interpersonal boundaries and self-control.

In summary, NSSI seems to be a maladaptive emotion regulation strategy with (internal and external) reinforcing and rewarding properties (32).

Neurobiology of NSSI

There are several neurotransmitter systems involved in NSSI. First, the endogenous opioid system, because it is involved in pain perception, pain relief and reduction of negative affect, reward and motivational processes (39, 40). Evidence for the relation between NSSI and the endogenous opioid system is based on altered endogenous opioid levels, reduced pain sensitivity and successful opioid antagonist treatment in NSSI (36, 40, 41). Risk factors for NSSI such as childhood trauma and disrupted attachment are also related to changes in opioid levels (39, 40, 42).

The opioid system modulates the dopaminergic (DA) system (42), which is also hypothesized to be involved in NSSI. In animal models with reduced DA neurons, self-biting behavior was observed when DA-agonists were administered, whereas DA-antagonists had a reversing effect on this behavior. Self-injury in animals was mainly observed when the animal was in isolation or physically restricted (43). As DA is the major neurotransmitter involved in reward processing (44), and reward is crucial in engagement and reinforcement of NSSI, altered DA levels in the reward circuit seem to be involved in NSSI. However, humane data on the role of DA in NSSI are lacking.

Another neurotransmitter that might be implicated in NSSI is the serotonergic (5-HT) system (40). Associations have been made between 5-HT and impaired emotion regulation and impulsivity (17), which are both psychological risk factors for NSSI. Also, 5-HT dysfunction has been linked to several psychiatric disorders associated with NSSI, such as depression, anxiety, BPD and eating disorders (17, 42). Genetic studies have found a correlation between polymorphisms in 5-HT transporters and increased probability of NSSI, particularly when mediated by stress exposure (34). However, other studies found no relation between NSSI and 5-HT levels (45).

Neuroimaging studies in patients with NSSI (with or without a specific psychiatric condition) suggest involvement of brain circuits related to negative valence, reward and habit formation, and cognitive control (36). For example, NSSI-expressing individuals seem to have more inhibitory control towards NSSI-related pictures than controls. Plener e.a (2012) (46) found increased activation in the limbic system (amygdala, anterior cingulate cortex) in response towards these pictures, which was related to increased levels of arousal. They also found increased activation in the prefrontal cortex, which was related to a controlling response towards the observed limbic over-activation. This could suggest that the initial arousing response towards NSSI was neutralized, probably because of the final rewarding experience of NSSI. Kraus e.a. (2010) (47) and Reitz e.a. (2015) (48) found similar imaging results related to NSSI-triggering acts and while experiencing physical pain. Ammerman et al. (2018) (36) stated that these findings support the regulative effects of NSSI on emotional processing.

Liu (2017) (41) proposes a habit model to explain NSSI. The author describes a shift from voluntary behavior (instrumental learning) to repetitive habitual behavior (stimulus-response learning) occurring over time. Similar to addiction, when the self-injury becomes a habit, it loses the sensitivity to the positive outcome. This shift is paralleled by a shift from the ventral to the dorsal striatum, as observed in addiction. Other research showed that NSSI decreased arousal mostly in individuals infrequently engaging in the behavior, which suggests that the reinforcing and rewarding effects are the strongest during the onset of the behavior. The positive effects of pain relief after NSSI were lower in frequent NSSI-patients, supporting NSSI as a habitual 'rewarding' experience (36). This implicates that risk factors for NSSI possibly change over time, just as NSSI and its neurobiological correlates might become more habitual over time (41).

An important conclusion of both Ammerman e.a. (2018) (36) and Liu (2017) (41) is that, based on most behavioral and imaging studies, NSSI is considered a conditioned, reinforcing behavioral act, aimed at emotion regulation, which results in a habitual rewarding experience. The reward system might therefore be of great interest when further investigating the neurobiological etiology of NSSI.

RESULTS: PSYCHOPATHOLOGICAL AND NEUROBIOLOGICAL OVERLAP BETWEEN AN AND NSSI

AN and NSSI: psychopathological overlap

As mentioned above, there is a high rate of co-occurrence between EDs and NSSI. Cucchi et al (2016) (49) found a lifetime prevalence of NSSI in 22% of the AN patients and in 33% of the bulimia nervosa (BN) patients. This seems logical because both NSSI and purging require proactive deliberate action, whereas restricting is a more passive action (50).

Claes & Muehlenkamp (2014) (51) define both NSSI and ED related behavior as 'harmful behaviors falling within a behavioral spectrum ranging from self-care to self-harm'. The behavioral symptoms of EDs and more specifically of both subtypes of AN (AN-R and AN-BP) do have a highly (self-) destructive character. Because of the level of self-destructiveness in AN (and other EDs), and the assumed function of eating disorder symptoms in emotion regulation, some authors even suggest to consider EDs itself as a form of non-suicidal self-injurious behavior (NSSI) (13).

The onset of both AN and NSSI is usually during adolescence, and both show a trend towards a higher prevalence in the female population. Both NSSI and EDs share important risk factors like experienced childhood trauma, especially sexual abuse, or other traumatic events. Claes & Muehlenkamp present a conceptual model based on the psychosocial risk factors that are shared by NSSI and EDs (**figure 1**, derived from Claes & Muehlenkamp (2014) (51).

In addition, Svirko and Hawton (2007) (13) systematically reviewed the literature on psychological associations between NSSI and EDs. The most important shared psychological factors besides affect/emotion dysregulation implicated in EDs and NSSI are impulsivity, obsessive-compulsivity, dissociation, self-criticism/self-punishment and a need for control. Furthermore, associations are found with perfectionism, body-dissatisfaction and identity-conservation (52).

Both NSSI and EDs are considered to be related to emotion dysregulation (49, 53-55). The behaviors function as maladaptive coping strategies that can be seen as a form of self-destructive behavior, to either escape or generate specific feelings. NSSI as well as eating-disordered behavior are

automatically negatively reinforced by the reduction of negative affect and potentially positively reinforced by an increase in positive affect (in case of dietary restriction this could be an increase in positive mood, control and accomplishment) and are thus maintained by reinforcement and habituation. Both NSSI and EDs symptoms have been reported by patients as forms of self-punishment.

In conclusion, there seem to be psychopathological links between NSSI and AN in emotion dysregulation, (maladaptive) coping behavior, and reinforcement or reward (56).

AN and NSSI: neurobiological overlap

The neurobiological evidence on AN and NSSI summarized above, suggests that processes related to reward are essential in their overlap. As described above, NSSI induces opioid related reward to compensate for lower levels of endogenous opioids (39, 42). If reduced sensitivity of endorphin receptors and/or low levels of endogenous opioids are typical for patients engaging in NSSI, NSSI and also anorectic/eating disordered behavior in these patients might be a way to self-stimulate the endogenous opioid system.

The endogenous opioid system and the reward system are closely linked, since opioid modulates DA pathways resulting in an increased DA release in for example the striatum. Furthermore, opioids are thought to be involved in the emotional value of reward, but also in modulating appetite and energy metabolism (17).

One class of opioids, beta-endorphin, is released during stress as well as during positive experiences and causes an euphoric rush and a reduced pain perception. NSSI, but also other impulsive behaviors like binge-eating, results in a release of beta-endorphin and its rewarding rush (39, 42, 45). Interestingly, as a consequence of malnutrition, beta-endorphin levels are reduced in AN-patients (17). NSSI, but possibly also the self-destructive eating disorder related behavior itself, in these patients could therefore be a way to self-stimulate and mobilize the last reserves of the endogenous opioid system (42). From this perspective, the state of malnutrition in AN-patients stimulates the engagement in self-destructive or other radical behavior. Besides NSSI, also binge-eating, food restriction and excessive exercising are ways to gain such an endorphin rush and thus to stimulate the reward system (39, 42, 57). In this way, self-destructive behavior is providing a short-term rewarding relief of the typical negative emotional state in AN-patients. Thereby, endogenous opioid dysfunctioning seems an important explanation for the neurobiological association between NSSI and AN.

Moreover, distilling the evidence summarized above on the neurobiology of AN and NSSI, both are linked to reward-related processes like DA dysregulation, serotonergic functioning and abnormal activation in the cortico-striatal neurocircuit.

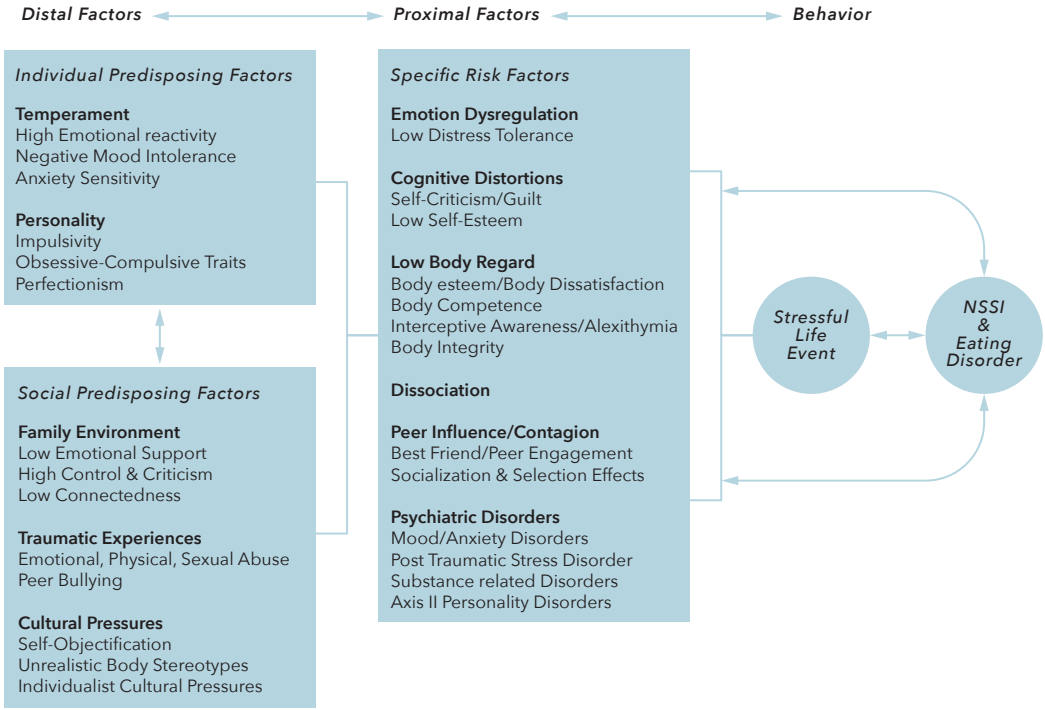

Figure 1 Claes and Muehlenkamp (2014) distinguish 'distal' risk factors that include temperament (high emotional reactivity, negative mood intolerance, anxiety sensitivity) and personality traits (impulsivity, obsessive-compulsive traits, perfectionism), cultural factors, family factors, and traumatic interpersonal experiences, and 'proximal' risk factors that include emotion dysregulation, cognitive distortions, low body regard, dissociation, peer pressure/contagion and comorbid psychiatric disorders. It is hypothesized that these risk factors interact with each other and with stressful events and that the internal distress caused by these interactions is regulated by behaviors of NSSI and/or EDs, which in turn can influence or reinforce the proximal risk factors.

The reward-centered model of AN (25) describing increased activation in striatal (bottom-up) networks and decreased activation in controlling cognitive (top-down) networks, is not only applicable for the engagement in anorectic behavior but also for NSSI. A study into the motivational processing of AN-compatible cues revealed that striatal DA modulation was relevant in the development of automated behavior regulated by the cortico-striatal circuit (58). This is consistent with the reward-based learning model of anorectic behavior and illness compatible cues proposed by the same authors.

Furthermore, the model of Liu (2017) (41) shows similarities with the model of O'Hara et al. (2015) (25), since both NSSI and anorectic behavior are initially a way to regulate negative affect, while repeated NSSI and AN-behavior is linked to habitual behavior or reward-associated learning.

The imbalance in the cortico-striatal circuit, with a focus on bottom-up processes of the striatal reward system, might be of great relevance for the reward associated learning of self-destructive behavior in AN and NSSI in general.

Because of the central role of reward in both NSSI and AN, the reward-associated brain areas and neurobiological mechanisms, we hypothesize that reward is a central and common factor in the pathophysiology of both AN and NSSI.

SUMMARY

Both AN and NSSI are characterized by disturbances in affect regulation, coping strategies, the psychological constructs of reward, and on a neurobiological level dysregulation of the reward circuitry and the opioid system.

DISCUSSION AND CONCEPTUALIZATION

AN and NSSI: conceptual hypotheses

We acknowledge the fact that in this review, we have placed ourselves in the difficult position of describing links between two constructs that are conceptually and structurally dissimilar. The conceptualization of both eating disorders and NSSI is a topic of much debate. Eating disorders, and AN in particular, may be perceived as disorders of feeding, but also as body-image disorders, psychosomatic disorders, neurotic or obsessive-compulsive disorders or even disorders with a psychotic component. Based on the psychopathological and neurobiological evidence outlined in our review, a reward-related or behavioral addiction disorder perspective seems applicable.
Self-destructive behavior has long been considered a symptom of several psychiatric disorders and has only been recently taken into consideration as a separate, affect regulation- and reward-related disorder.

Based on the overlap between AN and NSSI summarized above - in epidemiology, comorbidity, clinical picture, functionality, explanatory mechanisms and involvement of (partially) the same neurobiological systems - we propose several hypothetical models of the relationship between AN and NSSI and their underlying neurobiology: (1) a nosographical approach, (2) a research domain (RDoC) approach and (3) a network analysis approach. Central in these models is the overlap between AN and NSSI in affect regulation, body and/or pain disperception, punishment and reward.

AN and NSSI: a nosographical approach

Although there is considerable overlap between AN and NSSI, there are also differences. AN is a well-defined psychiatric disorder with specific diagnostic criteria. Although self-starvation, purging and over-exercising are highly self-destructive, the body image distortion and denial of the severity of the somatic condition in AN are not seen to this extent in people engaging in NSSI and seem to be specific to AN. NSSI on the other hand is increasingly being considered as a distinct disorder instead of a symptom of other disorders in the DMS-5. Based on these characteristics and differences in clusters of symptoms (i.e. a different *classification* of symptoms) it can therefore be hypothesized that NSSI and AN are *two separate disorders*, with some degree of overlap in neurobiology and functionality, leading to comorbidity (see **figure 2a**).

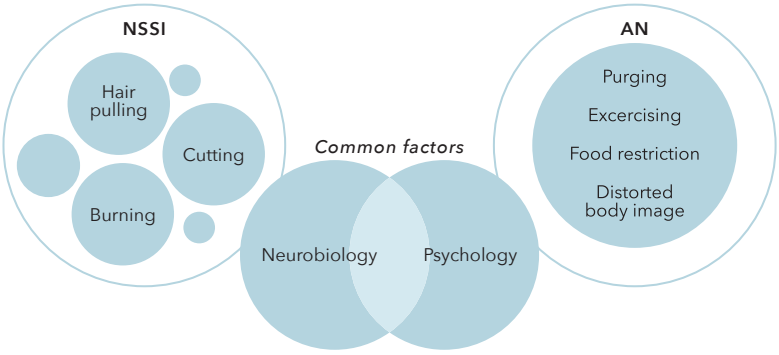

Figure 2a NSSI and AN as two separate disorders, with some degree of overlap in neurobiology and psychology, leading to comorbidity

One might also argue that NSSI is no separate construct or disorder at all. NSSI is prevalent in the context of many psychiatric disorders, especially disorders related to emotion regulation, impulsiveness, identity and interpersonal problems. Self-destructive eating disordered behavior and other forms of NSSI present during the course of AN could thus be seen as *a symptom of AN*, like NSSI is also often seen as a symptom in borderline personality disorder (see **figure 2b**). While the initial motivation to engage in food restriction and purging might be a drive for thinness, the existing predominant view of AN as a disorder of fear of weight gain might need to be revised. In accordance with the reward-based hypothesis of AN, AN could be considered as a disorder of emotion regulation and disrupted reward processing, with self-destructiveness, reflected by eating disordered behavior as well as NSSI in general, as a key symptom.

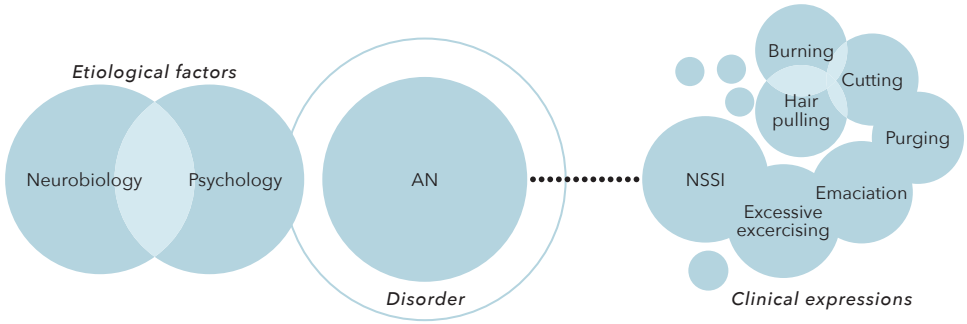

Figure 2b NSSI as a symptom of AN (like it can be a symptom of boulimia nervosa (BN) or borderline personality disorder (BPD))

Alternatively, yet in line with this view, the eating-disordered behavior seen in AN might be seen as *a form of NSSI*. In this perspective, NSSI would be considered a separate disorder with multiple (interchangeable) expressions. Purging, starvation, food restriction and over-exercising will in this model be in the same line with other forms of self-destructive behavior like for example self-cutting or self-burning. Self-destructive behavior is rewarding and reinforcing (e.g. in providing a relief of negative affect). This reinforcement is enhanced in AN due to the effects of starvation, which might explain why people engaging in eating disordered self-destructiveness tend to stick with the eating disordered behavior instead of changing to other forms of self-destructive behavior. In this model, AN, or the anorexia-related behaviors, can be considered as a form of internalized and positively reinforcing self-destructiveness or NSSI (see **figure 2c**).

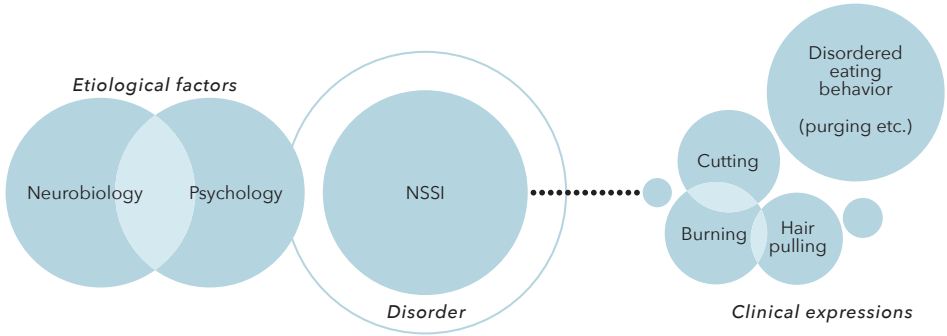

Figure 2c AN as a symptom of NSSI (with NSSI being considered as a separate disorder with multiple (interchangeable) expressions)

Based on the commonality in epidemiology, comorbidity, clinical features, functionality and neurobiological mechanisms a more fundamental relationship between NSSI and AN does not seem completely arbitrary. If a nosographical approach is conducted there seems to be consid-

erable overlap in the *intentionality* and *experience* of both NSSI and AN. This overlap consists of the concept of self-harm, but also the concepts of aberrant reward and punishment systems, the focus on the body or bodily structures, and the concept of affect dysregulation. In this perspective, both NSSI and AN could be conceptualized as *(disorders of) self-destructiveness*, driven by shared factors, with a different means of expression (see **figure 2d**).

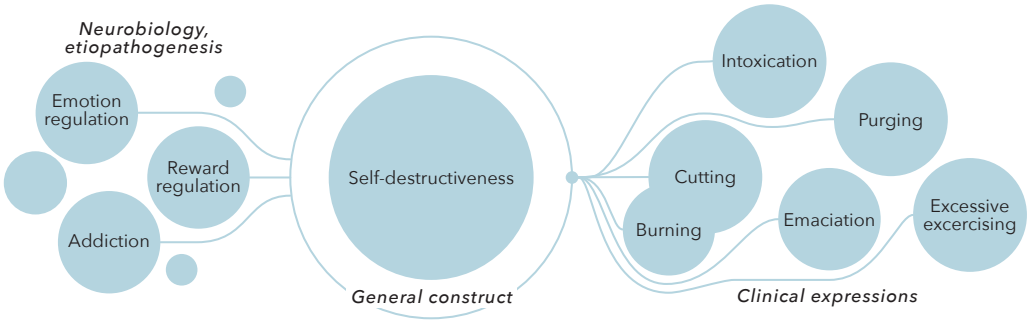

Figure 2d Self-destructiveness as new, DSM-transcending concept or psychopathological entity with a distinct neurological basis and a variety of clinical expressions

AN and NSSI: a research-domain centered approach

As shown above, AN and NSSI share various psychological concepts like reward and punishment, affect regulation and control. A relatively new but promising way to investigate mental disorders is through the Research Domain Criteria (RDoC) framework (National Institute of Mental Health). The RDoC framework aims at understanding the nature of mental health and illness in terms of varying degrees of dysfunction in general psychological and biological systems (59). The RDoC framework focuses on six major domains of human functioning. These domains consist of behavioral constructs, that are studied or assessed using different classes of variables (p.e. genetic, neurocircuit, behavioral, self-report).

In our review, we have focused on the clinical and especially neurobiological overlap between AN and NSSI. The RDoC framework could be of value in further exploring the overlap between AN and NSSI in terms of exploring the basic biological and cognitive processes underlying these disorders, to explain comorbidity and to create a dimensional conceptualization of the phenomena AN and NSSI (60).

According to our review, there seems to be overlap on several if not all six RDoC domains. In both disorders there is involvement of *negative valence systems* (e.g. fear, anxiety, nonreward), *positive valence systems* (p.e. reward, reward learning, habit formation), *cognitive systems* (p.e. self-perception, cognitive control), *systems for social processes* (p.e. self-perception, attachment), *arousal/regulatory systems* (p.e. homeostatic system, pain regulation) and *sensimotor systems* (motor actions, sensimotor dynamics). By using the RDoC framework it would be possible to research

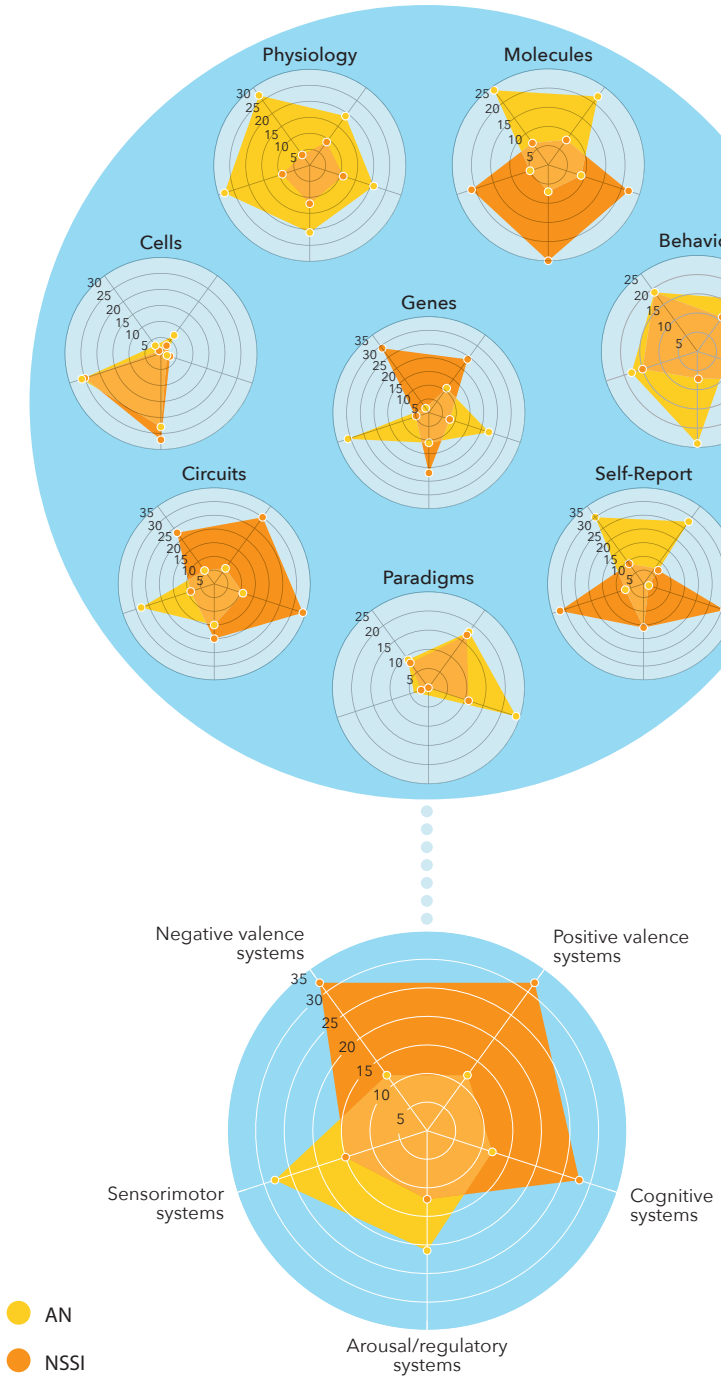

Figure 3 Conceptualization of the relationship between AN and NSSI via the RDoC framework

the more central domains and constructs of AN and NSSI, focusing on the underlying basis (and partially common) concepts. In this way the overlapping aspects can be investigated in a basic and dimensional way using genetic, neurobiological, behavioral and developmental data, leading to new (and maybe common) preventive and therapeutic options (**figure 3**).

AN and NSSI: a network analysis approach

Another way of researching clinical and neurobiological overlap is the network approach. In the network approach mental disorders are conceptualized as causal systems of mutually interacting symptoms (61). Statistical models provide ways to assess centrality of symptoms (i.e. how connected and clinical relevant a symptom is in a network) and to assess so-called 'bridge symptoms', that occur in both disorders.

In the network approach NSSI and AN are hypothesized to co-occur due to mutual interactions among (shared) symptoms. Moreover, besides symptoms, other variables like environmental factors, developmental factors, cognitive processes and laboratory and neurobiological measurements can also be included in a network analysis. A network analysis might reveal connections and bridges between variables that seem to overlap, like the symptoms of NSSI and AN itself (the various forms of expression of NSSI as well as food restriction, binging and purging), co-occurring affective symptoms regarding mood and anxiety, but also other variables like childhood trauma, impulsivity, obsessive-compulsiveness, perfectionism, focus on the body, self-criticism, need for control, emotion regulation and reward. Based on this review it is hypothesized that maladaptive coping and emotion regulation together with dysfunctional reward processing are central variables.

Although establishing centrality and shared symptoms might be of great value to explain co-morbidity, to predict the course of mental disorders, and to target treatment, the network analysis does not fully explain the direction and causality between connecting variables. It may however shed more light on the overlap between NSSI and AN and the shared etiopathogenetic and neurobiological processes underlying both phenomena. This might guide the phenomenological and research domain discussion elaborated on in the above paragraphs (**figure 4**).

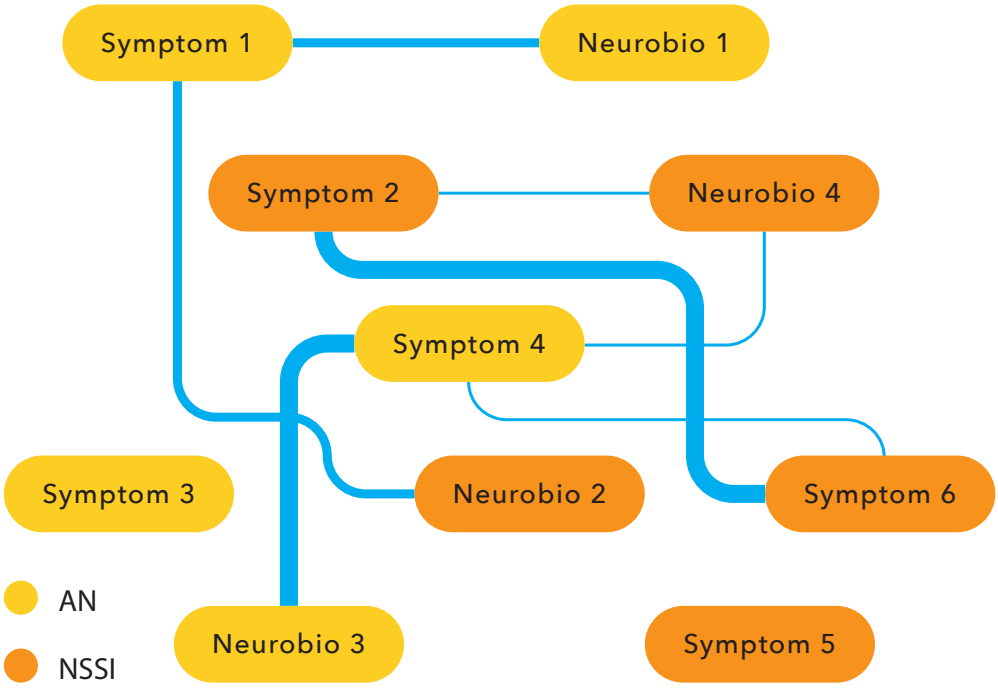

Figure 4 Conceptualization of the relationship between AN and NSSI via network analysis

LIMITATIONS

We described the (psychopathological and neurobiological) overlap between two distinct constructs: AN, which is a psychiatric diagnosis based on the internationally used psychiatric categorical classification system, and NSSI. NSSI has been included in the category 'Conditions for Further Study' in the DSM-5, suggesting a movement towards considering NSSI as a separate disorder. However, in the literature, NSSI is not studied as a separate disorder but as behavior occurring in patients with a range of (psychiatric) disorders as well as in patients with no disorder. Comparing two nosographically and conceptually different constructs may induce bias and complicates drawing conclusions on potential consistency. We have tried to minimize the risk of this bias by selecting literature on NSSI only, and excluding literature on self-destructive behavior and suicidality in general. Due to the use of various definitions of 'self-destructive behavior' or related terms, the differences in context in which self-destructive behavior is studied, and the conceptual nature of our literature synthesis, we conducted a narrative review. This narrative review may be a prelude to more systematic review with a formal search strategy related to the theories we formulated in this narrative review.

Studies on self-destructive behavior and/or NSSI in combination with EDs often do not distinguish between the different EDs but focus on the concept of EDs in general, or on disturbed eating as a symptom. In this narrative review, we chose to focus on AN because we think that AN is a more confined illness-concept with well-defined criteria, and because we hypothesize that the anorectic behavior (restricting, purging, over-exercising) and cognitions in particular have a highly self-destructive character. We used literature specific for AN in combination with NSSI. When no information specific for AN was available, we used literature on EDs in general as this was the best available evidence on this topic.

CONCLUSION

The aim of this review was to review the literature on the neurobiology of anorexia nervosa (AN), the neurobiology of non-suicidal self-injurious behavior (NSSI), and the possible clinical and neurobiological overlap between AN and NSSI, leading to a conceptual hypothesis of a shared etiopathogenesis (or etiopathological correlates) of AN and NSSI.

Based on the literature, both NSSI and EDs are related to emotion dysregulation, maladaptive coping and a dysfunctional reward system. In this conceptual review we formulate a *reward-centered hypothesis* explaining the overlap between AN and NSSI. Furthermore, we propose three approaches that can advance the understanding of the relationship between AN and NSSI, which integrate psychopathology and neurobiology: (1) a nosographical approach, (2) a research domain (RDoC) approach and (3) a network analysis approach. We believe that the approaches will enhance our knowledge of the underlying neurobiological substrates and may provide groundwork for the development of new treatment options for disorders of self-destruction, like AN and NSSI.

In conclusion, we hypothesize that self-destructiveness is a new, DSM-5-transcending concept or psychopathological entity that is reward-driven, and that both AN and (other forms of) NSSI could be conceptualized as *disorders of self-destructiveness*.

RECOMMENDATIONS FOR FURTHER RESEARCH

Our models on the possible relationship between AN and self-destructiveness are hypothetical, providing new inroads for scientific substantiation. We recommend the development of research initiatives that study AN and NSSI in the context of RDoC and through the network analysis and dynamic systems approach. This might increase insight in the mechanisms that cause the clinical and neurobiological overlap between AN and NSSI. To overcome nosologic difficulties we suggest to consider NSSI as a behavioral concept independent of diagnosis, and to research the overlap and differences with disturbed eating-related behavior instead of eating disorders or anorexia nervosa. This would lead to a more neuroscientific approach of defining and researching psychopathology conform the Research Domain Criteria (RDoC) Project (59, 62).

The involvement of the opioid system in both AN and NSSI is a point of interest, possibly creating an opportunity for new pharmacotherapeutical interventions in AN, NSSI or the combination (63). For example, N-Acetylcysteine is being studied as possible moderator in behavioral addiction (64).

A potentially promising intervention that is being researched in patients with severe, chronic treatment refractory AN is modulation of the reward circuitry with deep brain stimulation (DBS). Given the observed high levels of self-destructiveness (eating-disordered as well as non-eating disordered) and the affect regulation and reward-related abnormalities in these patients, DBS might be effective in the treatment of not only AN but also of self-destructiveness in general.
Neuroimaging studies focusing on the concepts of self-destructiveness, affect regulation and reward regulation of both AN and NSSI might increase knowledge of the underlying neurobiological substrates, providing tools for the development of new and targeted treatment options for both AN, NSSI and the combination of both.

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PART VI

Summary and discussion I

SUMMARY OF MAIN FINDINGS

Anorexia nervosa (AN) is a severe psychiatric disorder marked by low body weight, body image abnormalities, and anxiety and shows elevated rates of morbidity, comorbidity and mortality. Given the limited availability of evidence-based treatments, it manifests as a chronic condition in a significant percentage of patients. Consequently, there is an urgent need to investigate new therapeutic options that are informed by the disorder's underlying neurobiological mechanisms.

In this thesis, we explore the potential utility of deep brain stimulation (DBS) as a last-resort treatment for individuals suffering from AN. DBS has the advantage of being both reversible and adjustable. Existing studies have demonstrated that DBS can mitigate maladaptive neural activity and connectivity within the targeted region, thereby facilitating the re-establishment of healthier brain network dynamics. Furthermore, we assess the functional effects of DBS on AN through an array of methodologies, encompassing neuroimaging, electroencephalography, as well as metabolic and endocrinological evaluations. Finally, this work will situate AN within a broader theoretical framework, specifically focusing on its manifestation as a form of self-destructive behavior.

Part I

Part I contains the introduction of this thesis.

Part II

In the *first chapter* of this thesis, we conducted a comprehensive literature review to identify potential neurobiological correlates of anorexia nervosa (AN). Our analysis strongly implicates the fronto-striatal circuitry in the neuropathogenesis of AN, specifically the insula, ventral striatum (VS), and an ensemble of cortical regions including the prefrontal, orbitofrontal, temporal, parietal, and anterior cingulate cortices.
Given the symptomatology and neurocircuitry overlap between reward-related disorders such as obsessive-compulsive disorder (OCD) and AN, along with the proven efficacy of accumbal DBS in OCD, we postulate that DBS targeting the nucleus accumbens (NAc) and other reward-associated regions, like the anterior cingulate cortex (ACC), could potentially serve as an effective intervention for patients with chronic, treatment-resistant AN.
We hypothesize that this approach could facilitate not only weight restoration but also significant, sustained amelioration in the core symptoms, associated comorbidities, and complications of AN. Suggested DBS targets for AN include the ACC, the ventral anterior limb of the internal capsule (vALIC), and the VS.

Given the severity of AN and its evident neurobiological substrates, we argue that there exists a compelling rationale for considering an invasive modality such as DBS as a potential therapeutic

avenue for chronic, treatment-resistant AN. Through meticulous selection of stimulation targets, stringent inclusion and exclusion criteria, and rigorous oversight of safety protocols, DBS offers promise in addressing the core symptomatology of AN while concurrently expanding our understanding of its complex pathophysiological mechanisms.

Prior to initiating our DBS-AN study, several case reports had alluded to the potential impact of DBS on body weight and eating behavior. In 2010, our research team disseminated a frequently cited case report describing both smoking cessation and marked weight loss in an obese patient following DBS treatment for OCD (1) . To ascertain whether this isolated observation was replicable in a broader population, we conducted an analysis of weight changes in a more expansive cohort of patients undergoing vALIC-targeted DBS for either OCD or Major Depressive Disorder (MDD) (*Chapter 2*).
Our intention was to elucidate the global effects of DBS on weight and eating behavior. This is particularly relevant given the implicated role of the reward system in various eating behaviors and conditions, including obesity, binge eating, and AN.
Our results indicated no significant alteration in aggregate body weight post-vALIC DBS treatment for either OCD or MDD. Nonetheless, we observed a trending decrease in body mass index (BMI) within the subset of patients categorized as morbidly obese. Importantly, this trend did not mirror the dramatic weight loss depicted in our prior case study. It is worth noting that weight normalization or reduction was not a primary treatment objective in these cases, and no motivational therapy targeting weight loss was administered.

Part III

The core of this thesis is dedicated to a pilot study we conducted, aimed at evaluating the efficacy, safety, and tolerability of DBS in AN. To the best of our knowledge, this is the first study exploring vALIC DBS in the context of AN. Through an extensive optimization period coupled with comprehensive phenotyping, we provide nuanced insights into the psychological, somatic, and functional effects of this treatment modality.

In *Chapter 3*, we present the main results of the DBS-AN study. The average Body Mass Index (BMI) exhibited a substantial and statistically significant elevation by the conclusion of the follow-up period, increasing by 5.32 kg/m^2 (+42.8%, P=.017), thereby attaining the DSM-5 category of 'mild.' This increase was predominantly observed in two of the four participants, whereas the remaining pair manifested only modest BMI increase. A response rate of 50% on primary outcome BMI corroborates the findings of seminal works in this domain, including those by Liu et al. (2020) and Lipsman et al. (2017) (2, 3), which reported response rates of 61% and 57%, respectively.

Clinically, improvements were discernible, encompassing reductions in harmful eating behaviors such as purging, obsessive caloric counting, and body checking. Psychological metrics, as assessed

by the Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS), indicated a general enhancement relative to baseline measurements. Half of the patient cohort could be classified as responders, registering a symptom reduction of 35% or greater. Importantly, all participants noted a decline in eating-disorder related obsessions and compulsions, finding them less gratifying - an observation consistent with the Lipsman et al. (2017) study (3). Additional survey instruments corroborated these clinical improvements, signaling a considerable reduction in average symptoms of depression and anxiety - a crucial outcome given the high prevalence of comorbidities in AN.

Within the domain of Quality of Life (QoL), our study revealed ameliorations in the ED-QOL (physical health), MOS-SF-36 (physical function), and SDS (responsibilities) subscales. Nevertheless, other QoL subscales did not show a parallel enhancement, thereby underlining the enduring psychopathological struggles associated with AN and its comorbid conditions among this severely and chronically afflicted patient population. Notwithstanding these challenges, clinical outcome data indicated enhanced quality of life, and despite the persistence of severe pathology, no patients sought the deactivation or removal of the DBS device.

In summation, the data presented herein substantiate the assertion that vALIC DBS offers a promising, albeit investigational, avenue for the treatment of chronic, treatment-resistant AN. Despite the limitations of this small-scale pilot it serves as an invaluable preliminary investigation into the efficacy, major challenges, safety considerations, and feasibility parameters associated with this emerging treatment modality.

In *Chapter 4*, we present the first meta-analysis focused on the utilization of deep brain stimulation (DBS) in the treatment of anorexia nervosa (AN). Utilizing a random-effects model, the meta-analysis (4 studies with a total of 56 patients) revealed a statistically significant improvement in the primary outcome of BMI, registering a large effect size of 1.13. Notably, this result was accompanied by an absence of observed heterogeneity. Furthermore, the study delineated a favorable influence on comprehensive psychiatric symptom severity, achieving a similarly robust effect size of 0.89. Across four symptom domains - namely, depressive symptoms, obsessive-compulsive symptoms, symptoms of anxiety, and eating disorder symptoms - and in QoL the meta-analysis observed large effect sizes.

Collectively, these findings suggest that DBS exerts statistically significant and large-scale beneficial effects severe, treatment-resistant AN. The observed outcomes are congruent with the documented efficacy of DBS in the management of other psychiatric disorders, such as depression and OCD.

Moreover, the clinical efficacy of DBS, as elucidated by this meta-analysis, may yield valuable insights into the pathophysiology underlying AN. The studies incorporated into the meta-analysis

employed a range of stimulation sites, including the NAc, the subcallosal cingulate (SCC), and the vALIC. Despite these variances, the effects across different research investigations exhibited low heterogeneity. Such uniformity implies that DBS may be efficacious across a spectrum of neural targets, potentially reflecting multiple pathways to rectify dysfunctional neural circuitry.

Part IV

In this part of the thesis, the results of the studies on the functional effects of DBS in AN are described.

In the context of our DBS-AN study, we employed functional magnetic resonance imaging (fMRI) to investigate the neurobiological effects of vALIC DBS in patients with AN (*Chapter 5*). Two specialized tasks were administered: the Monetary Incentive Delay (MID) Task and a Food Viewing Task. The MID Task aimed to assess non-illness-specific, food-related reward processing, whereas the Food Viewing Task was tailored to explore illness-specific reward processing.

Contrary to findings from other investigations, our data did not disclose baseline activation disparities between AN patients and HCs. However, we did observe significant alterations in frontostriatal circuitry in AN patients post-DBS, specifically during both reward and loss anticipation. These changes entailed decreased activation in the right precuneus, right putamen, and right ventral striatum (VS), along with an increase in activation within the medial orbitofrontal cortex (mOFC). Conversely, HCs demonstrated augmented activation levels over time, indicating a differential response to DBS treatment in the AN cohort.

Despite our initial hypothesis suggesting an increase in activation in reward-related brain regions during the Food Viewing Tasks - especially when high-calorie food images were displayed as opposed to low-calorie ones - our empirical findings did not demonstrate statistically significant differences in activation pre- and post-DBS for any of the presented food stimuli. Such incongruence could potentially be ascribed to the limited sample size and the absence of a control group in this specific segment of our study.

In conclusion, our data offer preliminary evidence supporting the involvement of reward circuitry in the pathogenesis of AN, and indicate that DBS has the capability to modulate this aberrant neural activity.

In *Chapter 6* of this thesis, we delved into the effects of deep brain stimulation (DBS) on neural function, as assessed through electroencephalographic (EEG) measures. Contrary to the view that the impact of DBS would be constrained to localized effects around the stimulation site, our hypothesis posited a more expansive influence on the electrophysiological landscape in patients diagnosed with anorexia nervosa (AN).

Our analysis revealed robust empirical support for this hypothesis, as we observed significant and consistent alterations in oscillatory power across all patients. Within-subject these alterations were affecting a broad range of frequencies and extending across multiple brain regions and networks - even when the DBS device was deactivated.

These observations substantiate the notion that the neuromodulatory effects of DBS extend beyond localized regions, impacting broader pathological neural networks. Additionally, our findings suggest that the brain, following an initial period of disorganization, adapts to the perturbations induced by DBS, potentially reorganizing into a functionally more stable state.

In *Chapter 7* of our study, we investigated the endocrine and metabolic effect of deep brain DBS in patients with AN. Our pilot study posited that DBS would induce time-dependent alterations in endocrine and metabolic indices, correlating with AN and concurrent weight gain. We observed statistically significant reductions in testosterone (by 21.47%) and cortisol levels (by 47.39%). Other changes did not reach statistical significance, which may be attributed to the study's limited sample size and the pronounced individual variability.

The observed, albeit non-significant, elevation in leptin among DBS-responsive subjects further implies potential implications of DBS - or the weight gain it induces - on endocrine and metabolic profiles. These observations necessitate additional studies to unravel the intricate relationships among physiology, disordered eating behavior, and neuromodulation.

Although the generalizability of these data to broader AN or DBS populations is restricted, our exploratory study provides foundational insights into endocrine and metabolic shifts potentially induced by DBS.

Part V

As delineated in *Chapter 3*, we noted a statistically significant increase in self-destructive behaviors among the AN patients undergoing DBS treatment. In an effort to elucidate the potential relationship between AN and self-destructive tendencies, specifically non-suicidal self-injurious behavior (NSSI), we undertook a comprehensive review of extant literature (*Chapter 8*).
According to prevailing academic discourse, both NSSI and eating disorders (EDs) exhibit associations with emotional dysregulation, maladaptive coping strategies, and a dysfunctional reward system. Within the framework of this conceptual review, we advance a reward-centric hypothesis elucidating the common features shared between AN and NSSI. To further refine our comprehension of the interplay between AN and NSSI, we advocate for the adoption of three distinct methodological paradigms, each amalgamating elements of psychopathology and neurobiology: (1) a nosographical approach, (2) an approach based on Research Domain Criteria (RDoC), and

(3) a network analysis approach. We posit that the integration of these methodological vectors will augment our understanding of the salient neurobiological determinants, thereby potentially paving the way for the genesis of innovative treatment modalities for disorders characterized by self-destructive behavior, such as AN and NSSI.

In summary, we hypothesize that self-destructive behavior represents a novel, transcendent psychopathological entity, as defined beyond the confines of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Aberrant reward mechanisms ostensibly underlie this entity. Consequently, both AN and NSSI, among other manifestations, could be conceptualized as disorders inherently rooted in self-destructive tendencies.

GENERAL DISCUSSION

In this final chapter, we will first integrate the main findings of this thesis into a conceptual framework of AN. We will subsequently discuss methodological considerations, describe implications for clinical practice and provide recommendations for future research.

This study represents the first research project within the Netherlands to assess the efficacy, safety, and tolerability of DBS in the context of AN. On a global scale, the number of analogous trials are limited. We formulated hypotheses concerning the applicability of DBS as a last-resort therapeutic intervention for patients with chronic, treatment-resistant AN, subsequently constructing a comprehensive framework to probe the neurobiological substrates underpinning this disorder. This line of inquiry guided us to target the ventral anterior limb of the internal capsule (vALIC), an integral component of the brain's reward circuitry, for DBS intervention.

Beyond evaluating the primary effects of DBS on body weight, psychological metrics, and quality of life (QoL), we undertook a multifaceted assessment of its functional effects in AN. Using a variety of modalities - including functional fMRI, EEG, as well as endocrinological and metabolic analyses - we gathered empirical evidence supporting the hypothesis that DBS could serve as an efficacious treatment modality for patients with AN, whose *lives are on a scale*.

Furthermore, this research contributes substantively to the upcoming understanding of the neurobiological pathophysiology of AN, highlighting the brain's reward circuitry as a crucial factor. Lastly, our findings have generated additional hypotheses concerning the conceptual framework of AN, both as a psychiatric disorder and within the broader schema of self-destructive behaviors.

Integrating findings – neurobiology on a scale

The brain's reward circuitry plays a decisive role in the pathophysiology of AN. The mesocorticolimbic pathways are critically implicated in the motivational aspects of eating, and extant functional neuroimaging studies denote aberrant processing of both rewarding and aversive food-related stimuli in AN. Additionally, the cortico-striatal-thalamo-cortical circuits are instrumental in governing executive functions, habit formation, and reward processes relevant to eating behavior and eating disorders (4-9).

Our empirical investigations corroborate the central involvement of reward circuitry in the pathophysiology of AN through multiple avenues. In our DBS-AN study, we strategically targeted the vALIC, a key node within the reward circuitry. Subsequent clinical assessments indicated a diminution in the rewarding properties ascribed to eating disorder-related pathological behaviors. In a parallel fMRI study, we observed discernible alterations in frontostriatal circuit activity during phases of both reward and loss anticipation in AN patients post-DBS. Moreover, our data suggest that the AN cohort exhibits a differential neural response to DBS treatment compared to a healthy control group. Collectively, these findings support the hypothesis that reward circuitry is integral to the pathogenesis of AN and that DBS holds promise in modulating aberrant neural activity.
Our EEG study further substantiates the notion that DBS-induced effects transcend localized stimulation targets. EEG data reveal that the impact of DBS extends to diffuse pathological network activity. After an initial period of neural disorganization, the brain seems to undergo adaptive reorganization, potentially culminating in a more stable, healthier state. These observations align with extant literature on DBS, affirming its capacity to reduce maladaptive neural activity and restore pathological network activity.

Our meta-analysis on DBS in AN suggests that the therapeutic potential of this technique may extend across diverse neural targets. This pluralism in target efficacy may indicate multiple avenues for the normalization of aberrant neural activity within comparable brain circuits. This aligns with the emerging concept of connectomic DBS, where various implementation sites are linked to pathophysiologically relevant white matter tracts. The utilization of advanced connectomic methodologies could facilitate the identification of personalized pathological neural networks, thereby enabling more precise target selection tailored to individual patients.
Additionally, this suggests the possibility of transdiagnostic benefits, as the positive outcomes appear to extend to other psychiatric disorders where similar neural targets have been employed with therapeutic success.

The outcomes of our investigation align closely with extisting research elucidating the mechanisms of action underpinning DBS. DBS implies continuous modulation of neural structures integral to, or associated with, specific brain circuits. Historically, high-frequency stimulation exceeding 100 Hz has been posited to mediate its therapeutic effects by locally attenuating

pathological hyperactivity, akin to ablative surgical interventions. However, contemporary perspectives increasingly recognize the dual role of DBS in restoring normal neural function (10). It achieves this not only by inhibiting aberrant neural activity but also by stimulating specific neurons, thereby restoring proper network connectivity (11). This dual modulation enables a cognitive shift in patients, allowing them to transition from a habitual focus on disorder-related stimuli toward the re-establishment of goal-directed behaviors. Additional psychotherapeutical interventions could be helpful in sustaining this effect.

Despite these insights, the precise neurophysiological effects of DBS at the cellular and molecular tiers remain intricate, heterogeneous, and not fully elucidated (12). The long-term impact of this intervention on neural network restructuring, both within targeted areas and in adjacently connected regions, is yet to be fully characterized. This also applies to the influence of DBS on neurotransmitter kinetics - including release, uptake, and receptor sensitivity. The interaction between DBS and neural development in younger cohorts, as well as its role in neurodegenerative processes in older populations, also remains an enigmatic and underexplored domain. These uncertainties are particularly significant in conditions such as AN, where brain functioning and pathophysiology are further compromised due to prolonged exposure to malnutrition.

Integrating findings - conceptualization on a scale

The conceptualization of eating disorders, particularly AN, remains an area of considerable uncertainty and ongoing scholarly debate. Early psychoanalytical models, originating in the 1940s, attributed the etiology of AN to sexual drives. This perspective was later refuted by Hilde Bruch in her seminal 1982 lecture, wherein she proposed a more nuanced framework based on four principal domains: 1) body perception and interoceptive awareness; 2) attachment; 3) emotional perception, expression, and regulation; and 4) interpersonal functioning (13). This model has been updated by Treasure and Cardi in 2017, who incorporated genetic predispositions and obsessive-compulsive personality traits - such as inflexibility, attention to detail, and elevated standards - as additional risk factors (14).

Alternative models have sought to classify eating disorders as primarily disruptions in feeding or appetite, distortions of body image, or as disorders within the neurotic, psychotic, or psychosomatic spectra. The high prevalence of comorbidities, coupled with neurobiological overlaps with other psychiatric conditions, as well as shared genetic and environmental influences, all underscore the multifactorial etiology of AN. These complexities further highlight the challenges inherent in formulating a comprehensive and unified conceptual framework for the disorder.

In *Part V* of this thesis, we examine the clinical and neurobiological intersections between AN and self-destructive behaviors, navigating the complexities inherent in linking two fundamentally dissimilar constructs. While AN manifests through a specific set of symptoms - such as self-star-

vation, purging, and excessive exercise - these behaviors can be subsumed under a broader category of self-destructiveness. One of the participants of our study expressed this by saying that her eating disordered behaviors were giving her a form of satisfaction because of the 'active' balancing on the edge of life and death.

Historically, self-destructive behavior has been considered a symptomatic feature of various psychiatric disorders, such as borderline personality disorder. Alternatively, the self-destructive behaviors evident in AN could be conceptualized as a form of non-suicidal self-injury (NSSI), a category increasingly acknowledged as a separate disorder related to affect regulation and reward mechanisms.

The hypothetical models we propose in this thesis illuminate alternative perspectives: AN as an isolated diagnostic entity, and AN as a form of expression of reward-driven disorder of self-destructiveness. It is crucial to underscore the speculative nature of our models; the act of comparing two divergent, nosographically and conceptually distinct constructs inevitably introduces bias and complicates any efforts to draw definitive conclusions.

Nonetheless, we posit that our hypothetical models may offer novel avenues for empirical validation. Modulating the reward circuitry through DBS could prove efficacious not merely in the treatment of AN but also in addressing self-destructive behaviors more broadly. Moreover, supplementing DBS treatment with psychotherapeutic interventions targeted at underlying issues of emotion and impulse regulation could potentially amplify the therapeutic impact of DBS in AN, thereby improving clinical outcomes.

Integrating findings - ethics and philosophy on a scale

Employing an invasive, experimental neural intervention on a highly vulnerable patient population suffering from AN elicits a range of ethical and philosophical questions (15). Central to the discourse on medical ethics is the *principle of equipoise*.

Our DBS-AN study was categorized as high-risk due to several factors: the experimental nature of the investigation, the invasiveness of the procedure, and the critical medical condition of the patient population, which exhibited severe underweight conditions (BMI < 15 kg/m^2). The unique convergence of these variables renders risk-benefit calculations highly complex. However, in severe and enduring AN the exploration of innovative, albeit high-risk, therapeutic interventions seems warranted. AN has relatively clear neurobiological underpinnings, has high morbidity and mortality rates, has a proclivity for a chronic trajectory in a significant subset of patients, and evidence-based treatment modalities are scarce.

To secure authorization for this pilot study, we adhered to stringent and rigorous regulatory protocols, culminating in approval from our Medical Ethics Committee (MEC). The study was subjected to extensive monitoring, and a Data Safety Monitoring Board (DSMB) was instituted. Inclusion criteria were meticulously formulated to enlist only those patients with an extended illness duration (exceeding 10 years) who had exhausted all conventional treatment avenues and for whom the potential benefits of recovering from AN would be substantial.

To mitigate both medical and psychological risks, our patient cohort underwent rigorous pre-inclusion screening, facilitated by a comprehensive study protocol designed to enact safeguards. Throughout the study, the physical and psychological well-being of the participants was carefully monitored via weekly consultations with our nurse practitioner and consulting psychiatrist. In the perioperative phase or in instances of significant adverse events, patients were admitted to our Medical Psychiatric Unit (MPU) for more intensive evaluation and care.

Unlike psychiatric conditions such as OCD, the symptoms of AN are often ego-syntonic, meaning patients may perceive these symptoms as integral to their identity. Moreover, a lack of insight into, or trivialization of, the physical implications of the disorder is a characteristic feature among AN patients. These factors raise complex ethical issues regarding patient *autonomy* and the *capacity for informed consent*.

Although cognitive impairments can occur in AN patients due to prolonged malnutrition, their intellectual capabilities are generally preserved. However, their specific decision-making competence concerning their disorder may be compromised by their perception of the eating disorder as part of their identity, as well as by dysfunctional beliefs surrounding body weight, shape, and behaviors associated with AN.

Given that all conventional treatment avenues have typically been exhausted for these patients, the allure of a novel, experimental intervention like deep brain stimulation (DBS) and the *hope* for a positive outcome may exert a disproportionate influence on their decision to participate in the study. The unique opportunity to partake in the inaugural DBS trial for AN in the Netherlands - especially when only a handful of similar initiatives exist globally - may further skew consent. Patients may be inclined to overestimate the benefits and underestimate the risks, influenced both by *hope* and a sense of being 'special' or pioneering. These aspects, being important a-specific therapeutic factors, may also affect the clinical course and outcome of the study.

To address these ethical complexities, Park et al. (2017) have developed "The Oxford Neuroethics Gold Standard Framework for DBS in AN," aimed at guiding ethics committees and researchers in ensuring ethically robust conduct of such studies (16).

The application of DBS for psychiatric disorders in general introduces several complex philosophical issues that warrant consideration.

Firstly, intervening directly in the brain - a central locus of consciousness and personality - provokes questions about the potential alteration of a person's essential nature. Is the post-DBS *'self'* fundamentally the same, or does the intervention reshape it? Should any such alteration be considered a form of healing, or does it constitute the creation of a new or different individual? This is particularly pertinent in the context of AN, which often becomes deeply intertwined with a patient's identity. One of the participants of the study indicated that before DBS, the AN was her (sole) identity (that is, the AN was very *egosyntonic*). Only after treatment with DBS, she noticed the AN becoming more egodystonic, leaving room for her own identity to come to surface.

Secondly, questions surrounding *free will, autonomy, and the capacity to consent* are both ethically and philosophically intricate. If one accepts the brain as the seat of thought and behavior, direct manipulation of neural pathways challenges traditional notions of free will. Post-DBS, is an individual acting solely out of their own volition, or are their actions influenced - or even dictated - by the intervention? This bears implications for *personal responsibility* and *accountability*.

Additionally, employing DBS presupposes normative definitions of 'normal' and 'healthy' behavior and cognition. Who, then, is tasked with delineating these norms? While in the context of severe and enduring AN the issue may seem less controversial, psychiatric diagnoses largely rely on classifications and conceptual frameworks, leaving the boundaries between *normality* and disorder blurred. As DBS gains traction as a treatment for AN, ethical questions about pathologizing individual variance and the scope of its application for cognitive or emotional enhancement inevitably arise.

These concerns resonate with broader philosophical critiques, arguing that societal tendencies to medicalize life's challenges blur the lines between *personal and societal responsibility*. If we possess the tools to mitigate aspects of the human condition traditionally seen as integral to personal growth and spiritual development, what are the broader implications for human society?

The mechanistic worldview, as explored by philosophers like Martin Heidegger and Michel Foucault, considers the body as a machine to be optimized or fixed. Does the application of DBS perpetuate this perspective, and if so, what are the ramifications for our understanding of human existence?

While this thesis will not provide definitive answers to these multifaceted questions, they remain crucial considerations for the design and evaluation of future studies on DBS for psychiatric disorders, particularly AN. The complexities of *life* manifest *on numerous scales*, and a nuanced approach is imperative.

Limitations and strengths

Several limitations and strengths of the studies conducted for this thesis have been delineated in their respective chapters; however, some overarching considerations warrant mention.

One limitation is the small sample size, which is a consequence of the study's experimental nature, highly specific setting, and specialized patient population. This leads to low statistical power, potentially affecting the generalizability of our results. Additionally, the open-label provision of DBS could introduce placebo effects or other non-specific influences on the outcomes. Factors such as increased patient contact, the novelty of participating in a unique study, and patients' hope and expectations could inadvertently contribute to more positive results. We attempted to mitigate these limitations by incorporating a one-year follow-up period to investigate the durability of observed effects. Ethical considerations related to performing an invasive, experimental procedure on a medically vulnerable patient population necessitated the absence of a control group.

Patient selection in our study deserves particular attention. Participants were critically ill, displaying chronic, treatment-resistant AN. Previous pharmacological and psychotherapeutic interventions had proven ineffective, and the patients were functionally impaired in virtually all life domains. Preoperatively, they were in dire physical condition, severely underweight, and experiencing both acute and long-term complications from enduring malnutrition. With an average illness duration of 21 years, this cohort can be classified as chronic. Therefore, our findings are applicable exclusively to this narrow, severely affected patient subgroup and not to the broader population of individuals with AN. Moreover, our study did not differentiate between AN subtypes (i.e., restrictive or binge-purge), and participants exhibited a range of psychiatric comorbidities. Given these factors, the generalizability of our findings is limited.

On the one hand, it seems prudent to reserve new and experimental interventions for patients who have not responded to existing, standard treatment modalities - essentially, patients with limited options remaining. On the other hand, this specific patient population, characterized by treatment resistance and illness durations exceeding 10 years, inherently has a diminished likelihood of responding positively to any form of intervention.

Moreover, the precarious physical and psychological condition of this patient group elevated the risk of adverse events, not just perioperatively but throughout the duration of the study. This was evidenced by the elevated incidence of (severe) adverse events we observed. As a result, the anorexia nervosa (AN) patients participating in our study required considerably more frequent and intensive medical oversight, both in inpatient and outpatient settings, compared to patients with OCD who were treated with DBS.

Another challenge we encountered was the complexity of assessing outcomes in this patient population. Many studies on AN employ changes in BMI as the primary outcome measure. However, this approach is debatable, as the diagnostic criteria for AN only partially revolve around weight and BMI. The literature lacks consensus on the definitions of recovery and treatment refractoriness in AN, and studies often use a diverse array of psychological outcome measures. In our study, we selected changes in the Yale-Brown Obsessive Compulsive Scale for Eating Disorders (Y-BOCS-EDS) as the primary psychological outcome, aiming to quantify the severity of eating disorder-related obsessions and compulsions.

However, it's important to note that AN is a complex disorder, encompassing a broad range of psychopathologies beyond what is captured by the Y-BOCS-EDS. Additionally, while symptoms of OCD tend to respond more rapidly to DBS, the symptoms of AN - particularly in patients with enduring and chronic forms of the disorder - are more tenacious and deeply ingrained in patients' routines and identity. Consequently, it was less likely to observe significant changes in the Y-BOCS-EDS scores or other questionnaires on a weekly basis.

Given this complexity, we conducted weekly visits during the optimization period and added extensive narrative interviews, which proved to be both time-intensive and demanding for both the patients and the research team.

The major strength of this thesis is that it represents the first study in the Netherlands and one of a limited number globally to evaluate the efficacy, safety, and tolerability of DBS in the treatment of AN. Beyond assessing the primary impact of DBS on body weight, psychological parameters, and QoL, this research is novel in its comprehensive approach. We integrated evaluations of efficacy with critical examinations of the functional impact of DBS in AN, including fMRI, electro-encephalography EEG, as well as endocrinological and metabolic assessments. This thesis thereby deepens our understanding of the neurobiological underpinnings of AN and paves the way for future research and potential clinical applications of DBS in the management of severe and enduring AN.

Research and clinical future directions

In addition to the specific directions for future research and clinical practice outlined in individual sections of this thesis, we offer overarching recommendations concerning research design and clinical implications.

Eating disorders, especially AN, are disabling, and costly mental disorders that considerably impair physical health and disrupt psychosocial functioning (17). AN has the highest mortality of all psychiatric disorders, and in20% of cases, the disease takes on a chronic course (18). The recent COVID-19 pandemic further impacted young people with restrictive eating disorders as seen by

increased hospitalizations and requests for outpatient care (19). A recent systematic review of more than 63.000 participants from 16 countries found that about 22% of children and adolescents experience disordered eating (20). Future studies on prevention, etiopathogenesis and novel treatment options for AN are urgently needed.

Studies incorporating larger sample sizes are essential for establishing DBS as a standardized, last-resort treatment for this complex patient population. Future research should be meticulously designed, considering factors such as the severity and subtype of AN, the presence of physical and psychiatric comorbidities, and potential predictors of treatment response when selecting participants. Investigating a more homogenous subgroup of AN patients, who are less severely impacted by the long-term complications of AN and its comorbidities, could expedite the verification of DBS's efficacy.

Our pilot study suggests that DBS can be deemed a relatively safe intervention for patients with severe AN. Therefore, it appears reasonable to explore its applicability in a broader AN subpopulation, beyond just the most severe cases. Ethically speaking, the experimental and invasive nature of this research mitigates the need for a control group. Nonetheless, incorporating both "DBS-ON" and "DBS-OFF" phases into future study designs would offer valuable insights into the direct effects of DBS on clinical symptoms, as well as on neurobiological and endocrinological parameters.

Additionally, there is a pressing need for more comprehensive and standardized clinical outcome measures that extend beyond weight and BMI. This would necessitate greater uniformity in defining treatment outcomes and recovery in the context of AN. Our study did not incorporate specific outcome measures targeted at emotion regulation or self-destructive behaviors. Given our observations, subsequent studies employing vALIC DBS could prioritize these facets to yield further insights into novel perspectives on the underlying pathophysiological mechanisms in chronic, treatment-refractory AN.

A focal point for future research involves examining the variances and commonalities among the diverse DBS targets that have been employed. Our results suggest that targeting the brain's reward circuitry appears to be substantiated. However, this targeting can be further specified and refined. Investigations could explore both clinical and biological differentials in treatment effects. This might be accomplished through advanced clinical phenotyping coupled with an array of biological assessments, including advanced connectomic neuroimaging.

Important recent developments in DBS technology are electrodes with multiple independently controllable contacts and closed loop technologies. These advances could improve our understanding of psychiatric neurobiology and further specify and personify treatment options (21, 22).

Subsequent studies on DBS in AN should incorporate functional neuroimaging methods, deploying more disease-specific tasks to deepen our understanding of how reward responses correlate with the clinical features of AN. This could augment our knowledge of the etiopathological mechanisms underlying AN as well as the functional impacts of DBS. Establishing an international collaboration to conduct fMRI on a larger cohort of AN patients undergoing DBS treatment, or adopting a transdiagnostic approach that compares DBS in AN with DBS in OCD or MDD, would be invaluable for exploring the potential for individualized DBS targeting.

Our theoretical frameworks exploring the potential relationship between AN and non-suicidal self-injury (NSSI) offer novel avenues for empirical validation. We advocate for the initiation of research programs that examine AN and NSSI within the framework of the Research Domain Criteria (RDoC) as well as through network analysis and dynamic systems theory. Such approaches could enhance our understanding of the mechanisms responsible for the clinical and neurobiological overlaps between AN and NSSI. Neuroimaging investigations centered on the themes of self-destructiveness, affect regulation, and reward regulation in both AN and NSSI could illuminate the underlying neurobiological substrates. This would subsequently facilitate the development of targeted treatment options for AN, NSSI, and comorbid cases.

Another promising avenue for future research involves the synergistic combination of DBS and psychotherapy in the treatment of AN. Existing DBS studies in psychiatric conditions other than AN suggest that DBS may potentiate the efficacy of psychotherapeutic interventions. Given the clinical and neurobiological intersections between AN and NSSI, as well as their associated challenges in emotion regulation, it would be worthwhile to explore whether psychotherapy focused on enhancing emotion regulation could amplify the therapeutic impact of DBS.

Given the paucity of effective treatments for severe AN there is growing interest in the use of other brain stimulation techniques such as transcranial magnetic stimulation and transcranial direct current stimulation as possible treatments (23, 24). Other novel developments in the treatment of AN encompass the use of microbiome-based interventions such as fecal microbiota transplants and probiotics as adjuvants to standard AN therapies (25, 26). Recently, psilocybin therapy in AN in an open-label pilot study was reported as a safe and promising treatment option in AN (27).

One thing that stood out for me during the conduction of this study was that perhaps the most invaluable knowledge and comprehension of this fascinating disorder came from the participating patients themselves. During the countless study-visits, admissions at the MPU, or while waiting for yet another EEG of fMRI, we had (and still have) numerous in-depth conversations. For me their personal experiences with and thoughts on their symptoms, their eating disorder and their personality and identity, became crucial in understanding AN. Their personal narrative made it possible to connect and integrate the findings of our study with the clinical practice.

As a follow-up to this thesis, we plan to conduct semi-structured interviews with patients diagnosed with AN, both with and without DBS treatment. The objective is to capture and analyze their subjective experiences related to their eating disorder as well as their interactions with DBS. Such an investigation may enhance our understanding and conceptualization of AN, as well as its interrelationship with other disorders and constructs, particularly those related to reward and affect regulation.

Our study holds multiple dimensions of clinical significance. Importantly, it corroborates the role of the brain's reward circuitry in the etiopathogenesis of AN. This insight has the potential to inform the development or adaptation of alternative therapeutic modalities targeting the reward system, including both psychopharmacological and psychotherapeutic interventions. We anticipate that this study, along with forthcoming research, will eventually pave the way for the clinical utilization of DBS in AN. This could position DBS as either a last-resort treatment option or potentially as a standardized, evidence-based therapeutic approach for this patient population. In addition, this study contributes to the broader conceptualization of eating disorders.

This journey certainly has not answered all my questions. In fact, it has only increased my fascination with the undeniable interrelatedness of body and mind. It has inspired me to continue my clinical work with and develop future research projects on this complex, severe and intriguing disorder.

Ultimately, the stakes are exceedingly high for these patients, as their *lives are on a scale*.

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PART VII

Appendices I

9 Dutch summary/ Nederlandse samenvatting

DEEL I - INTRODUCTIE

Anorexia nervosa (AN) is een ernstige psychiatrische aandoening die gekenmerkt wordt door een intense angst om in gewicht aan te komen en een verstoord lichaamsbeeld. Er is sprake van een ernstig beperkte voedselinname en ander gedrag dat ertoe leidt dat patiënten niet in staat zijn om 'een minimaal gezond lichaamsgewicht vast te houden'. Vaak vinden patiënten AN niet dat zij een stoornis of probleem hebben, en hebben ze de neiging om de ernst van hun (vaak ernstig bedreigde) lichamelijke toestandsbeeld te bagatelliseren.
Patiënten met AN hebben door de slechte voedselintake en de ondervoede toestand vaak ernstige lichamelijke complicaties en de ziekte heeft bovendien een grote impact op het psychisch en sociaal functioneren en de kwaliteit van leven. AN heeft bij een significant deel van de patiënten een chronisch beloop. AN heeft de hoogste mortaliteit van alle psychiatrische aandoeningen, zowel vanwege de levensbedreigende lichamelijke complicaties als vanwege een sterk verhoogd suïciderisico.

De etiopathogenese van AN is multifactorieel en bestaat uit genetische, (neuro)biologische psychologische, en omgevingsgerelateerde factoren. Uit onderzoeken naar de onderliggende neurobiologische mechanismen komt naar voren dat het het zogenaamde 'beloningscircuit' in de hersenen, dat betrokken is bij beloning en straf, een belangrijke rol speelt in de pathofysiologie van AN. Gezien de beperkte beschikbaarheid van evidence-based behandelopties, is er een dringende behoefte aan het onderzoek naar nieuwe behandelopties die gebaseerd zijn op de onderliggende pathofysiologische mechanismen van de aandoening.

In deze thesis zullen we de potentiële effectiviteit van diepe hersenstimulatie (DBS) als laatste redmiddel voor de behandeling van patiënten met ernstige, chronische en therapieresistente AN onderzoeken. DBS is een behandeling waarbij elektrodes worden geïmplanteerd in specifieke hersengebieden, met als doel de neuronale activiteit in deze gebieden te beïnvloeden. In tegenstelling tot ablatieve neurochirurgie heeft DBS het voordeel dat het zowel omkeerbaar als aanpasbaar is. Studies hebben aangetoond dat DBS dysfunctionele neurale activiteit en connectiviteit binnen het doelgebied kan verminderen, waardoor er herstel van gezondere netwerkactiviteit kan optreden.

DBS is een aangetoond effectieve behandeling voor patiënten met een obsessieve compulsieve stoornis (OCD). Gezien de klinische en neurobiologische overeenkomsten tussen OCD en AN is onze hypothese dat DBS ook bij AN effectief zou kunnen zijn. Daarom hebben wij een onderzoeksprotocol opgesteld om de effectiviteit, veiligheid en toepasbaarheid van DBS bij AN te onderzoeken. Verder zullen we de functionele effecten van DBS bij AN onderzoeken door middel van een scala aan methodologieën, waaronder functionele magnetische resonantie imaging (fMRI), elektro-encefalografie (EEG), alsmede metabole en endocrinologische metingen. Tot slot

zal AN in deze thesis worden geconceptualiseerd binnen een breder theoretisch kader, specifiek gericht op de manifestatie ervan als een vorm van zelfdestructief gedrag.

DEEL II - DBS IN AN: HYPOTHESEVORMING

In het ***eerste hoofdstuk*** van deze thesis beschrijven wij een literatuurstudie om potentiële neurobiologische correlaten van AN te identificeren. In de literatuur komt duidelijk naar voren dat de fronto-striatale circuits - specifiek de insula, het ventrale striatum (VS), en de prefrontale, orbitofrontale, temporale, pariëtale en anterieure cingulate cortices - betrokken zijn in de neuropathogenese van AN.

Gezien de symptomatologische en neurobiologische overlap tussen verschillende beloningsgerelateerde aandoeningen zoals OCD en AN, en de bewezen effectiviteit van DBS bij OCD, stellen we dat DBS gericht op aan beloning gerelateerde gebieden, zoals de nucleus accumbens (NAc) en anterieure cingulate cortex (ACC), mogelijk een effectieve interventie zou kunnen zijn voor patiënten met chronische, therapieresistente AN.

Gezien de ernst van AN en het duidelijke neurobiologische substraat, beargumenteren we dat er een overtuigende reden is om een invasieve interventie zoals DBS te overwegen als een mogelijke behandeloptie voor chronische, therapieresistente AN. Door zorgvuldige selectie van het DBS-target, goed gedefinieerde inclusie- en exclusiecriteria, en strikte naleving van veiligheidsprotocollen, biedt DBS de kans om de kernsymptomatologie van AN aan te pakken, terwijl tegelijkertijd onze kennis van de complexe pathofysiologische mechanismen van AN wordt uitgebreid.
Wij stellen dat DBS niet alleen zou kunnen bijdragen aan gewichtsherstel, maar ook aan een significante, aanhoudende verbetering van de kernsymptomen van AN, de geassocieerde comorbiditeit en de complicaties van AN. Voorgestelde DBS-doelgebieden voor AN zijn de ACC, het ventrale anterieure deel van de interne capsule (vALIC) en het VS.

Voordat wij met onze DBS-AN-studie startten, suggereerden verscheidene casusrapporten al dat DBS een mogelijke impact zou kunnen hebben op lichaamsgewicht en eetgedrag. In 2010 heeft ons onderzoeksteam een veel aangehaald casusrapport gepubliceerd waarin beschreven werd dat BDS voor OCD bij een obese patiënte heeft geleid tot zowel het stoppen met roken als ook aanzienlijk gewichtsverlies. Om vast te stellen of deze geïsoleerde waarneming repliceerbaar was in een breder patiëntenbestand, hebben we zoals beschreven in ***hoofdstuk 2*** een analyse uitgevoerd van de gewichtsveranderingen in een uitgebreider cohort van patiënten die vALIC-gerichte DBS ondergingen voor óf OCD óf ernstige depressieve stoornis (MDD).

Onze intentie was om de algehele effecten van DBS op gewicht en eetgedrag in kaart te brengen. Dit is met name relevant vanwege de rol van het beloningssysteem bij eetgedrag en diverse eetgerelateerde aandoeningen, zoals obesitas, eetbuien-stoornis en AN.
Onze resultaten tonen geen significante verandering in het totale lichaamsgewicht na vALIC-gerichte DBS-behandeling voor zowel OCD als MDD. Desondanks observeren we een dalende trend in body mass index (BMI) binnen de subgroep van patiënten met morbide obesitas. Belangrijk is dat deze trend niet overeenkomt met het significante gewichtsverlies dat in ons eerdere casusrapport werd beschreven. Opgemerkt moet worden dat gewichtsnormalisatie of -vermindering geen primair behandeldoel was in de onderzochte populatie, en dat er geen sprake was van toegevoegde motivationele therapie gericht op gewichtsverlies.

Een opmerkelijke beperking van deze studie is het ontbreken van longitudinale BMI-gegevens tijdens de postoperatieve follow-up van met DBS behandelde patiënten. Dit kan grotendeels worden toegeschreven aan het ontbreken van gestandaardiseerde lichaamsgewichtsmetingen op vaste intervallen in dit cohort en wij een retrospectieve analyse hebben verricht van de beschikbare gegevens.

DEEL III - DBS IN AN: KLINISCHE EFFECTEN

De kern van deze thesis is gewijd aan een verkennende studie die we hebben uitgevoerd naar de effectiviteit, veiligheid en toepasbaarheid van DBS bij AN. Voor zover wij weten, is dit de eerste studie die vALIC DBS bij AN onderzoekt. Middels een uitgebreide optimalisatieperiode gekoppeld aan diepgaande fenotypering, bieden we genuanceerde inzichten in de psychologische, somatische en functionele effecten van deze behandelingsmodaliteit.
In ***hoofdstuk 3*** worden de primaire resultaten van de studie beschreven. Er is sprake van een aanzienlijke en statistisch significante stijging van de BMI aan het einde van de follow-up periode, met een toename van 5,32 kg/m^2 (+42,8%, P=.017). Deze verbetering wordt voornamelijk gezien bij twee van de vier proefpersonen, terwijl de overige twee proefpersonen slechts een bescheiden toename van de BMI-verhoging laten zien. Dergelijke responspercentages komen overeen met andere onderzoeken op dit domein.

Opvallend is dat wij klinisch duidelijke verbeteringen zagen, waaronder een afname van pathologisch eetgedrag zoals braken, het obsessief tellen van calorieën en het controleren van het lichaam. Psychologische metingen, zoals score van de Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS), tonen een algemene verbetering ten opzichte van de uitgangsmetingen. De helft van de proefpersonen kan als responder worden geclassificeerd, met een symptoomreductie van 35% of meer. Belangrijk om te vermelden is dat alle deelnemers een afname van eetstoornis-gerelateerde preoccupaties en obsessies vermelden, en dat deze eetstoornis-gedragingen duidelijk als minder voldoening-gevend worden ervaren.

Deze klinische verbetering wordt bevestigd door aanvullende metingen. Er was sprake van een aanzienlijke vermindering van symptomen van depressie en angst - belangrijk gezien de hoge mate van comorbiditeit bij AN. Op het gebied van kwaliteit van leven (QoL) vinden wij verbeteringen op subschalen van de ED-QOL (fysieke gezondheid), MOS-SF-36 (fysieke functie) en SDS (verantwoordelijkheden). Andere QoL-subschalen tonen geen significante verbetering, hetgeen wellicht samenhangt met de lange duur en ernst van de psychopathologie van AN en de comorbiditeit in deze ernstig en chronisch getroffen patiëntengroep. Klinisch geven de proefpersonen aan dat hun kwaliteit van leven sinds de DBS is verbeterd, en ondanks het aanhouden van ernstige pathologie, heeft geen van de patiënten tijdens de studie gevraagd om het uitzetten of verwijdering van het DBS-apparaat.

Samenvattend ondersteunen de gepresenteerde resultaten de hypothese dat vALIC DBS een veelbelovende behandeloptie zou kunnen zijn voor chronische, therapieresistente AN. Hoewel onze kleine, verkennende studie veel beperkingen heeft - hier wordt in de discussie uitgebreid op ingegaan - is deze studie een belangrijke aanzet tot het in kaart brengen van de belangrijkste uitdagingen en veiligheidsoverwegingen die geassocieerd zijn met onderzoek naar en eventuele toekomstige toepassing van deze opkomende behandelingoptie.

In ***hoofdstuk 4*** beschrijven we de eerste meta-analyse van de effectiviteit van DBS bij AN. Deze meta-analyse toont met behulp van een random-effects model een statistisch significante verbetering van de primaire uitkomst BMI, met een effectgrootte van 1,13. Verder schetst de studie een positief effect van DBS op de algehele psychiatrische symptoomernst, met een eveneens robuuste effectgrootte van 0,89. Over vier symptoomdomeinen - namelijk, depressieve symptomen (Hedges›s g = 0,98), obsessief-compulsieve symptomen (Hedges›s g = 0,72), angstsymptomen (Hedges›s g = 0,85) en eetstoornissymptomen (Hedges›s g = 0,98) - werden ook grote effectgroottes gevonden. Aanvullende analyse toont ook verbetering aan in kwaliteit van leven (Hedges›s g = 0,86).
Er is slechts beperkt sprake van publicatiebias, wat de validiteit van onze bevindingen versterkt.

Gezamenlijk suggereren deze bevindingen dat DBS bij ernstige, therapieresistente AN een statistisch significant en positief effect heeft op meerdere uitkomstmaten. De waargenomen uitkomsten komen overeen met de uitkomsten van studies naar de effectiviteit van DBS bij andere psychiatrische stoornissen, zoals MDD en OCD.

Bovendien kan de klinische effectiviteit van DBS, zoals verhelderd door deze meta-analyse, waardevolle inzichten opleveren in de pathofysiologie die ten grondslag ligt aan AN. De studies die in de meta-analyse zijn opgenomen, gebruikten aan aantal verschillende stimulatie doelgebieden, waaronder de NAc, de subcallosale cingulate (SCC) en de vALIC. Ondanks deze verschillen in doelgebieden zijn de effecten over verschillende onderzoeken relatief homogeen.

Deze uniformiteit impliceert dat DBS effectief is op meerdere doelgebieden, wat mogelijk een weerspiegeling is van het feit dat er meerdere wegen zijn om disfunctionele neurale circuits te beïnvloeden. Dit sluit aan bij het opkomende concept van connectomische DBS, waarbij verschillende doelgebieden zijn gekoppeld aan pathofysiologisch relevante witte stofbanen. Daarnaast zijn de positieve uitkomsten mogelijk te extrapoleren naar andere psychiatrische stoornissen waarbij vergelijkbare doelgebieden met effectief zijn gebleken, wat de transdiagnostische kennis vergroot.

DEEL IV - DBS IN AN: FUNCTIONELE EFFECTEN

Tijdens onze DBS-AN studie hebben we de neurobiologische effecten van vALIC DBS bij AN met behulp van functionele magnetische resonantie beeldvorming (fMRI) onderzocht (***hoofdstuk 5***). We hebben daarbij twee verschillende taken gebruikt: de Monetary Incentive Delay (MID) taak en een voedselplaatjestaak. De MID taak is gericht op het beoordelen van niet-ziektespecifieke, monetaire beloningsverwerking. De voedselplaatsjestaak meer gericht is op eetstoornis-gerelateerde beloningsverwerking. Onze aanvankelijke hypothese was dat AN-patiënten in vergelijking met gezonde controles (HCs) vóór de DBS-interventie verhoogde activatieniveaus zouden vertonen in hersengebieden die betrokken zijn bij beloningsverwerking tijdens de monetaire taken, met name verlies-condities. Dit zou overeenkomen met een eerder beschreven verhoogde gevoeligheid voor met name straf bij AN. Bovendien veronderstelden we dat deze abnormale neurale activatie zou normaliseren na de DBS-behandeling.
In tegenstelling tot bevindingen uit andere onderzoeken, laten onze gegevens geen basale activatieverschillen zien tussen AN-patiënten en HCs. We zien wel significante veranderingen in de frontostriatale circuits bij AN-patiënten na DBS, specifiek tijdens de anticipatie op zowel belonings als verlies. Deze veranderingen omvatten een afname van de activatie in de rechter precuneus, rechter putamen en rechter ventrale striatum (VS), en een toename van de activatie in de mediale orbitofrontale cortex (mOFC).

Ondanks onze aanvankelijke hypothese dat er tijdens de voedselplaatjes taak sprake zou zijn van een toename in activatie in de beloningsgerelateerde hersengebieden, vooral bij het bekijken van hoog-calorische voedselplaatjes, tonen onze empirische bevindingen geen statistisch significante verschillen in activatie voor en na DBS. Waarschijnlijk is dit toe te schrijven aan de kleine onderzoekpopulatie en de afwezigheid van een controlegroep.

Samenvattend ondersteunen onze preliminaire bevindingen de betrokkenheid van het beloningscircuit in de pathogenese van AN. Bovendien lijkt DBS abnormale neuronale activiteit te moduleren. Voor een beter inzicht zijn in de toekomst imagingstudies nodig met een grotere populatie, meer ziekte-specifieke paradigma's en een sham-conditie.

In ***hoofdstuk 6*** van onze studie hebben elektro-encefalografische (EEG) metingen verricht en geanalyseerd. In tegenstelling tot de vroegere opvatting dat de impact van DBS beperkt zou zijn tot gelokaliseerde effecten rond de stimulatieplaats, was onze hypothese dat de invloed van DBS op hersenactiviteit zich breder over meerdere hersengebieden zou verspreiden.
Onze analyse toont robuuste empirische ondersteuning voor deze hypothese. We zien significante en consistente veranderingen in oscillatoire power bij alle patiënten. De effecten van DBS zijn per proefpersoon wijdverspreid, waarbij een breed scala aan frequenties werd beïnvloed. Deze strekten zich uit over meerdere hersengebieden en netwerken - zelfs wanneer het DBS-apparaat was gedeactiveerd. De netwerkactiviteit op de verschillende meetmomenten in de tijd vormt een V-vormige curve, gekenmerkt door een initiële fase van desorganisatie, gevolgd door een daaropvolgende fase van reorganisatie. Er lijkt dus sprake van een verbetering van de functionele coherentie binnen deze netwerken bij langdurige stimulatie, gedurende een periode van meer dan een jaar.

Deze observaties ondersteunen het idee dat de neuromodulerende effecten van DBS verder reiken dan gelokaliseerde regio›s en invloed hebben op bredere pathologische neurale netwerken. Daarnaast suggereren onze bevindingen dat de hersenen zich, na een initiële periode van desorganisatie, aanpassen en mogelijk reorganiseren naar een functioneel meer stabiele toestand. De functionele implicaties van deze resultaten vereisen verder onderzoek. Vervolgstudies zouden de robuustheid van deze conclusies kunnen vergroten door de proefpersonenpopulatie te vergroten, de parameters te identificeren die het meest nauwkeurig therapeutische uitkomsten voorspellen, en de directe impact van DBS op EEG-activiteit nader te onderzoeken.

In ***hoofdstuk 7*** hebben we het effect van DBS bij AN op endocriene en metabole parameters onderzocht. Onze hypothese was dat DBS veranderingen in endocriene en metabole parameters zou induceren, correlerend met zowel de AN symptomen als gelijktijdige gewichtstoename. We zien in onze studie een statistisch significante daling in testosteron (met 21,47%) en cortisolspiegels (met 47,39%). Daarnaast zien we niet-statistisch significante, dalingen van progesteron, ACTH, GH, adiponectine, ADH, adrenaline en noradrenaline, en stijging van T3, IGF-1 en leptine. Het ontbreken van statistische significantie voor deze laatste parameters kan worden toegeschreven aan de beperkte steekproefomvang van de studie en de uitgesproken individuele variabiliteit in deze parameters.

Bepaalde uitkomsten, zoals de opvallende afname van plasma cortisol, wijzen op een mogelijke afname van initieel aanwezige hypercortisolemie. De niet-significante stijging van leptine bij DBS-responsieve subjecten impliceert eveneens een effect van DBS - al dan niet gemedieerd door de geïnduceerde gewichtstoename - op endocriene en metabole waarden betrokken bij de regulatie van voedselintake en energiehuishouding. Aanvullend onderzoek is nodig om de ingewikkelde relaties tussen fysiologie, verstoord eetgedrag en neuromodulatie te ontrafelen.

Vanwege de kleine onderzoekspopulatie zijn statistische correlaties tussen endocriene en metabole variabelen en veranderingen in gewicht of symptoomernst niet vast te stellen. AN wordt gekenmerkt door een scala aan endocriene en metabole afwijkingen, al dan niet gerelateerd aan ondervoeding. Bovendien was onze studie beperkt tot een zeer specifieke en heterogene subgroep van AN-patiënten met langdurige ernstige complicaties als gevolg van langdurige ondervoeding. Hoewel de generaliseerbaarheid van deze gegevens naar bredere AN- of DBS-populaties beperkt is, biedt onze verkennende studie fundamentele inzichten in de door DBS mogelijk geïnduceerde endocriene en metabole verschuivingen, waardoor nieuwe wegen worden geopend voor het begrijpen van zowel de mechanismen van DBS als de pathofysiologie van AN.

DEEL V - DBS IN AN: CONCEPTUELE HYPOTHESES

Zoals beschreven in hoofdstuk 3 zagen wij bij de patiënten in onze DBS-AN studie een significante toename van zelfdestructief gedrag. We beschrijven in ***hoofdstuk 8*** een uitgebreide literatuurstudie met als doel de mogelijke relatie tussen AN en zelfdestructief gedrag, specifiek niet-suïcidaal zelfbeschadigend gedrag (NSSI), te verhelderen. Onze focus lag op de neurobiologische basis van AN, de neurobiologie van NSSI, en de klinische en neurobiologische raakvlakken tussen deze twee fenomenen. Vervolgens hebben wij een conceptuele hypothese met betrekking tot de gedeelde etiopathogenese - of etiopathologische correlaten - van AN en NSSI geformuleerd.

Zowel NSSI als eetstoornissen (ES) zijn geassocieerd met emotionele dysregulatie, maladaptieve copingstrategieën en een disfunctioneel beloningssysteem. Binnen het kader van deze conceptuele review introduceren we een beloningsgerichte hypothese die de gemeenschappelijke kenmerken tussen AN en NSSI verduidelijkt. Vervolgens pleiten we voor de toepassing van drie verschillende methodologische paradigma›s, elk met elementen van psychopathologie en neurobiologie: (1) een nosografische benadering, (2) een benadering gebaseerd op onderzoeksdomeincriteria (RDoC), en (3) een netwerkanalysebenadering. We stellen dat de integratie van deze methodologische paradigma's ons inzicht in de relevante neurobiologische determinanten zal vergroten, waardoor mogelijk nieuwe behandelingsmodaliteiten kunnen ontstaan voor stoornissen die worden gekenmerkt door zelfdestructief gedrag, zoals AN en NSSI.

Samenvattend hypothetiseren we dat zelfdestructief gedrag een overstijgende psychopathologische entiteit vertegenwoordigt, zoals gedefinieerd buiten de grenzen van de Diagnostische en Statistische Handleiding van Psychische Stoornissen, Vijfde Editie (DSM-5). Deze entiteit wordt kennelijk aangedreven door een dysfunctioneel beloningssysteem. Als gevolg hiervan zouden zowel AN als NSSI kunnen worden geconceptualiseerd als 'zelf-destructiviteits-' stoornissen.

PART VI – SAMENVATTING EN ALGEMENE DISCUSSIE

In de discussie van dit proefschrift worden de bevindingen geïntegreerd en overkoepelend beschouwd.

Ons onderzoek ondersteunt op diverse manieren de betrokkenheid van het beloningssysteem bij de pathofysiologie van AN. Op basis van de beschikbare literatuur hebben wij de vALIC, onderdeel van het beloningssysteem, gekozen als doelgebied voor DBS. Wij zagen een afname van de belonende waarde van het eetstoornis-gerelateerde gedrag bij onze proefpersonen. Ook de fMRI- en EEG substudies lieten veranderingen zien in het beloningscircuit in de hersenen. Daarnaast toonden deze onderzoeken dat het effect van DBS niet alleen lokaal, maar wijder verspreid over de hele hersenen lijkt te zijn. Onze resultaten ondersteunen de hypothese dat DBS dysfunctionele netwerkactiviteit normaliseert.

Desondanks blijven de exacte werkingsmechanismen van DBS onbekend. Het is onduidelijk welk effect DBS heeft op neuroplasticiteit, cerebrale homeostase en neurotransmitters. Bovendien weten we niet wat de lange termijn effecten van DBS zijn op het functioneren van neuronale circuits. Tenslotte zijn er nog onvoldoende gegevens om te voorspellen wat de invloed van DBS is op enerzijds nog in ontwikkeling zijnde hersenen en anderzijds neurodegeneratieve processen. Deze vraagstukken zijn specifiek bij AN relevant, aangezien de hersenactiviteit en pathofysiologie bij AN in deze populatie ook beïnvloed wordt door soms langdurige perioden van ondervoeding.

Het conceptualiseren van eetstoornissen, en van AN in het bijzonder, is een al lang bestaand en voortdurend onderwerp van academische discussie en onderzoek. Er zijn talloze theorieën waarbij eetstoornissen vanuit verschillende domeinen beschouwd worden. Wij hebben ons gericht op de relatie met het beloningssysteem en zelfdestructief gedrag. We hebben een hypothese geformuleerd waarin we AN conceptualiseren als een uitingsvorm van zelfdestructiviteit, waarbij een dysfunctioneel beloningssysteem ten grondslag ligt aan zelfdestructiviteit in bredere zin.

Tenslotte gaan we in de discussie in op de ethische en filosofische aspecten van het doen van experimenteel invasief onderzoek in de hersenen bij een (zowel lichamelijk als psychisch) zeer kwetsbare groep patiënten. We gaan in op ethische constructen zoals de verhouding tussen risico's en voordelen van experimenteel wetenschappelijk onderzoek, op het begrip autonomie, de mentale capaciteit om in te stemmen met dergelijk onderzoek, en de invloed van factoren als hoop en exclusiviteit op zowel de motivatie tot deelname aan dergelijk onderzoek als de uitkomsten.

Filosofische vraagstukken rondom dit thema betreffen vragen rondom identiteit en het 'zelf', waarbij zowel de ziekte AN als manipulatie van hersenactiviteit middels DBS van invloed kan zijn op het zelf en de identiteit. Ook kan men zich afvragen in hoeverre DBS de vrije wil aantast, en in

hoeverre DBS invloed heeft op persoonlijke verantwoordelijkheid en toerekeningsvatbaarheid. Ook is het belangrijk om na te denken over de vraag waar de grens ligt tussen 'normaal' en 'pathologisch'. In de huidige maatschappij, die steeds meer gekenmerkt wordt door maakbaarheid, moeten we terughoudend zijn in het pathologiseren van variaties in gedrag en denken, om te voorkomen dat de grenzen rondom het toepassen van DBS vervagen en DBS geen behandeling van een ziekte maar een vorm van zelfverbetering wordt.

Hoewel deze vragen niet beantwoord worden in dit proefschrift, zijn bovenstaande overwegingen essentieel in het ontwikkelen van verder onderzoek naar en het klinisch toepassen van DBS bij psychiatrische stoornissen, en zeker bij ziektebeelden als AN.

De sterke punten en beperkingen van dit proefschrift en met name de DBS-AN studie worden besproken. De meest in het oog springende beperking is natuurlijk de zeer kleine proefpersonenpopulatie. Enerzijds is het vanwege de experimentele en invasieve aard van de studie gerechtvaardigd om dit in eerste instantie slechts bij een klein aantal proefpersonen uit te voeren, anderzijds beperkt dit vanzelfsprekend de power en generaliseerbaarheid van de resultaten. De inclusie van proefpersonen met langdurige, zeer ernstige en therapieresistente AN heeft tot gevolg dat de a priori kans op effect van een interventie gering is. Desalniettemin is deze in Nederland eerste DBS-AN studie een belangrijke stap in het onderzoek naar de effectiviteit, veiligheid en toepasbaarheid als ook de functionele effecten van DBS bij AN. Dit proefschrift draagt bij aan de kennis van de neurobiologische grondslag van AN en de ontwikkeling van nieuwe behandelmethoden voor AN.

Wij hopen dat dit proefschrift een eerste aanzet is voor verder onderzoek naar DBS bij AN, in grotere patiëntenpopulaties, waarbij de resultaten door meer homogeniteit m.b.t. AN subtype en comorbiditeit en het includeren van minder ernstig zieke patiënten beter generaliseerbaar worden. Uiteindelijk is het streven om een effectieve en toegankelijke nieuwe behandeloptie te kunnen bieden aan deze groep ernstig zieke patiënten, voor wie de prognose op dit moment slecht is, en wiens 'life is on a scale'.

10 List of Publications

Oudijn, M.S., Linders, J.T.W., Lok, A. et al. Neural effects of deep brain stimulation on reward and loss anticipation and food viewing in anorexia nervosa: a pilot study. J Eat Disord 2023 Aug 11: 140

Karaszewska D*, Cleintuar P*, **Oudijn M**, Lok A, van Elburg A, Denys D, Mocking R. Efficacy and safety of deep brain stimulation for treatment-refractory anorexia nervosa: a systematic review and meta-analysis. Transl Psychiatry. 2022 Aug 15;12(1):333.

Oudijn M, Linders J, Mocking R, Lok A, van Elburg A, Denys D. Psychopathological and Neurobiological Overlap Between Anorexia Nervosa and Self-Injurious Behavior: A Narrative Review and Conceptual Hypotheses. Front Psychiatry. 2022 May 11;13:756238.

Oudijn MS, Mocking RJT, Wijnker RR, Lok A, Schuurman PR, van den Munckhof P, van Elburg AA, Denys D. Deep brain stimulation of the ventral anterior limb of the capsula interna in patients with treatment-refractory anorexia nervosa. Brain Stimul. 2021 Nov-Dec;14(6):1528-1530.

Linssen RSN*, **Oudijn MS***, Mantione M, van den Munckhof P, Denys D, Schuurman PR. Body Weight Changes after Deep Brain Stimulation for Obsessive-Compulsive Disorder of Depression. Stereotact Funct Neurosurg. 2017;95(5):348-351.

Van Rooijen G, Strypet M, Maat A, Scheepens DS, **Oudijn MS**, Klopper KE, Denys D. Early introduction of clozapine after neuroleptic malignant syndrome may prevent malignant catatonia: A case report. Eur Neuropsychopharmacol. 2017 Jan;27(1):91-92.

Jagt YQ, Sutterland AL, Meijer JH, **Oudijn MS**, Kemperman PM, Vulink NC, de Haan L. Delusional infestation, a therapeutic challenge. Ned Tijdschr Geneeskd. 2014;158. Dutch.

Oudijn MS, Storosum JG, Nelis E, Denys D. Is deep brain stimulation a treatment option for anorexia nervosa? BMC Psychiatry. 2013 Oct 31;13:277.

Luigjes J, de Kwaasteniet BP, de Koning PP, **Oudijn MS**, van den Munckhof P, Schuurman PR, Denys D. Surgery for psychiatric disorders. World Neurosurg. 2013 Sep-Oct;80(3-4):S31.e17-28

Oude Elberink AM, **Oudijn MS**, Kwa VI, Van HL. Histrionic personality disorder with regression and conversion': a meningioma. *Tijdschr Psychiatr.* 2011;53(6):371-6. Dutch.

Oudijn MS. De relatie tussen 'household chaos', opvoedingsstijl en gedrag. *Tijdschr Psychiatr* 2007; 49 (4):269-270.

Oudijn MS, Vrijlandt CM, Casteelen G. Severe psychosis in an African woman due to the antiretroviral agent efavirenz. *Ned Tijdschr Geneeskd*. 2006 Mar 18;150(11):643-4; author reply 644. Dutch.

'Munchausen by Proxy: kinder- en jeugdpyschiatrische aspecten'. Referaat De Bascule, december 2006.

'De (on)macht van verstikkende liefde-Munchausen by Proxy: psychiatrische aspecten. Eindreferaat psychiatrie, juli 2006.

Jonkers MH, **Oudijn MS**, Baren R van, Aronson DC. Trichobezoar: an unusual cause of pancreatitis in a teenager. *Pediatric Clinics Amsterdam* 2000; 11(1): 6.

11 Portfolio

PHD TRAINING

	Year	ECTS
General courses		
- The AMC World of Science, Graduate School, University of Amsterdam (UvA), AMC	2010	0.7
		1.5
- BROK (Basiscursus Regelgeving en Organisatie voor Klinische onderzoekers), UvA-AMC	2011	1.5
		0.6
- Scientific writing in English , Graduate School, UvA-AMC	2012	1.5
- Course Clinical Epidemiology, Graduate School, UvA-AMC	2013	1.0
- OpenClinica, AMC Clinical Research Unit (CRU), UvA-AMC	2015	1.4
- BROK Recertification, VUmc	2015&2019	
- Course Practical Biostatics, Graduate School, UvA-AMC	2020	
Specific courses		
- ABCDE-training, AMC/European Resuscitation Counsil (2014, 2019, 2023)	2013	1.0
	2015&2021	1.4
	2014&2019 &2023	0.9
Seminars, workshops and master classes		
- Two-weekly research meetings Amsterdam UMC, AMC, department of psychiatry	2010-	4.0
- Monthly 'Eindreferaten' Psychiatry residents, Consortium of Psychiatry Noord-Holland	2010-	4.0
- Monthly meetings Utrecht Research Group for Eating Disorders (URGE)	2015-	4.0

Presentations

- 'Angst om te eten: de rol van walging bij specifieke angststoornissen', NVvP Spring Congress , Maastricht	2012	0.5
- 'Nothing tastes as good as skinny feels' (PechaKucha), AMC, department of psychiatry	2014	0.5
- 'Deep brain stimulation in anorexia nervosa', Utrecht Research Group for Eating Disorders (URGE)	2017	0.5
- 'Deep Brain Stimulation in patients with chronic treatment refractory Anorexia Nervosa: a pilot study, NVvP Spring Congress, Maastricht	2019	0.7
- Poster presentation DBS in AN, Annual Meeting of Eating Disorders Research Society (EDRS)	2019	0.5
- 'Deep Brain Stimulation of the Ventral Anterior Limb of the Capsula Interna in Patients with Chronic Treatment-Refractory Anorexia Nervosa', NVvP Spring Congress, Maastricht	2022	0.7
- 'Deep Brain Stimulation in treatment-refractory Anorexia Nervosa', NVvP Spring Congress, Maastricht	2023	0.7

(Inter)national conferences

- NVvP Spring congress, Maastricht, the Netherlands (yearly)	2010-2019	6.0
- Organisation 'Somatiek Symposium', NVvP, Department of hospital and consultative psychiatry		1.0

TEACHING

Lecturing

	Year	ECTS
- Minor course Crisis & Forensic Psychiatry, MSc Medicine, VU	2016-2018	0.9
- Cursus Pathofysiologie & Neurofarmacologie; BSc Psychobiologie, jaar 3, UvA	2018-2022	1.5

Supervising

- Marieke Schreuder, 'Symptom provocation in women with anorexia nervosa: a review of fMRI studies', MSc Brain and Cognitive Sciences, UvA	2014	3.0
- Rosalie Linssen, 'Effects of deep brain stimulation on eating behaviour and body weight', MSc Medicine, UvA-AMC	2016-2017	3.0
- Lara de Vries, 'Electroencephalography as a tool for measuring illeness and recovery in the anorectic brain', MSc Medicine, VUmc	2016-2017	3.0
- Valerie Rhemrev, 'Exploring the Neurobiology of Anorexia Nervosa by investigating Electrophysiological correlates during cognitive and behavioural tasks', MSc Biomedical Science, Faculty of Science, UvA	2017-2018	3.0
- Thomas van der Meer, 'Pharmacological treatment of anorexia nervosa: a review of literature', BSc Medicine, UvA-AMC	2017-2018	2.0
- Lois Deden, 'Early indicators for weight gain in anorexia nervosa patients', BSc Medicine, UvA-AMC	2017-2019	2.0
- Yudith Haveman, 'Effect of Deep Brain Stimulation on Resting State Activity using EEG in Treatment-refractory Anorexia Nervosa', MSc Neurosciences, VU	2018-2019	3.0
- Esmee Haverkort, 'The potential of Deep brain stimulation in anorexia nervosa: a Food viewing fmri sub-study', MSc Neurosciences VU	2018-2019	3.0
- Jara Linders, 'The Neurobiology of Self-Destruction in Anorexia Nervosa', MSc Brain & Cognitive Sciences, UvA	2018-2019	3.0
- Ritchie Wijnker, 'Deep brain stimulation in patients with chronic treatment refractory anorexia nervosa: sub analysis of the blood samples', MSc Medicine, UvA-Amsterdam UMC	2020-2021	3.0

Other

- Lectures and workshops in psychiatry for bachelor and master medical students, UvA, AMC/Amsterdam UMC	2010-	3.0
- 'Kleinschalig Klinisch Lijnonderwijs' (KKLO), UvA, AMC/ Amsterdam UMC	2010-2016	2.0
- Supervising of psychiatry residents, Department of psychiatry, AMC/Amsterdam UMC	2010-	5.0
- 'Basiskwalificatie onderwijs' (BKO) certification	2014	1.5
- Mentorship of MSc medical students	2021-	2.0

PUBLICATIONS

Peer reviewed

	Year
Oudijn, M.S., Linders, J.T.W., Lok, A. *et al.* Neural effects of deep brain stimulation on reward and loss anticipation and food viewing in anorexia nervosa: a pilot study. *J Eat Disord* 2023 Aug **11**: 140	2023
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12 Dankwoord

Dit proefschrift gaat over een ziekte waarbij de weegschaal een grote betekenis heeft. Voor mensen die kampen met een eetstoornis is het niet alleen hun gewicht dat zij op een weegschaal plaatsen. De weegschaal symboliseert voor hen (soms omgekeerd evenredig) ook het lichaamsbeeld, het zelfbeeld, de identiteit, soms zelfs de waarde van het leven. Het Engelse woord 'scale' betekent niet alleen 'weegschaal', maar ook 'waagschaal'. Mensen met een ernstige eetstoornis stellen hun leven dagelijks in de waagschaal, letterlijk en figuurlijk. Een patiënt beschreef der kern van haar eetstoornis ooit als 'continu op het randje moeten leven, niet perse met het doel om erover heen te gaan, maar wel met het altijd aanwezige risico er een keer overheen te gaan'.

Na jarenlang alle mogelijke behandelingen te hebben ondergaan hebben de deelnemers aan het onderzoek waar dit proefschrift over gaat het dappere besluit genomen om deel te nemen aan een experimentele ingreep. Een ingreep en behandeling waarvan niemand van tevoren wist hoeveel inspanning en inzet het van hen zo vergen, en wat de deelname aan het onderzoek voor hen persoonlijk zou betekenen, kosten en opleveren. Zij hebben hun leven opnieuw in de waagschaal gesteld, zich gecommitteerd aan een jarenlange verbintenis, en hebben hun strijd tegen deze levensbepalende ziekte voortgezet. Niet voor henzelf, maar voor de wetenschap en voor de vele (toekomstige) patiënten met anorexia die nog steeds naar een effectieve behandeling zoeken.

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13 About the author

Marloes Oudijn was born on the 12th of August 1975 in Gorinchem, The Netherlands. Her fascination with psychiatry started during her secondary education at the Gymnasium Camphuysianum in Gorinchem, where she wrote an essay on psychiatric disorders. Marloes relocated to Amsterdam persue a degree in Medicine at the University of Amsterdam (UvA) in 1993. Her keen interest in the human mind and psychiatry further manifested, through her participation in an elective course titled 'Literature and Psychiatry' during her studies. In 1994, she earned her Bachelor in Medicine ('propedeuse') with distinction (cum laude).

Upon completing her medical studies in 2001, Marloes began her medical career at Mentrum, working in the acute admission ward and with the crisis team. In 2003, she started her residency in psychiatry en child & adolescent psychiatry at the 'Academic Medical Center' (AMC; now Amterdam UMC) and the Bascule (now Levvel).

After successfully completing her residencies in psychiatry and child & adolescent psychiatry in 2008, Marloes took up a position as a psychiatrist at the Department of Psychiatry of the Amsterdam UMC, location AMC. In 2010, she initiated the Medical Psychiatric Unit (MPU), an academic unit dedicated to the diagnostics, treatment and research of intricate cases combining somatic and psychiatric pathology. Her clinical specializations include hospital psychiatry and complex eating disorders. In her practice, Marloes frequently navigates ethical dilemmas concerning mental competence, compulsory care, aggression, suicidality and end-of-life decisions. She has a profound interest in the ethical facets of medicine, especially psychiatry, and became am a member of the Ethical Committee of Patientcare at the Amsterdam UMC, location AMC. As of 2022, she serves as the chair of the Ethical Committee of the Amsterdam UMC.

Besides her clinical duties, Marloes is actively involved in the daily supervision of residents in psychiatry, and in teaching and supervising various medical and neuroscience bachelor and master programs. She also assumed the role of Deputy Medical Director ('Geneesheer Directeur') of the Department of Psychiatry, a position focusing on the legal and ethical affairs of the department.

Marloes' research centers on the efficacy, feasibility and neurobiological functionality of deep brain stimulation in patients with chronic, treatment refractory anorexia nervosa. Marloes resides in Abcoude and is the proud mother of two sons, aged 10 and 14.