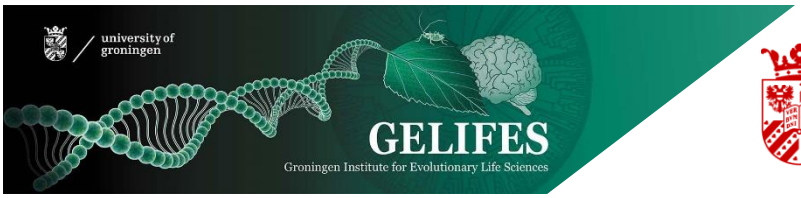

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Deep Brain Stimulation In Anorexia Nervosa

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Abstract

Ever since Anorexia Nervosa (AN) has been described in 1873, there have been no major improvements in the aetiology and treatment of the disorder. Anorexia Nervosa (AN) is a neuropsychiatric disorder in which the patients compulsively starve themselves, experiences anxiety, have a BMI of <17 kg/m^2, and has the highest mortality of any neuropsychiatric disorder. About 4% of women and 0.3% of men develop AN during their lifetime and 5% of AN patients do not survive the first 4 years after diagnosis. Deep Brain Stimulation (DBS) is used as a final resort to treat treatment-resistant neuropsychiatric disorders. In order to improve the DBS treatment of AN, the aetiology of AN should be clarified. The aetiology of AN is difficult to pinpoint as different aspects of the disorder overlap with aspects of addiction, Obsessive-Compulsive Disorder (OCD), and depression and anxiety. Patients with AN often show addictive behaviour towards exercise and weight loss. Obsessive-compulsive symptoms are also often seen in AN. Finally, patients with AN experience several depressive-like symptoms and experience social anxiety. In OCD, addiction, and depression and anxiety, the Nucleus Accumbens (NAc) is often targeted by DBS. The ventral Anterior Limb of the Internal Capsule (vALIC) is used as a DBS target in both OCD and depression and anxiety. The Bed Nucleus of the Stria Terminalis (BNST) is targeted by DBS only in OCD. Finally, the Subcallosal Cingulate Cortex (SCC) is targeted by DBS only in depression and anxiety. To conclude, AN shows great overlap in aetiology and symptomology with addiction, OCD, and depression and anxiety. The DBS targets of AN should be the SCC, NAc, and the vALIC, as these targets show promising results in AN.

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Introduction

Anorexia Nervosa (AN) was first described by Richard Morton in 1692 as a wasting of the body without further sickness (Pearce, 2004). Exactly 150 years ago, in 1873, two separate neurologists described AN. The French neuropsychiatrist Ernest Charles Lasègue described AN as a condition with refusal of food and a distorted body image (Pearce, 2004; Vandereycken & Van Deth, 1989). Further, British physician Sir William Gull also described AN as a disease of extreme emaciation mainly in females between the ages of 16 and 23 (Pearce, 2004; Vandereycken & Van Deth, 1989). Gull was also the first to use the term "anorexia nervosa", whereas Lasègue used the term "hysterical anorexia" (Vandereycken & Van Deth, 1989). Since then, many different treatments have been discovered. However, the mortality rate of AN is still 5% within the first four years of diagnosis (Westmoreland et al., 2022). Besides having the largest mortality rates of any psychiatric disorder, only 52% of patients with AN fully recover (Miskovic-Wheatley et al., 2023). Sadly, 26-31% of the patients who show full remission of AN experience relapse (Miskovic-Wheatley et al., 2023; Berends et al., 2018). This seems to suggest that treatment for AN is not as successful as hoped.

There are many different forms of treatment for AN, such as Specialist Supportive Clinical Management (SSCM), Enhanced Cognitive Behaviour Therapy (CBT-E), or Family-Based Treatment (FBT) (Zipfel et al., 2015). It is well known in the literature that these treatments for AN are far from perfect as there are high dropout rates and low success rates (Kiely et al., 2022). Further, it should be noted that there are only psychotherapies currently, as no medication is known to consistently and effectively treat AN (Clausen et al., 2023). SSCM is composed of two parts: clinical management and supportive therapy for AN (Jordan et al., 2019). CBT-E is a treatment which first focusses on helping the patient rethink their current physical state. This is followed by discussing the good and bad aspects of their physical state, which is followed by helping the patient increase their weight, with permission of the patient (Grave et al., 2013). The final most used treatment used for AN is FBT. FBT, or the Maudsley approach, is a psychotherapy that is designed to improve the health of patients with AN (Riencke, 2017). SSCM has a success rate of up to only 32% and CBT-E has a success rate of 27% (Purvis et al., 2023; Keßler et al., 2022). A more successful psychotherapy for AN appears to be FBT with a success rate of 40-49% (Rienecke, 2017). A meta-analysis by Zeeck and colleagues in 2018 has shown that there is no superior treatment. A large randomized controlled trial of 120 participants who received either SSCM, CBT-E, or FBT, showed a dropout rate of 40% in the first six months, with 52.5% of participants completing the 12-month follow-up (Byrne et al., 2017). This study showed a remission rate of 28.3% across all treatments (Byrne et al., 2017). It is clearly shown that treating AN is still a challenge. The treatment of AN is successful in not even half of the patients and there are very large dropout rates across all main treatment strategies.

Clearly, a new type of treatment is needed to treat patients with AN. An experimental treatment that is also experimentally used in other neuropsychiatric disorders is Deep Brain Stimulation (DBS). DBS has been used in experimental setting to treat AN by targeting several different brain structures (Hsu et al., 2022). However, there is not yet an obvious target for DBS in AN, as the brain mechanisms itself underlying AN is not yet known (Scharner & Stengel, 2019; Johnson et al., 2022). Brain areas such as the nucleus accumbens, subcallosal cingulate cortex, corpus callosum, and bed nucleus of the stria terminalis have been targeted by DBS in order to treat AN (Hsu et al., 2022). DBS has a success rate of about 25% in the aforementioned brain areas (Hsu et al., 2022), which is about as successful as treating AN by using psychotherapy. However, it should be mentioned that DBS is only used in treatment-resistant patients, which therefore increases the effectiveness of the treatment as it is the only successful treatment in these patients. The main question remains: which brain structures should be targeted by DBS in order to more effectively treat AN?

Main Body

In order to properly explain how Anorexia Nervosa (AN) could be treated, The aetiology and symptomology needs to be discussed. The symptomology and general information about AN will be discussed first, followed by an explanation of the aetiology. Since AN shows overlap in aetiology and symptomology with Obsessive-Compulsive Disorder (OCD), addiction, and depression, these three disorders will be explained and will be coupled to AN.

What is Anorexia Nervosa?

AN is the psychiatric disorder which gets diagnosed in about 4% of females and 0.3% of males during their lifetime (Van Eeden et al., 2021). The Diagnostic and Statistical Manuel of Mental Disorders, fifth edition (DSM-V) describes AN by three main characteristics. The first characteristic is restriction of energy intake, or self-starvation, which in turn leads to a significantly low body weight. This significantly low body weight corresponds with a BMI of at most 17 kg/m^2. The second characteristic described by the DSM-V is that the patient experiences extreme fear concerning weight gain, even though the patient is famished. The third and final characteristic of AN is that the perception of physical appearance of the patient is disturbed and there is a lack of recognition of the seriousness of the situation. The third characteristic has been demonstrated by Keizer and colleagues in 2013, who showed that patients with AN experience a turning reflex to get through a door much earlier than their body size suggests. Patients with AN started turning their torso when the apparatus was 40% wider than their shoulders while healthy controls rotated their torso when the apparatus was only 25% wider than their shoulders (Keizer et al., 2013). Besides the main characteristics of the disorder, patients who suffer from AN also suffer from emotional instability (Nalbant et al., 2019). Within AN, there are two separate types of the disorder, the restricting type and the binge-eating/purging type (American Psychiatric Association, 2013). The restricting type describes patients with AN who have achieved their low body weight primarily through fasting, dieting, and excessive exercise. The binge-eating/purging type describes people with AN who have lost weight by self-induced vomiting, and misuse of e.g. laxatives. The symptoms of AN are quite diverse and it is difficult to pinpoint a specific mechanism which could explain these symptoms.

AN is a complex disorder in which many brain structures have altered functioning (Scharner & Stengel, 2019). An important brain mechanism that is altered in AN is the reward system (Bischoff-Grethe et al., 2013). The reward system, or mesolimbic system, is the brain mechanism responsible for the experience of pleasure and motivation (Höflich et al., 2018). The reward system is composed of the following structures, which are all connected to the Ventral Tegmental Area (VTA): Nucleus Accumbens (NAc), which is located in the Ventral Striatum (VS), the Prefrontal Cortex (PFC), the amygdala, the hippocampus, and the insula (Lewis et al., 2021). Neuroimaging research has shown hypoactivation in the insula and VTA in patients with AN (Jiang et al., 2019). Another neuroimaging study by Kaye et al., (2020) has shown hypoactivation of the insula to caudal putamen which is responsible for motivating eating behaviours. This hypoactivation might lead to food avoidance and prolonged periods of self-starvation (Kaye et al., 2020). A more widely confirmed difference in reward processing in anorexia nervosa compared to healthy controls is the dysregulation of the NAc (Keating, 2010; Berner et al., 2019). A study by Kawakami et al., (2022) has shown that there is impaired connectivity between the NAc and VTA and thus results in impaired reward processing. Another brain area that is altered in AN is the Subcallosal Cingulate Cortex (SCC) (Lipsman et al., 2015). The SCC plays a major role in emotional processing of specifically negatively valenced emotions, such as sadness and fear (Rolls, 2019). Further, the SCC plays a major role in reward processing and social-learning (Du et al., 2021). The SCC in AN has disrupted connectivity and therefore impaired functioning (Hayes et al., 2015). Another brain structure that is altered in AN is the Bed Nucleus of the Stria Terminalis (BNST) (Wang et al., 2019). The function of the BNST is related to the intake of food and appetite, while a region within the BNST appears to have a function within fear and stress processing (Wang et al., 2019; Goode et al., 2019). It is clear that there is no obvious cause of AN, which has also been confirmed by other research (Johnson et al.,

2022). Instead of focussing solely on impaired brain functions, it might be more useful to focus on other neuropsychiatric disorder which show overlap with AN, such as OCD, addiction, and depression.

What Causes Anorexia Nervosa?

AN is a neuropsychiatric disorder that does not yet have a known underlying mechanism, but it does overlap with several other neuropsychiatric disorders of which the aetiology is better known of. AN overlaps with OCD, addiction, and depression and AN has often been described as being one of these disorders. By investigating these other, often comorbid, disorders, a possible cause or mechanism could be described for AN.

Is Anorexia Nervosa an Obsessive-Compulsive Disorder?

OCD is a disorder that is often named in the context of AN, as compulsive behaviours are seen in both AN and OCD (Thomas et al., 2022). A research by Serpell et al., in 2002 have found that the level of anxiety experienced by patients with AN and OCD are similar. Another research has found that patients with AN on average experience an at least moderate severity of obsessive-compulsive symptoms based on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Amianto et al., 2021). The DSM-V (American Psychiatric Association, 2013) describes several examples of OCD-like behaviours and symptoms in patients who suffer from AN. Patients with AN are often highly preoccupied with food and have food constantly on their mind, which is defined as an obsession with food. These obsessive thoughts, in this case, about food are a main symptom of OCD. Further, obsessive-compulsive symptoms in patients with AN have long been observed in studies (Amianto et al., 2021). It has been shown that there is a 55% genetic overlap between OCD and AN, indicating a possible shared aetiology (Levinson et al., 2019). OCD might be the cause of AN, since there are strong overlaps between the symptoms, obsessive-compulsive behaviours, and genetics.

Is Anorexia Nervosa an Addiction?

Besides OCD, compulsive behaviour has also been seen in addiction (Henden et al., 2013). This indicates overlap between addiction and AN. Unlike many other addictions, the substance that is addicting in AN is weight loss and physical activity (Barbarich-Marsteller et al., 2011). AN truly resembles a behavioural addiction when viewing the excessive physical activity and compulsive self-starvation. A qualitative study in 2015 by Godier and Park has investigated to what extent anorexia nervosa resembles an addiction. A majority of the participants (62.5%) explain a lack of control and inability to resist against their compulsions, which is a main symptom in addiction (Feltenstein et al., 2020). 35% of the participants experienced an escalation in the compulsions, such as increased weight loss goals. This behaviour is in line with the behaviour of increasing the dose of a substance over time in addictive disorders (Turton & Lingford-Hughes, 2016). A final similarity between AN and addiction is that the substance, dieting in AN, is used to modulate anxiety and mood (Barbarich-Marsteller et al., 2011). Thus, addiction shows clear similarities with AN in terms of behaviours and symptoms.

Is Anorexia Nervosa a Type of Depression/Anxiety?

Depressive and anxious behaviour are often observed in patients with AN (Calvo-Rivera et al., 2021; American Psychiatric Association, 2013). Many people with AN experience depressive symptoms such as a depressed mood, social withdrawal, irritability, and similar to many other disorder, insomnia. Similarly, many patients with AN experience a feeling of worthlessness and failure if they do not succeed in losing any more weight (Wade et al., 2015). These symptoms all indicate a strong overlap between AN and depression. When a patient with AN gains weight, this is perceived as a failure of self-control, which could lower the self-esteem of the patient further.

The depressive symptoms of AN are part of the disorder, as anxiety also plays a substantial role in AN. A main symptom of AN is the fear of gaining weight, which is accompanied by anxiety for accidentally gaining weight. This might seem very similar, however, fear is defined by the DSM-V as the emotional response to an imminent threat, while anxiety is the anticipation to a future threat. This fear

of gaining weight drives the persistent behaviour of losing weight. Further, patients with AN often have social anxiety and will therefore withdraw themselves from social environments. Since anxiety and depressive symptoms are highly prevalent in AN, these disorders might also be the cause of AN.

Obsessive-Compulsive Disorder

About 1% of men and 1,5% of women develop OCD during their lifetime, coming together to about 2-3% of the world population (Fawcett et al., 2020; Carmi et al., 2022). OCD is an anxiety disorder that is characterized by two main components as the name suggests: obsessions and compulsions (American Psychiatric Association, 2013). Obsessions are defined by the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.) as unwanted, intrusive thoughts, mental images, or urges which are recurrent and cause stress and anxiety. The most common obsessions are contamination, imagining disturbing scenes, or inflicting harm on others and/or themselves (American Psychiatric Association, 2013). Compulsions as defined by the DSM-5 are physical and/or mental acts, with very strict rules, which function to neutralize the anxiety caused by the obsessions and are often done repeatedly due to the strict rules and the need to do the compulsion "just right". Similar to obsessions, there are very common compulsions such as cleaning, counting, repeating specific words in a specific order (American Psychiatric Association, 2013).

AN is highly comorbid with OCD (Yılmaz et al., 2022; Levinson et al., 2019). Patients with AN are 9.6 times more likely to develop OCD in their lives when compared to healthy controls, leading to 44-62% of AN patients to develop OCD somewhere in their lives (Song et al., 2021; Mandelli et al., 2020; Riquin et al., 2021). As has been discussed above, there are clear similarities between the symptoms of both OCD and AN.

Many Deep Brain Stimulation (DBS) studies have focussed on the Nucleus Accumbens (NAc) as it appears to yield the best results and is relatively safe to stimulate (Cruz et al., 2022; Rezai et al., 2023). The NAc is a brain area that is dysfunctional in OCD (Ballester et al., 2015). The NAc is a structure that is positioned by the lower part of the striatum (Bayassi-Jakowicka et al., 2021). Further, the NAc is part of the limbic system, but due to its position next to the dorsal striatum, it also influences locomotion (Bayassi-Jakowicka et al., 2021). The NAc has inhibitory projections towards the basolateral amygdala, lateral hypothalamus, and the ventral pallidum (Xu et al., 2020). The NAc shows a decreased activation in patients with OCD compared to healthy controls (Figee et al., 2011). The less active inhibitory functions of the NAc leads to more activation in the aforementioned brain structures, specifically the basolateral amygdala, which in turn, is associated with high anxiety and addiction (Rau et al., 2015).

Denys et al., (2010) performed a study in which 16 patients with OCD got NAc Deep Brain Stimulation (DBS). The patients are aged between 18 and 65 years old, and the patients all have OCD according to the DSM-IV criteria. The patients were asked to fill out the Y-BOCS, which is a detailed questionnaire assessing the severity of obsessive and compulsive symptoms (Goodman, 1989). After 21 months, 9 out of the 16 patients responded to the DBS, bringing the response-rate to 56%. The obsessive-compulsive symptoms decreased with 52% and the overall improvement was 72% as the anxiety and depressive symptoms were halved (Denys et al., 2010). A negative side-effect of the treatment was however that some patients experienced hypomania or elevated mood, which has been found in many patients with DBS in the NAc. Similarly, DBS in the NAc and also in the internal capsule might lead to manic behaviour (Schüller et al., 2023).

Another brain area that is often targeted when treating OCD using DBS is the Bed Nucleus of the Stria Terminalis (BNST), an extension of the amygdala with functions in fear processing (Hulsman et al., 2021). Further, the BNST has an important role in processing of threat signals, which is disrupted in OCD (Goode et al., 2019). A study by Naesström et al., (2021) has investigated the effects of DBS in patients with OCD (n=11) when targeting the BNST. Similar to the results found by Denys et al., in 2010, the patients experienced hypomania in the first period after stimulation. In this study, 6 out of 11 patients responded to the DBS and 4 out of 11 patients responded partially. Of the responders, the score on the Y-BOCS was reduced with 49%.

Lastly, the ventral Anterior Limb of the Internal Capsule (vALIC) is a brain structure that contains fibres from the prefrontal cortex and the thalamus, and is responsible for motivation, decision-making, emotion, and cognitive processing (Haber & Behrens, 2014). This structure is often dysfunctional in psychiatric disorders, making it an excellent target for DBS (Safadi et al., 2018). A cohort study (n=70) by Denys et al., 2020 shows just how effective DBS in the vALIC is. After twelve months, 52% of the patients responded well, 17% of the patients were partial responders and the remaining 31% did not respond to the DBS treatment. On average, the Y-BOCS score were reduced by 40%, which reduced the symptoms from extreme severity to moderate severity (Goodman, 1989). Further, the study found that the Hamilton Anxiety Rating Scale (HAM-A), a measure of anxiety, was reduced by 55%, and the Hamilton Depression Rating Scale (HAM-D), a measure of depression, was reduced by 54%.

Addiction

AN can be seen as an addiction due to the excessive hyperactivity (e.g. running), and self-starvation despite the negative consequences. An addiction is defined as a risky behaviour that is repetitive, compulsive and excessive, and the patient is unable to stop this behaviour voluntarily (American Psychiatric Association, 2013). Addictions include substance abuse, such as alcohol or opioids, and behavioural addictions, such as gambling (Kuusisto et al., 2021; American Psychiatric Association, 2013). An addiction in composed of three main symptoms: continuity, tolerance, and withdrawal (American Psychiatric Association, 2013). When a patient is addicted, this person will have tolerance to the drug to a certain extent (Turton & Lingford-Hughes, 2016). The brain undergoes certain neuroadaptive changes that lead to a lower sensitivity of the drug, leading to a higher dose intake in order to achieve the desired effect (Turton & Lingford-Hughes, 2016). One of these neuroadaptive changes is a decrease in dopamine transporters in the ventral striatum and the NAc, lowering the sensitivity to the drug (Volkow et al., 2001). This lowered sensitivity, or tolerance, leads to continuity of drug abuse, since cessation of drug use leads to withdrawal symptoms due to the absence of the drug in a context where the body anticipates for the arrival of the drug, causing the patient to experience opposite effects to the effects of the drug (Turton & Lingford-Hughes, 2016). The withdrawal symptoms force the patients to feed their addiction (American Psychiatric Association, 2013).

About 16% of patients with AN also get diagnosed with substance use disorder, in contrast to only 0.7% of people worldwide in the same age group (Devoe et al., 2021). Similar to the high preoccupation with food that patients with AN experience, a high preoccupation with exercise is also seen often (Godier & Park, 2015; Kolnes, 2016). The high preoccupation with exercise is an important aspect of exercise addiction, which is seen in 48% of AN patients (Freimuth et al., 2011; Krivoschekov & Lushnikov, 2011). As explained before, many patients with AN experience similar symptoms to the symptoms of people suffering from substance use disorder (Godier & Park, 2015).

The Nucleus Accumbens (NAc) is a brain area of the mesolimbic system which is dysregulated in patients who suffer from addiction (Scofield et al., 2016). As described above, the less active NAc insufficiently inhibits the basolateral amygdala, leading to increased risk of anxiety and addiction (Figee et al., 2011; Rau et al., 2015). Therefore, a study was done by Bach et al., (2023) in which the effectivity of DBS in the NAc was investigated in people who suffer from alcohol addiction (n=9). The NAc DBS has resulted in a reduction of 47.4% of heavy drinking days in the patients after 6 months. After 18 months, the proportion of abstinence had increased by 74.2% in the patients. This study clearly demonstrates the success of NAc DBS in people who suffer from addiction.

Depression/Anxiety

Depression is a disorder which is a large problem worldwide, with a prevalence of 3.8% (4% of men and 6% of women) (WHO, 2023). There are several different depressive disorders: disruptive mood dysregulation disorder, major depressive disorder with single or recurrent episodes, persistent depressive disorder (dysthymia), and depressive disorder due to another medical condition (American Psychiatric Association, 2013). The disorder most often referred to as “depression” is Major Depressive

Disorder (MDD). MDD has three criteria, first of which being that the symptoms cause significant clinical distress and cause impairment in social or functional setting. The second criterium is that the symptoms are not caused by a substance or another medication condition. The last criterium is the symptoms of the condition. There is a list of nine symptoms of which five is sufficient to get diagnosed with MDD. Some of the symptoms are feeling depressed for most of the day, loss of pleasure and interest in activities, feeling worthless, insomnia or hypersomnia, or recurrent thoughts of death. Depression is often viewed in combination with anxiety.

Anxiety is a very broad term which includes many different disorders. Anxiety disorders include specific phobias, social anxiety, panic disorder, generalized anxiety disorder, or anxiety disorder due to another medical condition (American Psychiatric Association, 2013). Anxiety disorders are described broadly as disorders that cause excessive fear and anxiety with behavioural disturbances. An example of an anxiety disorder relevant for this thesis, is social anxiety disorder. This type of anxiety disorder is characterized by a fear of being in social interactions, or being observed. A very important aspect of social anxiety disorder is the fear that the subject is negatively viewed by other people. This anxiety disorder causes the subject to avoid interactions with other people, the subject withdraws itself.

Depression is highly comorbid with AN, about 60% of all patients with AN also develop depression (Calvo-Rivera et al., 2021; Calugi et al., 2014). Similarly, more than half of the patients with AN also suffer from social anxiety (Catone et al., 2021). As mentioned above, patients with AN experience many of the same symptoms as people with depression do. One symptom in particular appears to be overlapping with AN, depression, and social anxiety, which is social withdrawal. Social anxiety explains that social withdrawal is a consequence of feeling anxiety for the way people might judge the patient. Similarly, people with AN feel insecure about their body, and therefore might remove themselves from social situations.

Similar to OCD and addiction, the NAc is an important brain structure that has decreased volume and activation in depression and anxiety (Auerbach et al., 2022). In 2012, a study was done by Bewernick and colleagues in which the researchers treated 11 patients with treatment-resistant depression with NAc DBS. After 12 months, 45% of the patients were categorised as responders for at least four years. Besides the NAc, the SCC also shows disrupted functioning in depression (Dunlop et al., 2017). A study by Crowell et al., (2019) in which the long term effects of SCC DBS in treatment resistant depression patients (n=20) was investigated. This study had a response rate of >50% and a remission rate of >30%, with decreased global illness severity and increased global functioning. Another study was done by Bergfeld and colleagues in 2016, who investigated the effect of vALIC DBS in treatment-resistant depressive patients. This study was done with 25 patients, of who 10 patients responded to the DBS and 6 patients responded partially. Of the 25 patients, 5 patients managed to reach remission. These three studies indicate the success of NAc, SCC, and vALIC DBS in patients with treatment-resistant depression.

Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a treatment which is used in several treatment-resistant neurological disorders (Sullivan et al., 2021). DBS was first approved by the Food and Drug Administration (FDA) in 2002 for the treatment of Parkinson's disease (PD) (Gardner, 2013). With DBS, electrodes are implanted into the brain of the patient at the desired position to stimulate a specific brain area (Goyal et al., 2021). These electrodes stimulate the target areas with a specific frequency, current and pulse-width. A pacemaker-like device is implanted under the collar bone which powers the electrodes (Figure 1) (Professional, 2023). Finally, the device needs to be fine-tuned in order to avoid unwanted psychiatric changes in the patient (Senova et al., 2019). To treat PD, the brain mechanism needs to be established. The Substantia Nigra pars compacta (SNpc) has a modulatory role in the direct and indirect pathway of movement

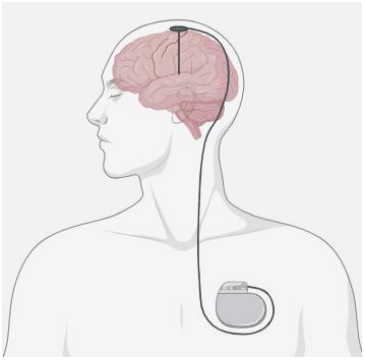

Figure 1: Schematic representation of the DBS device implanted into the chest and the electrode implanted into the brain, made using BioRender.com

(Young et al., 2023). The SNpc has dopaminergic neurons which activate the striatum, which in turn inhibits the Globus Pallidus internus (GBi) and the Subthalamic Nucleus (STN). In PD, there is dopaminergic cell loss in the substantia nigra (Bae et al., 2021). This dopaminergic cell loss disrupts the stimulation of the striatum and therefore the inhibition of the GBi and STN (Young et al., 2023). This explains why the subthalamic nucleus and the globus pallidus internus are the most used targets for DBS in PD (Honey et al., 2016). By stimulating the GBi and STN directly, the dysfunctional SNpc is bypassed, relieving the patient of many symptoms (Young et al., 2023; Honey et al., 2016).

PD is the only disease in which DBS is used as a treatment, but there have been many trials in neuropsychiatric disorders. As mentioned before, DBS has been experimentally used in OCD, addiction, and depression. However, this invasive treatment for several neurological diseases is not flawless, as it is successful in 72.5% of PD patients (Hitti et al., 2020). When DBS is used in treatment-resistant OCD, it has 49.5% success rate and 22.5% of patients respond partial to the treatment (Mar-Barrutia et al., 2021). DBS is also slightly more successful in addiction as 59.6% of patients improve (Shaheen et al., 2023). Finally, DBS in treatment-resistant depression has a response rate of 60% (Figee et al., 2022). The success of DBS in treatment-resistant psychiatric disorders indicates that DBS might also be a successful final resort for treating eating disorders such as anorexia nervosa.

Discussion

Anorexia Nervosa (AN) shows overlap with Obsessive-Compulsive Disorder (OCD), addiction, and depression and anxiety in terms of symptomology and altered brain functions (Godier & Park, 2015; Amianto et al., 2021; Bach et al., 2023; Denys et al., 2010; Liu et al., 2020; Naesström et al., 2021; Blomstedt et al., 2017; Barbier et al., 2011; Denys et al., 2020; Oudijn et al., 2021; Crowell et al., 2019; Bergfeld et al., 2016; Riquin et al., 2021; Lipsman et al., 2017). This overlap between the different disorders could be used to improve the Deep Brain Stimulation (DBS) treatment that is already being experimented with in AN. The different brain areas that are used as targets in OCD, addiction, and depression and anxiety are shown in table 1.

Table 1: Overview of the brain structure used in DBS in different disorders. Nucleus Accumbens: NAc; Subcallosal Cingulate Cortex: SCC; Bed Nucleus of the Stria Terminalis: BNST; ventral Anterior Limb of the Internal Capsule: vALIC; Obsessive-Compulsive Disorder: OCD.

	Disorder		
Brain Structure	OCD	Addiction	Depression/Anxiety
NAc	**X**	**X**	**X**
BNST	**X**		
vALIC	**X**		**X**
SCC			**X**

The DBS treatment of OCD shows many more potential targets for stimulation in the brain. The first brain structure that is mentioned is the Nucleus Accumbens (NAc). The NAc is a brain structure that shows impaired functioning in OCD and AN (Ballester et al., 2015; Keating, 2010; Berner et al., 2019). Similar to being a promising target in OCD, the NAc is also often targeted in treating treatment-resistant addiction (Denys et al., 2010; Chang et al., 2022). The NAc is a brain area that is dysregulated in AN, OCD, addiction, and depression, which are all highly co-morbid with AN (Kawakami et al., 2022; Ballester et al., 2015; Scofield et al., 2016; Xu et al., 2020; Auerbach et al., 2022). The study that is discussed shows promising results of NAc DBS in people who suffer from alcohol addiction with a success rate of 47.4% (Bach et al., 2023). A meta-analysis by Shaheen et al., (2023) provides a more reliable success rate of 59.6% of NAc DBS in people who suffer from substance abuse addictions. Similarly, the overall improvement patients with OCD who received NAc DBS is 72%, with a response rate of 52% (Denys et al., 2010). Luckily, the success of NAc DBS is not limited to the treatment of addictions and OCD, as the success rate of NAc DBS in AN is 61% (Liu et al., 2020). This study by Liu and colleagues in 2020 was performed with 28 patients with treatment-resistant AN. These success rates indicate that more than half of the patients with NAc DBS responded well, specifically in OCD and AN.

Addiction is a disorder that is not solely a problem in reward processing, it is also a habit disorder (Vandaele & Ahmed, 2020). The basal ganglia is the brain structure that is responsible for habit formation and is an important structure in addiction (Renteria et al., 2018). The importance of the basal ganglia in addiction might explain that the DBS in the NAc is not as successful as in OCD. The fact remains that the NAc is an excellent target for DBS in patients with AN.

The second brain structure that was discussed, is the Bed Nucleus of the Stria Terminalis (BNST). The BNST is a brain structure that is involved in the processing of threat signals, but also in regulating food intake and appetite (Goode et al., 2019; Wang et al., 2019). Further, the BNST regulates unpredictable threat processing, which plays an important role in social anxiety (Clauss et al., 2019). Social anxiety in turn, plays an important role in AN as it plays an important role in shame (Grabhorn et al., 2006). These functions of the BNST make it a very interesting brain structure for the treatment of OCD and AN, as the functions in threat processing and appetite, respectively, are main components of the disorders. The study by Naesström et al., (2021) has shown that targeting the BNST in OCD is indeed an successful option as 54.5% of patients responded well and 36.4% of patients responded partially. The responders showed a reduction in obsessive-compulsive symptoms of 49% (Naesström et al., 2021). The BNST has not yet been targeted by a larger DBS study with multiple participants since DBS in AN is still in its early stage, thus two case studies will be discussed. The two case studies were done by Blomstedt and colleagues in 2017, and Barbier et al. in 2011 and show promising results in two women with treatment resistant AN. Both patients in the case studies showed a disappearance of anxiety concerning food. It should be mentioned that the patient of Blomstedt et al., had no increase in BMI. Another important note is that the patient of Blomstedt et al., had AN with comorbid depression, similarly the patient of Barbier et al., had AN with comorbid OCD. Sadly, no clear percentages of improvement are given by the two case studies. However, the disappearance of the anxiety surrounding food indicates that BNST DBS in AN patients might have a similar success rate compared to BNST DBS in OCD. Despite the limitation of low quantity of patients, the treatments do show promising results. More clinical studies should be performed in which a large sample of patients with AN get BNST DBS, in order to properly confirm the success of this specific DBS target.

The next brain structure discussed in the analysis is the ventral Anterior Limb of the Internal Capsule (vALIC) which is responsible for motivation, decision-making, emotion, and cognitive processing (Haber & Behrens, 2014). The study by Denys and colleagues in 2020 showed that patients with OCD who received vALIC DBS showed a reduction of 40% on the Y-BOCS, 55% on the HAM-A, and 54% on the HAM-D. Further, 52% of the patients responded well to the DBS, and 17% of patients responded partially. Beside OCD, vALIC DBS also shows promising results in treating treatment-resistant depression. Bergfeld and colleagues (2016) treated 25 patients with depression with vALIC DBS. Of the 25 patients, 10 patients responded well to the treatment, and 6 patients responded partially. It is shown that vALIC DBS is a promising target for DBS in OCD and depression, but research has also found promising results in AN. Oudijn et al., in 2021 treated treatment-resistant AN with vALIC DBS. Although this study only has 4 participants, the patients showed a promising increase in BMI of 42.8%, a reduction of 47.9% on the HAM-A scores, and a reduction of 36.7% on the HAM-D scores. Overall, these results show that the vALIC is also a promising target for DBS in AN as the BMI of the patients increased significantly with 42.8%, placing the patients out of danger.

The last brain area discussed is the Subcallosal Cingulate Cortex (SCC), which is of high importance in both depression and AN. The SCC is a brain structure that is involved in the processing of reward, but also negatively valenced emotions (Rolls, 2019; Du et al., 2021). Patients with depression who received SCC DBS showed a response rate of more than 50% and a remission rate of more than 30% (Crowell et al., 2019). Similarly, in a study done by Lipsman et al. in 2017 treated patients with treatment-resistant AN (n=16) with SCC DBS. The patients showed a response rate of 60% and a remission rate of 40% (Lipsman et al., 2017). The results from these studies are quite interesting as SCC DBS in AN appears to be 10% more successful in both response rate and remission rate compared to SCC DBS in depression. These results show that the overlap of AN and depression is also seen in the brain as stimulation of the SCC in both disorders yields the same results.

It must be noted that DBS is not a perfect treatment. DBS can have very promising results, but this only occurs if the patient responds to the treatment, which is not the case in on average 33% of the cases (Hitti et al., 2020; Mar-Barrutia et al., 2021; Shaheen et al., 2023). However, of the 67% of patients that do respond to the treatment, there is also a percentage of people who only respond partially to the treatment (Mar-Barrutia et al., 2021). Further, DBS does not actually treat a disease permanently (Holtzheimer & Mayberg, 2011). After the battery of the implant dies, the psychiatric symptoms could return immediately as they were before the activation of the device (Holtzheimer & Mayberg, 2011; Vora et al., 2012). Further, DBS can have negative side effects, such as an increase in anxiety, but also an increase in impulsivity and hypomania (Van Westen et al., 2021; Denys et al., 2010). However, DBS does also help many patients who suffer from certain psychiatric disorder, as is demonstrated above. It is only used as a final resort when all other treatments have failed, as it is an invasive and experimental treatment.

Conclusion

The main question asked in the introduction was: which brain structures should be targeted by DBS in order to more effectively treat AN? The brain areas that would yield the best results as possible targets for DBS in AN are the NAc, vALIC, and SCC. The BNST could also be a good target since BNST DBS yielded good results in OCD patients, but more research is needed to confirm this. Further, the NAc is the most obvious target for DBS in AN, since the NAc is also targeted with DBS in OCD, addiction, and depression and anxiety. It is the only brain area that is targeted in all disorders that are highly comorbid with AN or could be the cause of AN. DBS of the vALIC showed good results in both OCD and depression, which are the disorders most similar to AN. Finally, the SCC was only targeted by DBS in depression, but this brain structure is often experimentally targeted by DBS in AN, showing promising results.

References

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Amianto, F., Secci, I., Arletti, L., Davico, C., Abbate-Daga, G., & Vitiello, B. (2021). Obsessive–compulsive symptoms in young women affected with anorexia nervosa, and their relationship with personality, psychopathology, and attachment style. *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity*, *27*(3), 1193–1207. https://doi.org/10.1007/s40519-021-01252-y

Auerbach, R. P., Pagliaccio, D., Hubbard, N. A., Frosch, I. R., Kremens, R., Cosby, E. A., Jones, R. J., Siless, V., Lo, N., Henin, A., Hofmann, S. G., Gabrieli, J. D. E., Yendiki, A., Whitfield-Gabrieli, S., & Pizzagalli, D. A. (2022). Reward-Related neural circuitry in Depressed and Anxious Adolescents: a Human Connectome project. *Journal of the American Academy of Child and Adolescent Psychiatry*, *61*(2), 308–320. https://doi.org/10.1016/j.jaac.2021.04.014

Bach, P., Luderer, M., Müller, U., Jakobs, M., Baldermann, J. C., Voges, J., Kiening, K., Lux, A., Visser-Vandewalle, V., Klosterkötter, J., Huys, D., Sommer, W., Weber, T., Bogerts, B., Kuhn, J., & Mann, K. (2023). Deep brain stimulation of the nucleus accumbens in treatment-resistant alcohol use disorder: a double-blind randomized controlled multi-center trial. *Translational Psychiatry*, *13*(1). https://doi.org/10.1038/s41398-023-02337-1

Bae, Y. J., Kim, J. M., Sohn, C., Choi, J. H., Choi, B. S., Song, Y. S., Nam, Y., Cho, S. J., Jeon, B., & Kim, J. H. (2021). Imaging the substantia nigra in Parkinson disease and other parkinsonian syndromes. *Radiology*, *300*(2), 260–278. https://doi.org/10.1148/radiol.2021203341

Ballester, J., Dvorkin-Gheva, A., Silva, C., Foster, J. A., & Szechtman, H. (2015). Nucleus accumbens core and pathogenesis of compulsive checking. *Behavioural Pharmacology*, *26*(1 and 2-Special Issue), 200–216. https://doi.org/10.1097/fbp.0000000000000112

Barbarich-Marsteller, N. C., Foltin, R. W., & Walsh, B. T. (2011). Does anorexia nervosa resemble an addiction? *Current Drug Abuse Reviews*, *4*(3), 197–200. https://doi.org/10.2174/1874473711104030197

Barbier, J., Gabriëls, L., Van Laere, K., & Nuttin, B. (2011). Successful anterior capsulotomy in comorbid Anorexia Nervosa and Obsessive-Compulsive Disorder: Case report. *Neurosurgery*, *69*(3), E745. https://doi.org/10.1227/neu.0b013e31821964d2

Bayassi-Jakowicka, M., Lietzau, G., Czuba, E., Steliga, A., Waśkow, M., & Kowiański, P. (2021). Neuroplasticity and multilevel system of connections determine the integrative role of nucleus accumbens in the brain reward system. *International Journal of Molecular Sciences*, *22*(18), 9806. https://doi.org/10.3390/ijms22189806

Berends, T., Boonstra, N., & Van Elburg, A. (2018). Relapse in anorexia nervosa. *Current Opinion in Psychiatry*, *31*(6), 445–455. https://doi.org/10.1097/yco.0000000000000453

Bergfeld, I. O., Mantione, M., Hoogendoorn, M. L., Ruhé, H. G., Notten, P., Van Laarhoven, J., Visser, I., Figee, M., De Kwaasteniet, B. P., Horst, F., Schene, A. H., Van Den Munckhof, P., Beute, G., Schuurman, R., & Denys, D. (2016). Deep brain stimulation of the ventral anterior limb of the internal capsule for Treatment-Resistant Depression. *JAMA Psychiatry*, *73*(5), 456. https://doi.org/10.1001/jamapsychiatry.2016.0152

Berner, L. A., Brown, T. A., Lavender, J. M., Lopez, E., Wierenga, C. E., & Kaye, W. H. (2019). Neuroendocrinology of reward in anorexia nervosa and bulimia nervosa: Beyond Leptin and Ghrelin. *Molecular and Cellular Endocrinology*, *497*, 110320. https://doi.org/10.1016/j.mce.2018.10.018

Bewernick, B. H., Kayser, S., Sturm, V., & Schläepfer, T. E. (2012). Long-Term Effects of Nucleus Accumbens Deep Brain Stimulation in Treatment-Resistant Depression: Evidence for Sustained Efficacy. *Neuropsychopharmacology*, *37*(9), 1975–1985. https://doi.org/10.1038/npp.2012.44

Bischoff-Grethe, A., McCurdy, D., Grenesko-Stevens, E., Irvine, L. E. Z., Wagner, A., Yau, W. W., Fennema-Notestine, C., Wierenga, C. E., Fudge, J. L., Delgado, M. R., & Kaye, W. H. (2013). Altered brain response to reward and punishment in adolescents with anorexia nervosa. *Psychiatry Research: Neuroimaging*, *214*(3), 331–340. https://doi.org/10.1016/j.pscychresns.2013.07.004

Blomstedt, P., Naesström, M., & Bodlund, O. (2017). Deep brain stimulation in the bed nucleus of the stria terminalis and medial forebrain bundle in a patient with major depressive disorder and anorexia nervosa. *Clinical Case Reports*, *5*(5), 679–684. https://doi.org/10.1002/ccr3.856

Byrne, S., Wade, T. D., Hay, P., Touyz, S., Fairburn, C. G., Treasure, J., Schmidt, U., McIntosh, V. V., Allen, K. L., Fursland, A., & Crosby, R. D. (2017). A randomised controlled trial of three psychological treatments for anorexia nervosa. *Psychological Medicine*, *47*(16), 2823–2833. https://doi.org/10.1017/s0033291717001349

Calugi, S., Ghoch, M. E., Conti, M., & Grave, R. D. (2014). Depression and treatment outcome in anorexia nervosa. *Psychiatry Research*, *218*(1–2), 195–200. https://doi.org/10.1016/j.psychres.2014.04.024

Calvo-Rivera, M. P., Navarrete-Páez, M. I., Bodoano, I., & Gutiérrez-Rojas, L. (2022). Comorbidity between anorexia nervosa and Depressive Disorder: A Narrative review. *Psychiatry Investigation*, *19*(3), 155–163. https://doi.org/10.30773/pi.2021.0188

Carmi, L., Brakoulias, V., Arush, O. B., Cohen, H., & Zohar, J. (2022). A prospective clinical cohort-based study of the prevalence of OCD, obsessive compulsive and related disorders, and Tics in families of patients with OCD. *BMC Psychiatry*, *22*(1). https://doi.org/10.1186/s12888-022-03807-4

Catone, G., Pisano, S., Muzzo, G., Corrado, G., Russo, K., Maiorano, A., Salerno, F., & Gritti, A. (2021). A glance into psychiatric comorbidity in adolescents with anorexia nervosa. *MINERVA Pediatrica*, *72*(6). https://doi.org/10.23736/s0026-4946.19.05202-2

Chang, R., Peng, J., Chen, Y., Liao, H., Zhao, S., Zou, J., & Tan, S. (2022). Deep Brain Stimulation in Drug Addiction Treatment: Research progress and perspective. *Frontiers in Psychiatry*, *13*. https://doi.org/10.3389/fpsyt.2022.858638

Clausen, L., Semark, B. D., Helverskov, J., Bulik, C. M., & Petersen, L. (2023). Pharmacotherapy in anorexia nervosa: a Danish nation-wide register-based study. *Journal of Psychosomatic Research*, *164*, 111077. https://doi.org/10.1016/j.jpsychores.2022.111077

Clauss, J. A., Avery, S. N., Benningfield, M. M., & Blackford, J. U. (2019). Social anxiety is associated with BNST response to Unpredictability. *Depression and Anxiety*, *36*(8), 666–675. https://doi.org/10.1002/da.22891

Crowell, A., Riva-Posse, P., Holtzheimer, P. E., Garlow, S. J., Kelley, M. E., Gross, R. E., Denison, L., Quinn, S., & Mayberg, H. S. (2019). Long-Term outcomes of subcallosal cingulate deep brain stimulation for Treatment-Resistant Depression. *American Journal of Psychiatry*, *176*(11), 949–956. https://doi.org/10.1176/appi.ajp.2019.18121427

Cruz, S., Gutiérrez-Rojas, L., González-Domenech, P. J., Díaz-Atienza, F., Martínez-Ortega, J. M., & Jiménez-Fernández, S. (2022). Deep brain stimulation in Obsessive-compulsive Disorder: results from meta-analysis. *Psychiatry Research*, *317*, 114869. https://doi.org/10.1016/j.psychres.2022.114869

Denys, D., Graat, I., Mocking, R. J. T., De Koning, P., Vulink, N., Figee, M., Ooms, P., Mantione, M., Van Den Munckhof, P., & Schuurman, R. (2020). Efficacy of deep brain stimulation of the ventral anterior limb of the internal capsule for Refractory Obsessive-Compulsive Disorder: a clinical cohort of 70 patients. *American Journal of Psychiatry*, *177*(3), 265–271. https://doi.org/10.1176/appi.ajp.2019.19060656

Denys, D., Mantione, M., Figee, M., Van Den Munckhof, P., Koerselman, F., Westenberg, H., Bosch, A., & Schuurman, R. (2010). Deep brain stimulation of the nucleus accumbens for Treatment-Refractory Obsessive-Compulsive Disorder. *Archives of General Psychiatry*, *67*(10), 1061. https://doi.org/10.1001/archgenpsychiatry.2010.122

Devoe, D. J., Dimitropoulos, G., Anderson, A., Bahji, A., Flanagan, J., Soumbasis, A., Patten, S. B., Lange, T., & Paslakis, G. (2021). The Prevalence of Substance use Disorders and Substance Use in anorexia nervosa: a systematic review and meta-analysis. *Journal of eating disorders*, *9*(1). https://doi.org/10.1186/s40337-021-00516-3

Du, Y., Wang, Y., Yu, M., Tian, X., & Liu, J. (2021). Sex-Specific functional connectivity in the reward network related to distinct gender roles. *Frontiers in Human Neuroscience*, *14*. https://doi.org/10.3389/fnhum.2020.593787

Dunlop, B. W., Rajendra, J., Craighead, W. E., Kelley, M. E., McGrath, C. L., Choi, K. S., Kinkead, B., Nemeroff, C. B., & Mayberg, H. S. (2017). Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with Cognitive-Behavioral therapy or antidepressant medication for major depressive disorder. *American Journal of Psychiatry*, *174*(6), 533–545. https://doi.org/10.1176/appi.ajp.2016.16050518

Fawcett, E., Power, H. A., & Fawcett, J. M. (2020). Women are at greater risk of OCD than men. *The Journal of Clinical Psychiatry*, *81*(4). https://doi.org/10.4088/jcp.19r13085

Feltenstein, M. W., See, R. E., & Fuchs, R. A. (2020). Neural substrates and circuits of drug addiction. *Cold Spring Harbor Perspectives in Medicine*, *11*(4), a039628. https://doi.org/10.1101/cshperspect.a039628

Figee, M., Riva-Posse, P., Choi, K. S., Bederson, L., Mayberg, H. S., & Kopell, B. H. (2022). Deep brain stimulation for depression. *Neurotherapeutics*, *19*(4), 1229–1245. https://doi.org/10.1007/s13311-022-01270-3

Figee, M., Vink, M., De Geus, F., Vulink, N., Veltman, D. J., Westenberg, H., & Denys, D. (2011). Dysfunctional Reward Circuitry in Obsessive-Compulsive Disorder. *Biological Psychiatry*, *69*(9), 867–874. https://doi.org/10.1016/j.biopsych.2010.12.003

Freimuth, M., Moniz, S., & Kim, S. R. (2011). Clarifying Exercise Addiction: differential diagnosis, co-occurring disorders, and phases of addiction. *International Journal of Environmental Research and Public Health*, *8*(10), 4069–4081. https://doi.org/10.3390/ijerph8104069

Gardner, J. (2013). A History of Deep Brain stimulation: Technological innovation and the role of clinical assessment tools. *Social Studies of Science*, *43*(5), 707–728. https://doi.org/10.1177/0306312713483678

Godier, L. R., & Park, R. J. (2015). Does compulsive behavior in anorexia nervosa resemble an addiction? A qualitative investigation. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.01608

Goode, T. D., Ressler, R. L., Acca, G. M., & Miles, O. W. (2019). Bed nucleus of the Stria terminalis regulates fear to unpredictable threat signals. *eLife*, *8*. https://doi.org/10.7554/elife.46525

Goodman, W. K. (1989). The Yale-Brown obsessive compulsive scale. *Archives of General Psychiatry*, *46*(11), 1006. https://doi.org/10.1001/archpsyc.1989.01810110048007

Goyal, A., Goetz, S., Stanslaski, S., Oh, Y., Rusheen, A. E., Klassen, B. T., Miller, K. J., Blaha, C. D., Bennet, K. E., & Lee, K. (2021). The development of an implantable deep brain stimulation device with simultaneous chronic electrophysiological recording and stimulation in humans. *Biosensors and Bioelectronics*, *176*, 112888. https://doi.org/10.1016/j.bios.2020.112888

Grabhorn, R., Stenner, H., Stangier, U., & Kaufhold, J. (2006). Social anxiety in anorexia and bulimia nervosa: the mediating role of shame. *Clinical Psychology & Psychotherapy*, *13*(1), 12–19. https://doi.org/10.1002/cpp.463

Grave, R. D., Calugi, S., Doll, H., & Fairburn, C. G. (2013). Enhanced Cognitive behaviour therapy for adolescents with anorexia nervosa: an alternative to family therapy? *Behaviour Research and Therapy*, *51*(1), R9–R12. https://doi.org/10.1016/j.brat.2012.09.008

Haber, S. N., & Behrens, T. E. (2014). The Neural Network Underlying Incentive-Based Learning: Implications for Interpreting circuit Disruptions in Psychiatric Disorders. *Neuron*, *83*(5), 1019–1039. https://doi.org/10.1016/j.neuron.2014.08.031

Hayes, D. K., Lipsman, N., Chen, D. Q., Woodside, D. B., Davis, K. D., Lozano, A. M., & Hodaie, M. (2015). Subcallosal cingulate connectivity in anorexia nervosa patients differs from healthy controls: a multi-tensor tractography study. *Brain Stimulation*, *8*(4), 758–768. https://doi.org/10.1016/j.brs.2015.03.005

Henden, E., Melberg, H. O., & Røgeberg, O. (2013). Addiction: choice or compulsion? *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00077

Hitti, F. L., Ramayya, A. G., McShane, B., Yang, A., Vaughan, K. A., & Baltuch, G. H. (2020). Long-term outcomes following deep brain stimulation for Parkinson's disease. *Journal of Neurosurgery*, *132*(1), 205–210. https://doi.org/10.3171/2018.8.jns182081

Höflich, A., Michenthaler, P., Kasper, S., & Lanzenberger, R. (2018). Circuit mechanisms of reward, anhedonia, and depression. *The International Journal of Neuropsychopharmacology*, *22*(2), 105–118. https://doi.org/10.1093/ijnp/pyy081

Holtzheimer, P. E., & Mayberg, H. S. (2011). Deep brain stimulation for psychiatric disorders. *Annual Review of Neuroscience*, *34*(1), 289–307. https://doi.org/10.1146/annurev-neuro-061010-113638

Honey, C. R., Hamani, C., Kalia, S. K., Sankar, T., Picillo, M., Munhoz, R. P., Fasano, A., & Panisset, M. (2016). Deep brain stimulation target selection for Parkinson's disease. *Canadian Journal of Neurological Sciences*, *44*(1), 3–8. https://doi.org/10.1017/cjn.2016.22

Hsu, T., Nguyen, A., Gupta, N., Godbole, N. N., Perisetla, N., Hatter, M. J., Beyer, R., Bui, N., Jagan, J., Yang, C., Gendreau, J., Brown, N. J., & Oh, M. (2022). Effectiveness of deep brain stimulation in treatment of anorexia nervosa and Obesity: a systematic review. *World Neurosurgery*, *168*, 179–189. https://doi.org/10.1016/j.wneu.2022.09.114

Hulsman, A. M., Terburg, D., Roelofs, K., & Klumpers, F. (2021). Roles of the bed nucleus of the stria terminalis and amygdala in fear reactions. In *Handbook of Clinical Neurology* (pp. 419–432). https://doi.org/10.1016/b978-0-12-819975-6.00027-3

Jiang, T., Soussignan, R., Carrier, E., & Royet, J. (2019). Dysfunction of the mesolimbic circuit to food odors in women with anorexia and bulimia nervosa: a FMRI study. *Frontiers in Human Neuroscience*, *13*. https://doi.org/10.3389/fnhum.2019.00117

Johnson, J., Cote, A., Dobbyn, A., Sloofman, L., Xu, J., Cotter, L., Charney, A., Birgegård, A., Jordan, J., Kennedy, M. A., Landén, M., Maguire, S., Martin, N. G., Mortensen, P. B., Thornton, L. M., Bulik, C. M., & Huckins, L. (2022). Mapping anorexia nervosa genes to clinical phenotypes. *Psychological Medicine*, *53*(6), 2619–2633. https://doi.org/10.1017/s0033291721004554

Jordan, J., McIntosh, V. V., & Bulik, C. M. (2019). Specialist Supportive Clinical Management for anorexia nervosa: What it is (and what it is not). *Australasian Psychiatry*, *28*(2), 156–159. https://doi.org/10.1177/1039856219875024

Kawakami, I., Iritani, S., Riku, Y., Umeda, K., Takase, M., Ikeda, K., Niizato, K., Arai, T., Yoshida, M., Oshima, K., & Hasegawa, M. (2022). Neuropathological investigation of patients with prolonged anorexia nervosa. *Psychiatry and Clinical Neurosciences*, *76*(5), 187–194. https://doi.org/10.1111/pcn.13340

Kaye, W. H., Wierenga, C. E., Bischoff-Grethe, A., Berner, L. A., Ely, A. V., Bailer, U. F., Paulus, M. P., & Fudge, J. L. (2020). Neural insensitivity to the effects of hunger in women remitted from anorexia nervosa. *American Journal of Psychiatry*, *177*(7), 601–610. https://doi.org/10.1176/appi.ajp.2019.19030261

Keating, C. (2010). Theoretical perspective on anorexia nervosa: The conflict of reward. *Neuroscience & Biobehavioral Reviews*, *34*(1), 73–79. https://doi.org/10.1016/j.neubiorev.2009.07.004

Keßler, U., Kleppe, M. M., Rekkedal, G. Å., Rø, Ø., & Danielsen, Y. S. (2022). Experiences when implementing enhanced cognitive behavioral therapy as a standard treatment for anorexia nervosa in outpatients at a public specialized eating-disorder treatment unit. *Journal of eating disorders*, *10*(1). https://doi.org/10.1186/s40337-022-00536-7

Keizer, A., Smeets, M. A. M., Dijkerman, H. C., Uzunbajakau, S., Van Elburg, A., & Postma, A. (2013). Too fat to fit through the door: First evidence for Disturbed Body-Scaled Action in Anorexia Nervosa during locomotion. *PLOS ONE*, *8*(5), e64602. https://doi.org/10.1371/journal.pone.0064602

Kiely, L., Touyz, S., Conti, J., & Hay, P. (2022). Conceptualising Specialist Supportive Clinical Management (SSCM): current evidence and future directions. *Journal of eating disorders*, *10*(1). https://doi.org/10.1186/s40337-022-00557-2

Kolnes, L. (2016). 'Feelings Stronger than Reason': Conflicting experiences of exercise in women with anorexia nervosa. *Journal of eating disorders*, *4*(1). https://doi.org/10.1186/s40337-016-0100-8

Krivoschekov, S. G., & Lushnikov, O. H. (2011). Psychophysiology of sports addictions (exercise addiction). *Human Physiology*, *37*(4), 509–513. https://doi.org/10.1134/s0362119711030030

Kuusisto, K., Evilampi, S., Ekqvist, E., & Juhila, K. (2021). Discourses of Behavioural Addiction, normalisation and Techniques of Governmentality in inpatient Substance abuse treatment. *Nordic Social Work Research*, *13*(2), 217–230. https://doi.org/10.1080/2156857x.2021.1950038

Levinson, C. A., Brosof, L. C., Ram, S. S., Pruitt, A., Russell, S., & Lenze, E. J. (2019). Obsessions are strongly related to eating disorder symptoms in anorexia nervosa and atypical anorexia nervosa. *Eating Behaviors*, *34*, 101298. https://doi.org/10.1016/j.eatbeh.2019.05.001

Lewis, R. W., Florio, E., Punzo, D., & Borrelli, E. (2021). The brain's reward system in health and disease. In *Advances in Experimental Medicine and Biology* (pp. 57–69). https://doi.org/10.1007/978-3-030-81147-1_4

Lipsman, N., Lam, E. W., Volpini, M., Sutandar, K., Twose, R., Giacobbe, P., Sodums, D. J., Smith, G. S., Woodside, D. B., & Lozano, A. M. (2017). Deep brain stimulation of the subcallosal cingulate for treatment-refractory anorexia nervosa: 1 year follow-up of an open-label trial. *The Lancet Psychiatry*, *4*(4), 285–294. https://doi.org/10.1016/s2215-0366(17)30076-7

Lipsman, N., Woodside, D. B., & Lozano, A. M. (2015). Neurocircuitry of limbic dysfunction in anorexia nervosa. *Cortex*, *62*, 109–118. https://doi.org/10.1016/j.cortex.2014.02.020

Liu, W., Zhan, S., Li, D., Lin, Z., Zhang, C., Wang, T., Pan, S., Zhang, J., Cao, C., Jin, H., Li, Y., & Sun, B. (2020). Deep brain stimulation of the nucleus accumbens for treatment-refractory anorexia nervosa: a long-term follow-up study. *Brain Stimulation*, *13*(3), 643–649. https://doi.org/10.1016/j.brs.2020.02.004

Mandelli, L., Draghetti, S., Albert, U., De Ronchi, D., & Atti, A. (2020). Rates of Comorbid Obsessive-compulsive Disorder in Eating Disorders: A Meta-analysis of the literature. *Journal of Affective Disorders*, *277*, 927–939. https://doi.org/10.1016/j.jad.2020.09.003

Mar-Barrutia, L., Real, E., Segalàs, C., Bertolín, S., Menchón, J. M., & Alonso, P. (2021). Deep Brain Stimulation for Obsessive-compulsive Disorder: A Systematic Review of Worldwide experience after 20 years. *World journal of psychiatry*, *11*(9), 659–680. https://doi.org/10.5498/wjp.v11.i9.659

Miskovic-Wheatley, J., Bryant, E., Ong, S. H., Vatter, S., Le, A., Touyz, S., & Maguire, S. (2023). Eating Disorder Outcomes: Findings from a rapid review of over a decade of research. *Journal of eating disorders*, *11*(1). https://doi.org/10.1186/s40337-023-00801-3

Nalbant, K., Kalaycı, B. M., Akdemir, D., Akgül, S., & Kanbur, N. (2019). Emotion regulation, emotion recognition, and empathy in adolescents with anorexia nervosa. *Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity*, *24*(5), 825–834. https://doi.org/10.1007/s40519-019-00768-8

Naesström, M., Hariz, M., Strömsten, L., Bodlund, O., & Blomstedt, P. (2021). Deep Brain Stimulation in the bed nucleus of Stria Terminalis in Obsessive-Compulsive Disorder—1-Year Follow-up. *World Neurosurgery*, *149*, e794–e802. https://doi.org/10.1016/j.wneu.2021.01.097

Oudijn, M., Mocking, R. J. T., Wijnker, R. R., Lok, A., Schuurman, P. R., Van Den Munckhof, P., Elburg, A., & Denys, D. (2021). Deep brain stimulation of the ventral anterior limb of the capsula interna in patients with treatment-refractory anorexia nervosa. *Brain Stimulation*, *14*(6), 1528–1530. https://doi.org/10.1016/j.brs.2021.10.387

Pearce, J. (2004). Richard Morton: Origins of Anorexia nervosa. *European Neurology*, *52*(4), 191–192. https://doi.org/10.1159/000082033

Professional, C. C. M. (30-10-2023). *Deep brain stimulation*. Cleveland Clinic. https://my.clevelandclinic.org/health/treatments/21088-deep-brain-stimulation

Purvis, F., Thorpe, A., Turner, H., & Lawrence, P. J. (2023). Evidence of effectiveness of specialist supportive clinical management for anorexia nervosa in routine clinical practice: Outcomes from a clinical case series. *International Journal of Eating Disorders*, *56*(10), 1941–1946. https://doi.org/10.1002/eat.24022

Rau, A. R., Chappell, A. M., Butler, T. R., Ariwodola, O. J., & Weiner, J. L. (2015). Increased basolateral amygdala pyramidal cell excitability may contribute to the anxiogenic phenotype induced by chronic Early-Life stress. *The Journal of Neuroscience*, *35*(26), 9730–9740. https://doi.org/10.1523/jneurosci.0384-15.2015

Renteria, R., Baltz, E. T., & Gremel, C. M. (2018). Chronic alcohol exposure disrupts top-down control over basal ganglia action selection to produce habits. *Nature Communications*, *9*(1). https://doi.org/10.1038/s41467-017-02615-9

Rezai, A. R., Mahoney, J. J., Ranjan, M., Haut, M. W., Wang, Z., Lander, L. R., Berry, J. H., Farmer, D. L., Marton, J. L., Tirumalai, P., Mears, A., Thompson-Lake, D. G., Finomore, V., D'Haese, P., Aklin, W. M., George, D. T., Corrigan, J., & Hodder, S. (2023). Safety and Feasibility Clinical trial of Nucleus Accumbens deep brain stimulation for treatment-refractory opioid use disorder. *Journal of Neurosurgery*, 1–9. https://doi.org/10.3171/2023.4.jns23114

Rienecke, R. D. (2017). Family-based treatment of eating disorders in Adolescents: Current insights. *Adolescent Health, Medicine and Therapeutics*, *Volume 8*, 69–79. https://doi.org/10.2147/ahmt.s115775

Riquin, É., Raynal, A., Mattar, L., Lalanne, C., Huas, C., Duclos, J., Berthoz, S., & Godart, N. (2021). Is the severity of the clinical expression of anorexia nervosa influenced by an anxiety, depressive, or Obsessive-Compulsive comorbidity over a lifetime? *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.658416

Rolls, E. T. (2019). The cingulate cortex and limbic systems for emotion, action, and memory. *Brain Structure & Function*, *224*(9), 3001–3018. https://doi.org/10.1007/s00429-019-01945-2

Safadi, Z., Grisot, G., Jbabdi, S., Behrens, T. E., Heilbronner, S. R., McLaughlin, N., Mandeville, J., Versace, A., Phillips, M. L., Lehman, J., Yendiki, A., & Haber, S. N. (2018). Functional segmentation of the anterior limb of the internal capsule: linking white matter abnormalities to specific connections. *The Journal of Neuroscience*, *38*(8), 2106–2117. https://doi.org/10.1523/jneurosci.2335-17.2017

Scofield, M. D., Heinsbroek, J. A., Gipson, C. D., Kupchik, Y. M., Spencer, S., Smith, A. C., Roberts-Wolfe, D., & Kalivas, P. W. (2016). The Nucleus accumbens: mechanisms of addiction across drug classes reflect the importance of glutamate homeostasis. *Pharmacological Reviews*, *68*(3), 816–871. https://doi.org/10.1124/pr.116.012484

Senova, S., Clair, A., Palfi, S., Yelnik, J., Domenech, P., & Mallet, L. (2019). Deep brain stimulation for Refractory Obsessive-Compulsive Disorder: towards an individualized approach. *Frontiers in Psychiatry*, 10. https://doi.org/10.3389/fpsyt.2019.00905

Serpell, L., Livingstone, A., Neiderman, M., & Lask, B. (2002). Anorexia nervosa: Obsessive–compulsive disorder, obsessive–compulsive personality disorder, or neither?. *Clinical Psychology Review*, *22*(5), 647–669. https://doi.org/10.1016/s0272-7358(01)00112-x

Scharner, S., & Stengel, A. (2019). Alterations of brain structure and functions in anorexia nervosa. *Clinical Nutrition Experimental*, *28*, 22–32. https://doi.org/10.1016/j.yclnex.2019.02.001

Sullivan, C., Olsen, S., & Widge, A. S. (2021). Deep brain stimulation for psychiatric disorders: from focal brain targets to cognitive networks. *NeuroImage*, *225*, 117515. https://doi.org/10.1016/j.neuroimage.2020.117515

Shaheen, N., Shaheen, A., Sarica, C., Singh, A. K., Zanaty, M., Johari, K., Yang, A., Zesiewicz, T. A., Dalm, B. D., Bezchlibnyk, Y. B., Lozano, A. M., & Flouty, O. (2023). Deep Brain Stimulation for Substance Use Disorder: A Systematic review and Meta-analysis. *Frontiers in Psychiatry*, *14*. https://doi.org/10.3389/fpsyt.2023.1231760

Schüller, T., Kohl, S., Dembek, T. A., Tittgemeyer, M., Huys, D., Visser-Vandewalle, V., Li, N., Wehmeyer, L., Barbe, M. T., Kuhn, J., & Baldermann, J. C. (2023). Internal Capsule/Nucleus accumbens deep brain stimulation increases impulsive decision making in Obsessive-Compulsive Disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *8*(3), 281–289. https://doi.org/10.1016/j.bpsc.2022.10.005

Song, W., Wang, W., Yu, S., & Lin, G. N. (2021). Dissection of the genetic association between Anorexia nervosa and Obsessive–Compulsive Disorder at the network and cellular levels. *Genes*, *12*(4), 491. https://doi.org/10.3390/genes12040491

Thomas, K., Birch, R. E., Jones, C. R. G., & Vanderwert, R. E. (2022). Neural correlates of executive functioning in Anorexia Nervosa and Obsessive–Compulsive Disorder. *Frontiers in Human Neuroscience*, *16*. https://doi.org/10.3389/fnhum.2022.841633

Turton, S., & Lingford-Hughes, A. (2016). Neurobiology and principles of Addiction and Tolerance. *Medicine*, *44*(12), 693–696. https://doi.org/10.1016/j.mpmed.2016.09.007

Van Eeden, A. E., Van Hoeken, D., & Hoek, H. W. (2021). Incidence, prevalence and mortality of anorexia nervosa and bulimia nervosa. *Current Opinion in Psychiatry*, *34*(6), 515–524. https://doi.org/10.1097/yco.0000000000000739

Volkow, N. D., Chang, L., Wang, G., Fowler, J. S., Franceschi, D., Sedler, M. J., Gatley, S. J., Miller, E. N., Hitzemann, R., Ding, Y., & Logan, J. (2001). Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *The Journal of Neuroscience*, *21*(23), 9414–9418. https://doi.org/10.1523/jneurosci.21-23-09414.2001

Wang, Y., Kim, J., Schmit, M. B., Cho, T. S., Fang, C., & Cai, H. (2019). A bed nucleus of stria terminalis microcircuit regulating inflammation-associated modulation of feeding. *Nature Communications*, *10*(1). https://doi.org/10.1038/s41467-019-10715-x

Westmoreland, P., Duffy, A., Rienecke, R. D., Grange, D. L., Joiner, T. E., Manwaring, J., Watters, A., & Mehler, P. S. (2022). Causes of death in patients with a history of severe anorexia nervosa. *Journal of eating disorders*, *10*(1). https://doi.org/10.1186/s40337-022-00716-5

Xu, L., Nan, J., & Lu, Y. (2020). The nucleus accumbens: a common target in the comorbidity of depression and addiction. *Frontiers in Neural Circuits*, *14*. https://doi.org/10.3389/fncir.2020.00037

Vandaele, Y., & Ahmed, S. H. (2020). Habit, choice, and addiction. *Neuropsychopharmacology*, *46*(4), 689–698. https://doi.org/10.1038/s41386-020-00899-y

Vandereycken, W., & Van Deth, J. W. (1989). Who was the first to describe anorexia nervosa: gull or lasègue? *Psychological Medicine*, *19*(4), 837–845. https://doi.org/10.1017/s0033291700005559

Van Westen, M., Rietveld, E., Bergfeld, I. O., De Koning, P., Vullink, N., Ooms, P., Graat, I., Liebrand, L. C., Van Den Munckhof, P., Schuurman, R., & Denys, D. (2021). Optimizing deep brain stimulation parameters in Obsessive–Compulsive Disorder. *Neuromodulation: Technology at the Neural Interface*, *24*(2), 307–315. https://doi.org/10.1111/ner.13243

Vora, A., Ward, H. E., Foote, K. D., Goodman, W. K., & Okun, M. S. (2012). Rebound symptoms following battery depletion in the NIH OCD DBS cohort: Clinical and reimbursement issues. *Brain Stimulation*, *5*(4), 599–604. https://doi.org/10.1016/j.brs.2011.10.004

Wade, T. D., Wilksch, S., Paxton, S. J., Byrne, S., & Austin, S. B. (2015). How perfectionism and ineffectiveness influence growth of eating disorder risk in young adolescent girls. *Behaviour Research and Therapy*, *66*, 56–63. https://doi.org/10.1016/j.brat.2015.01.007

World Health Organization: WHO & World Health Organization: WHO. (2023, 31 March). *Depressive disorder (depression)*. https://www.who.int/news-room/fact-sheets/detail/depression#:~:text=An%20estimated%203.8%25%20of%20the,among%20women%20than%20among%20men.

Yılmaz, Z., Schaumberg, K., Halvorsen, M., Goodman, E. L., Brosof, L. C., Crowley, J. J., Mathews, C. A., Mattheisen, M., Breen, G., Bulik, C. M., Micali, N., & Zerwas, S. (2022). Predicting eating disorder and anxiety symptoms using disorder-specific and transdiagnostic polygenic scores for anorexia nervosa and obsessive-compulsive disorder. *Psychological Medicine*, *53*(7), 3021–3035. https://doi.org/10.1017/s0033291721005079

Young, C. B., Reddy, V., Sonne, J. (2023, 24 July). *Neuroanatomy, basal ganglia*. StatPearls - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK537141/

Zeeck, A., Herpertz-Dahlmann, B., Friederich, H. C., Brockmeyer, T., Resmark, G., Hagenah, U., Ehrlich, S., Cuntz, U., Zipfel, S., & Hartmann, A. (2018). Psychotherapeutic Treatment for Anorexia Nervosa: A Systematic Review and Network Meta-Analysis. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00158

Zipfel, S., Giel, K. E., Bulik, C. M., Hay, P., & Schmidt, U. (2015). Anorexia nervosa: Aetiology, assessment, and treatment. *The Lancet Psychiatry*, *2*(12), 1099–1111. https://doi.org/10.1016/s2215-0366(15)00356-9