The role of the reward system in Anorexia Nervosa

Bachelor Thesis
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Abstract

Anorexia Nervosa (AN) is a complex mental disorder characterized by a significant reduction in food intake, leading to severe weight loss and emaciation. Despite its prevalence, especially among young adolescents, the exact causes of this multifactorial disease remain unknown, posing challenges for effective treatment. Patients with AN exhibit various neurobiological alterations, though it is unclear whether these changes result from the effects of starvation. Among these alterations, disruptions in dopaminergic transmission are notable. Worth noting, a study by Barbato et al. (2006) discovered that eye-blinking rate—a peripheral measure of central dopaminergic activity—is significantly increased in patients with restricting-type AN. Dopamine plays a crucial role in reward-associated pathways within the mesocorticolimbic circuits. Therefore, this thesis aims to address the question: *Can a reward-centered model explain the development and maintenance of AN*? After examining studies involving reward-based paradigms in response to food-related and illness-compatible cues, a theoretical framework is proposed. The current model suggests that reward-based learned associations can account for the progression of the disease, aligning with its pathological features. Additionally, the thesis highlights the striking similarities between addiction and AN and proposes new treatment strategies that target reward processing in AN patients.

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Introduction

Anorexia nervosa (AN) is a mental disorder of unknown etiology that has seen a global rise in incidence, particularly among young women (Nagy et al., 2022). This condition is characterized by an intense fear of gaining weight, leading to restricted food intake and excessive exercise. Patients with anorexia typically have a distorted perception of their body image and place excessive importance on body shape in self-evaluation. AN is a multifactorial disease with various risk factors, including genetics, childhood life events, personality traits such as perfectionism and criticism, and psychiatric comorbidities (Nagy et al., 2022).

Dopamine, a key neurotransmitter involved in reward, motivation, and control of food intake, is altered in AN patients. A 2006 study showed that the eye-blinking rate, a peripheral measure of central dopaminergic activity, is significantly increased in restricting-type AN patients (Barbato et al., 2006). Furthermore, polymorphisms in genes encoding dopamine receptors correlate with a higher risk of developing AN (Gervasini et al., 2013). While several studies have observed altered dopamine transmission and reward processing in anorexia, the neurobiology behind this complex disease remains unclear. Although it might seem intuitive that weight loss is rewarding due to external positive societal feedback on body image, it is less obvious why AN patients would find starvation and excessive exercise rewarding.

Given these observations, this thesis seeks to answer the following main question: *Can a reward-centered model explain the development and maintenance of Anorexia Nervosa?*

The following chapters will explore the characteristics of the disease, including its epidemiology and symptoms. Subsequently, the neurobiological aspects underlying AN will be examined, with a particular focus on dopamine and the reward system. Finally, studies linking reward processing and anorexia will be proposed to suggest a reward-centered model explaining the disease's development, ultimately aiming to open up new therapeutic strategies for treatment.

Chapter 1: Anorexia Nervosa

Anorexia Nervosa (AN) is a mental illness that is characterized by a reduction of food intake leading to significantly low body weight compared to age, sex, developmental trajectory, and physical health (The National Institute of Mental Health [NIMH], n.d.). The Diagnostic and Statistical Manual of Mental Disorders (7) has described two main subtypes of AN: 1) the binge-eating and purging type, and 2) the restrictive type. The person with the former subtype usually demonstrates actions like self-induced vomiting and laxative or diuretic abuse. The latter subtype is considered in a patient who abstains from regular binge eating and purging for a minimum of 3 months. A further classification of the disease into atypical anorexia has been made for patients not fulfilling the criteria of low body weight (American Psychiatric Association, 2013).

Epidemiology

Anorexia nervosa exhibits a global prevalence of up to 4% in females and 0.3% in males. Notably, there is a concerning trend of increasing incidence rates in younger populations below 15 years old, highlighting the importance of early intervention and prevention strategies (van Eeden et al., 2021). AN stands out for its elevated

mortality risk across mental disorders, with patients facing a five times more elevated risk of death (van Eeden et al., 2021). This elevated mortality risk can be attributed to various factors inherent to the diseases, in particular to physiological consequences of severe malnutrition and weight loss such as cardiac abnormalities, gastrointestinal issues, and weakened immune function. Additionally, the comorbidity of the disorder with other psychiatric conditions, in particular unipolar depression and anxiety disorders, elevates the risk of mortality due to suicide (van Eeden et al., 2021). Furthermore, while anorexia nervosa is commonly associated with young females in Western countries, it is crucial to recognize that individuals from diverse demographic groups can be affected by this disorder. This underscores the need for a comprehensive and inclusive approach to understanding and addressing anorexia nervosa beyond traditional stereotypes.

Symptoms

AN patients exhibit extreme fear of gaining weight, regardless of the severity of their weight loss. Furthermore, these symptoms are accompanied by a distorted body image and self-esteem highly influenced by body shape. Other symptoms that can develop over time are thinning of the bones (osteopenia), anemia, severe constipation, loss of menstruation, and low blood pressure (NIMH, n.d.). Another common clinical feature observed in these patients is hyperactivity, defined by excessive exercise (Kohl et al., 2004). Not all patients exhibit hyperactive behavior and although this symptom might be interpreted as a weight-loss strategy, studies have suggested a more complex etiology behind it. On one hand, the often-seen comorbidity of AN with other psychiatric conditions such as unipolar depression and anxiety, has suggested that overexercising could be a strategy to relieve discomfort. For instance, animal models reveal that rats with restricted food intake and access to a running wheel exhibit excessive activity and reduced food consumption. This paradoxical behavior named Activity-Based Anorexia is thought to arise from a dysfunction in brain regions regulating rest and activity (Epling et al., 1983). Additionally, alterations in the endocrine system and hormonal imbalances involving ghrelin and neuropeptide Y seem to play a role in the complex neurobiological changes involved in the disease (Scheurink et al., 2010).

Therapeutic strategies

Anorexia nervosa treatment involves three main approaches: nutritional rehabilitation, psychosocial treatments, and medications, with a combined approach being more effective than any single method alone (Nagy et al., 2023). Nutritional rehabilitation aims to restore healthy weight through proper nutrition and caloric intake and studies have shown that patients dehospitalized without reaching a healthy weight are more likely to relapse (Willer et al., 2005). Psychosocial treatments, including psychoeducation, and individual and family therapies, have demonstrated benefits through patient self-reporting and clinical experience. Cognitive behavioral therapy (CBT) has shown superior outcomes compared to nutritional rehabilitation alone, being associated with lower relapse rates and better overall outcomes (Pike et al., 2003). Lastly, pharmacological treatments for AN, though challenging, are also utilized. Some antipsychotic drugs, such as olanzapine, have shown potential benefits in reducing anxiety and depression, which in turn can promote weight gain. However, the use of antidepressants, such as fluoxetine, has demonstrated limited benefits in weight restoration (Nagy et al., 2023).

Chapter 2: Neurobiology of AN

Risk factors and disease-associated alterations

AN is a complex multifactorial disease resulting from the interaction between genetic factors, personality traits, comorbid psychiatric conditions, and psychosocial factors. Therefore, understanding the pathophysiology of this eating disorder has been the focus of many researchers to develop effective treatments. Altered brain functions have been observed in AN patients, however, it is hard to determine whether the observed abnormalities are consequences of malnourishment and weight loss or pre-existing conditions before the onset of the disease (Kaye et al., 2009). Hereafter, two categories of neurobiological alterations will be discussed: firstly, risk factors contributing to the development of the disease, and secondly, state-related alterations.

Twin and family studies reveal that genetic heritability accounts for 50-80% of the risk of developing AN and individuals with a family history of the disorder are 11 times more likely to develop AN compared to those with no such history (Barakat et al., 2023). Additionally, genetic research has highlighted polymorphisms in genes involved in serotonergic, dopaminergic, opioid, and appetite regulation pathways, suggesting their contribution to the disease's development (Donato et al., 2022). Strong genetic links have been found between AN and psychiatric comorbidities such as Obsessive-Compulsive Disorder (OCD), Major Depressive Disorder (MDD), and schizophrenia. In one study, MDD was found in 64% of individuals with restrictive-type AN, with mood disorders preceding the onset of AN in one-third of cases, indicating that depressive disorders can be both predictors and consequences of AN (Godart et al., 2015). Personality traits like anxiety, perfectionism, and obsessive-compulsivity are also associated with an increased risk of developing eating disorders. These traits significantly influence the severity of symptoms, treatment response, and risk of relapse (Barakat et al., 2023). For example, perfectionism, characterized by setting unrealistically high standards despite adverse outcomes, is strongly linked to AN psychopathology and tends to persist even after treatment. Given the shared features of rigidity and a need for control, it is not surprising that OCD frequently co-occurs with AN (Farstad et al., 2016). Additionally, body image concerns, including weight and shape overvaluation and the drive for thinness, are crucial risk factors for AN. Traditionally, research has focused on women's concerns with achieving a thin ideal but recent studies emphasize the muscular and lean ideal among men as well, especially in environments promoting strict dieting and excessive exercise such as those found in sports (Schroeder et al., 2023).

State-related alterations induced by starvation play an important role in the maintenance of the disease. These include a reduced brain volume, tending to normalize after recovery, and altered metabolism in frontal, cingulate, temporal, and parietal brain regions. (Kaye et al., 2009). Starvation-driven endocrine and metabolic changes in AN likely serve as compensatory mechanisms to conserve energy and stimulate hunger and feeding. Patients exhibit altered levels of neuropeptide Y (↑), leptin (↓), corticotropin-releasing hormone (↑), beta-endorphin (↓), and pancreatic polypeptide (↑) (Støving et al., 1999). These hormonal alterations can affect mood, cognitive function, impulse control, and autonomic and hormonal systems, contributing to the behavioral symptoms of AN. These changes may sustain AN behaviors by driving further dieting and weight loss (Jimerson et al., 2006). In Figure 1, a time course of AN showing the interaction between premorbid traits and state-dependent alterations is proposed. Specifically, risk factors increase an individual's vulnerability to the disease and are amplified by societal factors, stress and hormonal changes related to puberty. Once chronic dieting and weight loss are

achieved, secondary state-dependent neurobiological alterations further exacerbate rigidity, depression, and obsessionality (Kaye et al., 2009).

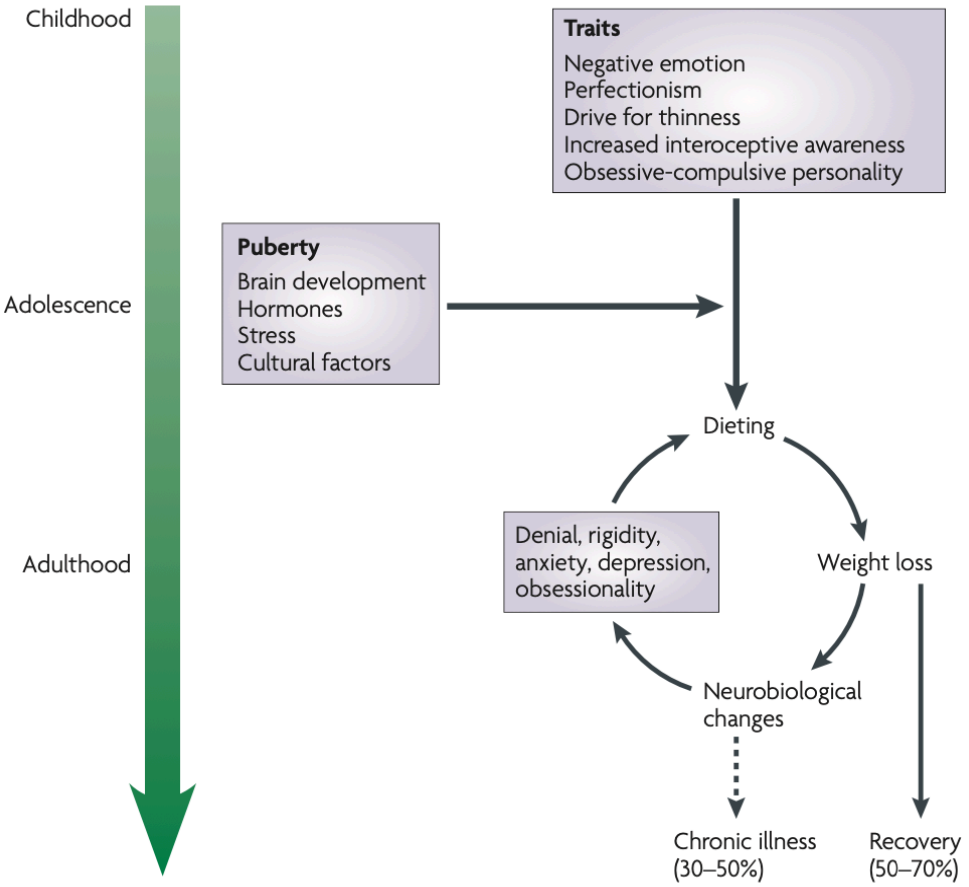

Figure 1. ***Time course of AN: interaction between risk factors and state-dependent neurobiological alterations.*** Adapted from Kaye et al. (2009).

Chapter 3: Dopamine and the Reward System

Dopamine is a monoamine neurotransmitter produced by dopaminergic neurons located in the ventral tegmental area (VTA), pars compacta of the substantia nigra (SNc), midbrain, and arcuate nucleus of the hypothalamus. From these nuclei, four main dopaminergic systems arise: the Nigrostriatal, Mesolimbic, Mesocortical, and Tuberoinfundibular pathways. These pathways transmit signals via dopamine receptors located in different brain areas. There are five subtypes of dopamine receptors: DRD1, DRD2, DRD3, DRD4, and DRD5. D1 and D5 receptors are mostly involved in post-synaptic excitation, while D2, D3, and D4 receptors are involved in both pre- and post-synaptic inhibition (Ayano, 2016).

The nigrostriatal pathway originates from the SNc and plays a major role in goal-directed locomotor activity and habitual actions. Disruptions in this system are often associated with Parkinson's disease, which can cause tremors and movement difficulties (Redgrave et al., 2010). The mesolimbic pathway, extending from the VTA to

mainly the nucleus accumbens (NAc) of the limbic system, is essential for reward and motivation. It shapes responses to pleasurable stimuli and drives behaviors related to reward-seeking and reinforcement. Dysregulation in this pathway can lead to addictive behaviors and mood disorders, highlighting its significant role in the interplay between emotions and motivations. The mesocortical pathway connects the VTA with the prefrontal cortex (PFC) and is essential for executive functions, emotional regulation, and cognitive processes such as attention and working memory. Because of the overlap between the mesolimbic and the mesocortical pathways, they are often referred to as the mesocorticolimbic system (Arias-Carrión et al., 2010). Lastly, the tuberoinfundibular pathway, linking the hypothalamus to the pituitary gland, regulates hormonal balance and reproductive functions, underscoring the connection between dopamine signaling and endocrine regulation (Ayano, 2016). An overview of the dopaminergic pathways mainly involved in reward is shown in Figure 2.

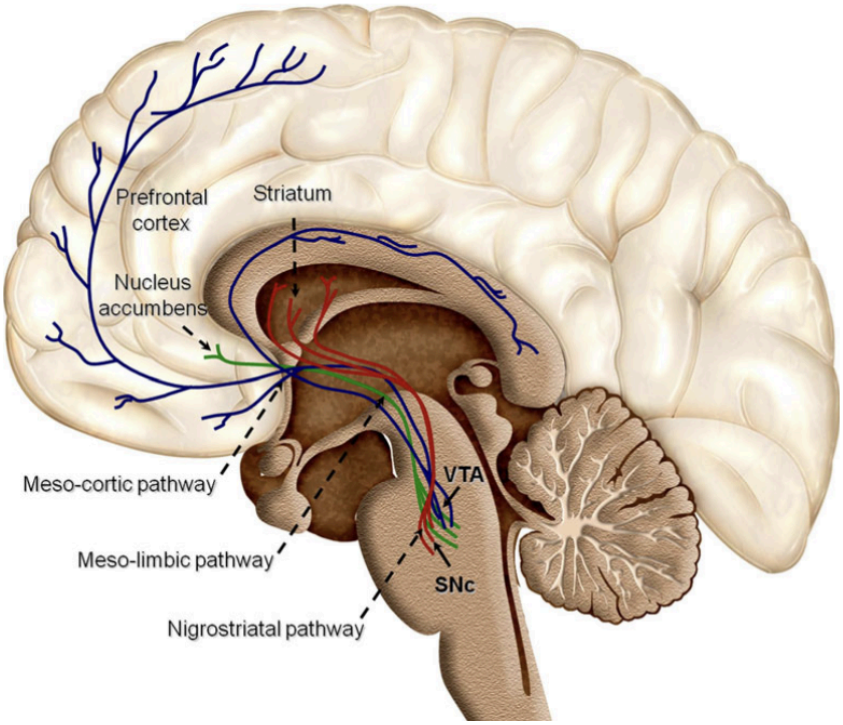

Figure 2. ***Overview of the brain's reward structures.*** Three dopaminergic pathways are shown: Nigrostriatal pathway (red) originating from the substantia nigra (SN), Mesolimbic (green) and Mesocortical (blue) pathways originating from the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAc) and prefrontal cortex (PFC) respectively. Adapted from Arias-Carrión et al. (2010).

The brain's reward system

Rewards are defined as objects or goals that we are willing to work for by investing time, energy, or effort. They represent anything we actively seek to obtain or achieve. Mesolimbic and mesostriatal dopamine projections have been suggested as the neural circuitry involved in reward processing. Evidence of dopamine systems mediating rewards mainly comes from studies of pharmacological blockade of dopamine receptors in animals. In particular, while several studies in humans have shown that presentations of rewards such as drug-associated stimuli, food, sexual behaviors, and even videogames increase dopaminergic activity, other studies have found

that dopamine antagonists reduce reward-directed consummatory behaviors (Berridge and Robinson, 1998; Koepp et al., 1998).

Considering the aforementioned aspects, it becomes clear that dopamine certainly plays an important role in reward. However, multiple hypotheses have been proposed on the exact role of this neurotransmitter and the mesocorticolimbic system in this process. A first interpretation, the anhedonia hypothesis, has been suggested by Wise (1982) and consists of the idea that the brain's dopamine systems mediate the pleasure induced by food and other stimuli such as sex and drugs, but also the conditioned pleasure induced by secondary reinforcers. This theory has been widely used to explain the observed anhedonic behavior during drug withdrawal in addicts, which can be only restored by seeking drugs that would re-establish a sort of "hedonic homeostasis" (Koob et al., 1997).

Another hypothesis regarding the role of dopamine in reward focuses on *incentive salience*, which involves attributing attentional value to otherwise neutral stimuli (Berridge et al., 1998). This theory suggests that reward processing can be divided into two components: "liking" and "wanting". The "liking" component is associated with neurochemical systems such as opioids, endocannabinoids, and GABA-benzodiazepines, which have been shown to enhance the hedonic response to rewarding stimuli in specific limbic structures known as "hedonic hotspots," located in the nucleus accumbens and the posterior ventral pallidum. In the context of incentive salience, conditioned stimuli (CS) acquire motivational properties through associative learning, becoming "wanted" and eliciting a motivational response even in the absence of the actual reward, the unconditioned stimulus (US). This process highlights the role of Pavlovian associative learning in shaping motivational behavior, habit formation and the influence of incentive salience on driving individuals toward seeking rewards (Berridge, 2009). Midbrain dopamine projections to the nucleus accumbens (NAc) and other regions of the striatum modulate incentive salience. Additionally, research indicates that inhibiting endogenous dopamine neurotransmission can diminish the "wanting" component of reward without affecting hedonic pleasure. This concept of incentive salience has been successful in explaining drug-seeking behavior and self-administration in addicts: it suggests that these behaviors result from the sensitization of the mesocorticolimbic dopamine system following repeated drug use, where the conditioned stimulus acquires new motivational significance, leading to "craving" the drug (Berridge, 2007).

Altered dopamine function in AN

Patients suffering from anorexia nervosa (AN) exhibit stereotyped behaviors, including compulsive dieting and excessive exercise, suggest alterations in the brain's dopamine system, which is critical for reward, motivation, and salience (Berridge et al., 2009). Furthermore, behaviors associated with AN such as dieting and exercising towards excessiveness have similarities with the clinical profile of addiction that, as described earlier in this chapter, displays a preoccupation with drug seeking- and self-administration (O' Hara et al., 2015). However, distinguishing between alterations caused by starvation and those that may contribute to the disease's onset is challenging. To address this issue, researchers have studied patients who have recovered from AN to avoid the confounding effects of malnutrition. For instance, Kaye et al. (1999) found reduced levels of homovanillic acid, a dopamine metabolite, in recovered restricting-type AN (RT-AN) patients. Numerous studies in both animals and humans have shown altered dopaminergic activity in RT-AN patients. Notably, Barbato et al. (2006) reported that Eye-Blinking Rate (EBR), a marker of dopamine activity, was higher in individuals with AN. Additionally, genetic studies have found correlations between polymorphisms in dopamine receptor (DRD2, DRD3 and

DRD4) genes and increased vulnerability to developing AN (Gervasini et al., 2013), as well as increased dopamine receptor DRD2/3 availability in the ventral striatum in RT-AN subjects (Frank et al., 2005).

Given the observed abnormalities in dopaminergic activity, researchers have employed reward-based paradigms to investigate reward processing in AN. The following chapter will present some findings from imaging and neuropsychological studies, alongside a theoretical framework for the disease's development, with a particular focus on the reward system and habit formation.

Chapter 4: Reward processing in AN

Hereafter, experimental findings on reward processing in AN will be presented in terms of food-associated stimuli and AN-associated cues, related to thinness and exercise.

Response to food-specific stimuli

Multiple studies on response to food-specific stimuli have shown altered activity in prefrontal, cingulate, insular and striatal regions in AN patients compared to healthy controls. In particular, a study in which sweet and savory foods were shown to ill and recovered AN patients, found increased activity in the medial PFC and anterior cingulate cortex (ACC) (Uher et al., 2003). Additionally, Cowdrey et al. (2011) have found that in response to the sight and taste of rewarding (chocolate) and aversive (moldy strawberries) food, recovered AN subjects showed increased activity in the ACC to an aversive food picture and in the medial PFC to an appetitive food picture. As seen in the previous chapter, the PFC plays a role in emotion regulation and motivation, as well as in the cognitive control network (Kaye et al., 2009). Furthermore, the ACC has been associated with the processing of reward and punishment. Therefore, hyperactivation of this region in AN patients has led to the hypothesis that this site is responsible for “reward contamination”, which consists in the idea that normally rewarding stimuli (i.e. chocolate) are perceived as punishing while normally punishing stimuli (e.g. starvation) as rewarding. This hypothesis, mainly focused on the ACC, has been further supported by the observation that individuals with AN find their behaviors highly valuable and rewarding at the early stages of the illness and over time, these behaviors become reinforced despite being punishing (Keating, 2010). Furthermore, these studies indicate that aversive reactions to food stimuli might be due to a cognitively driven reluctance to gain weight, rather than a general inability to experience reward (O’Hara et al., 2015).

In relation to food-specific stimuli, altered responses have been observed in insular and striatal regions as well. The insula plays an important role in the incentive value of cues related to tastes and physical properties of food, functioning as a connection between frontal and striatal regions while being involved in the integration of reward, motivated behaviors, and emotion processing (O’Hara et al., 2015). Recovered AN patients show increased activity in the ventral striatum in response to pleasant high-calorie tastes compared to controls, despite similar subjective ratings of 'pleasantness,' 'intensity,' and 'wanting'. Additionally, they exhibit heightened activity in the insula and putamen to aversive tastes, and in the caudate to aversive food images (Cowdrey et al., 2011). Interestingly, an fMRI study by Frank et al. (2012) used a reward paradigm to compare differences in dopamine reward systems between obese, healthy, and AN subjects. This test, involving learning the association between conditioned visual stimuli and unconditioned taste stimuli, as well as the unexpected violation of those learned associations, has shown differences between groups at the level of the ventral striatum, insula, and PFC, with

increased sensitivity in the AN group. Altogether, these findings show that both ill and recovered AN subjects, attribute greater salience to both rewarding and aversive food stimuli irrespective of valence, thereby suggesting that restricting food intake might be a way to control exposure to overwhelming food stimuli (O'Hara et al., 2015).

Response to illness-compatible stimuli

Frederich et al. (2010) have shown that AN patients exhibit heightened activation in regions involved in emotional and motivational processing, particularly the lateral PFC, insula, and putamen, when comparing self-body images to thin-idealized female bodies, in contrast to healthy controls. Additionally, these brain activity responses were accompanied by higher satisfaction ratings for thin-body images. The increased activation of these regions in response to thin body images suggests a greater attribution of motivational salience towards illness-related stimuli such as thinness.

Further supporting the role of the reward system in the disease, Fladung et al. (2010) found that in response to images of underweight female bodies, acute AN patients exhibit increased activity in the ventral striatum compared to healthy controls. This difference was not observed when comparing responses to normal weight body images, indicating that ventral striatal activity differences are specific to illness-related cues (i.e. thinness) and reinforcing the hypothesis of the reward system's pivotal role in maintaining the disease due to a starvation-dependence state.

Evidence that illness-compatible cues are rewarding for AN patients has also been suggested from a study involving dopamine depletion and Eye-Blink Startle responses (O'Hara et al., 2016). Startle eye-blink modulation (SAM) measures motivational states in terms of withdrawal and approach, with increased startle potentiation indicating an aversive response and decreased startle potentiation indicating an appetitive response. In response to underweight and active female body pictures, AN subjects showed decreased startle potentiation, indicating that these cues were rewarding for them. In contrast, healthy controls exhibited an aversive response to the same pictures compared to normal weight and non-active images. Repeating the test in a dopamine-depleted state eliminated the between-group difference in SAM response, further suggesting the observed aberrant reward processing in AN is dopamine-driven (O'Hara et al., 2016).

Chapter 5: A reward-centered model of AN

In the previous chapters, several findings on aberrant reward processing and dopaminergic activity in anorexia nervosa (AN) have been presented, along with hypotheses regarding their role in the disorder. The *anhedonia hypothesis* by Wise (1982) proposes dopamine as a key regulator of the hedonic component of rewards. Based on this hypothesis, it has been suggested that anhedonic behavior in AN patients could be due to a general inability to experience reward, stemming from a hyporesponsive dopaminergic reward system (Kaye et al., 2005). Contrary to this hypothesis, studies involving reward paradigms in AN patients have shown increased activity in ventral striatal reward-associated regions in response to food-specific stimuli and illness-compatible cues (Fladung et al., 2010; O'Hara et al., 2016; Friedrich et al., 2010). These studies also indicate increased sensitivity to both rewarding and aversive food stimuli in this group (Frank et al., 2012). As discussed in Chapter 4, a *reward contamination* theory has been proposed based on findings suggesting an overlap between neural

pathways processing reward and punishment in AN patients. This theory particularly focuses on the role of the anterior cingulate cortex (ACC) where reward, punishment, and conflict are integrated (Keating, 2010).

The reward-centered model currently proposed supports the role of the reward system in the development and maintenance of AN, emphasizing the involvement of dopamine in habit formation and motivated behavior (Walsh, 2013). In this model, when reward-related cues and associations are learned, they begin to predict their associated rewards, triggering the motivational "wanting" necessary to obtain the specific reward. This function is significantly influenced by dopamine (Berridge and Robinson, 1998; Berridge, 2009). Consequently, repeated behaviors risk becoming deeply entrenched and resistant to change due to potential interactions between striatal dopamine and habit-related regions of the frontal brain, such as the infralimbic cortex (Walsh, 2013).

Dieting initially starts as a goal-directed behavior to achieve weight loss, seen as positive and rewarding, and reinforced by socio-emotional factors. Dieting and other illness-associated behaviors, such as overexercising, become reinforced through "conditioned reinforcement" modulated by the dopaminergic reward system. Increased activation of the dopamine system promotes reward-association learning, ultimately leading to habit formation and the habitual cognitive bias towards AN-related preoccupations and behaviors observed in AN patients (O'Hara et al., 2015). In this context, as individuals continue to engage in anorectic behaviors and reinforce the reward-cue associations, top-down cognitive control comes into play. Top-down cognitive control, shaped by previously learned associations, drives cognitive reluctance to gain weight and exacerbates restricted eating behavior (O'Hara et al., 2015).

Furthermore, reward-related neurobiological states during illness are amplified by stressors, including starvation. Chronic stress induced by starvation in AN may stimulate dopamine reward circuits via the hypothalamic-pituitary-adrenal (HPA) axis, further amplifying the incentive value of behaviors and cues previously experienced as rewarding. Specifically, the reduction of food intake has been shown to increase dopamine release in the ventral striatum via corticotropin-releasing hormone (CRH), thereby mediating the reward experienced by dieting and contributing to the development of the disease, which is then maintained via conditioned learning (Bergh and Södersten, 1996).

Premorbid vulnerabilities play a crucial role in why only a small fraction of young adolescents who start dieting further develop the disease. Genetics (e.g., dopamine receptor polymorphisms), early childhood events (e.g., negative affect), and personality traits such as perfectionism, anxiety, and obsessivity significantly contribute to the development of AN (O'Hara et al., 2015). Vulnerable individuals may display abnormal activation of dopaminergic motivational circuits differently from healthy controls, resulting in the attribution of incentive salience to aversive stimuli (i.e., pathologic behaviors) because of differences in long-term goals, such as the pursuit of thinness and further weight loss, as shown in the dopamine-depletion experiment by O'Hara (2016). An overview of the interplay between premorbid vulnerability, triggers and reward association learning is shown in Figure 3.

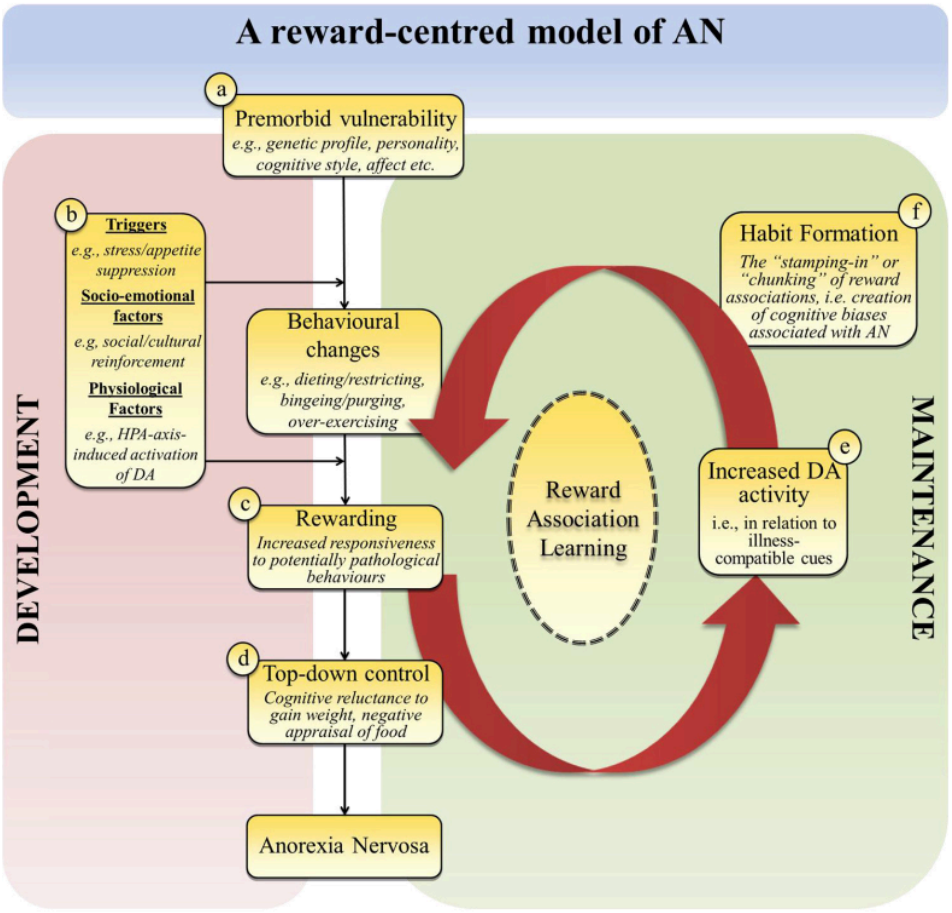

Figure 3. A reward-centered model for AN. Adapted from O'Hara et al. (2015).

Future research

It is now clear that the dopaminergic reward system plays a pivotal role in the development and maintenance of AN. However, only a few therapeutic approaches targeting reward-related processes are available. Positive Affect Treatment (PAT) is a novel psychotherapy intervention that has already been used to treat negative affect in depressive and anxiety disorders (Craske et al., 2019). Unlike commonly used therapeutic approaches such as CBT and weight restoration, PAT is a form of behavioral and cognitive therapy that targets the established associations between reward and illness-related behaviors, redirecting AN patients toward valuable life goals. Specifically, this therapeutic approach focuses on decreasing the positive affect associated with illness-compatible cues and behaviors and shifting these positive emotions to contexts independent of the disorder.

In this framework, it is first necessary to analyze the antecedents before the disease onset and understand why AN behaviors elicited positive affect in the subject. Then, PAT involves increasing and reinforcing alternative rewarding behaviors to replace the positive emotions resulting from pathological behaviors such as self-starvation and overexercise. This is accompanied by suggesting coping mechanisms to elicit positive affect

without engaging in pathological habits. Moreover, although weight gain is not a main target in this framework, it is expected as a by-product of increasing positive emotions related to food consumption. Therefore, this technique should help individuals suffering from AN to shift their focus to cues independent of the illness, thereby promoting healthier mechanisms to cope with negative affect (Hayanos et al., 2021).

Considering the model presented in this thesis, which emphasizes the role of reward-based learned associations leading to the formation of pathological habits in AN, a novel therapeutic approach could be to integrate Positive Affect Therapy (PAT) with Eye Movement Desensitization and Reprocessing (EMDR). This psychotherapeutic technique, first developed by Dr. Francine Shapiro in the 1990s, is based on the Adaptive Information Processing (AIP) model. The AIP model posits that psychopathology is driven by dysfunctionally stored memories that are activated in the present moment, leading to maladaptive behaviors. EMDR therapy works by facilitating the reprocessing of these dysfunctional learning experiences through bilateral stimulation, such as eye movements or taps (Markus et al., 2017). Eye movements lead to a weakening or desensitization of the original memory, and the chain of associations stimulates the modification of meanings (Landin-Romero et al., 2018).

This technique has been primarily used to reprocess traumatic events in individuals affected by post-traumatic stress disorder (PTSD), helping them integrate the traumatic memory with more adaptive information and alleviate associated emotional distress. In recent years, EMDR has shown promise in the treatment of addiction by targeting learned associations in the brain that lead to pathological behavior (Markus et al., 2017). In addiction, individuals often develop learned associations between substance use and certain cues or triggers in their environment. These associations are stored in memory and can lead to automatic, compulsive behaviors related to substance use. Addiction-focused EMDR (AF-EMDR) therapy facilitates the reprocessing of such associations, reducing the intensity of cravings and the power of triggers that lead to pathological behavior, ultimately promoting lasting behavioral changes (Markus et al., 2017). Furthermore, EMDR can specifically target core emotional issues (e.g., early childhood events, social stressors) that underlie the development of addictions. By addressing these core issues, EMDR helps individuals break the vicious cycle of addiction and promotes healthy coping mechanisms (Markus et al., 2017).

Given that AN shares various aspects with addiction, it is suggested that EMDR could be effective in the treatment of this eating disorder. In particular, AF-EMDR could be tailored to AN treatment to target reward-based associations that lead to restricted eating and excessive exercise. This could be achieved by reprocessing stored memories associated with “successful” weight loss while strengthening new associations with healthy eating behaviors and body acceptance, potentially increasing their reward value relative to anorexic behaviors. EMDR protocols have already been applied to eating disorders, showing better outcomes than CBT alone. This approach has been particularly effective in reworking eating disorder-related fears and core beliefs, specifically low self-esteem, clinical perfectionism, and negative body image (Zaccagnini et al., 2019). Considering these aspects, it is reasonable to think that an integrative approach of PAT and EMDR could address the current gaps in AN treatment by targeting a broader spectrum of features that this complex disease displays.

Lastly, the current theoretical framework focusing on reward processing suggests that targeting the dopaminergic system could be a valuable option in AN treatment. Indeed, a study by Frank et al. (2017) has found that treatment of AN with aripiprazole, a DRD2 antagonist, is associated with increased weight gain compared to no pharmacological intervention. This suggests that further research should be conducted to explore new treatment strategies focusing on dopamine transmission.

Conclusion

This thesis aims to answer the question: “Can a reward-centered model explain the development and maintenance of Anorexia Nervosa (AN)?” By presenting numerous findings involving abnormal dopaminergic activity and aberrant reward processing in AN patients, it concludes that the reward system regulated by dopamine plays a pivotal role in the development and maintenance of this eating disorder. Here it is proposed that AN is a reward-based learned behavior, where altered cognitions related to eating, weight, and shape impact the functioning of the striatal reward system. This leads to increased motivational salience attributed to illness-compatible cues, driving the establishment of pathological habits (i.e., self-starvation and overexercising) aimed at pursuing illness-related rewards, although dysfunctional and pathological (O’Hara et al., 2015). .

In this theoretical framework, premorbid vulnerabilities (e.g., genetics, personality traits such as perfectionism and compulsiveness) and socio-emotional factors increase an individual’s susceptibility to developing AN, explaining why not all adolescents who start dieting develop this disorder. This reward-centered model emphasizes dopaminergic reward processing as a key regulator in the development and maintenance of AN, with dopamine primarily involved in the attribution of motivational salience. This is consistent with findings from studies involving reward paradigms in response to food and illness-compatible stimuli (Fladung et al., 2010; O’Hara et al., 2016; Friedrich et al., 2010).

As discussed in Chapter 3, AN and addiction share similarities. Both conditions begin with initially rewarding behaviors—dieting in the case of AN and drug consumption in addiction. The reinforcement of these behaviors in both disorders is regulated by dopamine activity, which controls motivated behavior and further reinforces the establishment of pathological habits (Berridge, 2007). Additionally, individuals with AN and addiction display a loss of control over their behaviors, manifesting as a compulsive need to engage in these illness-related habits. However, despite these similarities, individuals with addiction typically exhibit different personality traits compared to AN patients, often associated with novelty seeking and impulsivity, while AN is linked to perfectionism, a need for control, and obsessional traits. Another key difference is that drugs elicit dopamine release in the mesocorticolimbic system more directly than food and illness-related cues (O’Hara et al., 2015).

Considering these aspects, further research is required to improve the understanding of the role of dopamine and the reward system in AN. Current data suggest that new therapeutic strategies are needed to treat AN, focusing on the proposed reward-related pathways associated with the illness. Addressing the reward-based learning associations that drive the establishment of pathological habits would target the core aspect that makes AN difficult to treat and would likely reduce the potential for relapses.

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