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Altered Cognitive Control and Reward Processing Mechanisms in Anorexia Nervosa: The Role of the Prefrontal Cortex

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Table of Contents

Introduction and Theoretical Background

Food constitutes one of the most fundamental human activities, going far beyond mere nourishment. It is deeply rooted in our social interactions, cultural practices and emotional experiences. Beyond its primary function of nourishment, food also serves as a powerful primary reward (Sescousse et al., 2013). While eating as a reward resembles a natural and necessary motivation to survive, it can also lead to dysfunctional behavior patterns with lasting physical and psychological consequences, as seen in eating disorders. Among these, Anorexia nervosa (AN) is distinguished as a particularly severe condition (Van Eeden et al., 2021).

AN is a disorder characterized by severe food restriction leading to a significantly low body weight, intense fear of gaining weight or persistent behavior that interferes with weight gain, as well as distortion in the perception of one's body weight or shape (American Psychiatric Association, 2013). A particularly high prevalence of anorexia nervosa is found in adolescent girls and young women in western countries (Sharan & Sundar, 2015; Smink et al., 2012). In men, however, the prevalence is considerably lower (Van Eeden et al., 2021). AN is one of the most lethal psychiatric disorders in adolescence and has the highest mortality rate of all psychiatric disorders across the general population (Keski-Rahkonen & Mustelin, 2016), which underscores the necessity for a comprehensive investigation of its etiology and the course of the disease, as well as a critical determination of the optimal therapeutic approach. The treatment of this restrictive eating disorder is constrained by a number of factors including a lack of clarity regarding the neurobiological underpinnings, comorbid illnesses that have an unfavorable impact on the development as well as on the course of the disorder, inadequate treatment methods, and high relapse rates of up to 31% even after multiple treatments (Berends et al., 2018). The regulation of eating behavior is a complex process that involves a metabolic state-dependent balance between brain networks responsible for maintaining homeostasis, processing food rewards, and regulating cognitive control (Chen et al., 2016; Kaye et al., 2013; Kouneiher et al., 2019). In the context of this balance, prior etiological research indicates alterations in the reward circuitry and heightened engagement of cognitive control mechanisms resulting in a dysregulation between top-down and bottom-up processes in the brain of AN patients (Kaye et al., 2009; Zastrow et al., 2009; Treasure & Schmidt, 2013).

When studying AN, it is crucial to examine the interplay between bottom-up and top-down processes. Bottom-up processing refers to the neural mechanisms involved in the detection of the emotional relevance of stimuli and the generation of corresponding affective responses. This system comprises ascending interoceptive pathways and brain regions that are linked to somatic states (e.g., hunger), including the hippocampus, amygdala, insula, ventral striatum, as well as ventral areas of the anterior cingulate cortex and orbitofrontal cortex. In contrast, top-down processing refers to neural modulatory mechanisms involved in cognitive evaluation, selective attention, and the

deliberate regulation of emotional states. These processes engage a cognitive control network comprising prefrontal cortical regions, including the dorsolateral prefrontal cortex (dlPFC), medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex (O'Hara et al., 2015).

From a bottom-up perspective, anorexia patients frequently demonstrate impairments in reward mechanisms (Keating et al., 2012; O'Hara et al., 2015; Wagner et al., 2007). Such impairments suggest that patients experience rewards associated with food and other stimuli in a way that differs from that of individuals without the disorder. This, in turn, may contribute to a reduction in their motivation to consume food. At the top-down level, it is particularly noteworthy that anorexia patients exhibit a tendency towards excessive self-control, as evidenced by a rigid thinking style and a strict set of rules regarding food intake (Ehrlich et al., 2015; Lavender et al., 2015; Steward et al., 2017). This excessive self-control gives rise to intense, goal-oriented behavior, which is then manifested in extreme eating habits and rigorous food regulation (Fairburn et al., 1999). This reciprocal relationship between opposing yet complementary processes may explain why individuals with AN feel no significant urge to consume food despite a markedly reduced body weight. In conclusion, previous research lines suggest that anorexia nervosa reveals a complex interplay between impaired reward perception and excessive self-control that significantly shapes the behavior of those affected and contributes to the maintenance of the disorder (Park et al., 2014). The corresponding processes and their neuronal correlates are described in detail in the subsequent sections.

Food and Reward: Unraveling the Basics

A reward is a natural process by which the brain establishes associations between various stimuli, such as substances, situations, occurrences, or activities, and positive or desirable outcomes. These associations result in behavioral adaptations that cause individuals to seek out the specific stimulus that produced the positively experienced effect (Lewis et al., 2022).

The human reward system is a complex network within the brain that exerts a significant influence on human behavior by offering rewards for specific actions, thereby shaping our future actions. Rather than functioning through a single pathway, it typically operates as a complex network of interacting components working together to generate and process rewards (Elliot et al., 2000; Berridge & Robinson, 2003). According to previous research, the experience of food reward involves two separate but interconnected neurological processes: "wanting" and "liking" (Berridge et al., 2009; Berridge & Kringelbach, 2014; Pool et al., 2016). In addition, association and predictive learning processes play a key role in the experience and processing of reward (Berridge et al., 2009). "Liking" refers to the actual pleasurable impact of reward and is constituted by a series of interactive hedonic hotspots in the brain (Berridge & Kringelbach, 2015). Conversely, the motivational aspect of reward can be divided into two categories: cognitive incentives, which are commonly known as

wanting, and incentive salience, which is referred to as "wanting" in this context (Berridge & Robinson, 2016). These two concepts may also be conceptualized as explicit and implicit aspects of wanting.

Cognitive incentives encompass goal-directed plans and explicit desires that ultimately align with a person's cognitive goals. Consequently, in the case of a desire, a declarative representation of the goal is typically present. This explicit form of wanting is most commonly recorded through the use of self-report methods (Van den Eynde et al., 2012), as evidenced in the present study, which employed a visual analog scale.

In contrast, incentive salience represents a form of motivational drive that encourages the pursuit and consumption of rewards (Berridge, 2018; Olney et al., 2018). In contrast to the cognitive facets of desire, which are typically associated with the term wanting and involve conscious goals or expectations of future outcomes and are predominantly regulated by cortical circuits, incentive salience operates at a more instinctive level, prompting approach behavior towards rewards (Berridge et al., 2009). In accordance with the incentive salience concept, this implicit component of wanting is significantly influenced by subcortical mesolimbic dopamine neurotransmission (Berridge et al., 2009). This implicit process enables the identification of specific stimulus representations within the brain that have Pavlovian associations with reward. Subsequently, this component of "wanting" can be strongly irrational, leading to a desire for a stimulus even without any cognitive reasoning behind it (Anselme & Robinson, 2016; Berridge et al., 2009). Given that implicit wanting typically occurs unconsciously, self-report measures are not applicable in this context. In previous studies, implicit wanting was assessed through indirect measurement techniques (Pool et al., 2016). To address this issue, this study employs a dynamometer as direct measure to quantify the force a person exerts to obtain a reward, thereby measuring implicit wanting on a more objective basis.

Neuronal Pathways of Reward Mechanisms

The neural system responsible for the experience of reward comprises a network of brain regions that, according to research findings, is undergoing expansion in both scope and complexity (Wise & Koob, 2014). As early as 1954, James Olds and Peter Milner conducted an experiment on rats that led them to hypothesize the existence of a human reward system. The researchers implanted electrodes in the brains of rats and allowed the rats to press a lever to receive mild electrical stimuli to the brain. When the electrodes were placed in the septal region of the brain, the rats pressed a lever for self-stimulation up to 2,000 times per hour over the course of the experiment, indicating their enjoyment of the stimulation of this particular region of the brain and providing preliminary evidence that specific regions of the brain are involved in the processing of rewards and positive reinforcement (Olds & Milner, 1954).

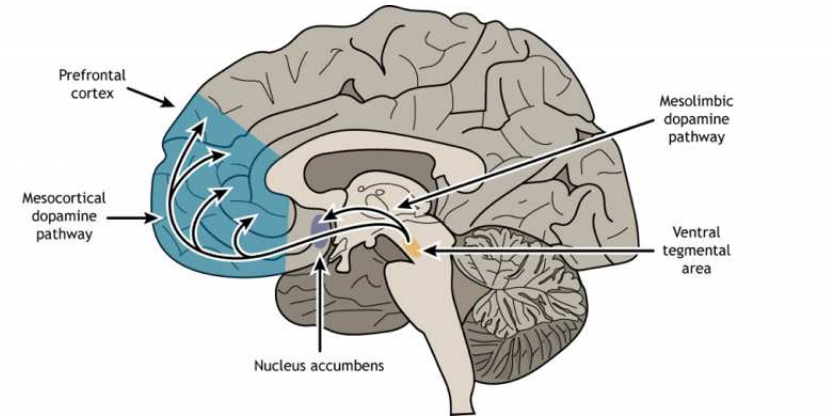
Based on these findings, the mesocorticolimbic dopaminergic pathway was later identified as a central component of the reward system generating wanting and liking. This pathway originates from dopaminergic neurons located within the ventral tegmental area (VTA) of the midbrain (D'Ardenne et al., 2008). In anticipation of or in response to a potentially rewarding event, such as the view or the taste of food, dopaminergic neurons are activated and transmit signals from the VTA to key regions in the limbic forebrain, particularly the nucleus accumbens (NA), as well as to the prefrontal cortex (Nestler, 2004; Haber, 2016). Dopamine release in the NA enhances the perception of reward and pleasure, directly influencing motivation. This region integrates sensory information and evaluates reward, thereby initiating motivated behaviors such as the desire to consume food (Day & Carelli, 2007). Subsequently, the prefrontal cortex (PFC) receives signals from the NA and then engages in decision-making and planning processes. This occurs by situating the reward within the context of long-term objectives and behavioral regulation. Finally, the PFC, in turn, sends descending projections back to the NA and the VTA (Nestler, 2004). The mesocorticolimbic circuit is therefore crucial in the final common pathway that processes reward signals and has been shown to control motivated behavior not only in rats (Olds & Milner, 1954), but also in humans (Weiland et al., 2014). The mesocorticolimbic dopaminergic pathway can be further subdivided into two distinct pathways: the mesolimbic dopaminergic and the mesocortical dopaminergic pathway.

The mesolimbic pathway can be subsumed under the so-called bottom-up processes and is typically referred to as most recognized component of the reward system. It encompasses the VTA and the NA, in addition to other limbic structures (Blaess et al., 2020). Regarding these brain structures, the mesolimbic pathway is of critical importance for the processing of reward and motivation, as it responds directly to reward and emotional stimuli (Berridge & Kringelbach, 2008; Nestler & Carlezon, 2006).

The mesocortical dopaminergic pathway on the other hand can be subsumed under the top-down processes. It also originates in the ventral tegmental area (VTA), but extends to the PFC, specifically the orbitofrontal cortex, ventromedial prefrontal cortex (vmPFC), medial prefrontal cortex, and anterior cingulate cortex. This sub-pathway of the mesocorticolimbic pathway is responsible for higher cognitive processing and control, planning, and decision-making (Malenka et al., 2009). Additionally, studies have demonstrated the involvement of the cortical components of the pathway in reward sensitivity (Grabenhorst, 2014), the neuronal response to receiving a reward (Oldham et al., 2018), higher-order cognitive processes in the wanting process, as well as the evaluation of the relative value of reward (Der-Avakian & Marakou, 2012).

Figure 1

Illustration of the Mesocorticolimbic Dopaminergic Pathway



Note: The illustration depicts the mesocorticolimbic pathway, which originates in the ventral tegmental area of the midbrain. From this point, dopaminergic neurons extend projections to both the limbic regions, specifically the NA and the PFC. Adapted from *Foundations of Neuroscience*, by Casey Henley, 2021. Copyright: Creative Commons Attribution Non-Commercial Share-Alike (CC BY-NC-SA) 4.0 International License.

Altered Reward Mechanisms in Anorexia Nervosa

Recent research has identified preliminary evidence indicating a potential involvement of altered reward processes in the etiology and persistence of AN (Berridge, 2009; Berridge & Kringelbach, 2015; Morales & Berridge, 2020). The prevailing body of research suggests that patients diagnosed with AN demonstrate analogous responses to the consumption phase of food rewards compared to healthy controls (Cowdrey et al., 2013; Dolan et al., 2022) indicating that the hedonic aspect of food consumption (liking) appears to largely remain intact in AN (Holsen et al., 2012). In contrast, previous studies have frequently demonstrated alterations in the wanting component of the reward process (Dolan et al., 2022a; Keating et al., 2012; Morales & Berridge, 2020).

In anorexia nervosa, many disorder models are based on the theory that the balance between top-down and bottom-up processes is disturbed (Lipsman et al., 2015; O'Hara et al., 2015; Sanders et al., 2015; Wierenga et al., 2015). Top-down processing can be defined as cognitive control exerted by the PFC, while bottom-up processing refers to the part of the reward circuit in which limbic and interoceptive processes take place (Ehrlich et al., 2015). Together, these processes regulate the body's homeostatic needs, execute motivation and shape rewards. There are various models that attempt to explain AN in terms of this dysregulation. O'Hara et al. (2015) suggest that the bottom-up mesolimbic system is downregulated leading to a diminished perception of reward. This hypothesis is supported by evidence of a downregulation of dopaminergic activity in the limbic system (Kaye et al., 2009). In individuals with anorexia nervosa, the perception of otherwise

rewarding stimuli as non-rewarding is referred to as anhedonia towards rewards (David & Woodside, 2002). This translates to a lack of pleasure or enjoyment associated with rewards.

In this context, the reward contamination model by Keating (2010) describes how individuals with anorexia nervosa perceive stimuli that should normally be perceived as rewarding as punishing and vice versa. For example, food is perceived as a punishment, whereas self-starvation and excessive exercise are perceived as a reward. These inverted rewards are then reinforced, leading to the development of pathological behaviors that are maintained over time. Consequently, the neural circuits of reward and punishment might overlap in AN patients and ultimately alter the corresponding dopamine system (Keating et al., 2012).

It is likely that dysregulation occurs not only in the mesolimbic pathway, but also in the mesocortical pathway, responsible for cognitive control systems (Chen & Bonci, 2018). In individuals with anorexia nervosa, this dysregulation may manifest as hyperactivation of top-down cognitive control processes inhibiting mesolimbic bottom-up reward processes (Brooks et al., 2011; Kaye et al., 2009;). An excessive cognitive control may suppress natural hunger signals and physiological needs, leading to rigid eating behavior and a persistent fixation on weight and body image (Kaye et al., 2013, O'Hara et al., 2015). This is supported by evidence of neuroimaging studies of AN patients showing heightened activity in top-down control regions, while at the same time reduced activity in somatosensory and hedonic regions (Celeghin et al., 2023).

The Prefrontal Cortex and its Role in Reward Processes

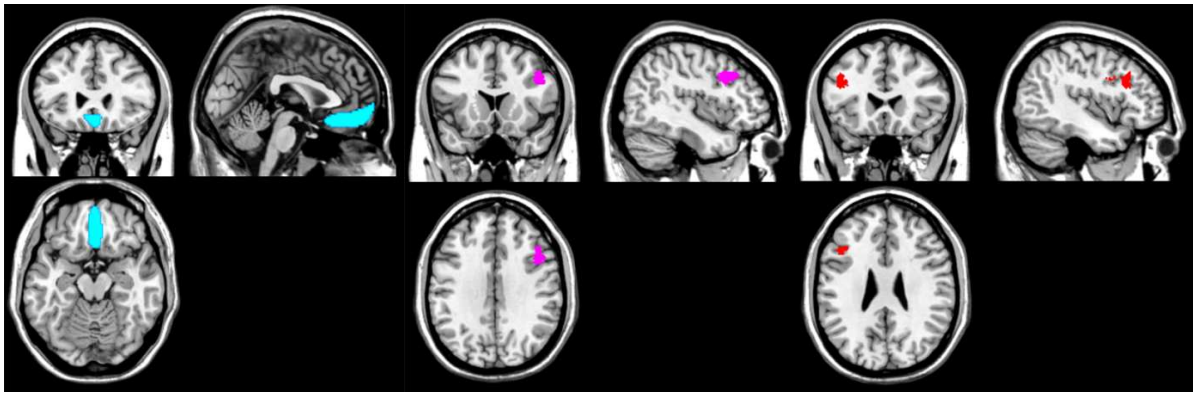
Central to these top-down process processes is the PFC, a region of the brain responsible for planning, decision-making and impulse control. In both evolutionary and individual development, the PFC matures more slowly and to a greater extent than most other brain structures, in terms of both size and weight (Kolk & Rakic, 2022). The human PFC does not reach full structural maturation, including cellular and connective development, until young adulthood (Arain et al., 2013). In 1848, our knowledge of the PFC changed fundamentally when Phineas Gage had a serious accident with an iron tamping rod that punctured the orbitofrontal lobe (Hathaway & Newton, 2023). The extensive alterations encompassed a broad range of changes, including significant personality shifts, impaired impulse control, and compromised decision-making abilities. Additionally, Gage experienced severe disturbances in social behavior, challenges with emotional regulation, and difficulties with both long-term and short-term planning, as well as general goal setting (Hathaway & Newton, 2023). This specific case exemplifies the profound importance of the brain region impacted by Gage's injury. 176 years later, research has reached a consensus that the PFC is involved in higher integrative functions such as information processing, thinking, understanding, attention, behavior, motivation, emotions, working memory and analysis (Friedman & Robbins, 2022; Kane & Engle, 2002).

In reward processes, the functions of planning, decision-making, and impulse control are of particular importance. In this context, the PFC serves as a top-down element in the interplay between cortical and subcortical structures, thereby significantly influencing reward processing in the human brain. This top-down element enables the modulation of immediate rewards in favor of long-term goals and ensures that behavioral adaptation to social and situational contexts is carried out (Buschman & Miller, 2014). Although the PFC is not considered a direct reward center, it is an integral component of the corticolimbic system, which is involved in emotion regulation and reward processing. The PFC is particularly connected to limbic structures, including the amygdala and the NA, and thus exerts influence over both emotional reactions and motivational states (Krämer & Gruber, 2015; Pessoa, 2009). It contains numerous regions that are involved in processes relating to the evaluation, decision-making and behavioral execution pertaining rewards (Ridderinkhof et al., 2004). The present study focuses more closely on two of these regions: the dlPFC and the vmPFC. Regarding reward processes, the dlPFC plays a significant role in cognitive control and executive functioning (Ghanavati et al., 2019; Kane et al., 2002), while the vmPFC is involved in reward evaluation and related emotion processing (Kim et al., 2010; Proudfit et al., 2015). The interaction between the two regions ensures that decisions are both rationally based and emotionally resonant (Hare et al., 2009). Figure 2 depicts the location of the vmPFC and dlPFC within the human brain.

Figure 2

Illustrations of the Ventromedial and Dorsolateral Prefrontal Cortex within the Human Brain

A *B* *C*



Note: Brain masks displayed on a brain template in MRIcron.

A: Bilateral vmPFC masks displayed in blue at MNI coordinates: x = 0, y = 26, z = -16.

B: Right dlPFC mask displayed in pink at MNI coordinates: x = 43, y = 17, z = 33.

C: Left dlPFC mask displayed in red at MNI coordinates x = -32, y = 23, z = 27.

Involvement of the Dorsolateral Prefrontal Cortex in Cognitive Control and Eating Behavior Modulation

The dlPFC is a crucial component of the cognitive control system (Miller & Cohen, 2001; Ridderinkhof et al., 2004). It is located in the middle frontal gyrus and corresponds to the lateral portions of Brodmann Areas 9 and 46 (Pommier et al., 2017). In humans with healthy psychological functioning, this brain region plays a key role in regulating the pleasurable drives associated with eating by exerting inhibitory control (Hollmann et al., 2011). It helps to balance the desire for food driven by pleasure, preventing overeating and promoting healthy eating habits (Chanaka et al., 2016).

The fundamental role of the dlPFC in mediating responses to food is supported by a study by Dillen & Steenbergen (2018). Healthy participants were exposed to an increased cognitive load while viewing pictures of high-caloric food, which resulted in heightened activity in the dlPFC and reduced reactivity in the NA. These findings suggest that engaging the cognitive system may influence the brain's hedonic responses to high-calorie food images, potentially through interactions between the dlPFC and NA. Moreover, the role of the dlPFC in modulating eating behavior was demonstrated by a study conducted by Camus et al. (2009), wherein inhibitory repetitive transcranial magnetic stimulation (rTMS) of the right dlPFC resulted in a shift in preference ratings for high-caloric food items. Similarly, high frequency rTMS to the right dlPFC was further associated with changes in food ratings and altered food preference in a computerized food choice task (Muratore et al., 2021). The participants provided higher ratings of healthiness for low- and high-fat foods and selected a significantly greater proportion of high-fat foods over a neutrally rated reference item while receiving stimulation. Moreover, the results of McClelland's randomized controlled trial (2016) indicated that repetitive transcranial magnetic stimulation to the left dlPFC was an effective intervention for reducing core symptoms of anorexia nervosa and for enabling improved decision-making abilities. In line with this research, a recent study by Dalton et al. (2020) demonstrated that the application of high frequency rTMS to the left dlPFC was able to significantly influence the food choices of patients with chronified AN. These findings indicate that the stimulation had an influence on participants self-control, resulting in an increased choice behavior for tasty, less healthy foods and an overall more flexible and less rigid choice of food.

Further, in a study conducted by Ehrlich et al. (2015), the response of recovered AN patients to monetary rewards was investigated. The findings revealed elevated dlPFC activity during the reward anticipation phase, coupled with an inability to deactivate this region during a feedback phase, where the increasing amount of monetary reward was presented. The findings of Ehrlich et al. (2015) indicate an elevated degree of cognitive control processes in response to rewarding stimuli while at the same time unaltered activation in the mesolimbic reward path regions. This suggests an

imbalance between brain systems that regulate bottom-up and top-down processes, which may serve as a trait marker of AN. Further, in a study by Brooks et al. (2012), AN acute patients of the restrictive subtype exhibited heightened activity in the dlPFC during the presentation of visual food cues, likely reflecting their efforts to suppress the urge to eat. In line with this research, Eddy et al. (2023) also presented food images to young females with AN or atypical AN and found a greater blood oxygen level dependent signal (BOLD) in reward-related brain regions and brain regions associated with cognitive control. Subsequently, the researchers indicated that enhanced cognitive control may exert a suppressive influence on the reward signal generated from limbic brain regions.

Importantly, none of the aforementioned experiments were designed to place an explicit demand on participants cognitive control abilities. Regarding structural changes, morphological studies indicated an increased gray matter volume of the dlPFC in AN patients. For instance, Brooks et al. (2011) found that acute AN patients revealed greater gray matter volume in the dlPFC compared to healthy controls (HC). Based on their analyses, the researchers propose that the elevated dlPFC volume observed in the AN group is potentially linked to excessive dietary restraint. Further, this finding is supported by evidence showing that neuroanatomical differences in the dlPFC predicted an individual's ability to exert control over dietary choices (Schmidt et al., 2018).

Involvement of the Ventromedial Prefrontal Cortex in Reward Processes and Eating Disorders

Another region that is associated with the processing of rewards, cognitive control mechanisms and is reciprocally connected to the dlPFC is the ventromedial part of the prefrontal cortex. Anatomically it is best designated as the innermost medial areas of the ventral frontal lobes encompassing Brodmann areas 10, 11, 12, 24, 25 and 32 (Clark et al., 2008). The vmPFC plays a crucial role in decision-making and the evaluation of subjective value (Lopez-Persem et al., 2016). It has reciprocal connections to memory brain regions like the hippocampus and has been found to exert top-down inhibitory control over emotional processing areas like the amygdala (Phelps et al., 2004; Urry et al., 2006). Furthermore, it maintains connections to higher-order sensory processing areas and the aforementioned dlPFC (Wood & Grafman, 2003). In light of vmPFC's functions, research has shown that patients with lesions in this brain region perform poor in judgements and show socially inappropriate and impulsive behavior (Damasio, 1994; Berlin et l., 2004). Other results from a study by Clark et al. (2008) using the Iowa Gambling Task showed that participants with dysfunction or lesions in the vmPFC showed a significantly poorer trade-off between long-term and short-term rewards compared to HC. Their behavioral tendencies were also indicative of a clear preference for risky decisions that had high short-term rewards but were loss-making in the long term (Clark et al., 2008). Furthermore, numerous meta-analyses of fMRI studies have also shown that the vmPFC is involved in value attribution for both abstract rewards, such as money, and primary

rewards, such as food (Arsalidou et al, 2020; Bartra et al, 2013; Chase et al, 2015; Levy and Glimcher, 2011; Sescousse et al, 2013).

Finally, in addition to examining gray matter volume in the dlPFC, a study by Schmidt et al. (2018) also examined gray matter volume in the vmPFC in relation to dieting behaviors. The researchers found that reductions in GMV in both the dlPFC and vmPFC were associated with greater adherence to restrictive dieting practices. This suggests that structural changes in these regions, which are critical for decision-making and self-regulation (Broche-Pérez et al., 2016; Mayeli et al., 2019), may contribute to the maintenance of restrictive eating behaviors in individuals with eating disorders such as anorexia nervosa. In a study conducted by Hare et al. (2009), the relationship between the dlPFC and the vmPFC was examined in a group of self-reported dieters who were subjected to functional magnetic resonance imaging (fMRI) while viewing a series of food images. The participants were required to make authentic decisions regarding which foods to consume, integrating considerations of healthiness and taste. The findings indicate that the vmPFC was primarily engaged when participants evaluated the subjective reward value of food, whereas the dlPFC was activated when individuals had to regulate their immediate food desires and select long-term objectives over immediate gratification. Overall, the study suggests that the dlPFC influenced the activity of the vmPFC and modulated the reward evaluation encoded by the vmPFC.

Conclusion

Anorexia nervosa is a severe eating disorder characterized by a restriction of energy intake, an intense fear of gaining weight and a distorted body image (APA, 2013). The high prevalence of anorexia nervosa (Smink et al., 2012) and the associated high mortality rate (Arcelus et al., 2011) underscore the urgent need to further clarify the etiological and perpetuating factors. Previous etiological research offers a range of evidence to shed light on the underlying causes of the disorder. In particular, it has been suggested that reward system and strengthened cognitive control mechanisms play a significant role in the maintenance of the disorder (Brooks et al., 2011; Kaye et al., 2009; Keating, 2010, O'Hara et al., 2015). Particularly the motivational component of reward (wanting) seems to be impaired in anorexia nervosa (Berridge, 2009; Dolan et al., 2022a; Keating et al., 2012; Morales & Berridge, 2020). Reward mechanisms are regulated by neurotransmitters, with the majority of studies focusing on dopamine. The mesocorticolimbic dopaminergic pathway appears to demonstrate differential reactivity to rewards in individuals suffering from AN (O'Hara et al., 2015). However, there are multiple potential explanations for this phenomenon, involving different regions of the brain and their distinct patterns of activation in reward-related experiments in AN patients. Further, studies investigating the proposed imbalance between bottom-up and top-down processing during the anticipation of reward yielded disparate results, with some indicating a clear inhibition of bottom-up processes by top-down processes (Eddy et al., 2023), while others reported

that only top-down processes were elevated, with bottom-up processes remaining comparable to those of healthy individuals (Ehrlich et al., 2015).

A significant number of studies that were primarily focused on the hypothesis of enhanced cognitive control repeatedly identified the involvement of the dlPFC in control and evaluation of food rewards (Brooks et al., 2011; Eddy et al., 2023; Ehrlich et al., 2015). Following these findings, additional high frequency rTMS studies observed changes in dietary preferences post-stimulation, leading to a more balanced choice between healthy and unhealthy foods. However, these studies stimulated either the right dlPFC (Camus et al., 2009; Muratore et al., 2021) or the left dlPFC (McClelland et al., 2016), making it difficult to draw clear conclusions about the specific lateralized functions of the dlPFC in exerting control over food behavior.

The vmPFC has been relatively understudied in the context of anorexia nervosa, despite its role in subjective reward evaluation and its close cooperation with the dlPFC. This is evidenced by morphological studies indicating that the gray matter volumes of both areas are equally related to adherence to dietary rules (Schmidt et al., 2018). It can be posited that the vmPFC represents a crucial target, given its integral function in fostering communication between the limbic structures and the dlPFC (Nejati et al., 2021). Its role in appraising the subjective value of rewards is particularly noteworthy, as it transmits the reward value information to the dlPFC, which bears responsibility for decision-making and the regulation of eating behavior.

Further, a definitive conclusion regarding alterations in the reward and cognitive control systems remains elusive, as studies have examined highly disparate groups of AN patients, encompassing variations in age, disease subtype (restrictive or binge-purge type) and disease stage (acute stage, partial or full remission). Furthermore, previous investigations on the reward system utilize both primary rewards and secondary rewards like money (Ehrlich et al., 2015), which are not consistently disease-specific stimuli. Additionally, the delivery modality and intensity of the stimuli varies, encompassing visual (Brooks et al., 2011) and gustatory stimuli (Frank et al., 2012), that may elicit different cognitive and emotional reactions in participants. Finally, when examining different stimulus intensities, previous research assumed all participants to perceive the administered stimuli as equally rewarding or equally unrewarding (Cowdrey et al., 2013; Holsen et al., 2014). However, this assumption neglected to consider individual preferences, which may suggest a differentiated perception of reward intensity.

The Present Study

Previous research on anorexia nervosa has revealed a number of challenges that the present study attempts to address through methodological enhancement. To gain a comprehensive understanding of reward and cognitive control mechanisms in anorexia nervosa, this study employed

a research paradigm that permits the differentiation between the anticipatory and the consummatory reward phase (Chiappini et al., 2022). Specifically, it incorporates the actual consumption of food, as opposed to purely visual or mental perception of food stimuli. The stimuli were presented in varying levels of intensity, allowing the participants to determine their individual preferences. This approach enabled us to hypothesize that some of the options were genuinely rewarding for the participants, rather than relying solely on the difference between low and high caloric food of previous research (Cowdrey et al., 2013; Eddy et al., 2023; Sanders et al., 2015). A significant proportion of prior research has frequently disregarded the objective component of wanting (Pool et al., 2016). In contrast, this paradigm permits a precise operationalization of both subjective and objective wanting, thereby avoiding bias in reward evaluation due to subjective beliefs or motivations.

As outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), both the restrictive and binge-purge types of anorexia are characterized by a common goal of weight loss through the use of unhealthy methods and a severely disturbed body image. The restrictive type of anorexia is characterized by a primary focus on weight control through dieting, fasting, and/or excessive exercise, with no binge eating or compensatory behaviors. In contrast, the binge-purge type involves not only restrictive behaviors but also includes episodes of binge eating and compensatory measures such as self-induced vomiting or the abuse of laxatives (Peat et al., 2009). It is assumed that the binge-purge subtype of anorexia nervosa is characterized by distinct neurobiological mechanisms concerning reward processes (Murao et al., 2017). In order to ensure internal validity and to minimize clinical heterogeneity, this thesis will focus on the restrictive subtype of anorexia nervosa, given the differences between the subtypes of this disorder.

Additionally, the sample was age-matched between HC and AN individuals and restricted to a specific age group that is in the critical transition phase between adolescence and young adulthood. This phase is distinguished by substantial neurobiological changes, particularly in the prefrontal cortex (Caballero et al., 2016). Moreover, only females were included in the study, given that anorexia nervosa predominantly affects young women (Smink et al., 2012).

In order to obtain a comprehensive understanding of the manifestations associated with anorexia nervosa, it is essential to consider the various stages of the condition. This results in a sample incorporating individuals in the acute phase of anorexia nervosa, as well as those in partial and full remission. By considering the different stages of the disease, it is possible to determine whether and how reward and cognitive control mechanisms change or persist in different stages of the disease allowing valuable conclusions to be drawn about the state and trait characteristics of AN.

This work explicitly focuses on two brain regions associated with reward processing and related cognitive control, examining them in young patients with AN at various stages. A particular emphasis is placed on the dlPFC, with a detailed examination of its lateralization, investigating the discrepancies in activity between the left and right part of the dlPFC. This permits a comprehensive analysis of the functioning of the lateralized dlPFC regions in comparison to HC, coupled with an investigation of their interactions with the vmPFC. Furthermore, the study additionally investigates how the interaction between dlPFC and vmPFC might change across different stages of AN, assessing whether the correlated activity between these regions may intensify or decouple as the disorder progresses.

Moreover, the study facilitates the establishment of correlations between brain activity and clinical measures of symptom severity and behavioral wanting data, thereby assisting in the identification of which alterations in these brain areas are particularly relevant to the experience of wanting and to the severity or worsening of symptoms. In conclusion, although this study does not focus explicitly on other regions associated with reward, it allows for exploratory whole-brain analyses, which may reveal alterations in brain activation in other brain regions not included in the primary analysis across various stages of the illness. Through these exploratory analyses, it might be possible to identify changes in areas more associated with bottom-up processes integrated into the mesocorticolimbic dopaminergic pathway, providing a broader understanding of the neural mechanisms involved in AN.

Research Questions & Hypotheses

Building on the previously outlined advancements of the study, this thesis will address the following research questions:

1. *Do individuals with anorexia nervosa exhibit lower explicit and implicit wanting measurements relative to healthy controls when actual food intake is involved?*

2. *How does activation of the dlPFC and vmPFC differ between individuals with anorexia nervosa and healthy controls during food reward anticipation?*

3. *Is activity in the dlPFC and vmPFC during the anticipation of food rewards correlated with explicit and implicit wanting ratings or measurements of symptom severity?*

It is postulated that an imbalance between top-down and bottom-up mechanisms may result in altered reward perception. In this model, the overactive cognitive control exerted by the prefrontal cortex determines the reward-evaluating component of the corticolimbic pathway. Prior studies have demonstrated that this impairment in reward evaluation is not exclusive to patients experiencing acute episodes but can also be observed in those in remission (Ehrlich et al., 2015).

Consequently, it can be predicted that there should be lower objective and subjective wanting for both reward intensities of food stimuli in AN patients (AN-A, AN-PR, AN-R) compared to HC (Hypothesis 1a). Nevertheless, the distinction between high and low rewards should be discernible in all groups, albeit to a lesser extent in the AN acute group (Hypothesis 1b).

In line with previous research (Dillen & Steenbergen, 2018; Eddy et al., 2023; Ehrlich et al., 2015), an elevated level of activation of the dlPFC in individuals with anorexia nervosa in comparison to HC is expected (Hypothesis 2a). This may be regarded as an indicator of enhanced cognitive control over eating behavior, particularly given that the experimental paradigm involves actual food consumption. This heightened activation should be particularly evident among those in the acute stage of the disease. Should lower activation in the dlPFC be observed in partially remitted and remitted participants at levels comparable to those of HC, it may be inferred that enhanced cognitive control is more likely a reflection of the disease state and may diminish as the disease progresses. Alternatively, if increased cognitive control in patients in remission persists beyond the acute phase, this could be indicative of a stable trait. Consequently, no directional effect is hypothesized when comparing partially and fully remitted patients with HC.

Prior research has indicated that the vmPFC is involved in the regulation of short-term and long-term goal attainment, processing of rewards and the subjective valuation of rewards (Arsalidou et al, 2020; Bartra et al, 2013; Chase et al, 2015; Levy and Glimcher, 2011; Lopez-Persem et al., 2016 Sescousse et al, 2013). Those suffering from anorexia nervosa may experience an imbalance in which short-term, reward-related stimuli, such as the anticipation of food rewards, counteract long-term goals, such as weight control and body image. In such cases, the vmPFC and the dlPFC might work together to modulate reward processing and bottom-up processes in order to align them with the long-term goal of weight control and achieving the ideal body image. The preceding research also suggests that individuals with AN process reward more extensively than HC. This finding can be aligned with the functions of the vmPFC. Consequently, it is hypothesized that AN-A patients exhibit hyperactivation of the vmPFC in anticipation of food reward stimuli compared to HC (Hypothesis 2b). Similar to the hypothesis concerning dlPFC activation, no directional effect is hypothesized for the AN-PR and AN-R groups.

In light of the observed interplay between the dlPFC and the vmPFC in anticipation of food-related stimuli in self-reported dieters (Hare et al., 2009), a significant positive correlation between the dlPFC (bilaterally) and the vmPFC in all AN groups is postulated (Hypothesis 3).

For the remaining possible correlations between measurements, no hypotheses are posited regarding the direction of the effects. Instead, it is merely assumed that the clinical, behavioral, and neurological data are related in some way, with the aim of fully exploiting the exploratory potential of the analysis. The correlations between dlPFC and vmPFC activity and measures of symptom severity (Eating Disorder Inventory 2 and Body Mass Index) could provide insights into whether brain activation patterns change over the course of the disease, potentially aligning with those observed in HC once remission is achieved. A significant positive correlation between Eating Disorder Inventory 2 (EDI-2) scores and brain activity might suggest that the enhanced cognitive control exerted by the dlPFC and the altered reward valuation by the vmPFC reflect a state associated with anorexia nervosa rather than a consistent trait. A significant negative correlation between Body Mass Index (BMI) and brain activity may indicate a similar underlying mechanism, whereby weight gain towards a normal BMI may result in a reduction in hyperactivity in the dlPFC and vmPFC, as reported for the dlPFC hyperactivity in recovered AN patients in Boehm et al. (2016). Moreover, the correlation analysis allows for an investigation of whether the objective wanting (effort) and subjective wanting (rating) measures are clearly related or whether some of the groups may exhibit more ambiguous relationships and discrepancies between the measures. A correlation between wanting and effort and measures of symptom severity may indicate how the variability of reward ratings is shaped by increasing symptom severity, thereby providing insight into the theories of impaired reward in AN. Ultimately, the correlation analysis enables the drawing of conclusions regarding the extent to which explicit and implicit wanting relates to potential hyperactivity in the dlPFC and vmPFC.

Methods

The following chapter provides a detailed account of the methodologies employed in this master's thesis as part of the AN-BEL study. First, an examination of the project's organizational background and objectives is presented, followed by a comprehensive description of the participants and the experimental paradigm. This is then followed by an overview of the experimental procedures and the resulting variables. Finally, the data analysis procedure is outlined.

Organizational Framework and Aim of the Research Project

This master thesis is drawn from the AN-BEL study focusing on reward processing in AN which is part of the collaborative project A translational psychiatric approach to adolescent AN between the Medical University of Vienna and the University of Vienna. Following a translational approach, the project's overarching goal is to investigate a reward-based mechanistic model of AN

within the human brain, with the aim of developing more precise therapeutic interventions. This is achieved through examining both the motivational ("wanting") and hedonic ("liking") aspects of food through food administration, as well as social rewards via touch stimuli, in individuals with anorexia nervosa compared to HC.

Data collection for this study is scheduled for 3 years until 2024 and conducted by the Clinical and Social Neuroscience Unit of the University of Vienna, situated at Vienna General Hospital. The unit operates under the supervision of Associate Professor Giorgia Silani, Privatdoz. PhD in close partnership with Professor Andreas Karwautz, MD.

The study is a s single center cluster study comparing 3 cohorts of patients with AN at different stages of the disease with a healthy sex- and age-matched comparison group. It consisted of a clinical part and a subsequent fMRI examination. The primary outcomes of the study are the subjective and objective measurements of reward (wanting, liking) of social (touch) and non-social types of rewards (food) measured by self-rating, effort used to obtain reward stimulus and facial muscle contraction (EMG). The secondary outcomes are the whole-brain neural activity during the reward task, differences between AN patients at different stages of the disease in terms of eating disorder pathology, neuropsychological parameters, quality of life, gut microbiota, compulsive exercise behavior, MR fingerprints and the influence of polygenic-risk scores in the course of the disease.

Participants and Recruiting

The target number of participants for the project is N = 100 (50 healthy and 50 anorexic individuals), to be reached in 2024. Only female participants were recruited since AN is mostly affecting young women (Smink et al., 2012). Most participants of the experimental group were directly recruited through the Department of Child and Adolescent Psychiatry at the Vienna General Hospital (in- and outpatients), as most of them where subjects in previous studies. The recruitment of HC was conducted by the psychological research team through the distribution of flyers, the promotion of the project on social media platforms including Instagram, Facebook, and TikTok, and via in-person presentations of the project at educational institutions in and around Vienna. Participants then registered independently by mail. A so-sci survey prescreening was sent to the participants to verify eligibility criteria. Provided the criteria were met, participants were contacted by email and an appointment was arranged. Fasting was required four hours in advance. Post-experiment, participants received a 3D image of their brain and a 70-euro reimbursement in form of a voucher on completion of the study.

Included were female participants between 12 and 30 with sufficient proficiency in German that provided informed consent or were provided informed consent by their legal guardians. The age of the control subjects ideally matched the current mean age of the experimental group of anorectic

participants. Participants of the control group were essentially healthy and did not exhibit any neurological or psychiatric disorder. Participants assigned to the AN patient group had a prior or current DSM-5 AN diagnosis including patients in acute, remitted and partially remitted status.

Individuals with an intellectual disability (IQ < 70), those experiencing an organic psychosyndrome or psychotic/bipolar disorder, pregnant individuals, and those with cardiovascular diseases, lung disorders, central nervous system conditions, and metabolic disorders were excluded from participation in the study. Additionally, individuals with contraindications related to the MRI examination, such as individuals with pacemakers, severe claustrophobia, and injuries or skin disorders affecting the somatosensory system of the left arm, were also excluded. Further, prospective controls were excluded on the premise of a history of severe dieting.

Participants were classified as anorexic if they fulfilled the three governing symptoms as described in the DSM-5 (American Psychiatric Association, 2013) – criteria A (low body weight), B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) and C (disturbances in self-perception of weight and shape). Further, participants were considered fully remitted when they no longer met any criterion and partially remitted when fulfilling only criterion B and/or C after having fulfilled the full criteria.

To date, N = 83 participants had already taken part in the study. For the present work, only the restrictive subtype (full syndrome, full remission and partial remission) as well HC were considered. By selecting a homogeneous sample, it can be ensured that the results of this work are applicable to the clearly defined subtype of restrictive AN while simultaneously reducing the potential variability that might arise from the inclusion of other subtypes or factors. Consequently, all participants diagnosed as binge-purging subtype or atypical AN were excluded (n = 10).

Two subjects were excluded following the refusal of food trials, six subjects due to missing data. Finally, a total of N = 65 participants were then included in the analysis of this study, comprising n = 19 participants in the acute stage of the disease, n = 11 participants in full remission, n = 16 participants in partial remission and n = 20 HC participants.

Experimental Paradigm

The study is based on a recently established and validated experimental paradigm by Chiappini et al. (2022), tailored to evaluate both the anticipatory (wanting) and consummatory (liking) responses to food (via food administration) and social reward (via touch administration). Both administration types had different intensities and speeds in order to achieve a modelling of three different reward levels (very low, low, high). For the food administration this was done by delivering three different types of milk: cocoa milk, sugared milk and a combination of both (cocoa milk 25% & sugared milk 75%). The touch was administered in three different stroke speeds: slow (6 cm/s), fast

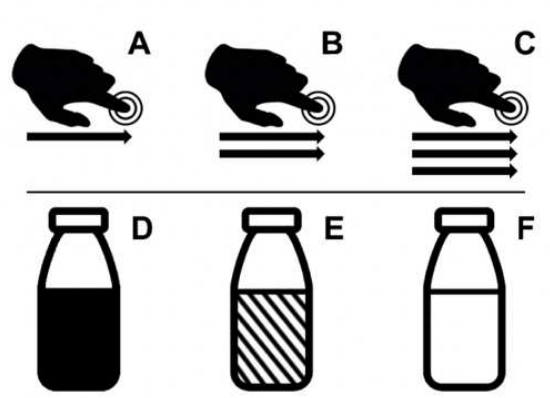
(21 cm/s) and very fast (27 cm/s). Participants were asked to rank their top two preferred stimuli. These rankings were then used to create two conditions for each type of stimulus in the experiment.

After a reward has been announced, participants gave subjective ratings for wanting and liking (explicit measures). Additionally, implicit wanting was assessed by measuring the force they exerted with a hand dynamometer. To measure implicit liking, electromyography (EMG) technology was used as a supplementary tool. Further employed was fMRI to provide detailed insights into the neural correlates.

In this study, only the food rewards in the anticipation phase and specific relevant clinical data (BMI, EDI-2) will be examined. It should be noted that all stimuli related to touch and assessments of liking will not be further described or considered for the analysis.

Figure 3

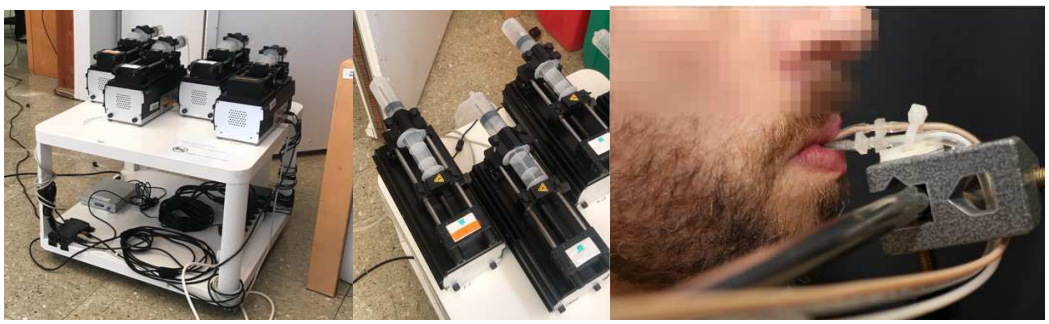
Experimental Stimuli



*Note***. Touch stimuli** - A: slow, B: fast, C: very fast. **Food stimuli** - D: Chocolate milk, E: combination of cocoa and sugared milk, F: sugared milk. These images were presented in the experimental FMRI reward trials.

Figure 4

Syringes and Pump Setup for Food Stimuli Delivery



Note. The four wired pumps to which the syringes are connected are situated outside the scanner room. The syringes, each equipped with a distinct mouthpiece, are then conveyed into the scanner room and taped to the head coil, thereby facilitating the straightforward administration of the food stimuli.

Procedure

The study is comprised of two distinct phases for each participant: a clinical examination and an experimental fMRI part. The subsequent sections will provide a comprehensive overview of the procedure.

Clinical Assessment

First, the participants were examined by clinical psychologists with an array of clinical questionnaires in the department of Child and Adolescent Psychiatry of the Medical University of Vienna: EDI-2, Eating Disorder Examination Questionnaire, Diagnostisches Interview bei Psychischen Störungen interview, Becks Depression Inventory, State/Trait Anxiety Inventory, Obsessive-compulsive inventory revised, Essener Trauma-Inventar, Modified Wisconsin Card sorting test, Rey-Osterreith Complex Figure Test, World Health Organization Quality of Life-BREF, Temperament and Character Inventory for adults, Gastrointestinal complaints questionnaire, Food protocol, Social Touch Questionnaire and Health and Taste Attitude Scales.

Reward Task

The second part of the study employed fMRI to investigate the effect of food and touch stimuli on brain activity and facial muscle activity. The participants were taken to the fMRI facility by an experimenter who accompanied them throughout the whole experiment. The participants were adequately prepared for the experiment, received an introduction to the scanner setting, were required to put on fMRI-compliant clothing, and underwent a cleansing process of the facial skin with water and an exfoliating lotion to facilitate the attachment of the five electrodes for the facial

electromyography. The measurements of the activity of the corrugator and zygomaticus constituted the implicit liking value. Subsequently, the subject was positioned within the scanner. The instructions and equipment, which included a button box, dynamometer, and emergency ball, were then explained. At this point, a confederate entered the scanner room and introduced themselves as a touch therapist. They then marked a 9-cm section on the participant's forearm with adhesive tape, where the participant would subsequently receive the touch stimuli. The experimenter then provided the participant with information regarding the safety precautions and potential risks associated with the procedure, after which the participant was placed within the scanner. Initially, a measurement of the participants' maximum voluntary contraction was undertaken via a dynamometer in their right hand. This served as a reference point for subsequent effort measurements throughout the experiment and across participants. Subsequently, all three stimuli of each reward type were administered, and individual preferences were assessed, where the participant was asked to rank the most and second liked of both reward types with a button box in their left hand. Importantly, participants were informed that all the milk stimuli contained the same number of calories, ensuring that their preferences were based on genuine taste preferences.

After the preference rating, the actual reward task began. Participants were initially presented with a fixation cross on the screen. This was followed by the announcement of a low or high reward stimulus. Participants were then instructed to rate their explicit desire for the reward on a scale, ranging from 'not at all' to 'very much', using the button box. Subsequently, their implicit desire was assessed using the dynamometer. They were instructed to exert force corresponding to their level of desire for the reward. The force was indicated by a visual feedback bar. Once this bar was completely filled, the probability of receiving the announced stimulus was 100%. Correspondingly, the probability that the announced stimulus would be administered decreased when less force was applied. The reward, determined by force and desire, was then administered, and participants were subsequently required to rate the stimuli obtained on the visual scale. Figure 5 illustrates the technical equipment and scales of the experimental wanting measurements, while Figure 6 depicts a full example of one food trial.

Figure 5

Scales and Technical Equipment of the Experimental Wanting Measurements

A

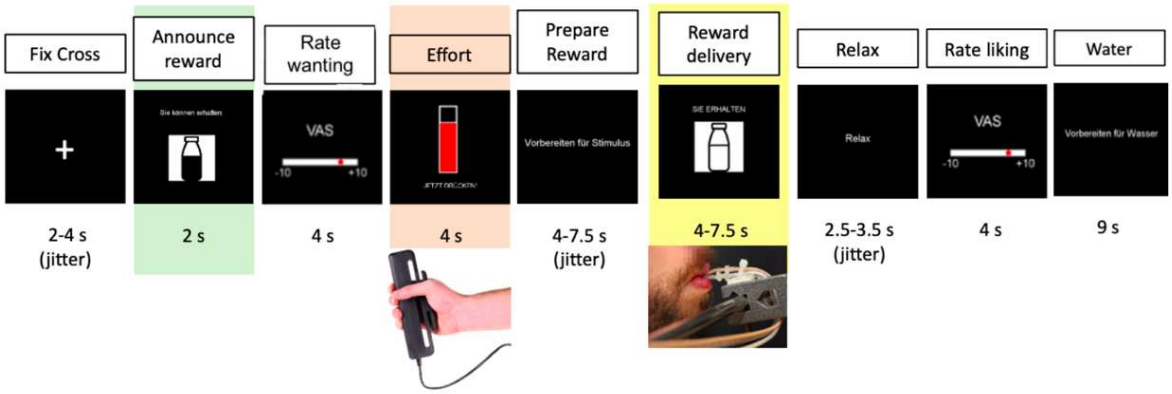
B

Note: **A:** Visual scale for measuring subjective wanting - participants were asked to move the slider with the different multi-colored buttons on the button box according to their desire for the announced stimuli. **B:** Visual Representation of the force exerted with the hand dynamometer.

The experimental part involved two phases. The first was a practice phase, which included two trials per reward type. The second was the actual experiment, which consisted of four blocks of 16 trials each. Each block consisted of eight high-reward and eight low-reward conditions, which were randomly dispensed to the participants. The duration of the experiment was approximately 50 minutes. The food blocks were completed in approximately 13 minutes, while the touch blocks required approximately 10 minutes. It is noteworthy that the blocks were always arranged in alternating order. Following the experimental trials, the participants were asked to complete the debriefing questionnaire.

Figure 6

Timeline of an Example Food Trial



Note: Timeline of a food reward task with a total duration of 50s. In this representative trial, the highest possible reward 'chocolate milk' could have been obtained by the participant (e.g., high reward). The participant provided medium to strong physical effort and a high explicit wanting rating on the scale. Then, the participant was informed that they would receive 'milk' (e.g., very low reward) instead. The very low reward was delivered, and after the relaxation phase the participant was asked to evaluate the level of liking. Finally, water was delivered to rinse the mouth and the participant was advised to prepare for the following trial.

fMRI Data Acquisition

MRI examinations were performed on a 3 Tesla Siemens Prisma MRI scanner (Siemens Medical, Erlangen, Germany) with a 64-channel head-neck coil at the Center of Excellence High-field MRI of the Medical University of Vienna. Further, the participants head was supported with No Motion Correction pads within the head coil. BOLD functional imaging was performed using a T2-weighted single-band echo planar imaging (EPI) sequence with the following parameters: Echo time (TE) = 36 ms, repetition time (TR) = 2.5 s, flip angle = 66°, 44 axial slices coplanar to the line connecting the anterior and posterior commissure, field-of-view = 140 x 140 x 132 mm, matrix size 96 x 96, voxel size = 1.45 x 1.45 x 3 mm, interslice gap = 3 mm. For each participant, 269 volumes per block were acquired during the anticipation of food stimuli.

Variables

Groups

For this examination, a categorical group variable with four values was created. Included were only patients of the restrictive AN subtype with full syndrome (AN-A), in full remission (AN-R) and in partial remission (AN-PR). Further, HC were included as fourth group.

Reward Conditions

Bases on initial individual preference ratings, three reward values were built for the food stimuli: high, low and very low. In the experimental food trials, only two reward levels were disclosed as the highest achievable options: the low and the high reward category. Hence, the reward condition was realized in the experiment as categorical binary variable with high and low reward level. Chocolate milk has consistently been ranked as the most preferred in pilot experiments (Chiappini et al., 2021). However, Korb et al. (2020a, 2020b) implemented a pre-main task preference ranking to address possible intergroup variability in preferences, which can pose a challenge in clinical group testing. Additionally, individual shifts in preferences may arise over the course of the experiment. To ensure the capture of individual preferences and changes in preference accurately, this study employed two methods of preference categorization. The first was a pre-ranking method, and the second was a subsequent adaptation of the categories to accommodate any alterations. The stimulus with the highest average wanting rating was classified as a high reward. If the wanting for this stimulus changes significantly over the course of the experiment, the categories are retrospectively adjusted accordingly.

Subjective Food Wanting

A visual analogue scale, ranging from 'not at all' to 'very much', is employed to measure subjective wanting. The midpoint of the scale is marked as 'do not care'. Participants are instructed to move the slider away from the midpoint and return it if they are indifferent to the stimulus. This additional requirement is implemented to ensure that a central rating reflects a considered evaluation rather than an inadvertent inability to engage with the scale.

A numerical value was then derived from the qualitative slider rating which can range continuously between -100 and +100. Thus, subjective food wanting is represented as a quantitative variable.

Objective Food Wanting

The effort exerted to obtain an announced reward constituted the objective wanting in this study. This was quantified using a hand dynamometer. The maximum voluntary contraction (MVC) measured before the experimental trials represented the reference measure for further effort measurements. To obtain the rewards in the experimental phase participants were required to press the dynamometer in accordance with their desire for the reward. This was quantified as a continuous scale ranging from zero up to the MVC reference measure taken pre-experiment. This objective measure complements subjective ratings by offering a reliable and robust method for capturing food wanting (Ziauddeen et al., 2014). It helps to mitigate biases and discrepancies often found in self-reported desires, ensuring a more accurate assessment of true wanting behavior.

Eating Disorder Inventory-2

The EDI-2 is a multidimensional psychometric self-report instrument for the assessment of the specific psychopathology associated with anorexia nervosa, bulimia nervosa, and other psychogenic eating disorders (Thiel & Paul 2006). It consists of 92 items distributed across 11 subscales measuring: drive for thinness, bulimia, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, maturity fears, asceticism, impulse regulation, and social insecurity. The questions are aimed at identifying distorted cognitions and behaviors characteristic of eating disorders. Responses are given on a six-point scale, ranging from one (absence of eating disorder-specific thoughts and behaviors) to six (indicating their constant presence). In addition, a total EDI-2 score is calculated by aggregating all subscale scores. Higher scores indicate greater severity of eating disorder-specific psychopathology (maximum value for symptom severity: 546). Importantly, the EDI-2 demonstrates excellent internal consistency (total EDI-2 score: Cronbach's alpha α = .90; Kappel et al., 2012).

Body Mass Index

The BMI is a marker of significantly low body weight and is used as diagnostic tool for anorexia (Hebebrand et al., 1996). It is calculated by dividing the patient's weight, in kilograms, by their height, in meters squared, and subsequently comparing this value to a fixed threshold. According to the American Psychiatric Association (2013) an adult patient with a BMI of less than 18.5 kg/m² can be described as significantly underweight.

Brain Activity

The neural activity, particularly in the dlPFC and in the vmPFC, resembles the dependent variable. To facilitate comparisons between different experimental groups, the individual BOLD signal amplitudes from the dlPFC and vmPFC are averaged within each group (AN-A, AN-PR, AN-R, HC). This averaging process enables the computation of group-level statistics and the comparison of neural responses across the four groups. Further, it serves as a comparative variable for analyzing behavioral and clinical data. Thus, the final quantified variable in this analysis is the amplitude of the BOLD signal reflecting the level of neuronal activity in the dlPFC and vmPFC in response to reward tasks.

Data Analysis

The analysis of neuroimaging data was performed with SPM12 (Statistical Parametric Mapping) in Matlab R2022a (version 9.12; Mathworks). Descriptive, behavioral, and clinical data analyses were conducted in JASP (version 0.16.2).

Behavioral Data

In order to ascertain the differences in subjective and objective wanting between the four groups, a mixed design was utilized, upon which a repeated-measures variance analysis was conducted. The repeated-measures factors were the type of measurement of wanting (subjective and objective) and the reward level (low and high), while the between-subject factor was group affiliation (AN-A, AN-R, AN-PR, HC). This enabled an investigation of the main effect of group, reward level, type of measurement, and corresponding interaction effects. Post-hoc group comparisons were performed as Bonferroni-corrected t-tests. To allow for a comparison of subjective and objective data, z-scores were calculated.

Neuroimaging Data

The neuroimaging data underwent a series of processing stages, from preparation to region of interest (ROI) analysis, which are described in further detail in the following paragraphs.

Preprocessing. The neuroimage data was preprocessed in several steps and optimized for subsequent analysis. First, data was imported and converted from DICOM (Digital Imaging and Communications in Medicine file format) to NifTI (Neuroimaging Informatics Technology Initiative file format). In the second step, the conversion from 3D to 4D took place in order to exclude a potential imbalance in the magnetic field and to control for slice sequence discrepancies. Subsequently, the spatial realignment and unwarping technique was performed to control for possible movement of the subject and to improve spatial accuracy, specifically using the x, y or z coordinates for directional and axial information. Then, the data was coregistered (functional and structural data were aligned) and segmented to classify grey matter, white matter and cerebrospinal fluid. In order to fit the data into a common anatomical template, the data was normalized within the standardized Montreal Neurological Institute (MNI) space with the transformations of zooms, shears and nonlinear deformations. Subsequently, spatial smoothing with a convolution coefficient of 6mm was applied to improve the signal-to-noise ratio and to reduce spatial noise between subjects. Finally, a mask was created to define the field of view during the experiment block, which allowed the subsequent analysis to be restricted to specific regions of interest.

First-Level Analysis. The preprocessing was followed by the first-level analysis, which was conducted on an individual basis, with the aid of a generalized linear model. This model facilitated the creation of a design matrix for each subject including regressors for each condition. The regressors included were fixation cross, anticipation (for high and low rewards), rating wanting, effort, delivery, relax, rating liking and the six movement regressors for translation and rotation (x, y, z, pitch, roll, yaw). Additionally, the parametric modulator (PM) of wanting was included in the

analysis to help explain additional variance in the data and record fluctuations in brain responses observed during the anticipation phase that occur from session to session. Further, a contrast image was generated for each subject, contrasting the BOLD response during the announcement of a reward (high and low) with the BOLD response during the presentation of a fixation cross.

Second-Level Analysis. The second-level analysis operates at group-level and employs the single subject contrast images created in the first-level analysis. To determine group differences, a one-way ANOVA was performed in SPM12 with all four groups (AN-A, AN-PR, AN-R, HC). This enabled to determine both a main effect of group and post-hoc t-tests to compare brain activity in the fixation cross/reward announcement contrast between and within the groups.

In order to target the analysis to specific neural regions, a small-volume correction with a significance level of p <.001 and a voxel threshold of > 0 was applied. The correction was performed with masks of the right and left dlPFC and the vmPFC (for an illustration of the ROIs see Figure 2). In order to create a brain mask for the dlPFC, a functional mask for cognitive control was generated in Neurosynth based on a meta-analytic analysis of 598 studies and 19614 activations. This mask was subsequently imported into MRIcron to extract bilateral regions of the dlPFC. The bilateral vmPFC mask was derived from a functional vmPFC mask utilized in a rTMS simulation trial involving patients with cocaine use disorder (Garza-Villarreal et al., 2021). Brain mapping was performed using the SPM toolbox Automated Anatomical Atlas 3 (AAL3). In the following results section, only clusters with a significance level of p_{FWE} <.05 are reported.

Correlational Analysis between Behavioral, Clinical and Neuroimaging Data. Pearson product-moment correlations were employed to investigate the relationships between clinical, behavioral and neuroimaging data. The variables of interest were BMI, EDI-2, subjective wanting ratings, level of effort exerted, and brain activity in the contrast reward announcement/fixation cross of the ROIs that were used in the previous analyses (right and left dlPFC, vmPFC).
The ROI activation values for the contrast images were calculated and extracted as averaged group values from the individual images of the first-level analysis using the SPM12 toolbox REX (Region Extraction tool). In order to include the behavioral data in the correlation analysis, a difference score was calculated for subjective wanting and exerted effort for each participant. This was achieved by subtracting the value of the low reward condition from the value of the high reward condition (the term "difference score" will be employed in subsequent discourse).

Results

The results section presents the findings of the respective analyses. Initially, the participants descriptive data is presented in tabular form, followed by an evaluation of the wanting measurements. Subsequently, the results of the brain activation data during food reward anticipation are outlined, accompanied by the results of the correlation analyses. Finally, the results of the exploratory whole-brain analysis are presented.

Descriptives

The participant sample of this thesis consisted of N = 65 female volunteers subdivided in full syndrome anorexic participants (n = 19), fully remitted (n = 11) or partially remitted participants (n = 16) and HC (n = 19). The age of the participants ranged from 13 to 24, with a mean age of M = 17.7 and a standard deviation of SD = 2.8. Significant group differences were found in age, BMI and in EDI-2 total scores, as shown in table 1. A post-hoc analysis showed that the AN-A group was significantly younger than the HC and AN-PR group. As expected in acute AN patients, the AN-A group had a significantly lower BMI compared to the HC, AN-PR and AN-R group. Further, the EDI-2 total score was significantly higher in the AN-A group compared to all other groups. There were no significant differences between the AN-R and HC group and between the AN-PR and AN-R group.

Table 1

Descriptive Statistics of Participants

Variable	AN-A Group (*n* = 19)	AN - R Group (*n* = 11)	AN-PR Group (*n* = 16)	HC Group (*n* = 19)	F	p	Significant Post-hoc Contrasts
Age	16.05 (*SD* = 2.53)	17.9 (*SD* = 2.07)	18.63 (*SD* = 2.9)	18.58 (*SD* = 2.65)	*F* (3,61) = 3.98	0.012	AN-A < HC (mean difference = -2.53, p_{tukey} = .02) AN-A < AN-PR (mean difference = -2.57, p_{tukey} = .024)
BMI	15.92 (*SD* = 1.96)	21.11 (*SD* = 2.67)	20.39 (*SD* = 3)	21.1 (*SD* = 2.83)	*F* (3,61) = 16.1	<.001	AN-A < HC (mean difference = -5.17, p_{tukey} = <.001) AN-A < AN-PR (mean difference = -4.47, p_{tukey} = <.001) AN-A < AN-R (mean difference = -5.18, p_{tukey} = <.001)

Variable	AN-A Group (*n* = 19)	AN - R Group (*n* = 11)	AN-PR Group (*n* = 16)	HC Group (*n* = 19)	F	p	Significant Post-hoc Contrasts
EDI-2 total score[a]	95.67 (*SD* = 32.06)	36.36 (*SD* = 32.98)	63.88 (*SD* = 34.78)	32.39 (*SD* = 17.09)	F (3,59) = 16.42	<.001	AN-A > AN-R (mean difference = 59.3, p_{tukey} = <.001) AN-A > HC (mean difference = 63.28, p_{tukey} = <.001) AN-A > AN-PR (mean difference = 31.79, p_{tukey} = .014) HC < AN-PR (mean difference = -31.49, p_{tukey} = .015)

Note. Table 1 presents means and standard deviations (*SD*) for age, BMI and EDI-2 total scores for each study group. Further, ANOVA results are presented with the corresponding post-hoc tests.

[a] EDI-2 total score values 1 missing for AN-A, 1 missing for HC

Concerning individual milk preferences, vegan milk was administered to n = 2 participants of the AN-A group, to n = 1 participant in the HC group, to n = 3 participants in the AN-PR group and to n = 1 participant in the AN-R group. Lactose-free milk was administered to n = 2 participants in the AN-A group, to n = 2 participants in the AN-PR group and to n = 1 participant in the AN-R group.

Subjective and Objective Food Wanting Measures

The AN-A group showed a lower desire to obtain high rewards in the subjective measurements compared to the AN-R, AN-PR and HC group. Further, a trend towards higher subjective and objective wanting is visible in the AN-A group for low rewards compared to all other groups. On average, there is less variation in wanting and effort between the high and low reward conditions in the AN-A group compared to all other groups (see Table 2).

Table 2

Descriptives of Subjective (Wanting) and Objective (Effort) Wanting Measurements of High and Low Reward

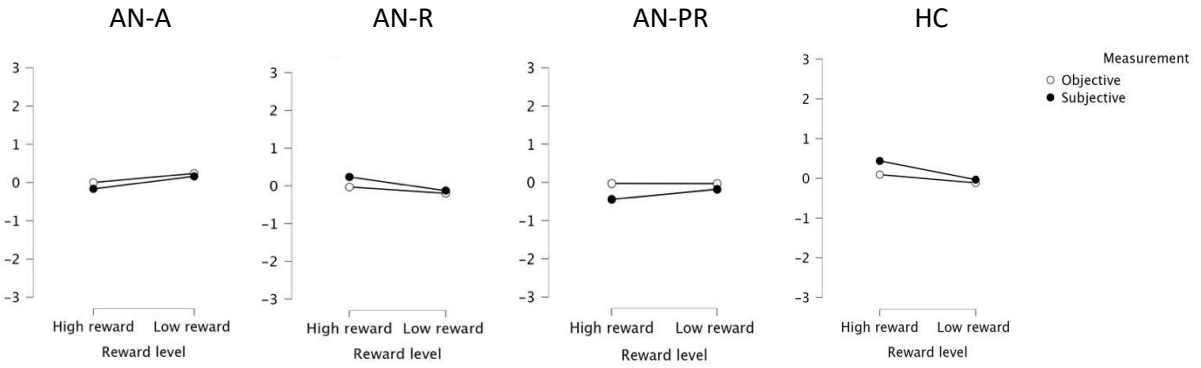
Measure	Group	High reward	Low reward	Difference Score	95% Confidence Interval	SD
Wanting	AN-A	26	10.29	15.71	[-74.5, 96.9]	41.68
	AN-R	44.45	-2.72	47.16	[-2.8, 118.8]	41.68
	AN-PR	13.27	-5.22	18.49	[-150, 123.7]	72.97
	HC	53.73	1.51	52.22	[-11.2, 195.3]	49.81
Effort	AN-A	73.34	70	3.33	[-29.1, 37.7]	14.48
	AN-R	72.61	58.14	14.47	[-1, 41.5]	17
	AN-PR	72.6	62.59	10	[-63.2, 109.3]	34.36
	HC	75.7	60.36	15.35	[-19.1, 77.3]	20.24

Note. This table shows measurements of high and low reward conditions, difference scores, 95% confidence intervals and standard deviations of food wanting ratings and exerted effort per participant group.

The values from low and high reward conditions were z-transformed to ensure the comparability of the measurement. The distributions of the values within each group, across different reward levels, and across different measurements were visually inspected for a normal distribution using quantile-quantile (QQ) plots. Figure A1 in the appendix displays the detailed graphs. Some groups exhibited deviations from normality. However, it can be assumed that the ANOVA is a sufficiently robust method to conduct the analysis while accounting for these deviations (Field & Wilcox, 2017). The following repeated measures ANOVA revealed a nonsignificant main effect of group *(F* (3, 61) = 0.66, *p* = .579), implicating no differences in food wanting between the AN-A, AN-R, AN-PR and HC groups. Overall, the repeated measures ANOVA with two factors did not reveal any other significant main or interaction effect, neither for the main effect of reward level *(F* (3, 61) = 0.17, *p* = .679) or measurement *(F* (3, 61) = 0.001, *p* = .97), nor for the interaction effect reward level x group *(F* (3, 61) = 1.85, *p* = .148), measurement x group *(F* (3, 61) = 0.61, *p* = .611), reward level x measurement *(F* (3, 61) = 0.05, *p* = .828) or reward level x measurement x group *(F* (3, 61) = 1.18, *p* = .324). Figure 7 illustrates the ANOVA results.

Figure 7

Food Wanting per Group, Reward Level Condition and Measurement



Note: The figure shows the averaged and z-transformed values of objective and subjective measurements of wanting within each group (AN-A, AN-R, AN-PR, HC).

Activity of the dlPFC and vmPFC during Food Reward Anticipation

The main effect of group (F-Contrast: (AN-A Reward Announcement – AN-A Fixation Cross) + (AN-R Reward Announcement – AN-R Fixation Cross) + (AN-PR Reward Announcement – AN-PR Fixation Cross)+ (HC Reward Announcement – HC Fixation Cross)) revealed two clusters with significantly different activation in the left dlPFC (F (4, 61) = 6.14, p_{FWE} = .043) and the right dlPFC (F (4, 61) = 10.49, p_{FWE} = .012). No main effect of group was found for activation of the vmPFC. Further post-hoc t-contrasts did not reveal any significant differences in right or left dlPFC and vmPFC activity in the groups, neither between nor within.

Table 3

Results from dlPFC (right and left) and vmPFC ROI Analysis contrasting Brain Activation during Reward Announcement versus Fixation Cross

Main Effect of Group (Reward Announcement > Fixation Cross)

Brain Region	**k**	**F**	p_{FWE}	**x**	**y**	**z**
Left dlPFC	2	6.14	.043	-50	12	32
Right dlPFC	17	10.49	.012	52	14	28

Post-hoc Between-Group Comparisons

Brain Region	k	F	p_{FWE}	x	y	z
AN-A > AN-PR						
No suprathreshold clusters						
AN-A > AN-R						
No suprathreshold clusters						
AN-A > HC						
No suprathreshold clusters						
AN-PR > AN-A						
No suprathreshold clusters						
AN-PR > AN-R						
No suprathreshold clusters						
AN-PR > HC						
No suprathreshold clusters						
AN-R > AN-A						
No suprathreshold clusters						
AN-R > AN-PR						
No suprathreshold clusters						
AN-R > HC						
No suprathreshold clusters						
HC > AN-A						
No suprathreshold clusters						
HC > AN-PR						
No suprathreshold clusters						
HC > AN-R						
No suprathreshold clusters						

Post-hoc Within-Group Comparisons

Brain Region	k	F	p_{FWE}	x	y	z
AN-A Food Reward Announcement > Fixation Cross						
No suprathreshold clusters						
AN-PR Food Reward Announcement > Fixation Cross						
No suprathreshold clusters						

Brain Region	k	F	p_{FWE}	x	y	z
AN-R Food Reward Announcement > Fixation Cross						
No suprathreshold clusters						
HC *Food Reward Announcement > Fixation Cross*						
No suprathreshold clusters						

Note. This table shows the BOLD activation results of the ROI analysis of the right dlPFC, left dlPFC and vmPFC using the PM of wanting. A threshold of p <.001 (with > 0 voxels) was utilized, followed by cluster-wise correction. Clusters were deemed statistically significant at p_{FWE} < .05.

Correlational Analysis between Behavioral, Clinical and Neuroimaging Data

A Shapiro-Wilk test was performed to test the normal distribution of the data, as the individual groups were small in size (N < 30). It revealed that the variables in all four groups were significantly deviated from normality (W(AN-A) = 0.56, p < .001; W(AN-R) = 0.622, p <.001; W(AN-PR) = 0.592, p <.001; W(HC) = 681, p <.001). Based on this outcome, Spearman's correlations were used as correlational method.

In all groups, the correlation between the difference scores of wanting and effort was found to be significantly positive ($r_{s\,(AN\text{-}A)}$ (57) =.649, p =.003; $r_{s\,(AN\text{-}R)}$ (57) =.836, p =.003; $r_{s\,(AN\text{-}PR)}$ (57) =.805, p <.001; $r_{s\,(HC)}$ (57) =.54, p =.018).

The coupling between the right and left dlPFC showed a strong positive correlation in all groups except for the HC group where only a small non-significant positive correlation was found ($r_{s\,(AN\text{-}A)}$ (57) =.475, p =.041; $r_{s\,(AN\text{-}R)}$ (57) =.709, p =.019; $r_{s\,(AN\text{-}PR)}$ (57) =.838, p <.001; $r_{s\,(HC)}$ (57) =.113, p =.664).

Further, the coupling between right dlPFC and vmPFC was correlated significantly positive with moderate to high effect size in the AN-A (r_s (57) =.663, p =.003) and AN-PR group (r_s (57) =.694, p =.004), while showing a non-significant small positive correlation in the AN-R (r_s (57) =.327, p =.327) and HC group (r_s (57) =.312, p =.194).

The interplay between left dlPFC and vmPFC revealed significant positive high correlations in all four groups with slightly higher correlations in the AN-PR and AN-R groups ($r_{s\,(AN\text{-}A)}$ (57) =.472, p =.043; $r_{s\,(AN\text{-}R)}$ (57) =.764, p =.009; $r_{s\,(AN\text{-}PR)}$ (57) =.706, p =.003; $r_{s\,(HC)}$ (57) =.572, p =.012).

In the context of the REX-extracted ROI data and its correlations with measures of wanting and effort, the AN-A group showed a significant high and negative correlation between activity in the right dlPFC and effort (r_s (57) = -.585, p =.008) and a marginally non-significant moderate negative correlation between right dlPFC activity and the subjective wanting measure (r_s (57) = -.425, p =.071), not visible to this extent in any of the other three groups. A similar picture can be drawn from the correlations between the left dlPFC and wanting and effort measurements. None of the groups

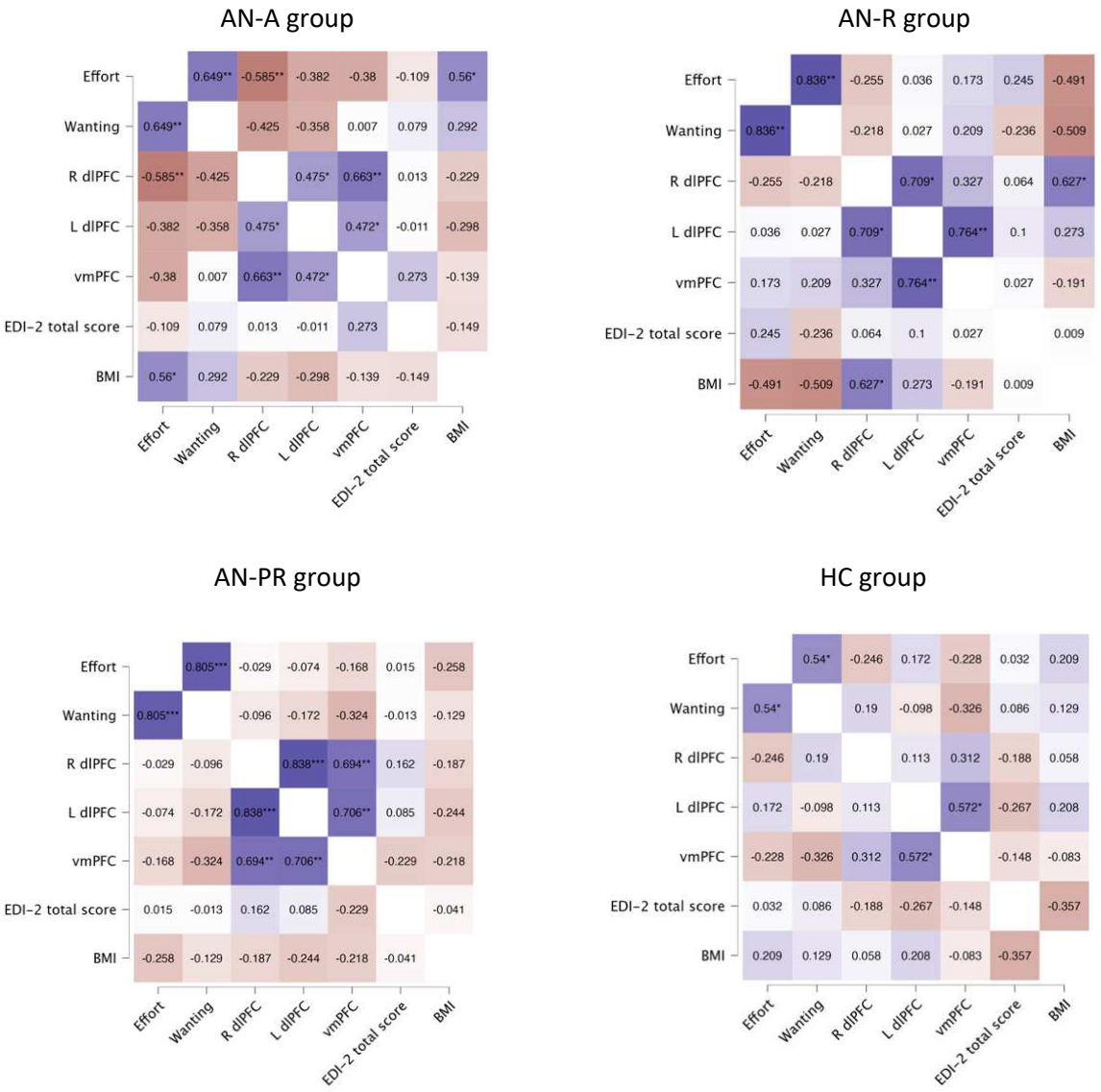
showed significant correlations, however in the AN-A group a trend towards a negative correlation with moderate effect size was visible for the pairing left dlPFC and wanting (r_s (57) = -.358, p =.133), and left dlPFC and effort (r_s (57) = -.382, p =.107).

The correlations between wanting data and symptom severity data revealed a significant positive correlation with moderate effect size between BMI and effort in the AN-A group (r_s (57) = .56, p =.013). Further, the AN-R group revealed a significant and strong positive correlation between BMI and activity in the right dlPFC (r_s (57) = .627, p =.044).

Conclusively, none of the groups exhibited a significant correlation between EDI-2 total score and activity in any of the predefined ROIs. Figure 8 shows the correlations patterns in form of Spearman's Rho heatmaps. The correlational matrices for each group are presented in the appendix of this thesis (Table A1).

Figure 8

Spearman's Rho Heatmaps



Note. Spearman's correlations between Effort and Wanting difference scores, right dlPFC, left dlPFC and vmPFC activity, EDI-2 total score and BMI are illustrated in these heatmaps. The darkness of a square represents the strength of the correlation (the darker the square, the stronger the correlation). Purple represents positive correlations, while red represents negative correlations. Significant correlations are flagged. * p <.05, ** p < .01, *** p <.001

Explorative Whole-Brain Analysis

In the whole-brain analysis examining the main group effect (F-Contrast: (AN-A Reward Announcement – AN-A Fixation Cross) + (AN-R Reward Announcement – AN-R Fixation Cross) + (AN-PR Reward Announcement – AN-PR Fixation Cross) + (HC Reward Announcement – HC Fixation Cross)), which contrasts activation between reward announcement and fixation cross, two significant clusters were identified.

The first cluster revealed a cluster with peak activation in the right superior occipital gyrus. This cluster, with a size of 75,826 voxels and a peak activation F-value of 40.24 (p_{FWE} < .001) at MNI coordinates x = 26, y = -94, z = 12, included several key regions contributing more than 1% to the cluster size: postcentral gyrus (r, l), precentral gyrus (r, l), lingual gyrus (r, l), fusiform gyrus (r, l), middle temporal gyrus (r, l), calcarine cortex (r, l), supramarginal gyrus (r, l), supplementary motor area (r, l), rolandic operculum (r, l), inferior temporal gyrus (l, r), superior temporal gyrus (r, l), inferior occipital gyrus (l), frontal inferior opercular gyrus (r), inferior parietal lobule (l), middle occipital gyrus (l), frontal mid 2 (r), cerebellum lobule VI (l), and superior parietal lobule (l). For a detailed composition of this cluster see Table A2 in the appendix of this thesis.

The second cluster had a total size of 230 voxels and exhibited a peak activation in the left anterior orbital gyrus with a F-value of 10.8 (p_{FWE} = .001) at MNI coordinates x = -22, y = 44, z = -14. The post-hoc between-group tests did not reveal any significant clusters. Detailed information about the activation of the clusters is provided in Table 4, activation of the two clusters is illustrated in Figure 9**.**

Table 4

Results Whole-Brain Analysis contrasting Brain Activation during Reward Announcement versus Fixation Cross

Main Effect of Group

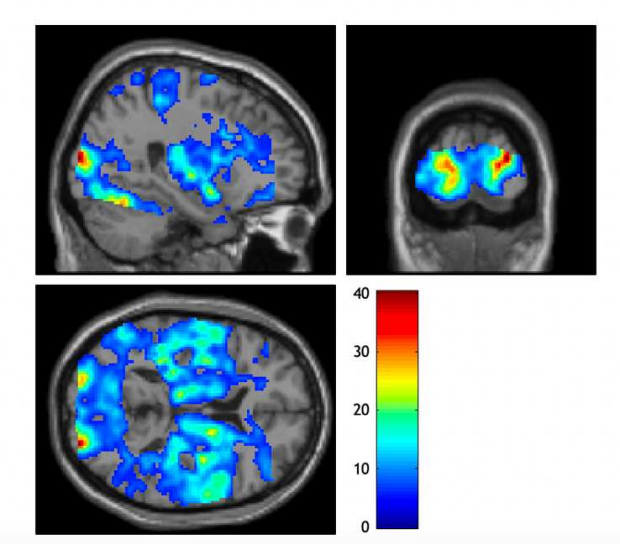
Brain region	**k**	**F**	p_{FWE}	**x**	**y**	**z**
Right Superior Occipital Gyrus	75826	40.24	.000	26	-94	12

Brain region	k	F	p_{FWE}	x	y	z
Left Anterior Orbital Gyrus	230	10.8	.001	-22	44	-14

Note: This table presents results from whole brain analysis across all groups contrasting reward announcement versus fixation cross as the wanting (PM) increases. Cluster size (k), F-values, p_{FWE}-values, and MNI coordinates are reported.

Figure 9

Whole-Brain Neural Activation for the Main Group Effect contrasting Food Announcement versus Fixation Cross



Note. Main group effect of BOLD activation across all AN-A, AN-PR, AN-R and HC groups (MNI coordinates x = 26, y = -94, z = 12). The color legend provides a visual representation of the size of the t-value.

Within the groups, several significant clusters were found in the brain activation comparison between food reward announcement and fixation cross. In the AN-A group, six significant clusters with peak activations in the postcentral gyrus (right and left), the right middle temporal gyrus, left supplementary motor area, and the right middle frontal gyrus were obtained. In the AN-R group, four significant clusters with peak activations in the left occipital inferior gyrus, left fusiform gyrus, left postcentral gyrus, and right fusiform gyrus were found. The AN-PR group revealed four significant clusters with peak activation in the left postcentral gyrus, right intralaminar thalamic nuclei, left supplementary motor area and the left middle frontal gyrus 2. The HC group showed five significant clusters with peak activation in the left lingual gyrus, right supplementary motor area, left middle

frontal gyrus 2 and the left superior parietal gyrus. Table 5 provides a detailed description of the clusters including t-values, p_{FWE} values and MNI coordinates. Figure 10 illustrates the BOLD activation within each of the analyzed group.

Table 5

Results Whole-Brain Analysis contrasting Brain Activation during Reward Announcement versus Fixation Cross Within-Groups

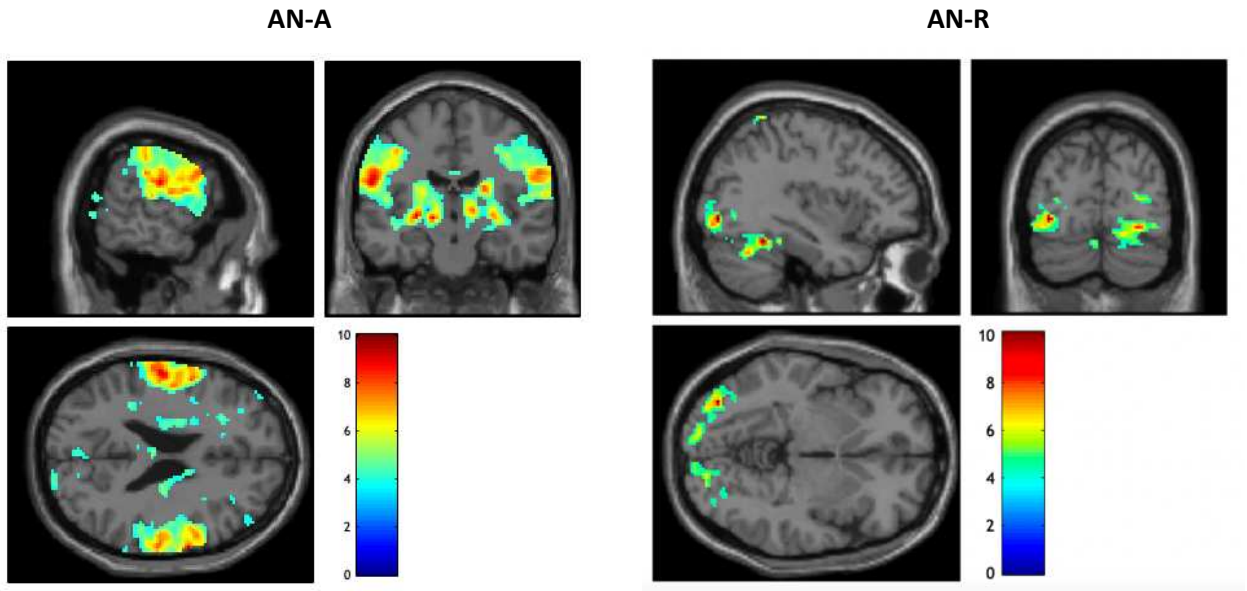
Brain region	**k**	**T**	p_{FWE}	**x**	**y**	**z**
AN-A Food Reward Announcement > Fixation Cross						
Right Postcentral Gyrus	9190	9.98	.000	68	-4	14
Left Postcentral Gyrus	17621	9.87	.000	-50	24	32
Right Middle Temporal Gyrus	176	6.24	.009	54	-62	6
Left Supplementary Motor Area	1358	5.85	.000	-2	-4	68
Right Postcentral Gyrus	285	5.68	.001	28	-32	54
Right Middle Frontal Gyrus	421	5.47	.000	42	42	6
AN-R Food Reward Announcement > Fixation Cross						
Left Occipital Inferior Gyrus	1047	10.11	.000	-36	-80	-4
Left Fusiform Gyrus	1164	10.01	.000	-38	-50	-20
Left Postcentral Gyrus	125	9.86	.047	-46	-42	62
Right Fusiform Gyrus	1861	9	.000	30	-78	-10
AN-PR Food Reward Announcement > Fixation Cross						
Left Postcentral Gyrus	8151	11.56	.000	-46	-20	42
Right Intralaminar Thalamus Nuclei	24153	10.05	.000	12	-22	0
Left Supplementary Motor Area	536	6.59	.000	-14	-18	50
Left Middle Frontal Gyrus 2	225	5.81	.001	-28	36	24

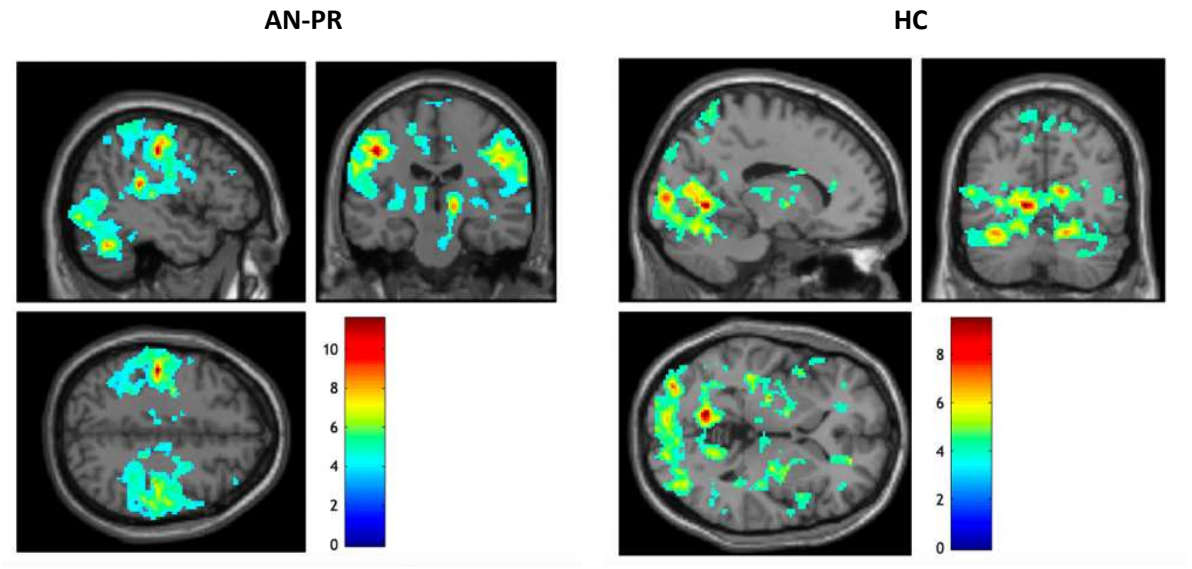
Brain region	k	T	p_{FWE}	x	y	z
HC Food Reward Announcement > Fixation Cross						
Left Lingual Gyrus	31052	9.48	.000	-14	-62	0
Right Supplementary Motor Area	791	7.22	.000	2	-2	68
Left Middle Frontal Gyrus 2	456	6.79	.000	-20	32	20
Left Middle Frontal Gyrus 2	309	5.42	.001	-36	34	48
Left Superior Parietal Gyrus	697	5.31	.000	-20	-54	66

Note: This table presents results from whole brain analysis within all groups contrasting reward announcement versus fixation cross. Cluster size (k), F-values, p_{FWE}-values, and MNI coordinates are reported.

Figure 10

Within-group AN-A Whole-Brain Neural Activation contrasting Food Reward Announcement and Fixation Cross





Note. BOLD activation within AN-A, AN-PR, AN-R and HC groups contrasting Food Reward Announcement versus Fixation Cross. MNI coordinates $_{AN\text{-}A}$ x = -60, y = -15, z = 25; MNI coordinates $_{AN\text{-}R}$ x = -36, y = -80, z = -4; MNI coordinates $_{AN\text{-}PR}$ x = -46, y = -20, z = 24; MNI coordinates $_{HC}$ x = -14, y = -62, z = 0. The color legend provides a visual representation of the size of the t-value.

In order to investigate potential differences without subdividing by disease stage and to identify persistent activation patterns even in remitted phases of anorexia, the activation patterns of all AN patients (AN-A, AN-PR and AN-R group) were compared with those of HC in the reward announcement versus fixation cross contrast. However, this analysis did not show any significantly different activation patterns.

Discussion

The objective of this thesis is to examine the role of reward and cognitive control processes in AN, with a particular focus on dlPFC and vmPFC activity and wanting measurements during food reward anticipation. It centers on young female patients with anorexia nervosa at different stages of the disease. The research aimed to ascertain whether individuals with anorexia nervosa exhibit discrepancies in explicit and implicit wanting measurements compared to HC when actual food intake is involved. Additionally, it investigated how dlPFC and vmPFC activity differs between different stages. Finally, the study assessed the correlation between the activation of these brain regions with wanting ratings and symptom severity to gain a broader understanding of the neurobiological underpinnings, underlying mechanisms, and interactions involved in the pathology of AN.

Subjective and Objective Food Wanting Measures

In contrast with the initial hypotheses, no significant main effect of group was observed in either objective or subjective wanting measures in anticipation of food rewards. One potential interpretation is that the participants in this study are currently in a developmental phase where alterations in the brain are still emerging. It is plausible that these changes have not yet become as firmly established as they typically do in adulthood. This could result in a less distorted perception of rewards in adolescent AN as indicated by prior research findings suggesting impaired reward processes that typically involved slightly older participants who are no longer defined within the adolescent age range (Cowdrey et al., 2013; Davis & Woodside, 2002; Frank et al., 2012). These findings demonstrate that reward processing is relatively unimpaired in adolescent AN patients.

However, this does not preclude the possibility that the reward processes may become impaired as the disease progresses, particularly given the presence of some trends already evident in the descriptive data. Although the main effect of group did not reach statistical significance, importantly the descriptive data of effort and wanting ratings suggests the presence of noteworthy discrepancies between the groups. In alignment with the proposed hypothesis, high reward was consistently rated higher than low reward across all subjective and objective rating scales in all experimental groups with least differentiation between reward levels in the AN-A group. However, based on the descriptive data for implicit and explicit wanting, the AN-A and AN-PR groups in particular only exhibited a minimal differentiation between reward types compared to the AN-R and HC groups, suggesting a reduced ability to experience different reward intensities in these groups. This is consistent with previous research on reward anhedonia in AN (Davis & Woodside, 2002; Keating, 2010). Moreover, it was observed that the difference score of the AN-R group approached that of the HC group for both implicit and explicit wanting measures. This suggests that a reduction in AN symptomatology could restore the differentiation between the two reward levels to a range more aligned with that observed in healthy individuals with normative reward processing. In contrast, previous research on remitted adult patients indicated that the altered reward response frequently persisted (Ehrlich et al., 2015; Cowdrey et al., 2011; Cha et al., 2016; Wagner et al., 2007). These findings indicate that alterations in the reward system during adolescence may be reversible by means of a reduction in AN symptoms, potentially explicable given that adolescence represents a critical period of enhanced neuroplasticity (Fuhrmann et al., 2015).

In the evaluation of the high reward, the AN-A and AN-PR participants showed the lowest average levels of subjective wanting in the group comparison, indicating that they demonstrated a lesser desire for the high rewards than the AN-R and HC groups. Further, it is noteworthy that the AN-A participants exhibited the highest average level of subjective wanting for the low reward in the group comparison, contrary to what one would anticipate from a healthy subject. The reward

contamination model (Keating, 2010) may account for the observed discrepancy in subjective wanting for high and low rewards among participants in the AN-A and AN-PR group. Accordingly, high rewards could be emotionally "contaminated" by negative associations such as fear of weight gain or loss of control over eating behavior, while low rewards are perceived as less stressful and therefore more rewarding. This contamination could drive reward processing in AN towards a paradoxical response in which lower stimuli are favored, although healthy individuals would typically value higher rewards more.

Notably, the relatively low subjective ratings for the high reward in the AN-A and AN-PR group did not align with the corresponding extended effort, exhibiting a level of exertion comparable to that observed in remitted patients and HC. This finding suggests that these groups may experience emotions (e.g., guilt, fear, and shame) and motivations (e.g., control over eating behavior and body image), which result in a subjective devaluation of the reward (Ehrlich et al., 2015; Holsen et al., 2012; Keating, 2012), without affecting the objective evaluation of reward.

Activity of the dlPFC and vmPFC during Food Reward Anticipation

The ROI analysis of the dlPFC revealed a significant main group effect of neural activation in two minor clusters in the right and left dlPFC. In the post-hoc contrasts, the difference between the groups was no longer apparent, which may be attributed to the relatively small sample size and potential heterogeneity of the groups, which may have limited the ability to withstand correction for multiple comparisons across the brain. Regardless, the increased dlPFC activity in acute AN patients compared to HC in anticipation of rewards observed in previous research (Brooks et al., 2012; Eddy et al., 2023; Ehrlich et al., 2015) is not supported by our data. However, these studies frequently employed visual representations of food rather than actual food consumption. Accordingly, when only images are viewed and no immediate food intake has to be feared by the participants, more time may be available for cognitive evaluation and control, which in turn activates the dlPFC to a greater extent. In contrast, when actual food is present immediately after the announcement, there may be less time for such cognitive processes. Consequently, the dlPFC may not demonstrate increased activation due to participants limited opportunity to engage in cognitive control mechanisms. Instead, the neural response of the AN patients in our sample may be more accurately characterized by rapid preparation for sensory stimuli related to actual food intake.

The results of the ROI analysis of the vmPFC are inconsistent with our initial hypotheses of higher vmPFC activation in AN groups based on earlier studies indicating the involvement of the vmPFC in reward processes (Arsalidou et al, 2020; Bartra et al, 2013; Chase et al, 2015; Levy and Glimcher, 2011; Sescousse et al, 2013). Neither a significant main effect of the group nor significant effects in post-hoc t-contrasts between or within the groups were revealed for the activation of the vmPFC. These results could again indicate high heterogeneity within the groups, a small sample size,

or insufficient sensitivity of the paradigm used to measure reward anticipation, whereby subtle differences in vmPFC activation were not recognized.

Correlational Analysis between Behavioral, Clinical and Neuroimaging Data

The study revealed a significant positive correlation with moderate to large effect sizes between explicit wanting and effort in all four groups, indicating that an increase in explicit wanting is associated with an increase in effort, regardless of group affiliation. This suggests that adolescents with AN do not experience a dissociation between implicit and explicit wanting during reward anticipation and that these mechanisms do not differ from those observed in HC, contrasting previous research on impaired reward mechanisms in AN (Cowdrey et al., 2013, Morales & Berridge, 2020).

Moreover, it was determined that the activity between the right and left dlPFC during reward anticipation was significantly positively correlated, with moderate to high effect sizes, in all groups except the HC group. These findings indicate that the collaboration between the two hemispheres of the dlPFC might represent an AN-specific dynamic that persists even in the remission phase.

In regard to the interaction between the dlPFC and the vmPFC, the initial hypothesis is partly supported by the data. Significant positive correlations with strong effect sizes between the activity of the right dlPFC and the activity of the vmPFC were observed in the acute and partially remitted groups. In contrast, the correlations in the HC and AN-R groups were only weak and not significant. The interaction between the left dlPFC and the vmPFC, however, demonstrated a relatively uniform correlation across all groups, with significant positive correlations and moderate to large effect sizes. This suggests that the right dlPFC and the vmPFC may be particularly engaged in a collaborative process in the acute and partially remitted groups, while the interaction between the left dlPFC and the vmPFC was relatively consistent across all groups and does not qualify as potential AN biomarker.

Upon examination of the REX-extracted data of the ROIs during reward anticipation and their interaction with the wanting and effort measures, a notable finding was the significant negative correlation of relatively strong effect size observed between the right dlPFC and exerted effort in the AN-A group. Furthermore, in the AN-A group a trend towards a significant moderate negative correlation was observed between the right dlPFC and subjective wanting ratings. A comparable pattern emerges with regard to the correlation between left dlPFC and both measurements of wanting. While the correlation is not statistically significant, a trend towards a negative correlation with a moderate effect size between left dlPFC and wanting and effort is observed exclusively in the AN-A group.

These outcomes suggest that hyperactivity of the dlPFC may exert an influence on the subjective evaluation of reward and the exerted effort during reward anticipation. As the activation of the dlPFC increases, the difference in ratings between high and low rewards in the AN-A group

decreases for both implicit and explicit wanting. This is in line with previous research on AN, which attributes an inhibitory effect of the dlPFC on reward processes in anorexia nervosa (Brooks, 2011; Eddy et al., 2023; Ehrlich et al., 2015; Wierenga, 2015). Significant negative correlations and negative significant correlation trends were exclusively observed in the AN-A group. Consequently, it can be posited that the activity within the dlPFC (bilaterally) exerts influence over the implicit and explicit wanting measurements in the acute phase of AN only. Importantly, in individuals with partial or remitted conditions, a correlational influence of the dlPFC could no longer be detected. Additionally, the AN-A group showed a significant positive correlation between BMI and effort. During the acute phase of the illness, a lower BMI may be associated with reduced variability in effort in response to different reward levels. Such reduced variability might indicate diminished sensitivity to reward differences or altered motivational processes, potentially reflecting the greater severity of the disorder in individuals with lower body weight.

The lack of a significant correlation between EDI-2 total scores and activity in the predefined ROIs suggests that the activations in these two brain regions may not be associated with the current severity of symptoms. Alterations in the activity in the vmPFC or dlPFC may be more affected by the duration of the disorder or the initial timepoint of disease manifestation, rather than symptom severity. This is corroborated by evidence indicating that specific psychological disturbances in AN such as excessive cognitive restraint of appetite, which is linked to DLPFC activation, become more pronounced with the progression of the disorder (Treasure & Russel, 2011).

Explorative Whole-Brain Analysis

The results of the whole brain analysis across all groups (main effect of group) revealed two significant clusters. The first and largest cluster comprised regions of the motor, somatosensory, visual, auditory and linguistic cortex. These brain regions are responsible for perceiving and processing sensory input, as well as complex visual and auditory stimuli and information (Bear et al., 2020). These findings are likely a reflection of the experimental design, which included the use of visual cues (pictures) to announce rewards, the requirement for participants to read instructions, and the delivery of auditory cues via an intercom system operated by the experimenter.

In contrast, the second cluster comprises regions that are of particular interest in the context of the preceding theoretical considerations. Maximum activation in this cluster was observed in the left anterior orbital gyrus, which has been demonstrated to play a role in the processing of rewards and punishments, as well as in complex emotional and social behavior (Kringelbach & Rolls, 2004). Additionally, the anterior orbital gyrus has been implicated in decision-making (Du et al., 2019) and specifically in the processing of reward information to guide decision-making (Wallis, 2007). Furthermore, research by Öngür and Price (2000) has demonstrated that this area is involved in the

orbital network that receives sensory information related to food and eating. These findings may suggest that during the anticipation of rewards, different activation occurred in the groups in regions responsible for processing rewards and making decisions regarding rewards, which may point in the direction of altered reward processing and cognitive control mechanisms in AN. However, these differences were no longer visible between the groups, which could indicate a certain heterogeneity in the groups.

The within-group comparisons revealed that, particularly in the AN groups, clusters showing a regional maximum in the left postcentral gyrus were significantly activated in anticipation of a reward. This region was not found to be significantly activated in the within-group analysis of HC; a result that aligns with the findings of a meta-analysis conducted by Zhong et al. (2023). This meta-analysis revealed an increased activation of the postcentral gyrus in individuals with anorexia nervosa compared to HC in tasks involving a reward-related fMRI task. This area may indicate that individuals in the AN groups anticipate increased or altered processing of sensory input, potentially engaging with the physical sensations of food (e.g., a feeling of fullness or the general sensation of food in the body) before the actual ingestion of food. This may be experienced more intensely or sensitively than in healthy individuals. Otherwise, the remaining clusters showing elevated activation in the within-group comparisons across the four groups displayed a high degree of similarity. The peak activation of these clusters was predominantly observed in visual and motor areas (as indicated by the main group effect), which is likely due to the nature of the experimental design.

Limitations

The experimental paradigm by Chiappini et al. (2022) offers many advantages, however, there are numerous limitations regarding the sample, study setting, and the generalizability of the results, which should be carefully considered when interpreting the results.

One major limitation was the considerably small sample size and unequal participant number between the analyzed groups, which restricts the statistical power and generalizability of the findings. A larger sample would have provided more robust data and increased confidence in the conclusions of this thesis.

The age range of participants presented challenges due to varying individual developmental stages. Adolescents and young adults, who constituted the majority of the sample, are still undergoing significant neurological development, particularly in the prefrontal cortex. This brain region undergoes continued maturation into the third decade of life (Arain et al., 2013), which may account for variability in participants' responses to the reward tasks. Such developmental differences could potentially introduce confounding effects in the results, as individual brain development trajectories may influence task performance.

Moreover, the lengthy duration of the study (approximately around five hours) could have led to fatigue or decreased motivation, affecting the participants engagement and, consequently, the quality of the data collected in the trials.

Due to the demanding nature of the experimental setup, frequent intervention and interaction by the experiment leaders were necessary to ensure the experiment was executed accurately and validly. These interventions were crucial for addressing technical issues and ensuring the well-being and safety of the adolescent participants. However, this constant interaction may have introduced a social desirability bias. Participants may have altered their responses to align with what they believed the experiment leaders expected or desired, thus compromising the authenticity of the data.

The controlled hospital and laboratory setting did not accurately reflect real-world eating behaviors. Eating in a natural, everyday environment involves complex social and psychological factors that are difficult to replicate in a clinical or laboratory setting. Further, the participants consumed the milk stimuli in a supine position, which is incongruent with their natural habitus.

Additionally, the milk stimuli used in the experimental task were minimal and the administration of the stimuli via tubes was unnatural and, for some of the hospitalized participants may have evoked associations with probing, a procedure they may have undergone during previous or current hospitalization. Subsequently, the procedure may have also induced stress in some patients, an aspect that was not assessed in the present study but may have influenced the participants natural wanting responses. Therefore, the findings from this study might not be fully applicable to typical eating behaviors outside of a controlled environment.

In summary, while the study provides valuable insights into anorexia nervosa, these limitations highlight the need for cautious interpretation of the results and suggest areas for improvement in future research. Addressing these issues could enhance the validity and applicability of findings in understanding and treating anorexia nervosa.

Summary and Future Directions

The study concentrated on altered processes of cognitive control and reward processing, with a particular focus on the functions of the dlPFC and the vmPFC during the anticipation of reward. Although the primary hypotheses were not confirmed, the descriptive data, correlative analyses and explorative brain analyses yielded valuable insights.

First, no significant group differences were identified in explicit and implicit wanting within this sample. Furthermore, the non-significant post-hoc between and within group tests of activation of the dlPFC and vmPFC indicate that reward and cognitive control processes are not affected to the same extent at this age as in adult AN patients.

However, a main effect of group was observed in clusters of the dlPFC, indicating a difference in activation between any of the groups that might potentially be more pronounced in larger and more homogeneous subgroups. In addition, the descriptive data (explicit and implicit) suggest that the acutely affected patients and those still in partial remission had fewer variations in the perception of reward intensity than the healthy or remitted comparison groups. Moreover, the findings indicate that a higher synchronicity between right and left dlPFC might represent a biomarker for AN at all stages of the disease, including remission. The study revealed potential interactions between the right dlPFC and the vmPFC in both acute and partially remitted patients during reward anticipation. In addition, the study showed that in acute patients, the activity of the bilateral dlPFC was more strongly associated with both aspects of reward processing-namely incentive salience and cognitive incentives-than in other disease states or in HC. Since most of these findings are supported only by trends rather than significant statements, and causality cannot generally be inferred from correlational data, further research and larger sample sizes are needed to fully capture the complexity of the disease mechanisms.

Future studies should concentrate on the age- and disease duration-related aspects of potential hyperactivation of the prefrontal cortex in AN to determine which factors contribute to the observation that the dlPFC is not yet as extensively engaged in the processing of reward and control mechanisms in the context of food rewards among individuals in the younger age group compared to adults. It may be beneficial to divide the sample into different age groups or to analyze the duration of the illness in order to draw conclusions about potential age effects or changes in dlPFC activity in the context of chronicity of AN.

Additionally, it could be advantageous to include other eating disorders in a comparison at the neuronal level. For instance, individuals with binge-eating disorder are positioned at the opposite end of the control spectrum as represented by the impulse control model by Brooks et al. (2012). They are characterized by impaired impulse control and excessive eating behaviors, which are likely to reflect opposing patterns in control and reward mechanisms compared to individuals with AN. Similarly, a comparison between individuals with AN and individuals with obesity could also provide further valuable insights into the contrasting neural processes that are operating.

Regarding study design, it would be advantageous to provide real food instead of milk or increase the quantity, thereby creating a more naturalistic setting. Additionally, it is important to use an alternative method of food administration to ensure that no association with a feeding situation involving a nasogastric tube arises for patients who are familiar with this procedure, whether in an acute or remitted state. Further, the unnatural eating situation may have induced stress in the participants, which may have biased the wanting. Future research should consider incorporating an evaluation of participants' stress level as an additional variable.

The inclusion of both high- and low-calorie foods in the study could prove beneficial, as it would allow researchers to examine how patients with active AN respond to varying caloric content, in addition to different levels of perceived reward. This approach could help to distinguish whether alterations in brain activity or behavioral responses are more influenced by the actual caloric value of the food or by the subjective perception of reward value. By comparing foods with different caloric contents, future research could gain insights into the underlying mechanisms of reward processing and caloric sensitivity in anorexia nervosa. The negative correlation between implicit and explicit wanting ratings and activity in the right and left dlPFC in the acute anorexia group, as identified by correlation analyses, suggests that these regions may be potential targets for rTMS. Previous studies have shown that rTMS can effectively normalize eating decisions in adults, leading to more balanced choices and increased inclusion of high-fat less healthy foods (Camus et al., 2009; Dalton et al., 2020; Muratore et al., 2021). Building on this research, future studies could explore the use of TMS of the dlPFC in younger patients to enhance variability in their evaluation of different reward levels, aiming to improve the flexibility of reward processing and support more balanced eating behaviors. The reciprocal interaction between the right dlPFC and vmPFC in the anticipation of food rewards was particularly evident in the AN-A and AN-PR groups. This neural interplay could be similarly targeted with rTMS to gain a deeper understanding of the specific role these regions play in cognitive, motivational and emotional processes in individuals with AN.

In conclusion, this study provides valuable insights into the cognitive control and reward mechanisms associated with food intake in adolescent patients with AN. Contrary to previous research suggesting enhanced cognitive control and altered reward systems in adult AN patients, the findings of this thesis indicate that such mechanisms are not present in adolescent AN patients. However, the correlations between neural activity, clinical data, and behavioral data suggest that, as the disease progresses, patterns of neural activity in adolescent patients may increasingly resemble those of adult patients. To address these discrepancies, future research should investigate the neural and behavioral mechanisms underlying anorexia nervosa in greater detail to enhance understanding of the disorder and provide a foundation for developing novel treatment approaches.

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List of Figures

List of Tables

List of Abbreviations

AAL3	Automated Anatomical Labeling
AKH	Allgemeines Krankenhaus Wien
AN	Anorexia Nervosa
AN-A	Acute Anorexia Nervosa patients
ANOVA	Analysis of Variance
AN-PR	Partially Remitted Anorexia Nervosa patients
AN-R	Remitted Anorexia Nervosa patients
BMI	Body Mass Index
BOLD	Blood Oxygen Level Dependent
DICOM	Digital Imaging and Communications in Medicine
dlPFC	Dorsolateral Prefrontal Cortex
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EMG	Electromyography
fMRI	Functional Magnetic Resonance Imaging
HC	Healthy Controls
ICD-11	International Classification of Diseases, 11th Revision
MNI	Montreal Neurological Institute
MVC	Maximum Voluntary Contraction
NA	Nucleus Accumbens
NifTI	Neuroimaging Informatics Technology Initiative
PFC	Prefrontal Cortex
REX	Region Extraction Tool
ROI	Region of Interest
SPM	Statistical Parametric Mapping
TMS	Transcranial Magnetic Stimulation
vmPFC	Ventromedial Prefrontal Cortex
VTA	Ventral Tegmental Area

Appendix

Abstract (EN)

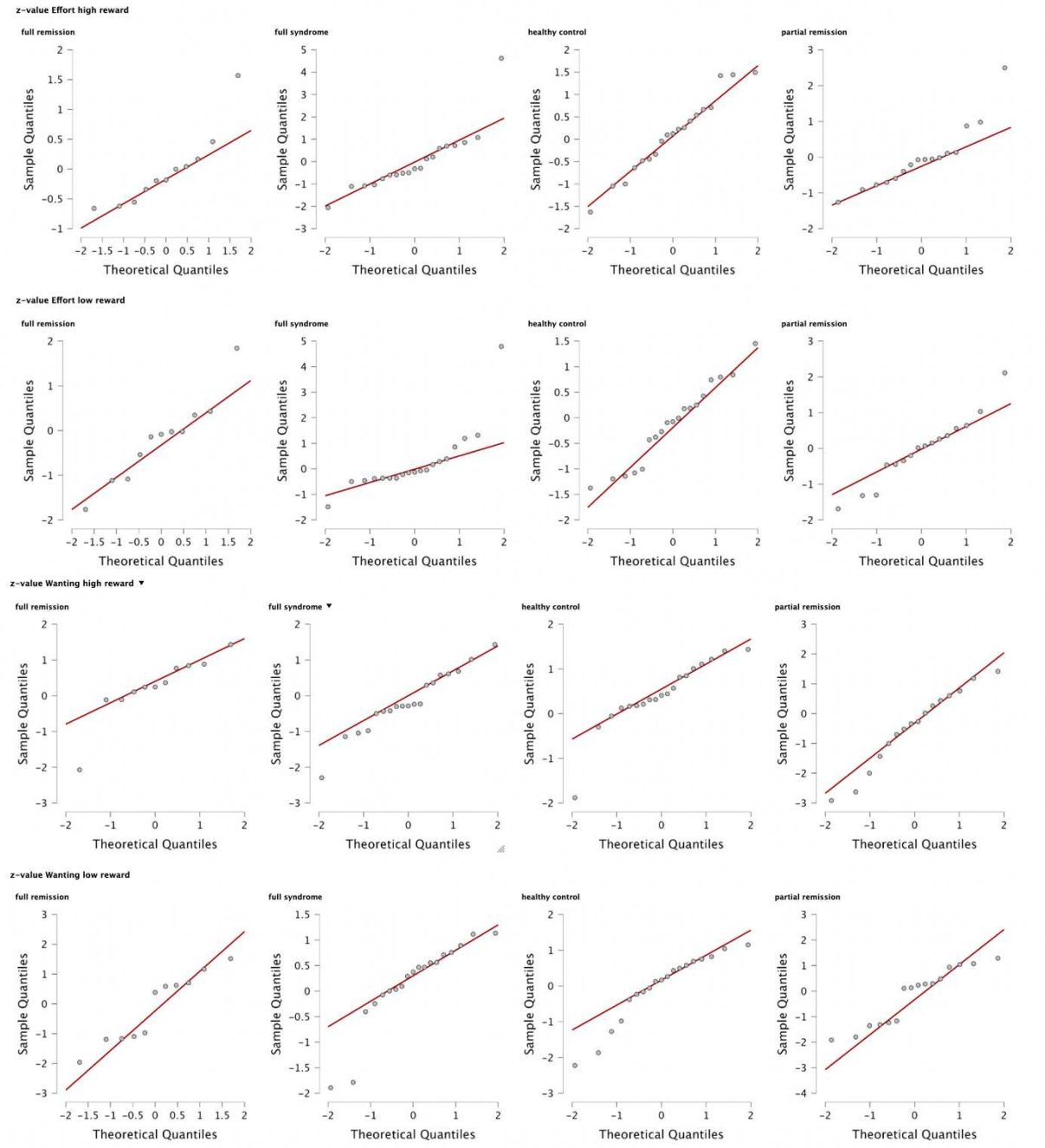
Anorexia nervosa (AN) is a severe eating disorder characterized by extreme food restriction, distorted body image and intense fear of gaining weight or becoming fat. While it has been proposed that enhanced cognitive control over eating behavior and altered reward processing constitute underlying mechanisms in adults with anorexia nervosa (AN), it remains elusive how these mechanisms manifest during adolescence. In this study, the focus is on two brain regions closely associated with these mechanisms, the dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC), investigating their roles in reward anticipation using an fMRI paradigm with real food consumption. 65 adolescent female participants, including those in the acute stage of AN, in partial and full remission, as well as HC, anticipated low and high food rewards based on their personal taste preferences. Region of interest analyses for the dlPFC and vmPFC were performed and explicit and implicit food wanting data was collected. Additionally, correlational analyses were conducted to investigate the relationships between neuroimaging findings, behavioral data and clinical measures of symptom severity. The results revealed no significant differences between groups in dlPFC or vmPFC activity during food reward anticipation, nor in explicit or implicit measures of food wanting. The correlation analysis revealed links within the groups between dlPFC and vmPFC activity, clinical data on symptom severity and implicit and explicit food wanting. Contrary to previous research highlighting heightened cognitive control and altered reward systems in adult patients with AN, these findings suggest that such mechanisms are not present in adolescents with AN. Preliminary correlational evidence indicates that as the disease progresses, adolescents' behavioral and neural patterns may increasingly align with those observed in adults.

Abstract (DE)

Anorexia nervosa (AN) ist eine schwere Essstörung, die durch extreme Nahrungseinschränkung, ein verzerrtes Körperbild und starke Angst vor Gewichtszunahme oder Übergewicht gekennzeichnet ist. Während bei erwachsenen AN PatientInnen eine verstärkte kognitive Kontrolle des Essverhaltens und eine veränderte Belohnungsverarbeitung als zugrundeliegende Mechanismen angenommen werden, ist bisher unklar, wie und ob sich diese Mechanismen in der Adoleszenz manifestieren. Der Schwerpunkt dieser Untersuchung liegt auf zwei Hirnregionen, die in engem Zusammenhang mit Belohnungs- und Kontrollmechanismen stehen: dem dorsolateralen präfrontalen Kortex (dlPFC) und dem ventromedialen präfrontalen Kortex (vmPFC). Die Rolle dieser Regionen wurde mithilfe eines experimentellen fMRT-Paradigmas während der Antizipation von Nahrung untersucht. 65 weibliche, jugendliche Teilnehmerinnen im akuten, partiellen und voll remittierten Stadium der AN (restriktiver Subtyp), sowie gesunde Kontrollpersonen, wurden mit niedrigen und hohen Nahrungsmittelbelohnungen auf der Grundlage ihrer persönlichen Geschmackspräferenzen konfrontiert. Es wurden Analysen der Gehirnaktivität im dlPFC und des vmPFC durchgeführt und Daten zum expliziten und impliziten Verlangen nach Nahrung erhoben. Des Weiteren wurden Korrelationsanalysen durchgeführt, um die Beziehungen zwischen den erhobenen Daten der Gehirnaktivität, den behavioralen Daten und den klinischen Daten der Symptomschwere zu untersuchen. Die Ergebnisse der vorliegenden Untersuchung weisen darauf hin, dass sich die dlPFC- und die vmPFC-Aktivität während der Antizipation von Nahrung, sowie die expliziten und impliziten Parameter des Nahrungsmittelverlangens zwischen den Gruppen nicht signifikant unterscheiden. Die Korrelationsanalyse wies innerhalb der einzelnen Gruppen Zusammenhänge zwischen der dlPFC- und vmPFC-Aktivität, den klinischen Daten zum Schweregrad der Symptome und dem impliziten und expliziten Verlangen nach Nahrung auf. Im Gegensatz zu früheren Untersuchungen, die eine erhöhte kognitive Kontrolle und veränderte Belohnungssysteme bei erwachsenen AN PatientInnen postulierten, deuten diese Ergebnisse darauf hin, dass eine Veränderung dieser Mechanismen bei jugendlichen AN PatientInnen nicht vorhanden ist. Die Korrelationsergebnisse lassen vermuten, dass sich die behavioralen und neuronalen Muster von jugendlichen AN PatientInnen mit fortschreitender Erkrankung zunehmend an die bei erwachsenen AN PatientInnen beobachteten Muster angleichen könnten.

Figure A1

Quantile-Quantile Plots for all Groups x Reward Level x Measurement



Note: These Q-Q plots enable the visualization of deviations from normal distribution of the data. One point indicates one measurement. When the data points are aligned with the diagonal line, it suggests a normal distribution of the data. In contrast, systematic deviations indicate potential deviations.

Table A1

Correlational Matrices between Behavioral, Clinical and Neuroimaging Data within the Groups (AN-A, AN-R, AN-PR, HC)

AN-A group

			Spearman's rho	p	Lower 95% CI	Upper 95% CI
Effort	–	Wanting	0.649**	0.003	0.277	0.852
Effort	–	R dlPFC	−0.585**	0.008	−0.821	−0.179
Effort	–	L dlPFC	−0.382	0.107	−0.712	0.088
Effort	–	vmPFC	−0.380	0.109	−0.711	0.090
Effort	–	EDI-2 total score	−0.109	0.666	−0.548	0.377
Effort	–	BMI	0.560*	0.013	0.142	0.809
Wanting	–	R dlPFC	−0.425	0.071	−0.737	0.037
Wanting	–	L dlPFC	−0.358	0.133	−0.699	0.115
Wanting	–	vmPFC	0.007	0.980	−0.449	0.460
Wanting	–	EDI-2 total score	0.079	0.754	−0.402	0.527
Wanting	–	BMI	0.292	0.225	−0.187	0.659
R dlPFC	–	L dlPFC	0.475*	0.041	0.027	0.765
R dlPFC	–	vmPFC	0.663**	0.003	0.299	0.859
R dlPFC	–	EDI-2 total score	0.013	0.961	−0.456	0.477
R dlPFC	–	BMI	−0.229	0.346	−0.619	0.251
L dlPFC	–	vmPFC	0.472*	0.043	0.023	0.763
L dlPFC	–	EDI-2 total score	−0.011	0.967	−0.476	0.458
L dlPFC	–	BMI	−0.298	0.215	−0.663	0.180
vmPFC	–	EDI-2 total score	0.273	0.271	−0.222	0.657
vmPFC	–	BMI	−0.139	0.571	−0.558	0.337
EDI-2 total score	–	BMI	−0.149	0.556	−0.576	0.342

* p < .05, ** p < .01, *** p < .001

AN-R group

			Spearman's rho	p	Lower 95% CI	Upper 95% CI
Effort	–	Wanting	0.836**	0.003	0.475	0.956
Effort	–	R dlPFC	−0.255	0.451	−0.741	0.408
Effort	–	L dlPFC	0.036	0.924	−0.576	0.623
Effort	–	vmPFC	0.173	0.614	−0.477	0.700
Effort	–	EDI-2 total score	0.245	0.468	−0.416	0.737
Effort	–	BMI	−0.491	0.129	−0.843	0.154
Wanting	–	R dlPFC	−0.218	0.521	−0.723	0.439
Wanting	–	L dlPFC	0.027	0.946	−0.582	0.617
Wanting	–	vmPFC	0.209	0.539	−0.447	0.719
Wanting	–	EDI-2 total score	−0.236	0.485	−0.732	0.424
Wanting	–	BMI	−0.509	0.114	−0.850	0.131
R dlPFC	–	L dlPFC	0.709*	0.019	0.190	0.918
R dlPFC	–	vmPFC	0.327	0.327	−0.339	0.775
R dlPFC	–	EDI-2 total score	0.064	0.860	−0.558	0.639
R dlPFC	–	BMI	0.627*	0.044	0.044	0.892
L dlPFC	–	vmPFC	0.764**	0.009	0.302	0.935
L dlPFC	–	EDI-2 total score	0.100	0.776	−0.532	0.660
L dlPFC	–	BMI	0.273	0.418	−0.391	0.750
vmPFC	–	EDI-2 total score	0.027	0.946	−0.582	0.617
vmPFC	–	BMI	−0.191	0.576	−0.710	0.462
EDI-2 total score	–	BMI	0.009	0.989	−0.594	0.606

* p < .05, ** p < .01, *** p < .001

Note: R dlPFC: Right Dorsolateral Prefrontal Cortex Activity, L dlPFC: Left Dorsolateral Prefrontal Cortex Activity, vmPFC: Ventromedial Prefrontal Cortex Activity.

AN-PR group

			Spearman's rho	p	Lower 95% CI	Upper 95% CI
Effort	–	Wanting	0.805***	< .001	0.515	0.930
Effort	–	R dlPFC	−0.029	0.917	−0.518	0.473
Effort	–	L dlPFC	−0.074	0.788	−0.549	0.438
Effort	–	vmPFC	−0.168	0.534	−0.612	0.358
Effort	–	EDI-2 total score	0.015	0.961	−0.485	0.507
Effort	–	BMI	−0.258	0.335	−0.668	0.273
Wanting	–	R dlPFC	−0.096	0.725	−0.565	0.420
Wanting	–	L dlPFC	−0.172	0.524	−0.615	0.354
Wanting	–	vmPFC	−0.324	0.221	−0.706	0.205
Wanting	–	EDI-2 total score	−0.013	0.961	−0.506	0.486
Wanting	–	BMI	−0.129	0.634	−0.587	0.392
R dlPFC	–	L dlPFC	0.838***	< .001	0.586	0.942
R dlPFC	–	vmPFC	0.694**	0.004	0.302	0.885
R dlPFC	–	EDI-2 total score	0.162	0.549	−0.363	0.609
R dlPFC	–	BMI	−0.187	0.488	−0.625	0.340
L dlPFC	–	vmPFC	0.706**	0.003	0.323	0.890
L dlPFC	–	EDI-2 total score	0.085	0.755	−0.429	0.557
L dlPFC	–	BMI	−0.244	0.361	−0.660	0.286
vmPFC	–	EDI-2 total score	−0.229	0.391	−0.651	0.300
vmPFC	–	BMI	−0.218	0.417	−0.644	0.311
EDI-2 total score	–	BMI	−0.041	0.879	−0.526	0.464

* p < .05, ** p < .01, *** p < .001

HC group

			Spearman's rho	p	Lower 95% CI	Upper 95% CI
Effort	–	Wanting	0.540*	0.018	0.114	0.799
Effort	–	R dlPFC	−0.246	0.310	−0.630	0.235
Effort	–	L dlPFC	0.172	0.480	−0.306	0.581
Effort	–	vmPFC	−0.228	0.346	−0.618	0.252
Effort	–	EDI-2 total score	0.032	0.900	−0.441	0.492
Effort	–	BMI	0.209	0.390	−0.271	0.606
Wanting	–	R dlPFC	0.190	0.437	−0.290	0.593
Wanting	–	L dlPFC	−0.098	0.689	−0.529	0.373
Wanting	–	vmPFC	−0.326	0.173	−0.680	0.150
Wanting	–	EDI-2 total score	0.086	0.735	−0.397	0.531
Wanting	–	BMI	0.129	0.598	−0.345	0.551
R dlPFC	–	L dlPFC	0.113	0.644	−0.359	0.540
R dlPFC	–	vmPFC	0.312	0.194	−0.166	0.671
R dlPFC	–	EDI-2 total score	−0.188	0.454	−0.602	0.305
R dlPFC	–	BMI	0.058	0.815	−0.407	0.499
L dlPFC	–	vmPFC	0.572*	0.012	0.159	0.815
L dlPFC	–	EDI-2 total score	−0.267	0.285	−0.652	0.229
L dlPFC	–	BMI	0.208	0.392	−0.272	0.605
vmPFC	–	EDI-2 total score	−0.148	0.558	−0.575	0.343
vmPFC	–	BMI	−0.083	0.737	−0.517	0.386
EDI-2 total score	–	BMI	−0.357	0.146	−0.706	0.132

* p < .05, ** p < .01, *** p < .001

Note: R dlPFC: Right Dorsolateral Prefrontal Cortex Activity, L dlPFC: Left Dorsolateral Prefrontal Cortex Activity, vmPFC: Ventromedial Prefrontal Cortex Activity.

Table A2

Components of the largest activated cluster of the main group effect in whole brain activation analysis

Working Dir : /Users/patriciadorner/Desktop/Final results/Anova Wanting PM
Main effect group
Labels : *volume summary (labels and percentages per cluster)*

x,y,z mm	Label	% Cluster	Nb Vx Cluster	% Label	Nb Vx Label
26 -94 12	OUTSIDE	20.10	75826	0.00	0
	Postcentral_R	3.86	75826	76.48	3823
	Postcentral_L	3.77	75826	73.38	3892
	Parietal_Inf_L	2.55	75826	79.12	2447
	Precentral_R	2.45	75826	54.90	3381
	Temporal_Mid_R	2.36	75826	40.55	4409
	SupraMarginal_R	2.19	75826	84.30	1974
	Calcarine_L	2.08	75826	69.93	2258
	Precentral_L	2.07	75826	44.58	3526
	Occipital_Mid_L	2.05	75826	47.53	3265
	Frontal_Mid_2_R	1.99	75826	31.03	4860
	Temporal_Mid_L	1.92	75826	29.42	4942
	Cerebelum_6_L	1.82	75826	81.64	1694
	Parietal_Sup_L	1.62	75826	59.32	2065
	Calcarine_R	1.59	75826	64.80	1861
	Supp_Motor_Area_R	1.56	75826	49.98	2371
	Rolandic_Oper_R	1.52	75826	86.33	1331
	Fusiform_L	1.46	75826	47.81	2309
	Lingual_R	1.43	75826	47.17	2300
	Lingual_L	1.43	75826	51.65	2095
	Temporal_Inf_L	1.36	75826	32.25	3200
	SupraMarginal_L	1.35	75826	81.53	1256
	Temporal_Inf_R	1.30	75826	27.66	3557
	Fusiform_R	1.30	75826	39.00	2518
	Temporal_Sup_R	1.28	75826	30.82	3141
	Temporal_Sup_L	1.26	75826	41.77	2296
	Occipital_Inf_L	1.18	75826	95.01	941
	Frontal_Inf_Oper_R	1.12	75826	60.90	1399
	Rolandic_Oper_L	1.08	75826	82.59	988
	Supp_Motor_Area_L	1.04	75826	36.70	2147
	Precuneus_L	0.97	75826	20.92	3528
	Occipital_Mid_R	0.96	75826	34.80	2098
	Parietal_Sup_R	0.95	75826	32.31	2222
	Insula_L	0.94	75826	38.16	1858
	Insula_R	0.93	75826	39.83	1770
	Putamen_R	0.92	75826	65.91	1062
	Precuneus_R	0.92	75826	21.35	3265
	Cerebelum_4_5_L	0.92	75826	61.78	1125
	Cuneus_L	0.91	75826	45.50	1521
	Occipital_Inf_R	0.91	75826	69.87	989
	Putamen_L	0.91	75826	68.77	999
	Frontal_Inf_Oper_L	0.91	75826	66.18	1038
	Cerebelum_Crus1_L	0.85	75826	24.78	2603
	Parietal_Inf_R	0.82	75826	46.17	1345
	Cuneus_R	0.82	75826	43.47	1424
	Frontal_Mid_2_L	0.81	75826	13.69	4507
	Cingulate_Mid_R	0.80	75826	27.37	2203
	Cerebelum_6_R	0.73	75826	30.97	1795
	Caudate_R	0.72	75826	63.53	861
	Frontal_Sup_2_R	0.62	75826	9.13	5126
	Vermis_4_5	0.59	75826	67.07	665
	Caudate_L	0.55	75826	51.93	805
	Cerebelum_4_5_R	0.50	75826	44.13	861
	Cingulate_Mid_L	0.50	75826	19.47	1941
	Occipital_Sup_L	0.45	75826	25.18	1366
	Frontal_Inf_Tri_R	0.45	75826	15.76	2151
	Vermis_6	0.42	75826	84.91	371
	Occipital_Sup_R	0.40	75826	21.51	1413
	ParaHippocampal_L	0.36	75826	27.61	978
	Frontal_Sup_2_L	0.35	75826	5.46	4870
	Thal_VL_L	0.34	75826	98.49	265
	Frontal_Inf_Tri_L	0.33	75826	9.92	2529
	Thal_VL_R	0.32	75826	93.05	259
	Pallidum_R	0.28	75826	76.07	280
	Heschl_R	0.27	75826	80.72	249
	Frontal_Inf_Orb_2_R	0.26	75826	22.31	874
	Amygdala_L	0.26	75826	88.18	220
	Pallidum_L	0.25	75826	64.16	293
	Amygdala_R	0.23	75826	71.37	248

table shows first local maximum per cluster.

Height threshold: F = 5.29, p = 0.001 (1.000)
Extent threshold: k = 0 voxels, p = 1.000 (1.000)
Expected voxels per cluster, <k> = 10.044
Expected number of clusters, <c> = 20.34
Expected false discovery rate, <= NaN

Degrees of freedom = [4.0, 61.0]
Smoothness FWHM = 11.3 11.0 10.5 {mm} = 5.6 5.5 5.2 {voxels}
Search vol: 1502712 cmm; 187839 voxels; 1088.9 resels
Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 161.76 voxels)
Page 1

Working Dir : /Users/patriciadorner/Desktop/Final results/Anova Wanting PM
Main effect group
Labels : *volume summary (labels and percentages per cluster)*

x,y,z mm	Label	% Cluster	Nb Vx Cluster	% Label	Nb Vx Label
	ParaHippocampal_R	0.23	75826	15.11	1132
	OFCant_R	0.22	75826	25.62	648
	Heschl_L	0.22	75826	73.33	225
	Angular_L	0.18	75826	11.34	1173
	Thal_VPL_L	0.16	75826	71.86	167
	OFCmed_R	0.15	75826	18.20	621
	Thal_VPL_R	0.15	75826	70.00	160
	Temporal_Pole_Sup_R	0.14	75826	8.07	1338
	Temporal_Pole_Sup_L	0.13	75826	7.39	1285
	OFClat_R	0.12	75826	48.40	188
	OFCpost_R	0.12	75826	15.69	561
	Paracentral_Lobule_L	0.11	75826	6.15	1349
	Thal_PuM_L	0.11	75826	43.24	185
	Cingulate_Post_L	0.09	75826	15.55	463
	Thal_VA_L	0.09	75826	83.33	84
	Hippocampus_R	0.09	75826	6.98	946
	Cerebelum_3_R	0.08	75826	29.95	207
	Thal_VA_R	0.07	75826	67.95	78
	OFCpost_L	0.06	75826	8.64	567
	Thal_MDm_L	0.06	75826	39.32	117
	Hippocampus_L	0.06	75826	4.72	932
	Thal_IL_R	0.06	75826	84.31	51
	Olfactory_R	0.06	75826	14.58	288
	Thal_IL_L	0.05	75826	80.39	51
	ACC_sup_R	0.05	75826	7.13	533
	Angular_R	0.05	75826	2.17	1752
	Thal_MDl_L	0.05	75826	83.33	42
	Thal_MDm_R	0.04	75826	25.98	127
	Thal_MDl_R	0.04	75826	83.33	36
	Cerebelum_3_L	0.04	75826	22.06	136
	Thal_PuA_L	0.04	75826	80.00	35
	Thal_PuA_R	0.04	75826	79.41	34
	Thal_PuL_L	0.03	75826	88.89	27
	Thal_PuM_R	0.03	75826	13.48	178
	Thal_LP_R	0.03	75826	85.71	28
	Olfactory_L	0.03	75826	6.53	291
	Thal_LGN_R	0.02	75826	37.50	48
	Thal_LP_L	0.02	75826	72.00	25
	Vermis_7	0.02	75826	8.25	194
	SN_pc_R	0.02	75826	45.45	33
	Thal_PuL_R	0.02	75826	51.85	27
	Cingulate_Post_R	0.02	75826	3.88	335
	SN_pr_R	0.02	75826	20.00	60
	SN_pr_L	0.01	75826	20.75	53
	Thal_AV_R	0.01	75826	44.00	25
	Thal_AV_L	0.01	75826	57.89	19
	Temporal_Pole_Mid_L	0.01	75826	1.46	755
	Red_N_R	0.01	75826	15.52	58
	SN_pc_L	0.01	75826	21.88	32
	Thal_PuI_R	0.01	75826	18.18	33
	Thal_MGN_R	0.01	75826	42.86	14
	Frontal_Sup_Medial_L	0.01	75826	0.20	2992
	Vermis_3	0.01	75826	1.75	228
	Paracentral_Lobule_R	0.01	75826	0.48	836
	OFCmed_L	0.00	75826	0.55	550
	Frontal_Inf_Orb_2_L	0.00	75826	0.37	814
	LC_R	0.00	75826	40.00	5
	ACC_pre_R	0.00	75826	0.31	648
	Thal_MGN_L	0.00	75826	11.11	18
	Cerebelum_Crus1_R	0.00	75826	0.08	2648
	Temporal_Pole_Mid_R	0.00	75826	0.17	1187
	Red_N_L	0.00	75826	1.75	57
	Rectus_R	0.00	75826	0.13	745
	Frontal_Sup_Medial_R	0.00	75826	0.05	2134
-22 44 -14	OFCant_L	40.00	230	20.77	443
	OFClat_L	17.83	230	20.81	197
	Frontal_Mid_2_L	15.22	230	0.78	4507
	Frontal_Inf_Orb_2_L	10.00	230	2.83	814
	OUTSIDE	6.96	230	0.00	0

table shows first local maximum per cluster.

Height threshold: F = 5.29, p = 0.001 (1.000)
Extent threshold: k = 0 voxels, p = 1.000 (1.000)
Expected voxels per cluster, <k> = 10.044
Expected number of clusters, <c> = 20.34
Expected false discovery rate, <= NaN

Degrees of freedom = [4.0, 61.0]
Smoothness FWHM = 11.3 11.0 10.5 {mm} = 5.6 5.5 5.2 {voxels}
Search vol: 1502712 cmm; 187839 voxels; 1088.9 resels
Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 161.76 voxels)

Working Dir : /Users/patriciadorner/Desktop/Final results/Anova Wanting PM
Main effect group
Labels : *volume summary (labels and percentages per cluster)*

x,y,z mm	Label	% Cluster	Nb Vx Cluster	% Label	Nb Vx Label
	Frontal_Sup_2_L	3.91	230	0.18	4870
	OFCmed_L	3.48	230	1.45	550
	OFCpost_L	2.61	230	1.06	567
-12 -46 20	OUTSIDE	88.24	17	0.00	0
	Cingulate_Post_L	11.76	17	0.43	463
52 -56 44	Parietal_Inf_R	93.55	31	2.16	1345
	Angular_R	6.45	31	0.11	1752
-46 28 -18	OFCpost_L	41.67	24	1.76	567
	OFClat_L	33.33	24	4.06	197
	Temporal_Pole_Sup_L	20.83	24	0.39	1285
	OUTSIDE	4.17	24	0.00	0
32 4 50	Frontal_Mid_2_R	93.33	15	0.29	4860
	Frontal_Sup_2_R	6.67	15	0.02	5126
12 32 -24	OFCmed_R	100.00	2	0.32	621
-54 18 -8	OUTSIDE	64.71	17	0.00	0
	Frontal_Inf_Orb_2_L	29.41	17	0.61	814
	Temporal_Pole_Sup_L	5.88	17	0.08	1285
14 -50 52	Precuneus_R	50.00	4	0.06	3265
	OUTSIDE	50.00	4	0.00	0
-52 -60 30	Angular_L	100.00	16	1.36	1173
0 -30 74	Paracentral_Lobule_R	72.73	11	0.96	836
	OUTSIDE	27.27	11	0.00	0
8 -28 80	Paracentral_Lobule_R	100.00	5	0.60	836
-10 -10 -36	OUTSIDE	100.00	4	0.00	0
-20 24 -18	OFCpost_L	50.00	4	0.35	567
	OFCmed_L	50.00	4	0.36	550
4 -48 18	Precuneus_R	100.00	2	0.06	3265
6 -36 76	Paracentral_Lobule_R	100.00	5	0.60	836
20 20 38	Frontal_Sup_2_R	100.00	2	0.04	5126
48 -52 34	Angular_R	100.00	2	0.11	1752
14 42 50	Frontal_Sup_2_R	100.00	2	0.04	5126
56 14 -22	Temporal_Pole_Mid_R	66.67	3	0.17	1187
	Temporal_Pole_Sup_R	33.33	3	0.07	1338
-38 22 18	Frontal_Inf_Tri_L	100.00	2	0.08	2529
68 -20 -4	Temporal_Sup_R	66.67	3	0.06	3141
	Temporal_Mid_R	33.33	3	0.02	4409
12 -42 26	Cingulate_Post_R	100.00	1	0.30	335
14 16 -16	Rectus_R	100.00	1	0.13	745
-4 -26 38	Cingulate_Mid_L	100.00	1	0.05	1941
16 -46 18	OUTSIDE	100.00	1	0.00	0
0 -24 -10	OUTSIDE	100.00	2	0.00	0

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Height threshold: F = 5.29, p = 0.001 (1.000)
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Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 161.76 voxels)