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Neural Correlates of Obsessive-Compulsive Symptoms in Anorexia Nervosa: A Voxel-Based Morphometry Study Across Illness Stages

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## Introduction and Theoretical Background

### Anorexia Nervosa

Anorexia nervosa (AN) is a complex mental health disorder that involves a combination of behavioral, psychological, and neurobiological factors. AN is classified as an eating disorder (ED) characterized by severe restriction of food intake, leading to significantly low body weight, an intense fear of gaining weight, and a distorted perception of body shape and weight, often with a lack of recognition of the seriousness of the condition (DSM-5; American Psychiatric Association, 2013). The significantly low body weight (Criterion A) required for AN diagnosis is typically assessed using the Body Mass Index (BMI). While for adults a value below 18.5 is considered indicative of significantly low weight, for children and adolescents, an age-adjusted BMI below the fifth percentile is used as the threshold. AN can be classified into three statuses: acutely ill (AI-AN), when all diagnostic criteria are met; partial remission (PR-AN), where some criteria (Criterion A) are no longer met but others such as intense fear of weight gain (Criterion B) or distorted body image (Criterion C) still persist; and full remission (FR-AN), where none of the criteria have been met for a sustained period. Further, AN can be categorized into two subtypes: the restricting type (AN-R) and the binge-eating/purging type (AN-BP). In AN-R weight loss is accomplished mainly through dieting, fasting, and/or excessive exercise, whereas AN-BP is characterized by episodes of binge eating or purging behavior. Purging in context of EDs refers to self-induced vomiting or the abuse of medications such as laxatives (DSM-5; American Psychiatric Association, 2013).

AN is most prevalent among adolescent females. According to van Eeden et al. (2021), lifetime prevalence of AN is up to 4% in females, and it is approximately 0.3% in males. Over the last decades, there has been in increase in the incidence rate in the high risk group of 15-19 year old girls (Smink et al., 2012). AN generally emerges in middle to late adolescence, with the peak age of onset between 15 and 19 years. However, recently, AN cases have been increasing among children and mid- to late-life individuals (Bulik et al., 2005; Micali et al., 2013). The course of the illness varies greatly: for some, it follows a chronic pattern with periods of relapse, remission, and crossover to other EDs such as bulimia nervosa (BN), while others experience a single episode and achieve full recovery after treatment. Approximately 50% of individuals with AN can be considered fully recovered after five years (Attia, 2010). However, the mortality in AN remains one of the highest among mental disorders (Arcelus et al., 2011).

Over their lifetime, individuals with AN show high rates of psychiatric comorbidities, with up to 73% experiencing at least one additional mental disorder (Salbach-Andrae et al., 2008). The most frequently observed comorbid disorders are mood disorders, particularly major depressive disorder (up to 64% of cases), at least one anxiety disorder (up to 72%), and obsessive-compulsive disorder (OCD) (up to 62%) (Godart et al., 2002, 2007). However, it needs to be noted that these comorbidity rates are highly variable across studies and depend on factors such as the severity of AN, age, subtype, and study methodology (Godart et al., 2002, 2007; O'Brien & Vincent, 2003).

The neurobiological mechanisms underlying the development and maintenance of AN remain poorly understood, limiting the development of new effective pharmacological and psychological treatments (Kaye, 2008). In response to the need of more effective interventions, transdiagnostic approaches have been proposed to investigate shared characteristics across different mental disorders (Conn et al., 2024; Godier & Park, 2014). Gaining a deeper understanding of these common features may help develop new theoretical models and treatments for AN. Compulsivity is one of these features and is suggested to be central to AN (Godier & Park, 2014). The following paragraph will explore obsessive-compulsive symptoms and their relevance in AN.

**Obsessive-Compulsive Behavior and Its Role in Anorexia Nervosa**

Compulsivity represents a tendency to perform repetitive behaviors in a habitual manner, even when they are inappropriate to the situation and persist despite lacking a clear connection to the overall goal, often resulting in negative consequences (Dalley et al., 2011). In individuals with AN, compulsive behavior manifests as patterns of control, avoidance, and perfectionism focused on weight loss. They particularly exhibit these behaviors in the form of excessive exercise to control shape and weight (Dalle Grave et al., 2008), along with rigid meal planning, and ritualistic eating patterns such as cutting the food into specific numbers of pieces (Steinglass & Walsh, 2006). Obsessing represents the cognitive aspect and refers to the tendency to experience intrusive or recurrent thoughts centered on a specific topic (Abramowitz et al., 2009).

Obsessive-compulsive behaviors in AN are often linked to those seen in OCD, with obsessions in AN typically centered on food, eating, weight, and body shape. These obsessions often cause distress or anxiety. Therefore, compulsive acts, such as excessive exercise or ritualistic eating, are performed to prevent or reduce distress or anxiety that is triggered by these thoughts (Steinglass & Walsh, 2006). Obsessive-compulsive symptoms are

highly prevalent in individuals with AN. For instance, Halmi et al. (2003) reported that the majority of AN patients had lifetime obsessive or compulsive symptoms, with almost similar rates in both AN subtypes: AN-R (68%) and AN-BP (79.1%).

### *The Role of Obsessive-Compulsive Behavior as a Risk Factor for Anorexia Nervosa*

Obsessive-compulsive traits, such as perfectionism and rigidity, have been identified as important psychological risk factors that may contribute to the development of AN. These traits may not only serve as predictors or contributors to the onset of AN but also as factors that help maintain the disorder over time (Anderluh et al., 2003). A review by Lilenfeld et al. (2006) also identified traits like perfectionism and obsessive-compulsive personality disorder (OCPD) as risk factors for AN, though these findings are primarily based on retrospective studies. In family studies elevated rates of OCPD in relatives of AN patients were found, suggesting that OCPD and AN may share a genetic basis (Lilenfeld et al., 1998). Furthermore, adolescent OCD has been found to significantly increase the risk of developing AN in early adulthood, with OCD emerging as a unique predictor of later AN (Buckner et al., 2010). Micali et al. (2011) showed a link between childhood OCD and the later development of AN, reporting that 12.7% of adolescents diagnosed with childhood OCD subsequently developed an ED, most commonly AN. Obsessive-compulsive symptoms, particularly obsessing (intrusive and repetitive thoughts) are closely linked to core AN symptoms, such as drive for thinness, purging, and body dissatisfaction. These associations were found regardless of weight status, indicating that obsessive thinking may be a key psychological risk factor underlying AN pathology (Levinson et al., 2019). As I explore further, it is also essential to examine how obsessive-compulsive symptoms might influence the outcome of AN once it has developed.

### *The Role of Obsessive-Compulsive Behavior for Anorexia Nervosa Outcome*

Obsessive-compulsive behaviors have been associated with significant clinical challenges, including poorer outcomes, higher risk of relapse, and increased chronicity. Although in a study by (Zubieta et al., 1995) initial levels of obsessive-compulsive symptoms did not predict long-term outcomes in individuals with AN, at follow-up higher levels of obsessive-compulsive symptoms were linked to lower body weight and more severe AN symptoms. This indicates that the influence of obsessive-compulsive symptoms may vary with illness stage and may be associated with a poorer outcome. Further, Strober et al. (1997) found that compulsive exercise at the time of discharge was associated with poorer long term

outcome and significantly predicted earlier relapse. Moreover, they found that extreme compulsivity in daily routines significantly prolonged the time to recovery. In individuals with AN, those with comorbid OCD were found to have an earlier onset and longer duration of illness compared to those without comorbid OCD (Milos et al., 2002). These results suggest that OCD with its characteristics may contribute to the chronic course of AN and act as a maintaining factor. A review examining the impact of OCPD traits, including perfectionism, on AN found that these traits are associated with a poorer prognosis and may influence the course and outcome of the disorder (Crane et al., 2007). Furthermore, using a lifetime diagnostic interview for retrospective assessment, researchers found that AN patients with childhood obsessive-compulsive personality traits such as perfectionism, rigidity, and inflexibility experienced longer durations of underweight status, severe food restriction, and excessive exercising. These findings suggest that such traits may contribute to the persistence and restrictive nature of the symptoms (Anderluh et al., 2009).

***The Course of Obsessive-Compulsive Behaviors in Anorexia Nervosa***

The development and course of obsessive-compulsive behavior in AN is complex, often emerging early in the illness and persisting throughout its progression. Pollice et al. (1997) investigated the relationship between obsessive-compulsive symptoms, measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), and the illness state in AN. Obsessive-compulsive symptoms were most severe in the underweight state, reduced after short-term weight restoration, and further reduced after long-term weight restoration. Importantly, long-term weight restored AN patients still exhibited higher levels of these eating disorder related obsessive-compulsive thoughts and behaviors than healthy controls (HC), indicating that such symptoms may persist even after physical recovery. Further, Srinivasagam et al. (1995) compared long-term recovered AN patients to HC on the Y-BOCS. They found significantly higher obsessive-compulsive scores in the recovered AN patients, but these were significantly lower than those they recalled having during their illness. Moreover, when they compared recovered and acutely ill AN patients, similar types of obsessive-compulsive symptoms – mainly concerns with symmetry, exactness, ordering, and cleanliness – were reported. Those who were acutely ill experienced these symptoms with greater intensity and impairment, suggesting that while the content of obsessive concerns remains stable across the illness, weight loss exacerbates severity. Similarly, Sysko et al. (2005) found that even after weight restoration, AN patients continue to exhibit persistent preoccupation with food, anxiety about weight gain, and difficulties with controlling food

intake and the urge to exercise. They suggested the continued presence of these thoughts and behaviors play a significant role in the chronic nature of AN and in the high relapse and mortality rates associated with the disorder. Holtkamp et al. (2005) extended previous research by demonstrating, through long-term follow-up at 3, 7, and 10 years, that even fully recovered AN patients continue to exhibit elevated obsessive-compulsive symptoms, supporting the view that these may represent enduring trait characteristics. Furthermore, a study that used the Obsessive-Compulsive Inventory-Revised (OCI-R) to assess obsessive-compulsive symptoms in individuals at different stages of AN found that the OCI-R total score was highest in acutely ill inpatients and then followed by weight restored community AN patients. Conversely to previous studies, they did not find a significant difference between weigh-restored patients and HC (Roberts et al., 2011). Supporting this, another study found a tendency for decreased Y-BOCS scores in AN patients from hospital admission to discharge (Mattar et al., 2012). Meule and Voderholzer (2022) confirmed this trend by demonstrating significantly lower obsessive-compulsive symptoms (OCI-R score) in AN patients after inpatient treatment, which did not primarily target these symptoms. Notably, the effect sizes in this study were small. However, it remains unclear whether the persistent obsessive-compulsive symptoms reflect a stable psychobiological trait or a state-dependent consequence of the illness. Additionally, it is uncertain which features of the symptoms are related to malnutrition and which existed prior to, or develop independently of AN.

### *Obsessive-Compulsive Behavior: Trait or State?*

This uncertainty has led to a central question in understanding obsessive-compulsive behavior in AN: are these behaviors primarily trait-dependent, state-dependent, or an interplay of both? Godier and Park (2014) proposed an etiological model of AN with which they tried to explain the development of compulsive starvation. Specifically, they proposed a self-reinforcing vicious cycle, in which obsessive-compulsive symptoms and malnutrition interact dynamically. Initially, weight loss behaviors are goal-directed and positively reinforced by dopamine-related reward mechanisms. Over time, repeated engagement with these behaviors strengthens their neural pathways, making them increasingly habitual and less dependent on reward. Starvation itself biologically enhances the rewarding and stress-related mechanisms that sustain these behaviors. Ultimately, weight loss behavior becomes compulsive. In short, the authors proposed that the reinforcement of starvation and goal-directed system abnormalities play a causal role in the onset of AN (Godier & Park, 2014). This theory indicates that obsessive-compulsive behavior in the context of food and eating is

rather state-dependent. Lloyd et al. (2017) extended this proposed model by adding anxiety to the emergence of compulsive starvation and other symptoms of AN.

Supporting the trait-perspective, Treasure and Schmidt's (2013) cognitive interpersonal model of AN highlights how certain premorbid obsessive-compulsive traits, such as being sensitive to detail and order, act as inherited vulnerabilities. These traits are linked to differences in brain circuits, specifically the cortico-striatal circuits, which can make individuals more prone to developing rigid habits. When dieting begins, these individuals might follow rules very strictly. As starvation progresses, brain function is further affected, intensifying the focus on dieting and making it even harder to break, thereby contributing to a cycle that maintains the disorder.

Building on this complexity, an important question remains: are obsessive-compulsive symptoms in AN an inherent part of the disorder, a direct result of starvation and malnutrition, or a combination of both? The Minnesota Starvation Experiment by Keys et al. (1950), as reviewed by Kalm and Semba (2005), informs this debate by showing how, under conditions of food restriction, healthy individuals developed obsessive-compulsive behaviors related to food and eating. This suggests the possibility that obsessive-compulsive behavior in AN may, at least in part, be secondary to starvation.

Clarifying whether these symptoms are driven by temporary physiological states, enduring traits, or a combination of both remains a central challenge – and one that needs to be further addressed. As conducting studies that examine obsessive-compulsive symptoms before, during, and after an episode of AN would be very complex, another possibility to address the state vs. trait debate is comparing these symptoms in AN with those in related clinical disorders, such as OCD.

### *Obsessive-Compulsive Behavior in Anorexia Nervosa and Obsessive-Compulsive Disorder: Overlap and Distinction*

In examining compulsivity in AN and its etiology, it is important to disentangle obsessive-compulsive symptoms that are part of AN from those suggesting comorbid OCD. This distinction helps in accurate diagnosis and identifies the unique neural mechanisms behind obsessive-compulsive behavior in AN. Understanding this symptom overlap is important because many individuals with AN show obsessive-compulsive behaviors similar to, but not exactly the same as those seen in OCD (Serpell et al., 2002). Many AN patients have elevated scores in questionnaires assessing obsessive-compulsive behavior (Bastiani et al., 1996; Halmi et al., 2003; Kaye et al., 1992). The comparison of AN patient's total scores

on the Yale-Brown Obsessive Compulsive Scale with those of OCD patients suggests a similar functional impairment from the obsessive-compulsive symptoms in both disorders. However, OCD patients showed a wider variety of OCD symptoms, while AN patients tended to show more symptoms that are related to symmetry and order (Bastiani et al., 1996). AN patients did not differ from OCD patients in the frequency of symmetry and somatic obsessions or in ordering and hoarding compulsions but showed significantly lower frequencies in all other categories. These partially overlapping obsessions and compulsions suggest that both disorders may share neural-behavioral mechanisms (Halmi et al., 2003).

Further, the two disorders differ according to how these obsessive-compulsive symptoms are perceived. In AN, behaviors like food restriction and thoughts of food and weight are typically ego-syntonic, as these behaviors and thoughts feel right or even necessary to the person, and they will be denied being abnormal. Whereas in OCD, symptoms are typically ego-dystonic, as individuals recognize their obsessions and compulsions as irrational, distressing, and unwanted, yet feel powerless to stop them (Bastiani et al., 1996; Kaye et al., 1992).

## Neuroimaging Findings in Anorexia Nervosa and Obsessive-Compulsive Disorder

### *Structural Brain Alterations in Anorexia Nervosa*

Multimodal neuroimaging and clinical research have increased the biological understanding of AN. However, the biological basis of its etiology remains unclear. Structural brain alterations, particularly changes in gray matter volume (GMV), have emerged as a consistent feature of AN, offering insights into is pathophysiology (Alfano et al., 2020; Seitz et al., 2016; Su et al., 2021; Titova et al., 2013; Van den Eynde et al., 2012). Magnetic resonance imaging (MRI) is a technique to detect global and regional brain volume alterations, including gray matter (GM), white mater (WM) and cerebrospinal fluid (CSF). To compare concentrations of GM, WM, and CSF, a voxel-by-voxel technique known as voxel-based morphometry (VBM) is often employed (Ashburner & Friston, 2000). Although neuroimaging research in AN has grown over the past 20 years, the results have been heterogeneous and often difficult to replicate (King et al., 2018).

A meta-analysis by Titova et al. (2013) demonstrated a significant and large reduction in global GMV in AN patients compared to HC. This finding was further corroborated and expanded by Seitz et al. (2014), who investigated GMV alterations across various AN stages, including weight-restored individuals. This work reported that in acutely ill AN patients, a global GMV reduction of 5.6% was observed compared to HC. Importantly, this meta-

analysis also indicated a degree of reversibility: global GMV alterations improved after short-term restoration, and approached normalization after two to eight years of remission. Seitz et al. (2016) extended these findings from their previous meta-analysis and explored age-related differences in GMV alterations, hypothesizing that the developing brain of adolescent patients might react uniquely to starvation. They found that the global GMV loss of acutely ill adolescent AN patients was 2.5 times that of adult AN patients. Interestingly, this age-related difference was not apparent in the short-term weight-restoration stage. However, less is known about how these patterns manifest in sustained periods of recovery, as data on long-term weight-restored adolescent AN patients is scarce. Roberto et al. (2011) conducted a longitudinal study on adult AN patients, assessing global GMV before and after short-term weight restoration (defined as reaching 90% of ideal body weight). They observed a significant increase in global GMV with weight-restoration, although it remained lower than in HC. Conversely, Lázaro et al. (2013) did not observe any difference in global GMV between HC and adolescent short-term recovered AN patients who had achieved 85% of their standard BMI, suggesting potential variability in recovery pattern between adults and adolescent AN patients.

Studies examining regional GMV alterations in AN, including different subgroups and stages of recovery, have reported widespread but heterogenous changes. Meta-analyses have consistently identified GMV reductions in cortical and subcortical regions, such as the hypothalamus, left inferior parietal lobe, right lentiform nucleus, and right caudate (Titova et al., 2013); as well as the bilateral median cingulate cortex (extending into the anterior and posterior cingulate and supplementary motor area (SMA)), precuneus, cerebellum, and left middle occipital gyrus (Su et al., 2021; Zhang et al., 2018). These findings suggest that the cingulate cortex, cerebellum, and regions within the frontal, parietal, and occipital lobes are particularly affected in AN. While meta-analyses point to some consistent structural alterations, individual studies continue to report both overlapping and divergent patterns of regional GMV alterations.

Consistent findings implicate the frontal lobes, particularly prefrontal and motor-related areas. GMV reductions have been observed in the SMA and precentral gyrus, both involved in motor planning and body-related actions (Amianto et al., 2013; Friederich et al., 2012; Lyall et al., 2024; Tose et al., 2024). Changes in the superior and middle frontal gyri, critical for cognitive control and executive function, are also consistently observed (Lyall et al., 2024; Mishima et al., 2021; Nickel et al., 2018; Tose et al., 2024). Reductions of GMV in the orbitofrontal cortex (OFC), involved in reward processing and decision-making (Lyall et

al., 2024), and the frontal operculum, implicated in gustatory and sensorimotor integration (Joos et al., 2010; Tose et al., 2024), further highlight the impact of AN on brain structure. Alterations across subregions have also been observed in the anterior cingulate cortex (ACC), which plays a central role in emotional regulation and conflict monitoring (Friederich et al., 2012; Joos et al., 2010). The insula, critical for interoception and bodily awareness, also shows consistent GMV reductions (Brooks et al., 2014; Curzio et al., 2020; Friederich et al., 2012; Tose et al., 2024), which is suggested to relate to disruptions in hunger signals and distorted body image. In the parietal lobe, reduced GMV has been found in regions involved in body representation and self-perception, including the right supramarginal gyrus (Amianto et al., 2013), inferior and superior parietal cortex (Lyall et al., 2024; Tose et al., 2024), postcentral gyrus (Lyall et al., 2024; Tose et al., 2024), precuneus (Fonville et al., 2014; Joos et al., 2010; Lyall et al., 2024; Mishima et al., 2021; Tose et al., 2024), angular gyrus (Mishima et al., 2021; Tose et al., 2024), and the left temporoparietal cortex (Joos et al., 2010). In the temporal lobe, observed reductions include the fusiform gyrus (Amianto et al., 2013; Brooks et al., 2011; Tose et al., 2024), which is critical for face and body perception, as well as the middle and superior temporal gyri, which are involved in social cognition, language, and multisensory processing (Lyall et al., 2024; Mishima et al., 2021; Titova et al., 2013), and parahippocampal gyrus (Brooks et al., 2011). Subcortical alterations include reduced GMV in the thalamus, central to sensory relay, (Amianto et al., 2013; Lyall et al., 2024; Tose et al., 2024), and hippocampus which is central to memory and emotional regulation (Amianto et al., 2013; Friederich et al., 2012; Lyall et al., 2024; Nickel et al., 2018). Furthermore, reduced volume in the putamen, involved in reward processing, and in the amygdala, relevant for emotional processing, were found (Bernardoni et al., 2016; Friederich et al., 2012). Additionally, GMV reductions in the cerebellum have been identified across multiple studies, which may reflect deficits in motor coordination and cognitive-emotional integration (Amianto et al., 2013; Brooks et al., 2011; Fonville et al., 2014; Joos et al., 2010; Mishima et al., 2021; Tose et al., 2024). Finally, changes in the occipital lobe, particularly in the inferior occipital gyrus and occipital-fusiform gyrus (Amianto et al., 2013; Fonville et al., 2014), may be linked to visual processing abnormalities, which could underlie altered body image perception in AN.

While most studies report decreased regional GMV, only few studies report regional GMV increase in AN compared to HC, including the left OFC, right insula (Frank et al., 2013), right dorsolateral prefrontal cortex (DLPFC) (Brooks et al., 2011), and the right paracentral lobule (Amianto et al., 2013). Given the heterogeneity of these findings in acutely

ill AN patients, focusing on alterations that persist even after weight restoration could help identify enduring neural traits of AN.

While most neuroimaging studies compare acutely ill AN patients with HC, there is only limited research of whether these regional structural brain alterations change with weight restoration or persist. As mentioned above, global GMV increases with weight restoration to almost normal levels (Seitz et al., 2016), whereas some regional GMV alterations persist even with weight restoration (Friederich et al., 2012; Joos et al., 2011). Many studies distinguish between short-term and long-term recovered AN patients, though previous studies did not use a unified criteria to define different stages. In short-term recovered adolescent AN patients, Bomba et al. (2015) re-evaluated one month following weight restoration (approximately at one year follow-up) and observed that regional GMV normalized. A study by Castro-Fornieles et al. (2009), on adolescents after 7 months of follow-up, showed that many brain areas normalized, though some smaller regions in the right temporal lobe and SMA still exhibited differences compared to HC. Similarly, Mainz et al. (2012) observed substantial regional GMV recovery in adolescents between their admission and discharge (on average, 4 months later). Only small clusters of reductions remained, mainly in premotor, frontal, and parietal regions, indicating relatively fast progress with weight gain.

When examining long-term recovered AN patients, only Wagner et al. (2006) reported no regional GMV differences in adult AN patients who had been free of any AN symptoms and had normal weight for at least one year, suggesting reversibility. However, other studies indicate more persistent reductions. Joos et al. (2011) reported persistent regional GMV reductions in previously severely ill adults who had been remitted for over five years, specifically in the precunues, but also in the ACC, frontal operculum, and parietal lobe. Consistently, Friederich et al. (2012) reported decreased regional GMV in weight-restored adult AN patients who had been symptom-free normal-weighted for at least 12 months compared to HC, particularly in the ACC, SMA, and inferior frontal operculum. Additionally, Mühlau et al. (2007) reported persistent decreases in GMV in the bilateral ACC in long-term recovered adults, defined by a BMI above 17 and regular menses for over 6 months. Notably, they used a more lenient definition of long-term recovery compared to the over 12-month criterion used in other studies. Oliva et al. (2020) observed decreased GMV in the inferior frontal gyrus in adults recovered for at least one year. While the specific regions identified vary across the studies, the consistent finding of persistent regional GMV reductions in long-term recovered patients suggests that these structural alterations may represent more trait-like

neural characteristics of AN, rather than changes that are driven by the acute underweight state.

### *Neural Correlates of Obsessive-Compulsive Behavior in Obsessive-Compulsive Disorder*

Since, to date, there is no literature specifically addressing the neural basis of obsessive-compulsive symptoms in AN, findings from OCD research may offer a point of reference for understanding potential neural mechanisms.

Neuroimaging studies of OCD consistently reveal neurobiological alterations, pointing to the cortico-striatal-thalamo-cortical (CSTC) circuits as a core pathway. Specifically, researchers have traditionally viewed dysfunctions in key regions of these circuits – including the OFC, anterior cingulate cortex (ACC), striatum, and thalamus – as important in mediating obsessive-compulsive behaviors (Piras et al., 2015; Tang et al., 2016; Yang et al., 2024). Early VBM studies, such as that by Atmaca et al. (2007) on treatment-naïve OCD patients, observed decreased GMV in the bilateral OFC and near-significant reduction in the left ACC, alongside increased GMV in the bilateral thalamus. These structural changes correlated with symptom severity, with Y-BOCS scores showing positive correlation with the left thalamus GMV and a negative correlation with bilateral OFC GMV. Further reinforcing the involvement of these key regions, Rotge et al. (2008) conducted a review of functional magnetic resonance imaging (fMRI) studies on OCD and found consistent activations in the OFC and ACC during symptom provocation, highlighting their role in obsessive-compulsive symptoms. The authors also observed activation in the dorsal frontoparietal network, including the DLPFC, which they suggested might reflect patients´ attempts to resist obsessive thoughts during symptom provocation. Subsequent structural analyses, such as the study of treatment-naïve OCD patients by Hou et al. (2013) expanded these findings by showing GMV increases in the left caudate, left thalamus, and posterior cortex, alongside GMV reductions in the bilateral OFC, left ACC, and left inferior frontal gyrus. These structural alterations were accompanied by abnormal functional integration within the CSTC circuits and the default mode network (DMN). Specifically, increased functional connectivity was observed in the CSTC circuit. Left thalamic GMV reductions correlated positively with the Y-BOCS total score, suggesting a link to clinical severity. More recently, research has increasingly pointed to the involvement of regions outside the CSTC circuits. A review of VBM studies by Piras et al. (2015) confirmed consistent abnormalities across two key components of the CSTC circuit: the “affective” fronto-striatal loop and the “executive” dorsolateral prefrontal-striatal loop, encompassing the lateral, frontal, and

posterior cortices. The review highlighted a consistent pattern of cortical volume reduction, increased deep GM structures at the limbic level, and hyperconnectivity between the thalamus, OFC, and ACC. They also identified structural alterations in various frontal regions and in posterior parts of the brain, including the parietal, temporal, and occipital lobes. These findings support the role of a broader fronto-striatal dysregulation in obsessive-compulsive behavior. More recently, multimodal neuroimaging techniques have advanced this understanding. A recent meta-analysis by Yang et al. (2024) identified increased GMV in the bilateral thalamus and the striatum. Decreased GMV was observed in the medial prefrontal cortex (mPFC), ACC, bilateral insula, left inferior frontal gyrus, and left precentral gyrus. Furthermore, Y-BOCS scores were positively correlated with decreased functional activity in the caudate nucleus, and illness duration correlated with bilateral mPFC and ACC GMV, suggesting an association between neural alteration and clinical expression and chronicity of obsessive-compulsive symptoms.

It is important to acknowledge the potential for neural corelates to differ across developmental stages. A meta-analysis by Hu et al. (2017) addressed this by investigating such age-specific distinctions in GMV alterations between youths and adults with OCD. While both groups consistently exhibited prefrontal-striatal abnormalities, unique age-related patterns were observed, suggesting that neurobiological presentations can vary developmentally. In summary, the literature on OCD consistently points to GMV alterations in brain regions that are involved in the CSTC circuits but also points to some other cortical and subcortical areas. However, findings can sometimes be inconsistent due to the wide symptom variety in OCD and differing medication statuses across studies.

The discovery of affected regions in OCD, particularly in the CSTC circuit, and their overlap with other compulsivity-related disorders, such as AN, suggest potential transdiagnostic mechanisms. For example, brain regions such as the ACC, putamen, and thalamus have also shown alterations in AN patients, potentially contributing to the persistence of obsessive-compulsive eating behaviors (Su et al., 2021; Tose et al., 2024). This overlap in neural findings has led to the assumption of shared neural mechanisms underlying obsessive-compulsive behavior in AN and OCD (Steinglass & Walsh, 2006). The following paragraph will further delve into these hypothesized neural mechanisms as they may underpin obsessive-compulsive behavior in AN.

**Potential Neural Mechanisms Underlying Obsessive-Compulsive Behavior in Anorexia Nervosa**

While research on obsessive-compulsive-specific brain alterations in AN is limited, in OCD key regions consistently associated with obsessive-compulsive behavior, including the OFC, ACC, striatal regions were identified (Hou et al., 2013; Piras et al., 2015; Rotge et al., 2009). Steinglass & Walsh (2006) proposed a cognitive neuroscience hypothesis that emphasizes the role of abnormal habit learning, mediated by the CSTC circuit, in the maintenance of AN. Their framework suggests that initial goal-directed weight loss behaviors become compulsive habits, persisting besides negative consequences. Godier and Park (2014) further expanded on this by suggesting a theoretical model of compulsivity in AN. This model suggested imbalances within these cortico-striatal circuits, where the striatal component (caudate nucleus) is suggested to drive compulsive behaviors, while the prefrontal component (OFC) exerts inhibitory control. Imbalances in this system, whether through hyperactivity or hypoactivity of either bottom-up striatal drive and top-down prefrontal control, may contribute to compulsive behaviors (Godier & Park, 2014). Despite evidence of structural and functional abnormalities in these regions in AN (Su et al., 2021; Titova et al., 2013; Zhang et al., 2018), their specific role in obsessive-compulsive behavior remains largely unclear. In an fMRI study, Rothemund et al. (2011) investigated the relationship between obsessive thoughts and compulsive behavior and regional brain activation in severely ill AN patients during high and low caloric food stimulation. They found that the degree of obsessive thoughts was related to the activation of several brain regions within the frontal-striatal circuits, whereas the degree of compulsive behavior was related to the deactivation of these circuits during both food conditions. These results underscore the important role of the fronto-striatal circuit in obsessive-compulsive symptoms in AN. However, most neuroimaging AN research has focused on general brain alterations rather than specifically investigating obsessive-compulsive-related mechanisms. This highlights a critical research gap: while the established neuroimaging findings in OCD provide a logical framework, further research is needed to explore whether structural alterations in the cortico-striatal circuit are directly associated with obsessive-compulsive behavior in AN. Specifically, it remains unclear whether these neural changes are state-dependent or persist as a stable risk factor for the disorder.

**Research Gap**

Research consistently shows elevated prevalence and severity of obsessive-compulsive symptoms in individuals with AN compared to HC. While obsessive-compulsive symptoms show a state-dependent pattern, being most prominent during acute illness and decreasing with weight-restoration, symptoms remain elevated in weight-restored AN patients compared to HC, suggesting a trait-like vulnerability (Holtkamp et al., 2005; Pollice et al., 1997; Roberts et al., 2011; Srinivasagam et al., 1995). This contradicting evidence is part of the ongoing state-trait debate of obsessive-compulsive behavior in AN, which has implications for understanding symptom etiology and optimizing treatment strategies. Elevated obsessive-compulsive symptoms in AN are clinically relevant because they appear as underlying psychological risk factors of AN pathology (Levinson et al., 2019) and negatively impact recovery, leading to poorer outcome and earlier relapse (Crane et al., 2007; Milos et al., 2002; Strober et al., 1997; Zubieta et al., 1995). Therefore, identifying whether obsessive-compulsive symptoms are state-dependent or reflect a stable trait is important for developing targeted interventions and improving long-term prognosis. Despite their clinical relevance, existing studies addressing obsessive-compulsive symptoms across AN illness stages face some methodological and conceptual limitations. Previous studies comparing obsessive-compulsive symptoms across different stages of AN recovery have been heterogeneous in their study designs and the operationalizations of recovery stages. For example, some studies compared groups at admission and discharge (Mattar et al., 2012; Meule & Voderholzer, 2022), while others contrasted different recovery stages with HC (Holtkamp et al., 2005; Srinivasagam et al., 1995), and some conducted within group comparisons (Pollice et al., 1997; Roberts et al., 2011). There is a lack of consistent criteria for defining these stages, which makes it difficult to compare findings and draw conclusions about the state-trait nature of obsessive-compulsive symptoms. This methodological inconsistency highlights an unmet need for research that establishes and utilizes standardized and distinct recovery stages to facilitate comparability across studies.

Despite growing evidence of structural GMV alterations in AN, the precise nature, progression, and long-term implications of these changes remain incompletely understood. While global GMV alterations in the acute stage of AN are well documented and appear to normalize with weight-restoration (Titova et al., 2013; Seitz et al., 2016), regional GMV alterations often persist even when weight is restored (Asami et al., 2022; Friederich et al., 2012; Joos et al., 2011; Roberto et al., 2011). While meta-analyses point to some consistent structural changes, mainly GMV reductions, findings from individual studies show a

divergent pattern of changes in heterogeneous brain regions (Titova et al., 2013; Zhang et al., 2018; Su et al., 2021). Most existing VBM studies compare acutely ill AN patients with HC, with relatively limited investigation of GMV changes during and after weight restoration. Furthermore, recovery is a heterogeneous process and distinctions in partially remitted and fully remitted stages are rarely addressed in neuroimaging research. This limits our understanding of how GMV changes over the process of weight restoration, which could inform about trait-like components and further contribute to the state-trait debate, as persisting GMV alterations in weight-restored stages could reflect a trait. Given the variability of findings across studies, further research is needed to replicate and clarify patterns of GMV alterations across different recovery stages of AN.

To summarize, previous studies have shown elevated obsessive-compulsive symptoms and structural GMV alterations in individuals with AN. However, to my knowledge, no study to date has investigated how these two aspects may be interrelated across different stages of illness and recovery, including acute, partially remitted, and fully remitted AN patients, as well as HC. By integrating behavioral and neuroimaging data across these stages, a novel perspective on how obsessive-compulsive symptoms and brain structure may be interrelated and how these patterns shift with recovery could be detected. This would help disentangle the state vs. trait aspects for both obsessive-compulsive symptoms and GMV alterations and potentially reveal underlying neural mechanisms of symptom and GMV alteration persistence. While speculative, identifying brain regions consistently associated with obsessive-compulsive symptoms across stages could eventually inform treatment approaches. More broadly, this approach may support the development of stage-specific, personalized interventions. By addressing this gap — the lack of research examining the association of GMV and obsessive-compulsive symptoms across illness stages — this study aimed to contribute new insights into the neural underpinnings of symptom persistence and recovery in AN.

**Research Questions and Hypotheses**

The overall aim of my master's thesis was to investigate how obsessive-compulsive behaviors are associated with structural brain differences across different stages of AN patients, including acutely ill (AI-AN), partially remitted (PR-AN), fully remitted (FR-AN), and healthy controls (HC). More specifically, I examined (1) differences in obsessive-compulsive symptom severity, (2) differences in structural GMV, and (3) associations between obsessive-compulsive symptoms and GMV and how these associations vary across

illness stages. By examining both behavioral and neuroimaging data, a particular focus was on how these patterns change from the acute phase through partial and full remission. Based on previous research, I formulated a set of confirmatory and exploratory hypotheses to address the following research questions:

RQ 1: How does obsessive-compulsive behavior differ between AN patients (acutely ill, partially remitted, fully remitted) and healthy controls?

- H1a: Acutely ill AN patients show higher levels of obsessive-compulsive symptoms (OCI-R score) compared to patients in partial remission, full remission, and healthy controls.
- H1b: AN patients in partial remission show higher levels of obsessive-compulsive symptoms (OCI-R score) compared to patients in full remission and healthy controls.
- H1c: AN patients in full remission show higher levels of obsessive-compulsive symptoms (OCI-R score) compared to healthy controls.

RQ 2: Are differences in obsessive-compulsive behavior associated with structural brain differences in AN patients?

- H2: Acutely ill, partially remitted, and fully remitted AN patients show altered GMV across the whole brain compared to healthy controls, after controlling for age and total intracranial volume (TIV).
- H3: Across all participants, obsessive-compulsive symptoms (OCI-R score) are associated with GMV variations across the whole brain, after controlling for age and TIV.
- H4: The association between OCI-R scores and GMV is different across all groups (acutely ill, partially remitted, fully remitted, and healthy controls), after controlling for age and TIV.

Hypotheses H1a, H1b, H1c, and H2 are confirmatory, based on prior literature and theoretical expectations, and are intended to replicate and extend previous findings. Hypotheses H3 and H4 are exploratory, aiming to investigate potential associations between obsessive-compulsive symptoms and GMV across the brain.

# Methods

## Study Design

The data used in this master's thesis were part of the "AN-BEL" cluster project, which is a cooperative research project of the University of Vienna and the Medical University of Vienna. The project uses a translational psychiatric approach and focuses on reward processing in AN. It includes various psychological assessments and both functional and structural MRI scans. For my master's thesis, only clinical data and structural MRI data were analyzed. In my analysis I used data that were collected between February 2022 and March 2025 within this larger research project.

The present study used a cross-sectional design to compare obsessive-compulsive symptoms and differences in GMV across different stages of AN (acutely ill, partially remitted, and fully remitted) and heathy controls. Additionally, associations between obsessive-compulsive symptoms and GMV variations were investigated across the whole sample and separately in each of the four groups.

## Participants

### *Power Analysis and Sample Size*

An a priori power analysis was conducted using G*Power (Faul et al., 2007) for the primary behavioral analysis, which involved comparing group differences in obsessive-compulsive symptoms scores (OCI-R). While several prior studies examining obsessive-compulsive symptoms in AN have predominantly used the Y-BOCS, only a few have employed the OCI-R. However, due to differences in study design, sample characteristics, definition of AN recovery stages, and reporting effect sizes, it remains inappropriate to directly apply those findings to the current analysis. Therefore, a conservative medium effect size (Cohen's $f = 0.25$) for a one-way analysis of variance (ANOVA) was assumed. This analysis indicated that a total sample size of 180 participants, with 45 per group, would be required to detect group differences with 80% power at an alpha level of .05.

However, the sample size for my master's thesis follows the recruitment plan of the "AN-BEL" project, which aimed to include 90 clinical participants (with $n = 30$ per AN subgroup) and 60 healthy controls, for a total of 150 participants. While this is smaller than the 45 participants per group suggested by the power analysis for the primary behavioral analysis, it was determined that proceeding with the "AN-BEL" project's plan is appropriate given the practical constraints and the overall goals of the study.

No power analysis was performed for the voxel-based morphometry (VBM) analyses. These analyses explored GMV differences among AN subgroups and HC and examined associations between GMV and obsessive-compulsive symptoms across participants. This approach is in line with previous neuroimaging studies in AN (Frank, 2013; Seitz et al., 2014). The current study aimed to align with common practice in the field, while maintaining methodological rigor through appropriate covariate control and statistical correction procedures, and by including the maximum number of participants available within the framework of the larger project.

### *Recruitment*

The participants (AN patients and HC) were recruited through social media advertisement (Facebook and Instagram), flyers, research participant platforms and lectures of the psychological research team in schools. Additionally, many of the AN patients, both in-patient or out-patient, were recruited through practitioners from the Department of Child and Adolescent Psychiatry at the Medical University of Vienna / Vienna General Hospital. Some of the AN patients were re-recruited as they have already participated in previous studies. As incentive participants received a voucher of 70 Euros after completing the psychological interviews, tests and scan.

### *Inclusion and Exclusion Criteria*

The inclusion criteria for the study were as follows: participants had to be female, between 12 and 30, possess sufficient German language skills, and provide written consent by themselves or through their legal guardians if under 18. For inclusion in the AN patient group, a current or past diagnosis of AN according to DSM-5 criteria was required. Once included, AN patients were further categorized into specific subgroups based on their current state of illness: acutely ill, partial remitted, and fully remitted. To be considered acutely ill, participants had to fulfil all diagnostic criteria according to the DSM-5 at the time of the study. Participants were assigned to the partially remitted group if they had a BMI above 18.5 and no longer restricted food intake, engaged in binge eating episodes, or vomited but still had a fear of weight gain or body image disturbances. Additionally, their total Eating Disorder Examination (EDE) score had to be within two standard deviations of the normal score, and they had to maintain this status for at least 3 months. To be considered fully remitted, participants had to reach a BMI above 19 or reach 85% of their ideal weight, with no food intake restriction, binge eating episodes, or vomiting. Unlike the partially remitted

group, they also had to be free of fear of weight gain and body image disturbances. Their total EDE score had to be within 1.5 standard deviations of the normal score, and this status had to be maintained for at least 12 months.

Healthy controls were required to be free from any psychiatric or neurological disorders, both current or in their past. Additional exclusion criteria for all participants included intellectual disabilities, psychotic or bipolar disorders, organic psychosyndrome, cardiovascular diseases, lung disorders, metabolic disorders, and pregnancy. Participants were also excluded based on MRI-related criteria. Specifically, those with claustrophobia or metal implants in their bodies, such as pacemakers, were not eligible for the study.

As of the time of writing this thesis, a total of 145 participants were enrolled in the study. Due to missing data across different measures and exclusion criteria, the number of participants included in each analysis varied. For the behavioral analysis of Hypothesis 1, 22 participants were excluded: 7 participants due to a current excluding psychiatric diagnosis and 17 due to missing data on the OCI-R questionnaire. For the VBM analysis of Hypothesis 2 and 3, additional 12 participants were excluded due to various reasons related to scan availability, including poor scan quality, technical issues, or participants opting out of the scanning procedure. Final sample sizes for each analysis are reported in the respective results sections.

**Procedure**

As described in the recruitment section above, there were several methods how participants learned about the study. Once prospective participants contacted the research team, they received a link to an online survey to test their eligibility and provide general information about the study. After they screened and found eligible, participants were invited to take part in the study. Via Mail they received further information about the testing procedures, and an appointment was scheduled. One week before the in-person appointment at the Medical University of Vienna, participants were asked to fill out several online questionnaires, including the OCI-R. They were also provided with a written consent form, which they were required to bring with them signed to the testing day. The in-person testing at the Medical University of Vienna was divided into two parts. The first part included various neurological assessments and a structured clinical interview. Additionally, only the AN participants completed the EDE interview, which was used to assess eating disorder symptoms and to determine subgroup allocation within the AN group. The second part of the session involved the experimental fMRI task, including a structural MRI. For the structural

MRI, participants lay for about 15 minutes in the scanner. After completing both parts of the study, participants were debriefed and received a voucher as compensation.

## Measurements

### *Eating Disorder Symptomatology*

To assess the current state of the illness for AN-subgroup allocation, eating disorder symptoms were assessed by using the German version of the Eating Disorder Examination (EDE) (Hilbert & Tuschen-Caffier, 2016). The EDE is a semi-structured clinical interview to assess the specific ED psychopathology in children and adults. The interview consists of four subscales: Restraint, Eating Concern, Weight Concern, and Shape Concern. The Restrained subscale measures the attempt to restrict food intake. The Eating Concern Scale assesses anxiety, guilt, and preoccupation with eating. The Weight Concern Scale captures concerns and dissatisfaction with body weight. The Shape Concern Scale measures worries and discomfort related to body shape. The EDE assesses the frequency and intensity of ED-specific behavior over the past 28 days, using a seven-point scale (0-6). A score of zero indicates the absence of eating disorder specific behavior, while a score of six indicates that the behavior was present daily or with extreme severity. It provides subscale scores and a total EDE score, with higher scores indicating greater psychopathology. The total score of the interview demonstrates good reliability (Cronbach's $\alpha$ of .93).

### *Obsessive-Compulsive Symptoms*

To assess obsessive-compulsive symptoms, a German version of the Obsessive-Compulsive Inventory-Revised (OCI-R) was used (Gönner et al., 2007). The OCI-R is a self-report questionnaire that assesses the major symptoms of OCD on six subscales: Washing, Checking, Ordering, Obsessing, Hoarding, and Neutralizing. It consists of 18 items that are rated on a 5-point Likert scale from 0 (not at all) to 4 (extremely). The items describe obsessive-compulsive symptoms in the form of self-reports and are rated according to the degree of impairment/distress they caused during the past month. The total score ranges from 0 to 72 and the subscale scores range from 0 to 12. Higher sum scores indicate higher obsessive-compulsive symptomatology. The OCI-R demonstrated good to excellent internal consistency, with Cronbach's alpha ranging from .76 to .95 for the total score and most subscales, while the Neutralizing subscale showed satisfactory reliability. The factor structure of the original English version was confirmed in the German sample (Gönner et al., 2008). The German version of the OCI-R exhibited good to excellent convergent validity and good

divergent validity, confirming it as a reliable and valid measure of obsessive-compulsive symptoms (Gönner et al., 2007).

### *Structural MRI Data Acquisition*

Structural MRI data were acquired using a 3T Siemens fit MRI whole body scanner (Siemens Healthineers, Erlangen, Germany), equipped with a 64-channel headcoil at the MR Center of Excellence, Medical University of Vienna. High-resolution T1-weighted anatomical images were obtained, using a magnetization-prepared two inversion time rapid gradient-echo (MP2RAGE) sequence with the following parameters: repetition time (TR) = 500 ms, echo time (TE) = 2.8 ms, flip angle = 4°/5°, field of view (FOV) = 256 × 216 × 160 mm, and voxel size = 1 × 1 ×1 mm.

## Data Analysis

Statistical analysis of descriptive and clinical data was performed using Statistical Package for Social Sciences (SPSS), version 30 (IBM Corp., 2020). The estimation of effect sizes was conducted using JASP (version 0.19.3) as SPSS did not provide these values directly. A significance level of $\alpha = .05$ was used in all analyses. Given the exploratory nature of the multiple regression analyses, a more liberal threshold was used, and uncorrected p-values are reported. Generative AI models (ChatGPT by Open AI and Google Gemini by Google) were used to help with statistical analyses and language refinement.

### *Statistical Analysis of Demographics*

Prior to addressing the main research questions, exploratory analyses were conducted to examine the demographic characteristics of the sample. Assumptions of normality and homogeneity of variances were assessed. While Levene's test indicated that the assumption of homogeneity of variances was met for both age and BMI, Shapiro-Wilk tests, showed that two of the four groups showed deviations from normality in these same analyses. Therefore, in addition to the standard one-way analysis of variance (ANOVA), a non-parametric Kruskal-Wallis test was also conducted to check for consistent results across methods. When the results converged, the standard ANOVA was used for reporting to ensure consistency and ease of interpretation, a common practice when robust analyses yield similar conclusions despite assumption violations (Field, 2024; Glass et al., 1972). When significant group differences were found, Tukey's Honestly Significant Difference (HSD) post-hoc tests were

performed for the ANOVA and Bonferroni-corrected pairwise comparisons were conducted for the non-parametric analyses to determine specific group differences.

### *Statistical Analysis of Hypothesis 1a, 1b, and 1c*

To examine research question 1 — whether compulsivity levels (OCI-R total score) differed between the four groups — I performed an ANOVA. Before that, I tested the assumptions of ANOVA. Normality was assessed using the Shapiro-Wilk test. Three of the four groups showed deviations from normality. Levene's test indicated that the assumption of homogeneity of variances was also violated. Due to these assumption violations, I additionally performed a robust ANOVA based on the Welch's test and a non-parametric Kruskal-Wallis test to check whether results were consistent across different methods. As the results were consistent across all three approaches, the standard ANOVA was chosen for primary reporting due to its broad interpretability and familiarity. Since the ANOVA was significant, post-hoc pairwise comparisons were conducted using Tukey's HSD test to determine specific group differences. No additional corrections for multiple comparisons were necessary, as the Tukey's HSD test already includes error control. In addition to significance testing, I reported Cohen's *d* effect sizes for each pairwise comparison, calculated using JASP (version 0.19.3). This allowed for an estimation of the magnitude of group differences.

As an exploratory check for potential confounding effects of age on obsessive-compulsive symptoms, an analysis of covariance (ANCOVA) was conducted. Group served as the fixed factor, OCI-R total scores as the dependent variable, and age as the covariate. For any significant main effects involving group as the fixed factor, pairwise comparisons of the estimated marginal means were performed using a Bonferroni adjustment to control for Type I error rate. Age was considered a confounder only if its inclusions substantially altered the significance or pattern of group differences observed in the original ANOVA. Because no such changes were observed, the standard ANOVA was retained for the main analysis to ensure consistency and interpretability.

### *MRI Scan Pre-Processing*

Prior to preprocessing, all T1-weighed images were visually inspected for motion and anatomical abnormalities. All images were of sufficient quality for further analysis. T1-weighted structural MRI data were pre-processed using the Computational Anatomy Toolbox (CAT12; http://dbm.neuro.uni-jena.de/cat/) implemented in Statistical Parametric Mapping

(SPM12; https://www.fil.ion.ucl.ac.uk/spm/) running under MATLAB R2023b (https://www.mathworks.com). The default voxel-based morphometry (VBM) preprocessing pipeline in CAT12 was used without modifications. All images were segmented into GM, WM, and CSF. Spatial normalization to Montreal Neurological Institute (MNI) space was performed using the integrated Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) registration, with modulation to preserve volume. The resulting GM segments were smoothed with an 8-mm full widths at half maximum (FWHM) Gaussian kernel to create a local weighted average of surrounding voxels. Additionally, total intracranial volumes (TIV) were computed for each subject using the CAT12 toolbox. Quality control included both automated sample homogeneity checks and image quality ratings provided by CAT12. All scans met quality criteria and were included in further analysis.

***Statistical Analysis of Hypothesis 2***

To test whether GMV differs between AI-AN, PR-AN and FR-AN patients compared to HC, a whole-brain voxel-wise analysis was performed using CAT12 implemented in SPM12. The smoothed GM segments were entered into a full factorial model with one factor (group) comprising four levels: AI-AN, PR-AN, FR-AM, and HC. TIV and age were included as covariates to control for individual differences in brain size and age-related effects on GMV. This model corresponds to a voxel-wise analysis of covariance (ANCOVA). An absolute threshold of 0.1 was applied for masking, and implicit masking was used to exclude non-brain voxels. Planned two-sided *t*-contrasts were used to examine specific between-group comparisons between AN subgroups and HC: HC > AI-AN, AI-AN > HC, HC > PR-AN, PR-AN > HC, HC > FR-AN, FR-AN > HC, and within AN subgroups: FR-AN > AI-AN, AI-AN > FR-AN, PR-AN > AI-AN, AI-AN > PR-AN, FR-AN > PR-AN, PR-AN > FR-AN. The statistical threshold was set at $p < .05$, corrected for family-wise error (FWE) at the voxel level, with a minimum cluster extent threshold of $k > 20$ voxels, to reduce the likelihood of false-positive results (Ashburner & Friston, 2000).

***Statistical Analysis of Hypothesis 3***

To test whether compulsivity levels are associated with GMV across the entire sample, a whole-brain multiple regression analysis was performed in CAT12 implemented in SPM12, including all participants (AI-AN, PR-AN, FR-AN, and HC). The smoothed GM segments were used as input. OCI-R total scores served as the regressor of interest. TIV and age were included as covariates to control for individual differences in brain size and age-

related effects on GMV. Both types of associations between OCI-R scores and GMV were tested: a positive association indicates regions where higher OCI-R scores are associated with greater GMV, whereas a negative association indicates regions where higher OCI-R scores are associated with lower GMV. An absolute threshold of 0.1 on the GM probability map was applied to exclude voxels with low GM tissue probability, and implicit masking was used. To identify potentially subtle effects, a voxel-wise height threshold of $p < .001$ uncorrected was used. Additionally, a minimum cluster extent threshold of $k > 20$ voxels was applied.

### *Statistical Analysis of Hypothesis 4*

To test whether the association between OCI-R scores and GMV differs across the groups, separate whole-brain voxel-wise multiple regression analyses were done within each group individually (AI-AN, PR-AN, FR-AN, and HC). These analyses were performed using CAT12, with the smoothed gray matter segments as input. In each model OCI-R total score was included as the regressor of interest, and age and TIV were entered as covariates to account for individual differences in brain size and age-related effects. An absolute GMV threshold of 0.1 and implicit masking were applied, consistent with previous analyses. Again, to identify potentially subtle effects, a voxel-wise height threshold of $p < .001$ uncorrected was used. Additionally, a minimum cluster extent threshold of $k > 20$ voxels was applied.

## Results

### Sample Characteristics

Due to missing data across different measures, the number of participants included in each analysis varied. For the behavioral analysis of H1, the final sample included 121 participants, consisting of 29 AI-AN, 35 PR-AN, 21 FR-AN patients, and 36 HC. For the MRI analyses of H2, H3, and H4, the final sample included 109 participants: 25 AI-AN, 33 PR-AN, 19 FR-AN patients, and 32 HC. Age and BMI values reported below are based on the final sample included in the analysis of H1.

As an exploratory analysis, participant demographics for age and BMI were examined. Although parametric assumptions were not fully met for age and BMI, standard one-way ANOVAs with Tukey's HSD post-hoc contrasts were used for group comparisons of age and BMI. To confirm the robustness of these findings, a non-parametric Kruskal-Wallis H test was also conducted, with the detailed results of all assumption and robustness checks presented in the Appendix.

For age, ANOVA found a significant group effect ($F(3, 117) = 5.68$, $p = .001$). Tukey's HSD post-hoc tests demonstrated that the AI-AN group was significantly younger than the HC ($p = .023$), FR-AN ($p = .014$), and PR-AN groups ($p = .001$). No significant differences were found between PR-AN and FR-AN ($p = .989$), PR-AN and HC ($p = .736$), or FR-AN and HC ($p = .942$). Participants ranged in age from 12 to 30 years.

For BMI, a significant group effect was found ($F(3, 117) = 33.9$, $p < .001$). Tukey's HSD post-hoc tests indicated that the AI-AN group had a significantly lower BMI compared to HC ($p < .001$), FR-AN ($p < .001$), and PR-AN groups ($p < .001$). No significant differences were found between PR-AN and FR-AN ($p = .893$), PR-AN and HC ($p = .886$), or FR-AN and HC ($p = 1.00$). Participants ranged in BMI from 13.00 to 29.70.

As shown in Table 1, the means and standard deviations for age and BMI reflect these differences, with descriptive and inferential statistics reported for these demographic variables alongside OCI-R scores, which are analyzed further below.

**Table 1**

*Descriptive and Clinical Characteristics for Behavioral Analysis*

| Variable | HC (A) ($n = 36$) | | FR-AN (B) ($n = 21$) | | PR-AN (C) ($n = 35$) | | AI-AN (D) ($n = 29$) | | ANOVA (*df*, *F*, *p*) | Tukey's HSD Post-hoc |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | | |
| Age (years) | 19.5 | (3.3) | 20.1 | (3.1) | 20.3 | (3.4) | 17.1 | (3.4) | 3, 5.68, .001 | A, B, C > D |
| BMI ($kg/m^2$) | 21.1 | (2.2) | 21.2 | (2.2) | 20.7 | (2.5) | 16.1 | (2.1) | 3, 33.9, < .001 | A, B, C > D |
| OCI-R, total score | 14.2 | (8.3) | 10.7 | (9.5) | 16.4 | (10.3) | 28.5 | (14.7) | 3, 13.7, < .001 | D > A, B, C |

*Note.* HC: healthy controls, FR-AN: fully remitted anorexia nervosa, PR-AN: partially remitted anorexia nervosa, AI-AN: acutely ill anorexia nervosa, BMI: Body Mass Index, OCI-R: Obsessive-Compulsive Inventory-Revised.

**H1: Group Differences in Obsessive-Compulsive Symptoms**

Prior to conducting ANOVA, assumptions of normality and homogeneity of variances were assessed. Normality was assessed using the Shapiro-Wilk test for each group. The assumption of normality was violated for the HC ($W$ = .930, $p$ = .025), FR-AN ($W$ = .889, $p$ = .022), and PR-AN groups ($W$ = .929, $p$ = .026). The AI-AN group demonstrated normal distribution ($W$ = .978, $p$ = .773). Homogeneity of variances was assessed using Levene's test, which revealed a significant result ($F$(3, 117) = 3.31, $p$ = .023), indicating that the variances were not homogeneous across groups.

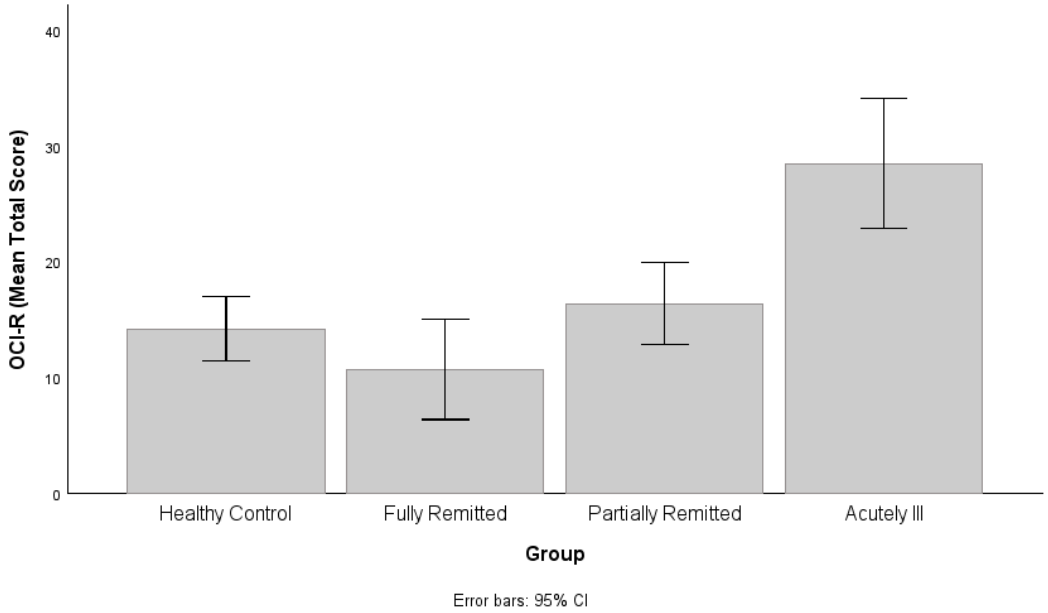
Although parametric assumptions were not fully met, standard one-way ANOVA with Tukey's HSD post-hoc contrasts was used for initial group comparisons. As shown in Table 1, a significant group effect for OCI-R total score was found ($F$(3, 117) = 13.7, $p$ < .001). Planned Tukey's HSD post-hoc contrasts showed that the AI-AN group reported significantly higher OCI-R scores than the HC ($p$ < .001, Cohen's $d$ = -1.307), FR-AN ($p$ < .001, Cohen's $d$ = -1.629), and PR-AN groups ($p$ < .001, Cohen's $d$ = -1.107). No significant differences were found between PR-AN and FR-AN ($p$ = .239, Cohen's $d$ = -0.521), PR-AN and HC ($p$ = .835, Cohen's $d$ = -0.200), and FR-AN and HC ($p$ = .646, Cohen's $d$ = 0.322). These group differences are illustrated in Fig. 1 and Table 1. The measured effect sizes reflect very large differences between the AI-AN group and all other groups, while differences between both remitted and HC groups were small to medium and nonsignificant (Cohen, 2013). To confirm the robustness of these findings given the assumption violations, a robust Welch's ANOVA and a non-parametric Kruskal-Wallis H test were also conducted, with their detailed results presented in the Appendix.

***Exploratory Analysis: Age as a Potential Confounder***

In an exploratory analysis, age was assessed as a potential confounder. An exploratory ANCOVA was conducted to investigate the potential confounding effect of age on OCI-R total scores. The ANCOVA results indicated that age did not have a statistically significant effect on OCI-R total scores ($F$(1, 116) = 2.11, $p$ = .149, $\eta_p^2$ = .018). The main effect of group membership remained statistically significant after controlling for age ($F$(3, 116) = 10.61, $p$ < .001, $\eta_p^2$ = .215). Given that age was not a significant covariate and its inclusion did not alter the pattern of group differences compared to the original analysis without controlling for age, the primary findings regarding group differences were reported based on the results of the original one-way ANOVA. For completeness, the detailed ANCOVA-adjusted results, including pairwise comparisons of estimated marginal means, are reported in the Appendix

**Fig. 1**

*Group Differences in OCI-R Total Scores*




*Note.* This bar chart displays differences in obsessive-compulsive symptoms, as measured by the Obsessive-Compulsive Inventory-Revised (OCI-R), between healthy controls, fully remitted, partial remitted, and acutely ill anorexia nervosa patients. Error bars represent 95% confidence intervals (CI).

## H2: Group Differences in GMV

### *GMV Differences Between AN Subgroups and HC*

VBM analysis revealed that, compared to HC, AI-AN patients showed significantly reduced regional GMV in frontal, temporal, and cerebellar regions. No regions showed significantly increased GMV in the AI-AN group relative to HC. Compared to HC, PR-AN showed significantly reduced regional GMV in temporal, parietal, and subcortical regions. No regions showed significantly increased GMV in the PR-AN group relative to HC. Compared to HC, no significant regional GMV increases or decreases were observed in FR-AN. Detailed results for these comparisons are presented in Table 2 (AI-AN vs. HC) and Table 3 (PR-AN vs. HC). Figure 2 visualizes the brain regions exhibiting significant GMV differences between the groups.

***GMV Differences Between AN Subgroups***

Compared to FR-AN, PR-AN showed significantly lower regional GMV in temporal and anterior cingulate regions. No significant regional GMV increases were observed in the PR-AN group compared to FR-AN. Compared to FR-AN, AI-AN showed significantly lower regional GMV in cerebellar and anterior cingulate regions. No significant regional GMV increases were observed in the AI-AN group compared to FR-AN. No significant regional GMV increases or decreases were observed in the AI-AN group compared to PR-AN. A summary of significant results is presented in Table 4 (FR-AN vs. PR-AN) and Table 5 (FR-AN vs. AI-AN).

**Table 2**

*Regions of GMV Differences Between AI-AN and HC*

| | | | | | MNI coordinates[b] | | |
|---|---|---|---|---|---|---|---|
| Contrast | Brain region | $p$[a] | Cluster size | $T$ ($Z$)[b] | x | y | z |
| HC > AI-AN | **R** cerebellar lobule VI | < .001 | 386 | 6.02 (5.55) | 34 | -68 | -22 |
| | **L** cerebellum | .001 | 204 | 5.93 (5.47) | -34 | -51 | -40 |
| | **R** superior frontal gyrus (subregion 2) | .004 | 87 | 5.18 (4.87) | 24 | 28 | 45 |
| | **L** cerebellar crus I | .008 | 60 | 5.29 (4.96) | -42 | -57 | -26 |
| | **R** middle temporal gyrus | .017 | 27 | 4.69 (4.68) | 58 | -33 | 4 |
| AI-AN > HC | No regions | | | | | | |

*Note.* MNI: Montreal Neurological Institute, HC: healthy control, AI-AN: acutely ill anorexia nervosa, R: right, L: left

$k > 20$

[a] FWE-corrected at the voxel level, $p < .05$

[b] of peak of $t$-score ($z$-score), voxel level

**Table 3**

*Regions of GMV Differences Between PR-AN and HC*

| Contrast | Brain region | $p$[a] | Cluster size | $T$ ($Z$)[b] | MNI coordinates[b] | | |
|---|---|---|---|---|---|---|---|
| | | | | | x | y | z |
| HC > PR-AN | **R** putamen | .008 | 300 | 5.31 (4.97) | 27 | 2 | -9 |
| | **R** amygdala | | | 5.26 (4.93) | 20 | -3 | -12 |
| | **L** putamen | .004 | 147 | 5.47 (5.11) | -28 | -14 | -3 |
| | **R** parahippocampal gyrus | .003 | 66 | 5.56 (5.18) | 24 | -22 | -22 |
| | **L i**nferior parietal lobule | .010 | 36 | 5.25 (4.93) | -38 | -42 | 48 |
| | **L** middle temporal gyrus | .014 | 20 | 5.16 (4.85) | -52 | -58 | 14 |
| PR-AN > HC | No regions | | | | | | |

*Note.* MNI: Montreal Neurological Institute, HC: healthy control, PR-AN: partially remitted anorexia nervosa, R: right, L: left
$k > 20$
[a] FWE-corrected at the voxel level, $p < .05$
[b] of peak of $t$-score ($z$-score), voxel level

**Table 4**

*Regions of GMV Differences Between FR-AN and PR-AN*

| Contrast | Brain region | $p$[a] | Cluster size | $T$ ($Z$)[b] | MNI coordinates[b] | | |
|---|---|---|---|---|---|---|---|
| | | | | | x | y | z |
| FR-AN > PR-AN | **L** parahippocampal gyrus | .008 | 51 | 5.31 (4.97) | -26 | -16 | -28 |
| | **L** pre-genual anterior cingulate gyrus | .003 | 44 | 5.53 (5.15) | -8 | 45 | -3 |

| | |
|---|---|
| PR-AN > HC | No regions |

*Note.* MNI: Montreal Neurological Institute, FR-AN: fully remitted anorexia nervosa, PR-AN: partially remitted anorexia nervosa, R: right, L: left

$k > 20$

[a] FWE-corrected at the voxel level, $p < .05$

[b] of peak of *t*-score (*z*-score), voxel level

**Table 5**

*Regions of GMV Differences Between FR-AN and AI-AN*

| | | | | | MNI coordinates[b] | | |
|---|---|---|---|---|---|---|---|
| Contrast | Brain region | $p$[a] | Cluster size | $T$ ($Z$)[b] | x | y | z |
| FR-AN > AI-AN | **R** cerebellar lobule IV | .003 | 136 | 5.53 (5.15) | 33 | -69 | -20 |
| | **L** subgenual anterior cingulate cortex | .018 | 71 | 5.08 (4.78) | -3 | 24 | -10 |
| AI-AN > FR-AN | No regions | | | | | | |

*Note.* MNI: Montreal Neurological Institute, FR-AN: fully remitted anorexia nervosa, AI-AN: acutely ill anorexia nervosa, R: right, L: left

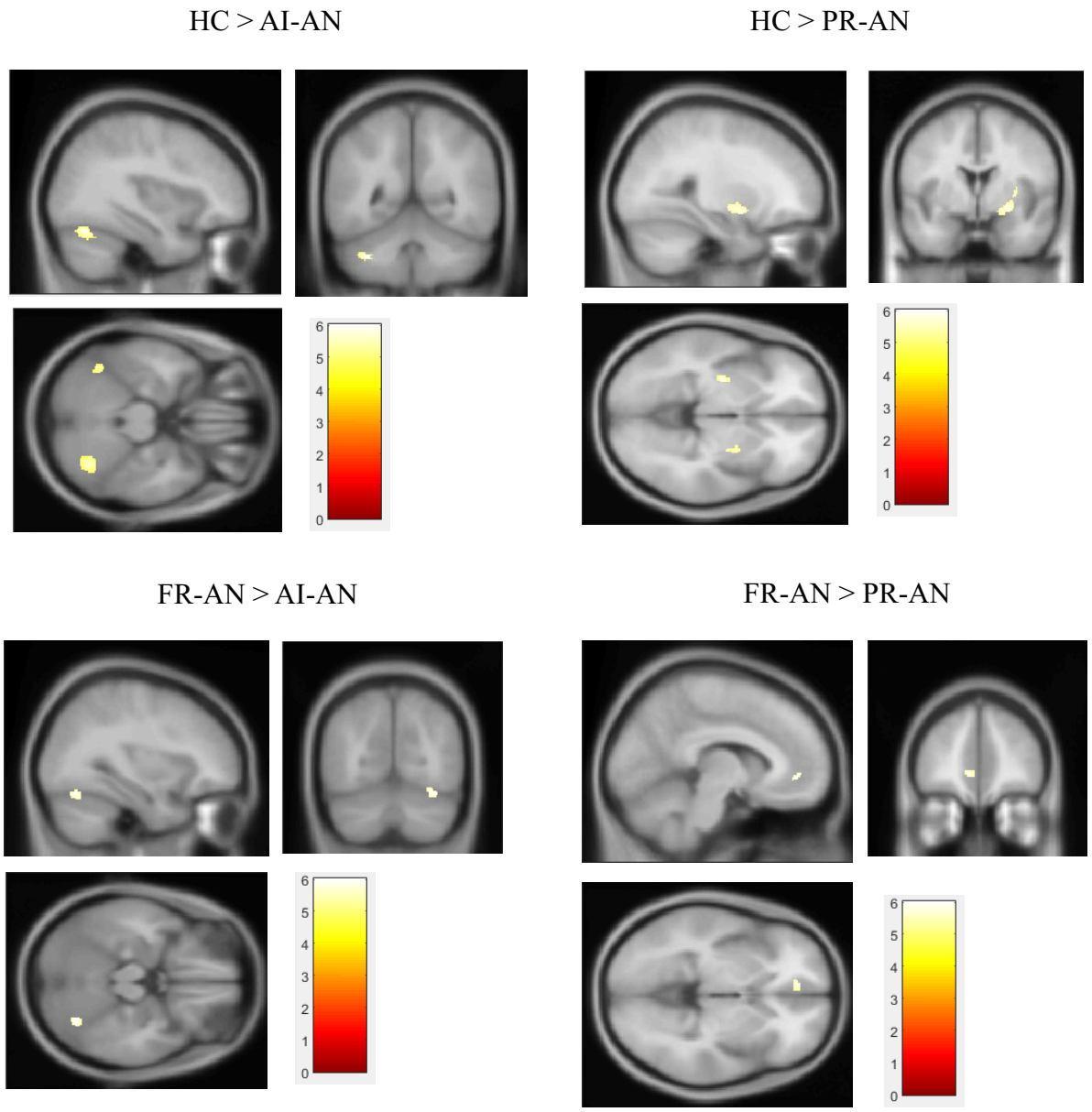
$k > 20$

[a] FWE-corrected at the voxel level, $p < .05$

[b] of peak of *t*-score (*z*-score), voxel level

**Figure 2**

*Brain Regions Showing Significant Between-Group Differences in GMV*




*Note.* GMV differences between AI-AN patients vs. HC (MNI coordinates: x = 36, y = -51 , z = -26) and FR-AN patients (MNI coordinates: x = 33, y = -69 , z = -19); and PR-AN patients vs. HC (MNI coordinates: x = 27 , y = 0 , z = -4 ) and FR-AN patients (MNI coordinates: x = -7, y = 45 , z = -3 ) are displayed. Significance threshold: voxel-level FWE-corrected $p < .05$ ($k > 20$). Color bar indicates *t*-values.

MNI: Montreal Neurological Institute, AI-AN: acutely ill anorexia nervosa, PR-AN: partially remitted anorexia nervosa, FR-AN: fully remitted anorexia nervosa, HC: healthy control, GMV: gray matter volume, FWE: family-wise error

**H3: Association of OCI-R Score with GMV**

An explorative voxel-wise multiple regression analysis to examine the relationship between OCI-R scores and GMV across all groups (AI-AN, PR-AN, FR-AN, and HC), controlling for age and TIV, was performed. The analysis revealed a significant positive association in one cluster in the left middle temporal gyrus ($p < .001$ uncorrected; 144 voxels; peak MNI coordinates: x = -40, y = -60, y = 14), with a minimum cluster extent threshold of $k > 20$ voxels. This indicates that higher OCI-R scores are associated with higher GMV in this region. No significant negative association between OCI-R scores and regional GMV was found.

**H4: Group Differences in Association Between OCI-R Scores and GMV**

Four separate explorative voxel-wise multiple regression analyses were conducted to examine the relationship between OCI-R scores and GMV within each group (AI-AN, PR-AN, FR-AN, and HC), controlling for age and TIV. Within-group associations between OCI-R scores and GMV revealed distinct patterns across the groups.

In AI-AN, the analysis revealed significant positive associations between OCI-R score and GMV in three clusters located in occipital, frontal, and temporal regions (see Table 6). No significant negative associations between OCI-R and GMV in AI-AN were observed.

In PR-AN, the analysis revealed significant positive associations between OCI-R score and GMV in five clusters in the parietal and temporal lobe. Further, significant negative associations in three clusters in the parietal and temporal lobe were detected (see Table 7).

In FR-AN, the analysis revealed significant positive associations between OCI-R score and GMV in four clusters in cingulate, frontal, and occipital regions (see Table 8). No significant negative associations between OCI-R and GMV in FR-AN were observed.

In HC, the analysis revealed significant positive associations between OCI-R score and GMV in two clusters in the frontal and temporal lobe. Further, significant negative associations in three clusters in frontal and cingulate regions, and in the frontoparietal operculum were detected (see Table 9).

A visual representation of positive associations is presented in Appendix Figure A 1, while negative associations are summarized in Appendix Figure A 2.

**Table 6**

*Regions of GMV Associated with OCI-R Score in Acutely Ill Anorexia Nervosa*

| | | | | | MNI coordinates[b] | | |
|---|---|---|---|---|---|---|---|
| Association | Brain region | $p$[a] | Cluster size | $T$ ($Z$)[b] | x | y | z |
| Positive | **R** middle occipital gyrus | < .001 | 106 | 5.07 (4.05) | 36 | -74 | 14 |
| | **R** superior frontal gyrus, subregion 2 | < .001 | 93 | 4.95 (3.99) | 26 | 69 | 20 |
| | **L** middle temporal gyrus | < .001 | 60 | 4.86 (3.94) | -42 | -60 | 16 |
| Negative | No regions | | | | | | |

*Note.* MNI: Montreal Neurological Institute, L: left, R: right

$k > 20$

[a] $p < .001$ uncorrected at the voxel level

[b] of peak of $t$-score ($z$-score), voxel level

**Table 7**

*Regions of GMV Associated with OCI-R Score in Partially Remitted Anorexia Nervosa*

| | | | | | MNI coordinates[b] | | |
|---|---|---|---|---|---|---|---|
| Association | Brain region | $p$[a] | Cluster size | $T$ ($Z$)[b] | x | y | z |
| Positive | **L** inferior parietal lobule | < .001 | 187 | 5.13 (4.29) | -57 | -36 | 40 |
| | **R** superior parietal lobule | < .001 | 71 | 3.86 (3.44) | 14 | -64 | 70 |
| | **L** postcentral gyrus | < .001 | 56 | 4.03 (3.56) | -54 | -33 | 56 |
| | **L** precuneus | < .001 | 38 | 3.76 (3.36) | -10 | -51 | 60 |
| | **L** middle temporal gyrus | < .001 | 23 | 3.66 (3.29) | -39 | -62 | 15 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Negative | **L** inferior temporal gyrus | < .001 | 76 | 4.74 (4.05) | -54 | -28 | -20 |
| | **L** postcentral gyrus | < .001 | 23 | 3.95 (3.50) | -60 | -20 | -15 |
| | **R** inferior temporal gyrus | < .001 | 22 | 3.60 (3.24) | 55 | -60 | -24 |

*Note.* MNI: Montreal Neurological Institute, L: left, R: right

$k > 20$

[a] $p < .001$ uncorrected at the voxel level

[b] of peak of *t*-score (*z*-score), voxel level

**Table 8**

*Regions of GMV Associated with OCI-R Score in Fully Remitted Anorexia Nervosa*

| | | | | | MNI coordinates[b] | | |
|---|---|---|---|---|---|---|---|
| Association | Brain region | $p$[a] | Cluster size | $T$ ($Z$)[b] | x | y | z |
| positive | **L** middle cingulate gyrus | < .001 | 171 | 4.86 (3.71) | -10 | 0 | 36 |
| | **R** supplementary motor area | < .001 | 77 | 4.24 (3.38) | 3 | 12 | 50 |
| | **L** precentral gyrus | < .001 | 33 | 4.31 (3.42) | -51 | -3 | 46 |
| | **R** lingual gyrus | < .001 | 27 | 4.23 (3.38) | 9 | -60 | 3 |
| Negative | No regions | | | | | | |

*Note.* MNI: Montreal Neurological Institute, L: left, R: right

$k > 20$

[a] $p < .001$ uncorrected at the voxel level

[b] of peak of *t*-score (*z*-score), voxel level

**Table 9**

*Regions of GMV Associated with OCI-R Score in Healthy Controls*

| Association | Brain region | $p$[a] | Cluster size | $T$ ($Z$)[b] | MNI coordinates[b] | | |
|---|---|---|---|---|---|---|---|
| | | | | | x | y | z |
| Positive | **L** hippocampus | < .001 | 273 | 4.30 (3.73) | -15 | -10 | -18 |
| | **L** middle frontal gyrus (subdivision 2) | < .001 | 196 | 4.45 (3.84) | -45 | 42 | 24 |
| Negative | **R** rolandic operculum | < .001 | 53 | 3.99 (3.52) | 64 | 10 | 10 |
| | **L** pregenual anterior cingulate cortex | < .001 | 20 | 3.81 (3.39) | -12 | 39 | 0 |
| | **R** middle frontal gyrus (subdivision 2) | < .001 | 20 | 3.60 (3.24) | 44 | -6 | 58 |

*Note.* MNI: Montreal Neurological Institute, L: left, R: right

$k > 20$

[a] $p < .001$ uncorrected at the voxel level

[b] of peak of $t$-score ($z$-score), voxel level

## Discussion

The overall aim of this study was to investigate the neural correlates of obsessive-compulsive behavior across different AN subgroups at various stages of recovery. Specifically, the study examined whether obsessive-compulsive behavior, measured by the OCI-R, differs among AI-AN, PR-AN, FR-AN, and HC. Additionally, the study assessed whether GMV differs between the AN subgroups and HC. In an exploratory analysis, the association between OCI-R scores and GMV was examined, including whether these associations differ between AN subgroups and HC. Although exploring these associations was a key objective of this thesis, the preliminary and exploratory nature of these findings, together with significant methodological limitations (to be discussed in detail later), leads me to primarily focus this discussion on the more robust findings of differences in obsessive-compulsive symptoms and GMV.

**Obsessive-Compulsive Behavior**

The first research question examined differences in obsessive-compulsive behavior across the AI-AN, PR-AN, FR-AN, and HC groups, as measured by the OCI-R. A significant overall group difference was found. In line with H1a, planned post-hoc contrasts demonstrated that individuals in the AI-AN group exhibited significantly higher obsessive-compulsive symptoms than those in the PR-AN, FR-AN, and HC groups. These group differences were not only statistically significant, but also associated with very large effect sizes, indicating substantial clinical differences in symptom severity. However, H1b and H1c were not supported: the results did not demonstrate significantly higher obsessive-compulsive symptoms in PR-AN compared to FR-AN or HC, nor did the FR-AN group differ significantly from HC. While the comparison between PR-AN and FR-AN yielded a moderate effect size, indicating higher obsessive-compulsive symptoms in PR-AN, this difference did not reach statistical significance. Furthermore, although the HC group descriptively had higher obsessive-compulsive symptoms than the FR-AN group, the corresponding effect size was small and not statistically significant. Similarly, comparisons between PR-AN and HC also showed small effect sizes, which were again not significant. These findings suggest that obsessive-compulsive symptoms are most elevated during the acute phase of AN. While symptoms appear to diminish with remission, the study did not find significant differences in symptom severity between partially remitted, fully remitted, and HC groups. This suggests that once remission is achieved, whether partial or full, obsessive-compulsive symptoms may no longer significantly differentiate these groups, or that the sample size was too small to detect these differences.

These results are partially in accordance with previous research, which has consistently reported elevated obsessive-compulsive symptoms in acutely ill AN patients compared to HC (Fonville et al., 2014; Holtkamp et al., 2005; Pollice et al., 1997; Roberts et al., 2011). Notably, some previous studies that compared obsessive-compulsive symptoms across different recovery stages of AN and HC observed a graded decrease in these symptoms, from highest in acutely ill individuals, to intermediate in weight-restored patients, to lowest in HC. Importantly, in these studies with a graded pattern, obsessive-compulsive symptoms in weight-restored individuals often remained significantly elevated compared to HC (Holtkamp et al., 2005; Pollice et al., 1997). These results suggest a combination of state-dependent and trait-like components. That is, while symptoms may diminish with weight restoration, they may not fully normalize, implying a persistent vulnerability. However, the findings from the present study offer a slightly different perspective. Since no significant

differences were found between partially and fully remitted AN groups compared to HC, the results suggest a primarily state-dependent profile, in which symptoms decrease substantially with weight restoration and no longer exceed those seen in HC. This finding aligns with a study by Roberts et al. (2011) who similarly used the OC-R and found no significant differences between weight-restored groups and HC. This supports the idea that obsessive-compulsive symptoms in AN are largely influenced by acute illness-related factors, such as malnutrition.

Several factors may explain the absence of a graded pattern in my sample. First, the relatively small sample sizes across the groups likely resulted in a lack of power to detect smaller differences. While some comparisons showed small to moderate effect sizes, these did not reach statistical significance, suggesting that subtle differences might exist in the population but were not reliably detected in the current study. Furthermore, definitions of partial and full remission vary across studies and inconsistent operationalization may make it hard to detect subtle differences in symptom profiles. Additionally, sample characteristics such as illness duration, age of onset, comorbidities, or treatment history may have influenced symptom expression and masked smaller group differences. The choice of measurement, OCI-R versus other instruments like the Y-BOCS may also have influenced sensitivity to changes across stages.

Interestingly, the HC group reported higher OCI-R scores than the fully remitted AN group. However, this finding should be interpreted with caution, as the difference was not significant and the effect size was small. One possible explanation may be that the FR-AN group may have underreported symptoms to affirm their recovery and psychological well-being or due to social desirability. In contrast, the HC may have answered more open, as they did not have any ED history. Future research with larger sample sizes and additional objective measures, which may reduce the impact of self-report biases, may help clarify this finding.

To further address the trait-versus-state debate, future research should incorporate standardized definitions of recovery, consider both behavioral and physiological indicators, and ideally use longitudinal designs. Prospective studies assessing individuals prior to AN onset would be needed in identifying predisposing traits. However, such designs are difficult to implement. Nonetheless, the current findings provide evidence that obsessive-compulsive symptoms are most elevated in the acute state of the illness, and may diminish with remission, reducing the likelihood of them representing a stable trait in individuals with AN.

## GMV Differences

### *GMV Differences Between AN Subgroups and HC*

The current study revealed widespread GMV reductions in AI-AN and PR-AN compared to HC, while FR-AN showed no significant GMV differences compared to HC. These findings suggest that GMV reductions are most pronounced in the acutely ill and partially remitted stages and may normalize with longer and more comprehensive recovery. These results are partially in line with Hypothesis 2, which suggested alterations in GMV across the whole brain in the AN groups compared to HC.

More specifically, relative to HC, AI-AN patients demonstrated significant reductions in the right cerebellar lobule VI, left cerebellum, left cerebellar crus I, right superior frontal gyrus (subregion 2), and right middle temporal gyrus. The GMV reductions in the cerebellum, specifically in the right cerebellar lobule VI, left cerebellum, and left cerebellar crus I, confirm previous studies that also found cerebellar GMV reductions in AN (Amianto et al., 2013; Boghi et al., 2011; Brooks et al., 2011; Joos et al., 2010; Mishima et al., 2021). However, some previous studies have suggested bilateral cerebellar volumetric reductions to be a late consequence of AN, as these reductions were pronounced in adult AN patients with a longer disease duration of at least 9 years (Boghi et al., 2011). Brooks et al. (2011) confirmed this observation and further suggested the cerebellum to be a key region for starvation-induced GMV loss. However, my findings suggest that these cerebellar reductions might already occur at an earlier stage of illness. The current study observed the reduction in adolescent acutely ill patients with an average age of 17.1 years, which contrasts the assumption that such reductions are a late consequence of long-term illness. Furthermore, Seitz et al. (2015) found that cerebellar GMV reductions predicted weight at one year follow-up, suggesting the cerebellum to have a predictive role. Seitz et al. (2016) also proposed that the cerebellum may be particularly susceptible to semi-starvation, potentially leading to the development of a “cerebellar scar”. Another possibility is that a smaller cerebellar GMV may pre-exist and act as a risk factor for AN or its chronic course.

Next to the well-established involvement in sensorimotor control, the cerebellum is involved in cognitive and emotional functions. Reductions in the cerebellar lobule VI and crus I have been associated with emotional processing and executive functioning, both domains that are affected in AN (Stoodley & Schmahmann, 2009). Schmahmann et al. (2007), who related case histories of patients with cerebellar lesions, identified several symptoms relevant in AN, including compulsive and ritualistic behaviors, obsessional thoughts, difficulty shifting focus of attention, anxiety, and depression, suggesting that

cerebellar dysfunction may contribute to the cognitive and emotional disturbances in AN. A recent meta-analysis examining task-based fMRI studies in AN patients found both hyperactivation and hypoactivation in the cerebellum during food-related and emotional processing tasks, highlighting the cerebellum's involvement in key domains affected by the disorder (Zhong et al., 2023). The consistent findings of altered structural GMV and functionality in cerebellar regions underscores the important role of this region in AN pathology.

In line with previous research, I also found in AI-AN GMV reductions in frontal regions, particularly in the right superior frontal gyrus (Mishima et al., 2021; Nickel et al., 2018; Tose et al., 2024). Mishima et al. (2021) additionally reported reduced cortical thickness in the superior frontal gyrus. This region has been suggested to be functionally diverse, being involved in cognitive control, the default mode network, and executive functions (Li et al., 2013). Impairments in these functions may be associated with the often-observed rigid cognitive styles in AN like ritualized eating patterns or fixation on calorie counting, and compulsive behaviors (Miles et al., 2020).

The reductions in GMV in the right middle temporal gyrus confirmed previous findings (Kohmura et al., 2017; Lyall et al., 2024; Mishima et al., 2021). Specifically, Kohmura et al. (2017) not only observed reduced GMV in the right middle temporal gyrus but also in the right superior temporal gyrus, positing that these two regions work together for body recognition. They further reported a correlational group difference between body dissatisfaction and GMV in the superior temporal gyrus, suggesting that decreased GMV in both the superior and middle temporal gyrus may contribute to the frequently observed body dissatisfaction and abnormal body image perception in AN. Moreover, Zhong et al. (2023) showed altered activity in the right middle temporal gyrus in AN patients, with increased activity during cognitive-related tasks and decreased activity during food-related tasks. They indicated this altered activity may be relevant in the development of AN, potentially heightening patients' sensitivity to cognitive and food-related stimuli. Thus, my finding underscores the central role of the right temporal lobe in acute AN.

Compared to HC, PR-AN patients showed significant GMV reductions in the bilateral putamen extending to the right amygdala, right parahippocampal gyrus, left inferior parietal lobule, and left middle temporal gyrus. My finding of reduced subcortical limbic-striatal GMV in partially remitted AN patients compared to HC partially contradicts the claim that these changes are linked to an acute, underweight state and resolve with weight restoration. For example, Friederich et al. (2012) reported reduced GMV in the amygdala and putamen in

acutely ill AN patients but found no reduced subcortical GMV when long-term-recovered AN patients were compared to HC, supporting a state-dependent model. It is important to note that their long-term-recovered AN patients are not directly comparable to my partially remitted group; they rather align to my fully remitted AN group. Similarly, Bernardoni et al. (2016) observed reduced subcortical GMV in acutely ill AN patients, including the amygdala and putamen, which normalized with partial weight restoration, showing no longer differences compared to fully recovered AN patients or HC. However, literature on these subcortical regions is not completely consistent. For example, a recent study investigating the volume of key basal ganglia regions found no significant difference in putamen volume between acutely ill AN and HC, though it did report group differences in the shape of these regions (Leppanen et al., 2020). Beyond structural alterations, these limbic-striatal regions are critical in understanding the pathophysiology of AN. The amygdala plays a central role in emotional processing, fear, and reward (Baxter & Murray, 2002; Davis, 1992), which are relevant to eating behaviors. Consistent with this, Joos et al. (2011) found in restricting-type AN patients increased activation in the right amygdala while looking at food photographs. Moreover, this amygdala activity was negatively associated with disgust ratings, highlighting its role in the disorder and indicating its complex involvement in emotional aspects of eating behavior. Another fMRI study using a body-related paradigm reported increased activity in the right amygdala when AN patients viewed a photograph of another woman's body (Vocks et al., 2010).This further underscores the importance of the amygdala in AN, both structurally and functionally. The observed alterations in the putamen and amygdala align with neurobiological models of AN emphasizing altered reward processing. O'Hara et al. (2015) suggested the striatal reward system to be central to the development and maintenance of AN, where reward-based learned behaviors become anorectic habits. The persistent subcortical limbic-striatal GMV reductions observed in the partially remitted AN group, particularly in the putamen and amygdala, may underscore an enduring contribution to the pathophysiology of AN, even after partial weight restoration. These findings, together with the established functional roles of these regions in emotional and reward processing, provide further support for neurobiological models that suggest altered reward and emotional processing in the maintenance of the disorder.

My finding of reduced GMV in the left inferior parietal lobule, which is composed of the angular gyrus and supramarginal gyrus, is consistent with a large body of prior research. Importantly, while my observation was made in PR-AN, many of the corroboration studies were conducted in AI-AN. This distinction is important, as it may suggest that the alterations

in the left inferior parietal lobule represent a more persistent neurobiological feature, potentially acting as a vulnerability marker or a persistent feature that remains even after some symptom remission. Several previous VBM meta-analyses (Su et al., 2021; Titova et al., 2013) and individual studies (Amianto et al., 2013; Gaudio et al., 2011; Mishima et al., 2021; Tose et al., 2024) provide evidence for this finding in acute AN. The consistent identification of parietal lobe alterations, particularly within the inferior parietal lobule, suggests functional implication for AN. Lyall et al. (2024) proposed these alterations could be an early indicator of the brain's response to weight loss in AN. Gaudio et al. (2011) supported a regionally specific vulnerability in areas important for mental self- and body image representation, noting early GMV decreases in short-illness AN. My contrasting findings of reduced GMV in PR-AN compared to similar findings in acutely ill AN is important to note. This persistence suggests that these alterations may not only be effects of acute malnutrition. Instead, they may represent more stable neurobiological underpinnings of AN, potentially contributing to the enduring risk of relapse or persistent body image disturbance, even after some symptoms have remitted. Daprati et al. (2010) suggested that the left parietal cortex is important for creating and monitoring an internal model of one's own movements. Consequently, reduced GMV in the left inferior parietal lobule, observed in both acutely ill and partially remitted AN, likely impairs this function. This impairment could help explain the distorted body perception in AN, as individuals struggle to integrate sensory and motor information for a coherent body representation. The persistence of these structural changes in remission suggests that the neural basis for accurate self-perception remains affected, hindering full body image recovery.

Two clusters of reduced GMV in the temporal lobe were found in partially remitted AN patients compared to HC: the parahippocampal gyrus and the left middle temporal gyrus. Consistent with Brooks et al. (2011), but contrary to Frank et al. (2013) who observed increased volumes, I found reduced GMV in the parahippocampal gyrus. This regions, part of the limbic system, is involved in learning, memory formation, and the emotional regulation of food intake (Aminoff et al., 2013; Rosenbaum et al., 2008). A recent meta-analysis also found increased resting-state functional activity in the parahippocampal gyrus extending to the amygdala and middle temporal gyrus in AN patients (Su et al., 2021). Another fMRI study observed poorer activity in the bilateral parahippocampal cortex during set-shifting in AN patients, suggesting its contribution to impaired cognitive flexibility in AN (Sato et al., 2013). Thus, the parahippocampal gyrus may play an important role in cognitive dysfunctions in AN.

Like in the acute AN group (on the right side), I found reduced GMV in the temporal gyrus in the partially remitted group, though in contrast, this reduction was on the left side. As previously discussed, regarding the general temporal gyrus, this broader anatomical region encompasses the middle and superior temporal gyri. My observation of reduced GMV in the left temporal gyrus is consistent with previous literature (Boghi et al., 2011; Lyall et al., 2024; Rothemund et al., 2011). Mishima et al. (2021) also reported bilateral middle temporal gyrus reductions, and Phillipou et al. (2018) further observed reductions in both the left middle and superior temporal gyri. The persistence of this left-sided reduction in my partially remitted group is particularly noteworthy when considering recovery studies. While Nickel et al. (2018) reported decreased temporal gyri in acute AN compared to HC, their recovered AN group (defined almost identically to my fully remitted group) showed higher GMV in the superior temporal gyrus than the acute AN group, indicating some degree of structural normalization. For the middle temporal gyrus, they observed only a trend toward recovery. This contrasts with Bomba et al. (2015), who found full recovery of left superior temporal gyrus GMV after weight restoration in AN patients. This inconsistency suggests that the recovery journey of GMV in the left temporal gyrus may vary depending on the sub-region and extent of remission, with my finding in partially remitted AN indicating incomplete structural normalization in certain left temporal regions.

Unlike some prior studies, my results showed no significant regional GMV differences between fully remitted AN patients and HC, aligning with research suggesting GMV normalization with sustained recovery (Bomba et al., 2015; Wagner et al., 2006). This apparent normalization in my fully remitted AN group could be interpreted as complete GMV recovery and may be attributable to the particularly strict and multi-dimensional definition of full remission applied in this study, which included being symptom-free and at a normal weight for at least 12 months. However, the literature on GMV normalization in long-term-recovered individuals remains inconsistent, with other studies reporting persistent regional GMV reductions even in long-term-recovered individuals (Friederich et al., 2012; Joos et al., 2011; Mühlau et al., 2007; Oliva et al., 2020). This ongoing debate, whether AN-related regional GMV changes are state- or trait-dependent is further complicated by the use of varying definitions and criteria for recovery stages across studies. Another important consideration when interpreting my finding is the relatively small sample size of the fully remitted group ($n$ = 19) that reduces the statistical power to detect subtle differences that might exist. This highlights the need for future longitudinal research with larger sample sizes of fully remitted individuals to clarify the extent and permanence of GMV normalization.

***GMV Differences Between AN Subgroups***

To further obtain insight into neural mechanisms that go along with remission, GMV differences between AN subgroups were compared. The study revealed significant GMV reductions in AI-AN compared to FR-AN, and significantly lower GMV in PR-AN compared to FR-AN. Importantly, there were no significant GMV differences between AI-AN and PR-AN, suggesting that partial remission may not be sufficient for full neuroanatomical recovery, despite some weight restoration and improvements in clinical symptoms. Specifically, relative to FR-AN, AI-AN exhibited GMV reductions in the right cerebellar lobule IV, (consistent with the comparison with HC), and in the left subgenual ACC. Furthermore, compared to FR-AN, PR-AN had GMV reductions in the left parahippocampal gyrus, (consistent with the comparison with HC), and in the left pregenual ACC.

The right cerebellar lobule IV and parahippocampal GMV were reduced in acutely ill and partially remitted AN patients also when compared to fully remitted AN may suggest a degree of reversibility of brain structural changes in full remission. The reductions in these regions appear to be state-dependent characteristics that may tend to normalize with full recovery.

The finding of reduced GMV in specific subregions of the ACC in acutely ill and partially remitted patients, when compared to fully remitted patients, aligns with previous research highlighting the important role of this region in AN pathology. The ACC is thought to be part of a neural circuit that is involved in regulating cognitive and affective processing, with the dorsal part being involved in cognitive and the rostral and ventral parts in emotional and motivations processing (Bush et al., 2000). It has consistently been implicated in both structural and functional brain alterations in AN (Su et al., 2021). Previous meta-analyses corroborate widespread structural impairment in the cingulate cortex in AN (Su et al., 2021; Zhang et al., 2018). While some studies, like McCormick et al. (2008), have observed significant reductions in the ACC GMV in acute AN, particularly in the right dorsal ACC, they also demonstrated that this GMV loss can normalize with weight restoration. Similarly, Joos et al. (2011) found that while dorsal ACC was lower in acute patients, it showed no significant difference between recovered individuals and HC, further supporting recovery-related normalization. Conversely, Friederich et al. (2012) demonstrated persistent reductions in the right dorsal ACC in weight-restored AN patients, pointing to the variability within the recovered population. My observation that fully remitted patients show a recovery of ACC GMV supports the view that some structural deficits, particularly those related to the state of acute illness, may be reversible. This aligns with findings suggesting that structural brain

changes in AN are, at least partially, state-dependent and normalize with recovery (McCormick et al., 2008). However, the specific subregional reductions observed in the current study (subgenual ACC in AI-AN, pregenual ACC in PR-AN) point to the assumption that specific parts of the ACC might show differential recovery patterns or enduring vulnerabilities, potentially contributing to persistent symptoms in partially remitted states. It needs to be considered that this was a cross-sectional study, making it impossible to make causal inferences from the findings. Besides structural alterations, various functional neuroimaging studies have consistently shown altered neural activity within the ACC in AN patients. These studies suggested the involvement of the ACC in aberrant reward processing (Kaye et al., 2009), body dissatisfaction (Friederich et al., 2010), and impaired cognitive-behavioral flexibility (Zastrow et al., 2009). In conclusion, my findings could be interpreted as ACC GMV normalization in fully remitted patients, suggesting a degree of recovery in the ACC with weight restoration. However, the ACC is a complex brain area, important for both emotion and cognition. This complexity, combined with its role in AN, suggests it to be a key region that may experience both illness-state-dependent changes and potential lasting vulnerabilities.

In summary, distinct patterns of GMV differences across AN subgroups were found. AI-AN and PR-AN demonstrated widespread GMV reductions compared to HC, particularly in cerebellar, frontal, temporal, and subcortical limbic striatal regions. Importantly, the lack of significant GMV differences between AI-AN and PR-AN might suggest that partial remission, despite improvements in clinical symptoms and some weigh restoration, may not be sufficient for full GMV recovery. In contrast, these GMV reductions seem to be largely absent in fully remitted AN patients, which could indicate a significant degree of GMV normalization with sustained recovery, defined as being symptom-free and at normal weight for at least 12 months. By comparing AN subgroups with each other, my findings highlight the reversibility of some brain alterations, with GMV reductions in the cerebellum, parahippocampal gyrus, and ACC appearing to be state-dependent and tending to normalize with full recovery. These findings underscore the dynamic nature of brain structure in AN and emphasize the potential for GMV recovery, while also highlighting the possible persistence of GMV reductions in partially-remitted states and the potential importance of long-term recovery and full remission for complete neuroanatomical normalization.

**Association of OCI-R Score with GMV**

The main aim of this study was to investigate the association between obsessive-compulsive symptoms and structural GMV across different illness stages of AN patients and HC. Given the highly exploratory nature of these analyses and significant methodological limitations (to be discussed in detail below), the primary focus of this discussion is the more robust group-level GMV differences. Nevertheless, an exploratory analysis revealed some associations between obsessive-compulsive symptoms and GMV. However, given the lack of research on the association between obsessive-compulsive symptoms and structural GMV in AN, this discussion will focus on the findings in areas that are consistently implicated in OCD, such as components of the CSTC circuits and other regions with strong functional associations (Piras et al., 2015).

Across all participants, a single positive association between obsessive-compulsive symptoms and GMV in the left middle temporal gyrus was observed, providing limited support for the exploratory hypothesis H3 that proposed associations across the whole brain. Notably, this positive association was also present in the AI-AN and PR- AN groups individually. This finding suggests that higher levels of obsessive-compulsive symptoms may relate to increased GMV in this region. Davey et al. (2016) proposed the left posterior middle temporal gyrus to play a role in flexibly integrating automatic semantic processing with controlled, goal-oriented cognition. This region might be related to the rigid, inflexible, and maladaptive thought patterns and behaviors that characterize obsessive-compulsive symptoms in AN. A dysfunction in this region could lead to the inability to use broader and more adaptive semantic meanings, which could lead to a very narrow-minded thinking. However, this interpretation is highly speculative, and future research should investigate the functional role of the left middle temporal gyrus on obsessive-compulsive symptoms in AN.

The exploratory hypothesis H4 that proposed these associations between obsessive-compulsive symptoms and GMV would differ between the groups was supported by the data revealing very distinct patterns of associations within each individual group. For example, the AI-AN group demonstrated positive associations in occipital, frontal, and temporal regions. In contrast, the PR-AN group showed positive and negative associations in various parietal and temporal regions. The FR-AN group and HC likewise demonstrated distinct, non-overlapping patterns of associations. It is important to note that in the PR-AN group, the left postcentral gyrus showed positive and negative associations with obsessive-compulsive symptoms.

In the FR-AN group, a positive association between obsessive-compulsive symptoms and GMV in the left middle cingulate gyrus was found. Previous research has implicated the anterior midcingulate cortex in disorders marked by compulsive behaviors, such as OCD and ADHD. In particular, the anterior midcingulate cortex has been linked to checking symptoms, a core feature of OCD (Vogt, 2016). Its involvement in AN may reflect shared neurobiological mechanisms related to cognitive control and compulsivity across disorders. Furthermore, in the HC group, a negative association in the left pregenual anterior cingulate cortex was found. Together with the middle cingulate gyrus, this region has a central role in the CSTC circuits, whose dysfunction is closely linked to the onset and maintenance of obsessive-compulsive symptoms in OCD (Saxena et al., 2009). Dysfunctions in areas related to the CSTC circuits may also be relevant in the maintenance of obsessive-compulsive symptoms in AN.

A positive association between obsessive-compulsive symptoms and GMV in the left hippocampus was found in the HC group. Literature has proposed the hippocampus to be involved in the pathophysiology of OCD through its mediating effect on affective and cognitive processes. For instance, a study by Rao et al. (2018) found a negative correlation between compulsion scores and the left posterior hippocampus in OCD patients. While my finding was observed in the HC group, existing research mainly investigates hippocampal GMV in OCD patients. For example, Reess et al. (2018) reported significant differences in hippocampal GMV across various OCD symptom profiles, observing lower hippocampal GMV in patients with higher severity of ordering and checking symptoms compared to HC. My findings in HC might suggest a complex involvement of the hippocampus in obsessive-compulsive symptoms beyond what is typically observed in clinical OCD populations, or hint at subclinical mechanisms.

Taken together, these exploratory findings may suggest that the neurobiological correlates of obsessive-compulsive symptoms in AN are not uniform but rather shift with illness stage. It is also noteworthy that some brain areas that showed associations, particularly those within the cingulate cortex and related to CSTC circuits, are well-documented as relevant in OCD, potentially underscoring common underlying neurobiological pathways for obsessive-compulsive behaviors across disorders. However, these findings should be interpreted with extreme caution due to significant methodological limitations. The exploratory nature of these analyses, together with small and uneven group sizes, limits their generalizability and statistical power. Thus, these findings should be seen as preliminary and primarily used for hypothesis generation. Future studies with larger sample sizes and ideally

longitudinal designs are needed to replicate those findings and further investigate the dynamic relationship between obsessive-compulsive symptoms and brain structure throughout the course of AN.

**Limitations**

It is important to acknowledge certain limitations of this study. One of the primary limitations is the relatively small sample size of each subgroup, which ranged from 19 to 33 participants. This reduces the statistical power of the results and can increase Type 1 errors (false positives). Furthermore, such small sample sizes are insufficient to reliably detect small brain-behavior associations. Recent literature suggests that while the median neuroimaging study sample size is around 25, very large sample sizes of thousands of individuals are required for robust brain-behavior associations (Button et al., 2013; Marek et al., 2022). However, such standards are difficult to meet in studies involving well-characterized clinical subgroups, as the specific diagnostic and clinical criteria make recruitment of large samples difficult. Within the framework of the larger project, I aimed to address this by including the maximum number of participants available. Furthermore, group sizes are unequal, with larger sample sizes in the HC and PR-AN groups, which may have selectively increased power in these groups and thereby skewed the results.

Moreover, the use of the lenient statistical threshold of $p < .001$ without multiple comparisons correction in the brain-behavioral analysis can increase type 1 errors, making findings more vulnerable to noise. This approach was chosen due to the explorative nature of the study, aiming to identify potential associations. Therefore, these findings should be treated with caution, as false positives are expected at a higher rate than usual.

Age was an inherent factor of the study design; for instance, acutely ill AN patients are logically younger than fully remitted patients, as achieving full remission requires being symptom-free and at normal weight for at least 12 months. Consequently, participants in the AI-AN group were significantly younger than those in the other groups. This demographic difference was addressed by controlling for age in the MRI analyses. For the behavioral analysis, preliminary tests showed that the inclusion of age did not alter the significance of the main findings, allowing standard ANOVA to be used. While groups were not matched for age, the decision to include age as a covariate in all relevant analyses addressed the potential confounding effects of age on the results.

Due to the cross-sectional design, interpretations regarding the reversibility of obsessive-compulsive symptoms and GMV alterations should be treated with caution as prior

state or causality cannot be ascertained. However, conducting a longitudinal study would be very complex and difficult, given the low prevalence of the disorder, the high relapse rate, and the long time required for individuals to achieve full remission. It is also important to note that structural GMV differences do not necessarily indicate that there are any functional brain differences. To show functional alterations of brain areas, fMRI studies with specific tasks are needed.

A further limitation is that I did not control for comorbid psychiatric disorders, medication use, or different types of therapy received by the participants. These factors could have potentially confounded my results. Particularly, the absence of an OCD diagnostic assessment may have masked scores elevated due to OCD comorbidity, thereby leading to misinterpretations of the prevalence of obsessive-compulsive symptoms that are inherent to AN.

Finally, another important limitation is that I only looked at the OCI-R total score that indicates obsessive-compulsive symptom severity, rather than analyzing the subscales. Analyzing the obsessive-compulsive subscales separately, especially in the brain-behavior analysis, might have revealed more specific results, as literature suggests certain subscales are more relevant in AN (Bastiani et al., 1996). Additionally, employing an ED-specific measure for obsessive-compulsive symptoms would have been beneficial, as this would have allowed for a more accurate assessment of how these symptoms manifest within the context of AN, potentially revealing unique patterns or specific areas for intervention that general OCD measurements might miss.

**Future Directions**

Building upon the insights gained from this study, several important directions emerge for future research. A primary focus should be on replicating and expanding these findings in larger, more diverse populations to enhance statistical power and generalizability, specifically, to be able to reliably detect brain-behavior correlations between obsessive-compulsive symptoms and GMV. Subsequent studies could do multi-center collaborations to achieve larger sample sizes. Longitudinal investigations are warranted to truly see individual changes over time and establish causality, rather than using cross-sectional designs. To address the imbalance in age distribution across groups, future research should perform age-matching when cross-sectional designs are used. Furthermore, studies should include more comprehensive data, including psychiatric comorbidities, medication, and type and length of therapy, to better be able to control for potential confounding effects. Furthermore, additional

use of OCI-R subscales or integrating other assessment tools, such as ED-specific measures for obsessive-compulsive symptoms, would provide a more comprehensive picture. Future research employing fMRI next to structural MRI, including obsessive-compulsive specific tasks, could further provide insight into the underlying neural mechanisms of these symptoms in AN. Future research should first focus on replicating and extending the identification of the aberrant brain regions identified in the brain-behavior analyses. Once these findings are established, investigations into their functional roles are warranted. Understanding the role of these regions in the context of AN recovery could provide important insights into the involvement of obsessive-compulsive symptoms in the recovery process, potentially leading to more targeted interventions.

**Conclusion**

This study contributes to the ongoing trait-or-state debate by combining behavioral and neuroimaging data across different illness stages of AN. My findings provide evidence that obsessive-compulsive symptoms are primarily state-dependent, as they are most elevated in the acute stage and tend to diminish with recovery and are not significantly elevated in the PR-AN and FR-AN groups compared to HC. This indicates that these symptoms may be reversible rather than fixed traits, highlighting the importance of sustained recovery. Furthermore, the findings of the VBM analysis comparing GMV across the groups indicate that GMV also normalize with full recovery, suggesting that GMV alterations are also, at least in part, state-related. Moreover, key brain regions with altered GMV in acutely ill AN patients of previous studies could be replicated, solidifying the neurobiological understanding of the acute illness stage. Specifically, while AI-AN and PR-AN demonstrated widespread GMV reductions compared to HC, the lack of significant GMV differences between AI-AN and PR suggests that partial remission may not be sufficient for full GMV recovery. In contrast, these apparent GMV reductions were largely absent in FR-AN patients, indicating a significant degree of GMV normalization with sustained recovery. This study provides initial evidence that the neurobiological correlates of obsessive-compulsive symptoms in AN are complex and stage-specific. The exploratory analysis revealed distinct patterns of associations between obsessive-compulsive symptoms and GMV across illness stages. These findings suggest that these neural correlates may shift with recovery progression, with some implicated brain areas aligning with those observed in OCD. While preliminary and subject to methodological limitations, these hypothesis-generating results, requiring caution, point

toward complex stage-specific neurobiological mechanisms of obsessive-compulsive symptoms in AN that warrant further investigation.

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## List of Abbreviations

| | |
|---|---|
| **ACC** | Anterior Cingulate Cortex |
| **AI-AN** | Acutely Ill Anorexia Nervosa |
| **AN** | Anorexia Nervosa |
| **AN-BP** | Anorexia Nervosa Binge-Eating/Purging Type |
| **ANCOVA** | Analysis Of Covariance |
| **ANOVA** | Analysis Of Variance |
| **AN-R** | Anorexia Nervosa Restricting Type |
| **BMI** | Body Mass Index |
| **BN** | Bulimia Nervosa |
| **CAT** | Computational Anatomoy Toolbox |
| **CSF** | Cerebrospinal Fluid |
| **CSTC** | Cortico-Striatal-Thalamo-Cortical |
| **DARTEL** | Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra |
| **DLPFC** | Dorsolateral Prefrontal Cortex |
| **DMN** | Default Mode Network |
| **ED** | Eating Disorder |
| **EDE** | Eating Disorder Examination |
| **fMRI** | Functional Magnetic Resonance Imaging |
| **FR-AN** | Fully Remitted Anorexia Nervosa |
| **FWE** | Family-Wise Error Rate |
| **FWHM** | Full Width At Half Maximum |
| **GM** | Gray Matter |
| **GMV** | Gray Matter Volume |
| **HC** | Healthy Control |
| **HSD** | Honestly Significant Difference |
| **IQR** | Image Quality Ratings |
| **L** | Left |
| **MNI** | Montreal Neurological Institute |
| **mPFC** | Medial Prefrontal Cortex |
| **MRI** | Magnetic Resonance Imaging |

| | |
|---|---|
| **OCD** | Obsessive-Compulsive Disorder |
| **OCI-R** | Obsessive-Compulsive Inventory-Revised |
| **OCPD** | Obsessive-Compulsive Personality Disorder |
| **OFC** | Orbitofrontal Cortex |
| **PR-AN** | Partially Remitted Anorexia Nervosa |
| **R** | Right |
| **SMA** | Supplementary Motor Area |
| **SPM** | Statistical Parametric Mapping |
| **SPSS** | Statistical Package For Social Sciences |
| **TIV** | Total Intracranial Volume |
| **VBM** | Voxel-Based Morphometry |
| **WM** | White Matter |
| **Y-BOCS** | Yale-Brown Obsessive-Compulsive Scale |

# Appendix

## Abstract (EN)

Anorexia nervosa (AN) is a complex psychiatric disorder which often encompasses elevated obsessive-compulsive behavior and gray matter volume (GMV) alterations, but it remains unclear how these two aspects interrelate across different illness stages. This study aimed to elucidate the relationship between obsessive-compulsive symptoms and GMV in female adolescents with AN at various illness stages. Obsessive-compulsive symptoms were measured by the Obsessive-Compulsive Inventory-Revised (OCI-R) in a cohort of 121 participants, comprising acutely ill (AI-AN), partially remitted (PR-AN), and fully remitted (FR-AN) AN patients, alongside healthy controls (HC). A subset of 109 participants underwent structural neuroimaging, and voxel-based morphometry was employed to analyze GMV. The results revealed significantly higher OCI-R scores in the AI-AN group compared to all other groups, which did not differ from one another. AI-AN and PR-AN showed no GMV differences between each other, but reductions in cerebellar, frontal, temporal, and subcortical regions compared to HC, while FR-AN notably displayed no GMV differences compared to HC. An exploratory analysis examining differences in associations between OCI-R scores and GMV across groups found a single positively associated region shared by all groups, while distinct patterns of associations were found within individual groups. These findings indicate that obsessive-compulsive symptoms and brain structural alterations in AN are largely state-dependent, tending to normalize with sustained remission. While the neural correlates of obsessive-compulsive behavior potentially shift across illness stages, this preliminary observation is limited by methodological shortcomings.

**Abstract (DE)**

Anorexia nervosa (AN) ist eine komplexe psychiatrische Störung, die häufig mit ausgeprägter Zwangssymptomatik und Veränderungen im Volumen der grauen Substanz einhergeht. Der Zusammenhang beider Aspekte über verschiedene Krankheitsstadien hinweg ist jedoch unklar. Die vorliegende Studie zielte darauf ab, die Beziehung zwischen Zwangssymptomen und dem Volumen der grauen Substanz bei weiblichen Adoleszenten mit AN in unterschiedlichen Krankheitsphasen aufzuklären. Die Zwangssymptomatik wurde mittels des Obsessive-Compulsive Inventory-Revised (OCI-R) bei 121 Teilnehmerinnen erfasst, darunter akut kranke, teilremittierte und vollständig remittierte Patientinnen sowie gesunde Kontrollpersonen. In einer Subgruppe von 109 Teilnehmerinnen wurde das Volumen der grauen Substanz mittels struktureller Neurobildgebung und voxelbasierter Morphometrie analysiert. Die Ergebnisse zeigten signifikant höhere OCI-R-Werte bei akut kranken AN-Patientinnen im Vergleich zu allen anderen Gruppen, die sich nicht voneinander unterschieden. Die akut kranken und teilremittierten Patientinnen zeigten untereinander keine Unterschiede im Volumen der grauen Substanz, jedoch Reduktionen in zerebellaren, frontalen, temporalen und subkortikalen Hirnarealen im Vergleich zu den Kontrollpersonen. Bemerkenswerterweise wiesen die vollständig remittierten Patientinnen keine Unterschiede im Volumen der grauen Substanz zu den Kontrollpersonen auf. Eine explorative Analyse, die die Unterschiede in den Assoziationen zwischen OCI-R-Werten und dem Volumen der grauen Substanz über alle Gruppen hinweg untersuchte, fand ein einzelnes positiv assoziiertes Hirnareal, das sich in allen Gruppen zeigte, während innerhalb der Gruppen unterschiedliche Assoziationen gefunden wurden. Diese Befunde deuten darauf hin, dass Zwangssymptome und hirnstrukturelle Veränderungen bei AN größtenteils vom aktuellen Krankheitsstand abhängen und sich mit anhaltender Remission normalisieren. Die neuronalen Korrelate zwanghaften Verhaltens könnten sich über die Krankheitsstadien hinweg verändern; diese vorläufige Beobachtung ist jedoch durch methodische Mängel limitiert.

**Robustness Checks for Analyses**

To ensure the robustness of my primary findings, I performed supplementary analyses using non-parametric and robust parametric tests.

***Age***

The Shapiro-Wilk test revealed significant deviations from normality in two of the four groups: HC ($W$ = .888, $p$ = .002) and AI-AN ($W$ = .916, $p$ = .024). Normality was given in PR-AN ($W$ = .956, $p$ = .174) and FR-AN ($W$ = .958, $p$ = .468). Levene's test indicated homogeneity of variances across groups ($F(3, 117) = 0.320$, $p$ = .811).

A non-parametric Kruskal-Wallis H test was performed to examine group differences in age. The Kruskal-Wallis H test revealed a significant effect for age across all groups ($\chi^2(3) = 16.683$, $p < .001$). Pairwise comparisons with Bonferroni correction for multiple tests to identify specific group differences were performed. The pairwise comparisons showed that the AI-AN group was significantly younger than the HC ($p$ = .026), FR-AN ($p < .011$), and PR-AN group ($p$ = .001). No significant differences were found between PR-AN and FR-AN ($p > .999$), PR-AN and HC ($p > .999$), and FR-AN and HC ($p > .999$).

***BMI***

The Shapiro-Wilk test revealed significant deviations from normality in two of the four groups: HC ($W$ = .876, $p < .001$) and AI-AN ($W$ = .869, $p$ = .002). Normality was given in PR-AN ($W$ = .957, $p$ = .189) and FR-AN ($W$ = .978, $p$ = .900). Levene's test indicated homogeneity of variances across groups ($F(3, 117) = 0.674$, $p$ = .570).

A non-parametric Kruskal-Wallis H test was performed to examine group differences in BMI. The Kruskal-Wallis H test revealed a significant effect for BMI across all groups ($\chi^2(3) = 54.128$, $p < .001$). Pairwise comparisons with Bonferroni correction for multiple tests to identify specific group differences were performed. The pairwise comparisons showed that the AI-AN group had significantly lower BMI than HC ($p < .001$), FR-AN ($p < .001$), and PR-AN groups ($p < .001$). No significant differences were found between the PR-AN and FR-AN ($p > .999$), PR-AN and HC ($p > .999$), and FR-AN and HC ($p > .999$).

***Obsessive-Compulsive Symptoms***

Descriptive statistics for OCI-R total scores revealed the following: AI-AN group (Median = 27.00, IQR = 18.00 - 40.00 ; Mean = 28.48 , SD = 14.75), PR-AN group (Median = 14.00, IQR = 9 - 22, Mean = 16.40, SD = 10.35), FR-AN group (Median = 8.00,

IQR = 3.50 - 12.50; Mean = 10.71, SD = 9.53), and HC (Median = 12.00, IQR = 8.00 - 19.00; Mean = 14.22, SD = 8.25).

Robust Welch's ANOVA was conducted to examine if there were significant group differences in OCI-R scores. It revealed a significant group effect for OCI-R total scores across all groups ($F(3, 58 = 9.4, p < .001$). Games-Howell post-hoc contrasts showed that the AI-AN group reported significantly higher OCI-R scores than HC ($p < .001$), FR-AN ($p < .001$), and PR-AN groups ($p = .003$). No significant differences were found between the PR-AN and FR-AN ($p = .171$), PR-AN and HC ($p = .762$), and FR-AN and HC ($p = .503$).

A non-parametric Kruskal-Wallis H test was performed to examine group differences in OCI-R scores. The Kruskal-Wallis H test revealed a significant effect for OCI-R total scores across all groups ($\chi^2 (3) = 20.183, p < .001$). The overall median OCI-R total score was 15. Pairwise comparisons with Bonferroni correction for multiple tests to identify specific group differences were performed. The pairwise comparisons showed that AI-AN reported significantly higher OCI-R scores than HC ($p = .001$), FR-AN ($p < .007$), and PR-AN ($p = .001$). No significant differences were found between the PR-AN and FR-AN ($p > .999$), PR-AN and HC ($p > .999$), and FR-AN and HC ($p > .999$).

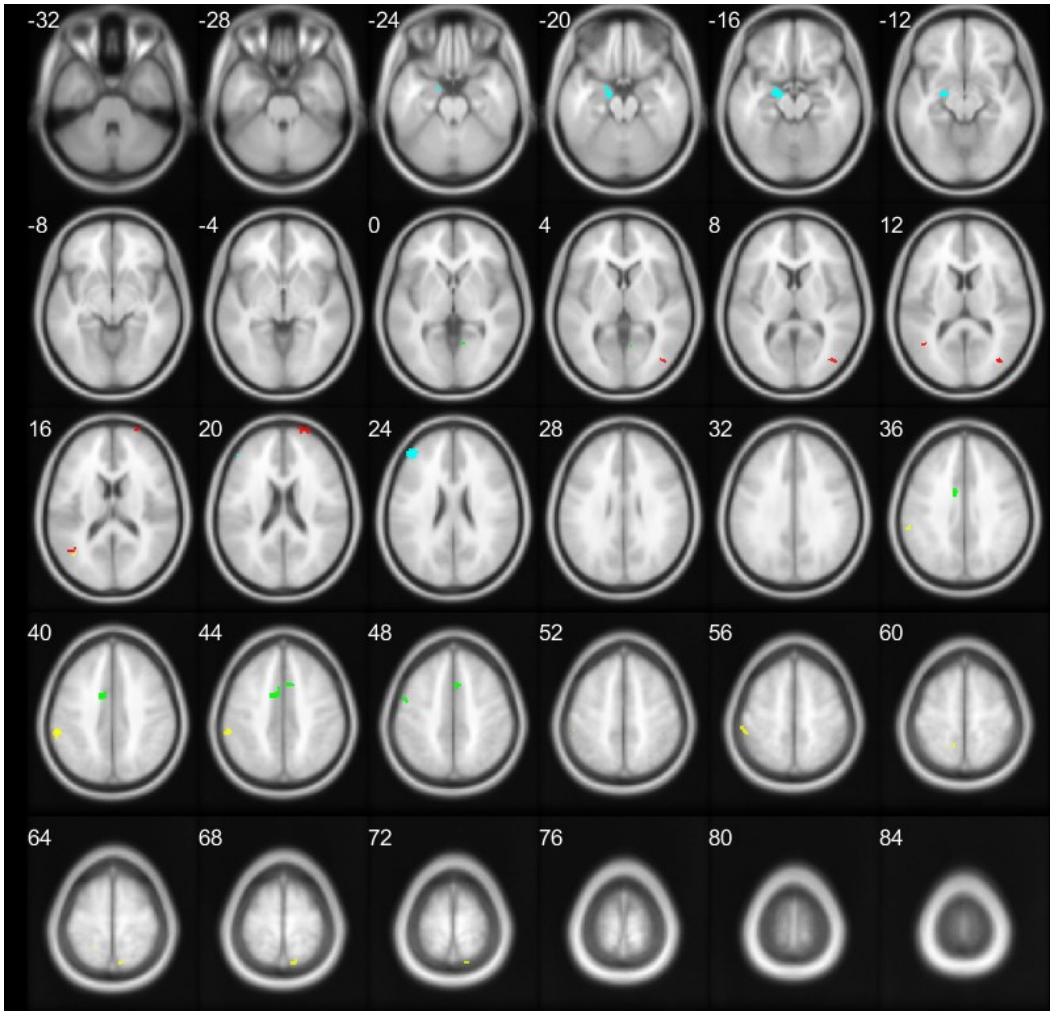
**Detailed Exploratory ANCOVA Results**

An exploratory ANCOVA was conducted to assess the potential confounding effect of age on OCI-R total scores. The ANCOVA revealed that age did not have a significant effect on OCI-R total scores ($F(1,116) = 2.11, p = .149, \eta_p^{2 =} .018$). After controlling for age, the main effect of group remained significant ($F(3,116) = 10.61, p < .001, \eta_p^2 = .215$). Post-hoc comparisons using the Bonferroni adjustment revealed that the AI-AN group (adjusted $M = 27.54$, standard error (SE) = 2.12) reported significantly higher OCI-R scores than HC (adjusted $M = 14.33$, SE = 1.81) $p < .001$, FR-AN (adjusted $M = 11.05$, SE = 2.38) $p < .001$, and PR-AN groups (adjusted $M = 16.87$, SE = 1.86) $p = .002$. No significant differences were found between the PR-AN and FR-AN ($p = .330$), PR-AN and HC ($p > .999$), and FR-AN and HC ($p > .999$).

## Supplementary Figures

### Figure A 1

*Brain Regions Showing Positive Associations Between Gray Matter Volume and Obsessive-Compulsive Symptoms Across Groups*



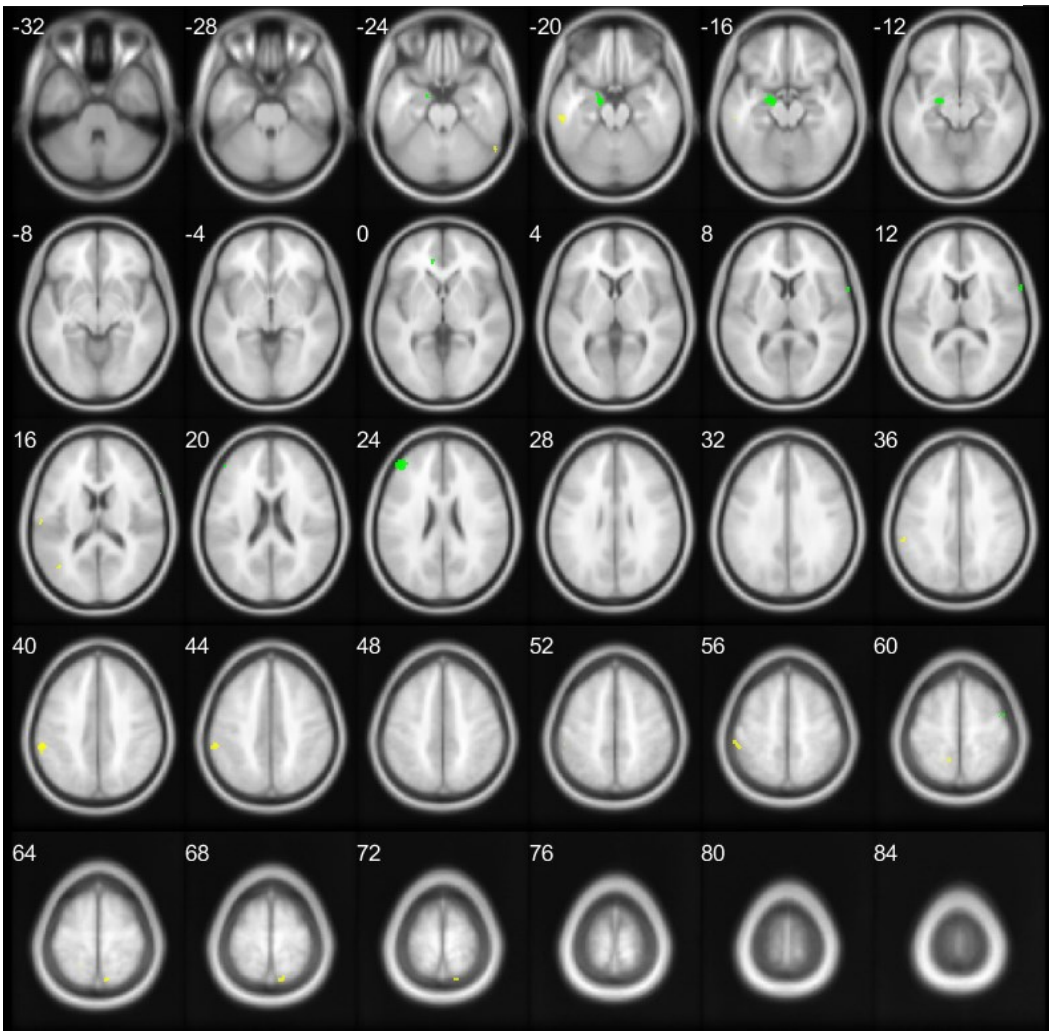

*Note.* Brain regions showing positive associations between gray matter volume and obsessive-compulsive symptoms in acutely ill (red), partially remitted (yellow), fully remitted (blue) anorexia nervosa patients, and healthy controls (green) are displayed

Statistical threshold of $p < .001$ uncorrected

$k > 20$

**Figure A 2**

*Brain Regions Showing Negative Associations Between Gray Matter Volume and Obsessive-Compulsive Symptoms in PR-AN and HC*




*Note.* Brain regions showing negative associations between gray matter volume and obsessive-compulsive symptoms in partially remitted anorexia nervosa patients (yellow) and healthy controls (green) are displayed.
Statistical threshold of $p < .001$ uncorrected
$k > 20$
HC: healthy control, PR-AN: partially remitted anorexia nervosa