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Titel | Title

Special Features of the Anorexia Nervosa Brain

Associations between gray matter volume and cognitive flexibility across different stages of anorexia nervosa in adolescents and young adults compared with healthy controls

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Introduction

Anorexia nervosa (AN) is a psychiatric disorder with global prevalence and morbidity and mortality rates higher than any other psychiatric illness (Attia, 2010; Smink et al., 2012; Van Eeden et al., 2021).

According to DSM-5, three main criteria must be met for being diagnosed with anorexia nervosa (American Psychiatric Association, 2013). The first criterion is met if there is a restriction of energy intake in relation to actual body needs (American Psychiatric Association, 2013). This restriction leads to a significantly reduced body weight (American Psychiatric Association, 2013). The second criterion is met if weight gain causes severe anxiety or if the patient engages in persistent behaviors that prevent weight gain (American Psychiatric Association, 2013). The last criterion is met if the patient experiences anxiety about body weight or shape, if body weight or shape affect their self-esteem, or if they ignore the health consequences of being underweight (American Psychiatric Association, 2013).

There are two different types of Anorexia nervosa defined by DSM-5 (Eddy et al., 2015). The two types are restrictive AN and AN with the bulimic symptoms binge and purge (Eddy et al., 2015). Patients with restrictive AN achieve weight loss mainly through the restriction of their food intake (Eddy et al., 2015). AN patients with bulimic symptoms, as well as restricting food, purge their food, either with or without binge eating (Eddy et al., 2015). The main distinction between AN with bulimic symptoms and bulimia nervosa is the patients´ low body weight (Attia, 2010).

Anorexia nervosa usually emerges during adolescence (Bohon et al., 2020). It is particularly prevalent among young women (Smink et al., 2012). The highest-risk group is girls aged 15 to 19 (Smink et al., 2012). In recent decades, the incidence rate in this group has increased, although the overall prevalence of anorexia nervosa has remained relatively stable (Smink et al., 2012; Van Eeden et al., 2021). In women, the lifetime prevalence of AN is 4 percent (Van Eeden et al., 2021).

Cognitive flexibility in anorexia nervosa

Evidence-based treatments for anorexia nervosa often have a high relapse rate (Khalsa et al., 2017). The current treatments focus primarily on restoring weight (Treasure & Schmidt, 2013) rather than addressing the underlying factors that contribute to the maintenance of the disorder. Endophenotypes and genetic predisposition associated with AN may prevent successful treatment (Attia, 2010; Weinbach et al., 2019). Individuals with eating disorders

(ED) often exhibit inflexible behaviors, which are mostly related to eating, weight, and body shape (Friederich et al., 2012; Tchanturia et al., 2012). They are trapped in their anorexic behavior, which includes counting calories, ritualizing eating behaviors and excessive exercising (Friederich et al., 2012; Tchanturia et al., 2012). These behaviors reinforce their illness (Tchanturia et al., 2012). Studies attribute this behavior to impairments in cognitive flexibility (Tchanturia et al., 2012).

Cognitive flexibility is the process of adapting thoughts and behavior to changing circumstances (Deák, 2004; Fuglset, 2021). Set shifting, the mental ability to flexibly switch tasks or behavior in response to changing rules, is one of the best-known measurable constructs of cognitive flexibility (Miles et al., 2020; Shott et al., 2012). Cognitive flexibility can be tested when the requirements of a situation are unpredictable or changeable, making automated responses impossible (Deák, 2004). The Wisconsin Card Sorting Test (WCST) is a neurological test to assess set shifting ability (Tchanturia et al., 2012). The most important parameter for measuring set shifting is perseveration (Tchanturia et al., 2012). Perseveration is defined as continuing an old reaction to a stimulus, rule, or situation after a change has occurred and feedback indicates that the old reaction is no longer appropriate (Tchanturia et al., 2012).

Impairments in cognitive flexibility, particularly set shifting, are one of two core characteristics identified in numerous neuropsychological studies of anorexia nervosa (Tchanturia et al., 2011). Moreover, set shifting skills in AN are independent of body mass index (BMI), anxiety and depression (Fuglset, 2021).

Some evidence suggests that weak cognitive flexibility could be an endophenotype of anorexia nervosa (Treasure & Schmidt, 2013). The criteria that define an endophenotype are that it is associated with the illness, heritable, largely independent of the current disease state, co-segregates with the disorder within families, and occurs in family members at a higher rate than in the general population (Gottesman & Gould, 2003). The last criterion is supported by findings showing impairments in cognitive flexibility observed in unaffected sisters of AN patients (Holliday et al., 2005; Roberts et al., 2010).

Previous literature about cognitive flexibility in anorexia nervosa

A common finding across previous literature is that acute AN adults show impairment in set shifting (Danner et al., 2012; Holliday et al., 2005; Tchanturia et al., 2011, 2012). In line with this is the systematic review and meta-analysis by Roberts et al. (2007). They found that

individuals with eating disorder exhibit impairments in set shifting across multiple neuropsychological tests.

In contrast Miles et al. (2022) found no significant group differences in cognitive flexibility between low-, medium-, and high-risk groups of AN as well as between participants with lifetime AN across neurocognitive tests. The researchers clustered the participants into low-, medium-, and high-risk groups based on their level of depression, neuroticism, and weight concerns. Additionally, they explored self-reported cognitive flexibility in adults with AN. The researchers observed significantly weaker cognitive flexibility in the high-risk AN group compared to the low and medium-risk AN groups. The medium-risk AN group had exhibit weaker cognitive flexibility than the group with the low-risk of AN. Individuals with lifelong AN reported significantly weaker cognitive flexibility compared to the low and medium-risk groups.

Furthermore, the majority of studies that assessed set shifting using the WCST reported that adults with acute AN showed significantly more perseveration errors compared to healthy control subjects (Fitzpatrick et al., 2012; Lang et al., 2014; Shott et al., 2012; Steinglass et al., 2006; Westwood et al., 2016). Additionally, adults with AN performed significantly worse than healthy controls in most domains of the WCST (Tchanturia et al., 2012).

Conversely, Talbot et al. (2015) found no significant difference in performance between acute AN adults and healthy controls when evaluating with the WCST.

Moreover, previous literature found evidence of impairments at cognitive flexibility in different AN stages. Across studies, fully remitted AN patients perform poorer in set shifting compared to healthy controls as measured by the Berg's Card Sorting Test (Danner et al., 2012; Lindner et al., 2014).

When evaluated with the WCST, partially and fully remitted AN patients showed significantly more perseverative errors compared to healthy controls, which could signal impairments in cognitive flexibility (Talbot et al., 2015). In the study by Tchanturia et al. (2012), fully remitted AN adults performed better in the WCST than the acute AN adults. Compared to healthy controls, they showed significant impairments in perseverative errors, conceptual level responses and in the numbers of categories completed in the WCST.

At the same time, the studies by Roberts et al. (2010) and Tchanturia et al. (2011) were unable to find this significant differences in cognitive flexibility between fully remitted AN

adults and healthy controls. Additionally, in the study of Tchanturia et al. (2011) fully remitted AN adults did not significantly differ from the acute AN adults. The researcher concluded that fully remitted AN patients demonstrated an intermediate cognitive flexibility profile between acute AN adults and healthy controls.

While evidence on impaired set shifting in adults with anorexia nervosa after weight restoration and full recovery is inconsistent (Miles et al., 2020), impairments in adults with acute AN have been well established in previous studies (Danner et al., 2012; Holliday et al., 2005; Tchanturia et al., 2011, 2012). However, it remains unclear whether these impairments are also present in the younger AN population (Lang et al., 2014). The literature on set shifting in adolescents and young adults delivers contradictory and inconsistent findings (Weinbach et al., 2019).

The majority of previous studies found no significant difference in cognitive flexibility between children and adolescents with AN and healthy controls across different neurological tests (Fitzpatrick et al., 2012; Lang et al., 2014; Shott et al., 2012; Westwood et al., 2016). As research in this population is in its early stages, findings indicating no significant differences should be interpreted with caution (Lang et al., 2014). Additionally, due to limited sample sizes in children and adolescents AN studies, the not significant results may be due to type II errors (Westwood et al., 2016).

McAnarney et al. (2011) registered significantly poorer set shifting performance in acute AN adolescents compared to healthy controls across neurological tests. Similarly, Lang et al. (2015) recorded significantly more perseverative errors and perseverative responses in children and adolescents with AN compared to healthy controls. The study participants, aged 11 – 18, were evaluated with the WCST.

In contrast, the meta-analysis of Lang et al. (2014) could not show on a significant level that children and adolescents with AN performed poorer at set shifting than the healthy controls.

While literature on cognitive flexibility ability of adolescents and young adults with acute AN is already limited, even fewer studies have investigated adolescents and young adults in recovery stages of AN, and their findings are highly heterogeneous.

In the study by Weinbach et al. (2019), partially remitted AN adolescents demonstrated superior visual-motor and verbal set shifting abilities compared to healthy controls. However, when the researchers investigated only set shifting abilities while controlling for inhibitory

abilities, partially remitted AN adolescents performed poorer compared than HC. In contrast, Bohon et al. (2020) found no significant difference in perseverative errors between partially remitted AN adolescents and healthy controls.

To the best of my knowledge, no previous study has investigated set shifting in full remitted adolescents and young adults with anorexia nervosa.

Cognitive flexibility in the AN brain

Impairments in cognitive flexibility in patients with AN may indicate underlying brain abnormalities (Steinglass et al., 2006). There is growing evidence of brain abnormalities associated with AN (Castro-Fornieles et al., 2019), but little is known about the relationship between cognitive flexibility and anorexia nervosa in the younger patient population (Lang et al., 2015).

General GMV differences in AN

A previous meta-analysis of nine voxel-based morphometry (VBM) studies involving a total of 228 adults and adolescents with AN and 240 healthy controls revealed a reduction in gray and white matter in patients with acute AN compared to healthy controls (Titova et al., 2013). Reduction in acute AN patients in gray matter volume (GMV) is supported by previous studies (Castro-Fornieles et al., 2009; Seitz et al., 2016). In addition, Seitz et al. (2016) found that adolescents with acute AN showed a significantly greater reduction in gray matter (GM) than adults with AN.

The existing literature reveals patterns regarding which brain regions are affected by AN. Acute AN patients demonstrated reduced GMV in the left hypothalamus, left inferior parietal lobe (Brodmann area 39), right caudate and right lentiform nucleus (Titova et al., 2013). These regions are associated with the regulation of appetite and somatosensory perception (Titova et al., 2013). This perception is often affected by anorexia nervosa (Titova et al., 2013). Moreover, no significant increases as well as no significant difference in hemisphere lateralization was revealed (Titova et al., 2013). The results of Friederich et al. (2012) support these findings, as they also did not find significant increases in GMV in patients with AN compared to healthy controls. Their findings regarding GMV decreases align with the findings of Titova et al. (2013) only on the adjacent, non-overlapping region of the putamen. In addition to this region, Friederich et al. (2012) found decreases in GMV in the right amygdala/insula extending in the putamen, left hippocampus extending in the amygdala and putamen, the right dorsal ACC and the supplementary motor area (SMA) in acute AN

patients compared to healthy controls. Previous literature supports decreases in the left hippocampus (Amianto et al., 2013) as well as in the SMA (Amianto et al., 2013; Boghi et al., 2011) of acute AN patients. Additionally, Amianto et al. (2013) found GMV decreases in the cerebellum, right precentral gyrus, right supramarginal gyrus, right occipital inferior gyrus, left fusiform gyrus and right thalamus in AN patients compared to healthy controls. Previous literature supports decreases in acute AN patients in the GMV in the cerebellum and left fusiform gyrus (Boghi et al., 2011; Brooks et al., 2011). The results of Nickel et al. (2018) support decreases in GMV in acute AN patients in the hippocampus, but they found decreases in the right hippocampus. Moreover, they found reduced GMV in acute AN patients in the right inferior frontal gyrus and left middle inferior frontal gyrus.

Friederich et al. (2012) findings revealed no regions with greater GMV in partially remitted AN patients compared to healthy controls. Partially remitted adults showed an enduring GMV reduction (Seitz et al., 2016). They also showed decreased GMV in the right dorsal ACC, right SMA and the right inferior frontal operculum compared to healthy controls (Friederich et al., 2012). Castro-Fornieles et al. (2009) found decreases in GMV between PRAN and HC. More specifically, GMV decreases in the SMA, cingulum and paracentral lobule. On the contrary, other studies found no differences in GMV in partially remitted AN adolescents when comparing them to healthy controls (Lázaro et al., 2013; Mainz et al., 2012). When Mainz et al. (2012) applied a less stringent statistical threshold ($p < .001$, uncorrected, with an extent threshold of 100 voxels), they observed differences in GMV between PRAN and HC primarily in premotor, frontal, and parietal regions.

There were no regions that showed greater GMV in acute AN patients compared to partially remitted ones (Friederich et al., 2012). Acute AN patients showed when compared to partially remitted AN patients decreased GMV in the left amygdala, both sides of the putamen, and the left inferior temporal cortex (Friederich et al., 2012).

Previous research found no significant GMV reduction between fully remitted AN women and healthy controls (Bang et al., 2016; Nickel et al., 2018; Seitz et al., 2016). Joos et al. (2011) reported no significant differences in GMV between FRAN and HC in the dorsal anterior cingulate cortex, which indicates full recovery in this region. G. Frank et al. (2013) found reduction in GMV in the caudate and putamen volume and greater GMV in the left orbitofrontal cortex and right insula in FRAN compared to HC.

Previous studies found greater GMV in fully remitted AN patients compared to acute AN patients (G. Frank et al., 2013; Joos et al., 2011; Nickel et al., 2018). G. Frank et al. (2013) found decreased GMV in the right dorsal caudate in fully remitted AN patients compared to acute AN patients. Nickel et al. (2018) conducted a ROI-based analysis of GMV derived from VBM. They reported significant greater GMV in fully remitted AN patients compared to those in acute phase in several brain regions, including the superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, left middle orbitofrontal gyrus, lateral orbitofrontal gyrus, left gyrus rectus, right superior parietal gyrus, left angular gyrus, superior temporal gyrus, right middle temporal gyrus and right hippocampus.

Associations between GMV and cognitive flexibility

Specific brain abnormality could explain why AN patients have difficulties with cognitive flexibility (Steinglass et al., 2006). Previous studies and a meta-analysis have shown that increased GMV in the right anterior insula and lateral part of the prefrontal cortex correlates with greater cognitive flexibility (Müller et al., 2015; Yuan & Raz, 2014). In addition, Zhu et al. (2019) revealed that decreased GMV in the temporal cortex is associated with greater cognitive flexibility. Moreover, GMV in the temporal regions can significantly predict individual differences in cognitive flexibility (Zhu et al., 2019). This indicates the important role of the temporal cortex in cognitive flexibility performance (Zhu et al., 2019).

Association between GMV and cognitive flexibility in AN

In the specific population of AN patients little is known about the association between cognitive flexibility and structural brain differences due to limited VBM studies. Friederich et al. (2012) found a positive correlation between cognitive flexibility and right amygdala GMV in AN patients. However, after multiple testing this correlation was gone. Furthermore, they found a negative correlation between cognitive flexibility and right ACC gray matter volume in healthy controls.

Examining which regions of the brain are consistently active during cognitive flexibility tasks using functional magnetic resonance imaging studies (fMRI) could provide additional insights about important regions for cognitive flexibility performance in AN.

In several fMRI studies, reduced brain activity was observed during set shifting tasks (Castro-Fornieles et al., 2019; Sato et al., 2013; Zastrow et al., 2009). Castro-Fornieles et al. (2019) found reduced activation in the inferior and middle occipital and lingual gyri, fusiform gyri and cerebellum in 30 patients with AN aged 12 -17 during a set shifting task compared

to a control task. However, this significant difference disappeared after six months of treatment and restoration of nutrition. In the 2009 Zastrow et al. study, patients with AN showed reduced activation in the cerebellum during behavioral response shifting compared to healthy controls. Adding to that, the researchers found reduced activation during these tasks in the sensorimotor regions, left and right thalamus, anterior cingulate cortex and ventral striatum. This indicates that weak behavioral response shifting in AN might be connected with reduced activation in the ventral anterior cingulate-striato-thalamic loop (Zastrow et al., 2009). This loop is part of the motivation-behavior system (Zastrow et al., 2009). Sato et al. (2013) instructed their subjects to perform the WCST while undergoing fMRI and found that AN patients showed reduced activation in the right ventrolateral prefrontal cortex and bilateral parahippocampal cortex compared to healthy controls.

However, AN patients showed greater brain activation during set shifting tasks as a dominant activation in frontal and parietal brain regions, more specifically in the right ventral frontoparietal network (Zastrow et al., 2009). This activation suggests that a demanding and supervisory cognitive control is needed during behavioral response shifting in AN (Zastrow et al., 2009). During the WCST, AN patients showed a greater activation in the cingulate cortex and striatum, insula, and occipital cortex (Sato et al., 2013).

In previous fMRI studies, healthy controls showed greater activation in the subcortical brain regions such as the thalamus and striatum, the dorsolateral prefrontal cortex, the anterior insula/ventrolateral prefrontal cortex, the parietal cortex, premotor brain regions reaching into the dorsal anterior cingulate cortex, and the cerebellum (Zastrow et al., 2009). During the WCST, healthy controls demonstrated a correlation between higher performance and greater ventrolateral prefrontal activity compared to AN patients (Sato et al., 2013). These results indicate that impaired cognitive flexibility in AN is caused by impairments in the ventrolateral prefrontal cortex and parahippocampal cortex (Sato et al., 2013). Furthermore, healthy controls exhibited activity in the LPFC, cingulate cortex, PHC and basal ganglia in both hemispheres while performing the WCST (Sato et al., 2013).

The present study

Although previous studies have investigated cognitive flexibility in individuals with anorexia nervosa, findings for adolescents and young adults at different stages of the illness are inconsistent (Lang et al., 2014) and limited. Moreover, as of today, little is known about the association between cognitive flexibility and structural brain differences due to limited

VBM studies. This lack of understanding highlights the need for further investigation. This study´s aim is to fill this gap.

Our study extended the previous research not only by the chosen age group, but also by adding an additional illness stage: partially remitted anorexia nervosa. Therefore, our study included all three different illness stages of AN: acute AN, partially remitted AN and fully remitted AN (Brodrick et al., 2021; Tchanturia et al., 2012). For this reason, our results may provide a deeper understanding of the anorexia nervosa recovery processes related to cognitive flexibility, as well as different brain abnormalities (Brodrick et al., 2021). This also may provide valuable insights into the recovery process of affected brain regions in adolescent AN patients, whose brains may be more plastic than those of adults due to ongoing development (Mainz et al., 2012).

It is especially important to examine cognitive flexibility in adolescence and young adults, as adolescence is the age in which AN most commonly develops (Fitzpatrick et al., 2012). Furthermore, cognitive functions develop rapidly in the period from ten to fifteen years (Fitzpatrick et al., 2012; Tervo-Clemmens et al., 2023; Timko et al., 2024) until they stabilize in late adolescence or young adulthood (Tervo-Clemmens et al., 2023; Timko et al., 2024).

The understanding of whether adolescents and young adults with AN also exhibit set shifting impairments could provide evidence for cognitive flexibility to be an endophenotype for AN (Fitzpatrick et al., 2012; Lang et al., 2015). If there is no association, this suggests that impairments in cognitive flexibility in adults are more likely to be a consequence of AN (Fitzpatrick et al., 2012; Lang et al., 2015).

Another indication that cognitive inflexibility is a consequence of AN would be if impairments in cognitive flexibility improved with recovery from the illness (Miles et al., 2020). To develop an understanding of this, we are investigating in this study different illness stages of AN (Miles et al., 2020).

If the role of cognitive flexibility is confirmed to be an endophenotype of AN, cognitive flexibility could be used as a marker for the diagnosis of AN in the future (Lang et al., 2015). Moreover, it could support the differential diagnosis of AN (Lang et al., 2015).

Additionally, with our study we improve the general understanding of the neurobiological and genetic basis of AN in the younger population (Lang et al., 2015). Clarifying neurocognition in adolescents and young adults with AN would be beneficial for the

development of effective treatments (Lang et al., 2015). For adults with AN, cognitive remediation therapy (CRT) is a popular and effective treatment therapy (Lang et al., 2015). CRT is a behavioral intervention with the main goal of improving cognitive impairments as cognitive flexibility (Lang et al., 2014; Timko et al., 2024). Therefore, knowing if cognitive flexibility is impaired in adolescents and young adults with AN helps target the right impairments in therapy (Lang et al., 2014).

Research questions and hypotheses

The research questions of this study are the following.

RQ1: How does cognitive flexibility differ among participants with acute, partially, and fully remitted anorexia nervosa, as well as healthy controls?

The hypotheses are as follows:

- **H1a:** Participants with acute anorexia nervosa show weaker cognitive flexibility compared to those who are partially remitted, fully remitted, or healthy controls.
- **H1b**: Participants with partially remitted anorexia nervosa show weaker cognitive flexibility compared to those who are fully remitted or healthy controls.
- **H1c:** Participants with fully remitted anorexia nervosa show weaker cognitive flexibility compared to healthy controls.

RQ2: Do acute, partially, and fully remitted participants with anorexia nervosa and healthy controls show structural brain differences associated with variations in cognitive flexibility?

The hypotheses are as follows:

- **H2a:** Participants with acute, partially remitted and fully remitted anorexia nervosa and healthy controls demonstrate altered GMV across the whole brain compared to each other after controlling for age and TIV.
- **H2b:** Across acute, partially remitted and fully remitted anorexia nervosa patients and healthy controls cognitive flexibility is associated with altered GMV across the whole brain after controlling for age and TIV.
- **H2c:** The association between cognitive flexibility and GMV across the whole brain differs for acute, partially remitted and fully remitted anorexia nervosa patients and healthy after controlling for age and TIV.

Methods

This master´s thesis is part of the interdisciplinary project “AN-BEL cluster project - a translational psychiatric approach to adolescent anorexia nervosa - from genes to brain systems and behaviors.” This project is a collaboration between the University of Vienna and the Medical University of Vienna under supervision of Univ. Prof Dr. Silani and Univ.-Prof. Dr. med. univ. Karwautz. Data collection started in February 2022 and is expected to continue until November 2025.

Power analysis

An optimal sample size of 40 participants was determined a priori with G*Power (Faul et al., 2007) for the behavioral analysis. This calculation was based on a large effect (Cohen's f = 0.56) of set shifting, more specifically the parameter perseverative errors, in acute AN adults, fully remitted AN and healthy controls (Danner et al., 2012), with an α-error probability of 0.05 and a statistical power of 0.80. The study of Danner et al. (2012) differed from our study by investigating set shifting abilities in three groups instead of four. We additionally investigated set shifting abilities in partially remitted AN patients. Moreover, Danner et al. (2012) used a different measurement tool, the Berg´s Card Sorting Test, and tested adults instead of adolescents and young adults. Hence, the a priori optimal sample size should be interpreted with caution.

As previous studies did not report effect sizes for voxel-based morphometry analyses, it was not possible to conduct a priori power analyses.

Participants

The target number of participants for the AN-BEL cluster project is 150. This includes 30 per AN group and 60 healthy control subjects (HC).

To date, the sample comprises 139 participants. For this master’s thesis, 21 participants were excluded due to their prior exposure to the CKV in previous studies. Additionally, six participants were excluded due to missing CKV data. This left a total of 112 participants for the behavioral data analysis (see figure 1). The healthy control group contains 47 participants, the acute AN group 28, the partially remitted AN group 25 and the fully remitted AN group 12.

Furthermore, the brain data for 21 participants were missing, incomplete, or corrupted and therefore excluded from the voxel-based morphometry (VBM) analysis, resulting in a sample size of 91 (see figure 1). This left 35 participants in the healthy control group, 22 in

the acute AN group, 24 in the partially remitted AN group and 10 in the fully remitted AN group.

The inclusion criteria for participation in the AN-BEL project were identifying as female, being between 12 and 30 years old, and to be fluent in German. Participants in the AN group additionally had to have met the DSM-5 criteria for Anorexia Nervosa either currently or in the past (American Psychiatric Association, 2013).

The exclusion criteria for participation were an intellectual disability, organic psychosyndrome, psychotic disorder, bipolar disorder, current pregnancy, intolerance or dislike of milk, any condition that would prevent fMRI scanning, and any condition that impair the somatosensory function of the left arm. An additional exclusion criterion for healthy control participants was a history of eating disorders. Healthy controls were also excluded if they had any current psychological disorder. Additional exclusion criteria for acute AN participants included the presence of any eating disorder other than AN, either as primary or comorbid diagnosis.

Based on the Eating Disorder Examination interview, the AN participants were assigned to groups: acute AN (AAN), partially remitted AN (PRAN) or fully remitted AN (FRAN).

The criterion for the acute AN group was that participants met all DSM-5 diagnostic criteria for Anorexia Nervosa (American Psychiatric Association, 2013).

The criteria for the partially remitted group were a BMI above the 10th percentile for participants under 18 years of age and a BMI $\geq$ 18.5 for participants aged 18 or older. In addition, participants had to have a fear of gaining weight and/or a disturbance of body image. Restrictive eating behavior, binge eating or vomiting were not allowed. The total EDE score had to be within 2 standard deviations of the normal score and the status had to have lasted for at least three months.

The criteria for the fully remitted group were a BMI of at least 19 or a body weight of at least 85% of ideal body weight. Participants had to show no significant fear of gaining weight or disturbance of body image. In addition, they had to have no restrictive eating behavior, binge eating or vomiting. The total EDE score had to be within 1.5 standard deviation of normal score and the remission status had to have lasted for at least 12 months.

Participants were recruited at the department of Child and Adolescent Psychiatry at the Medical University of Vienna, via advertisements on social media, in schools, through a mailing list for people interested in research participation and through flyer campaigns in

Vienna. Participants received a 70 Euro voucher and a structural brain image as compensation for participation.

Study design

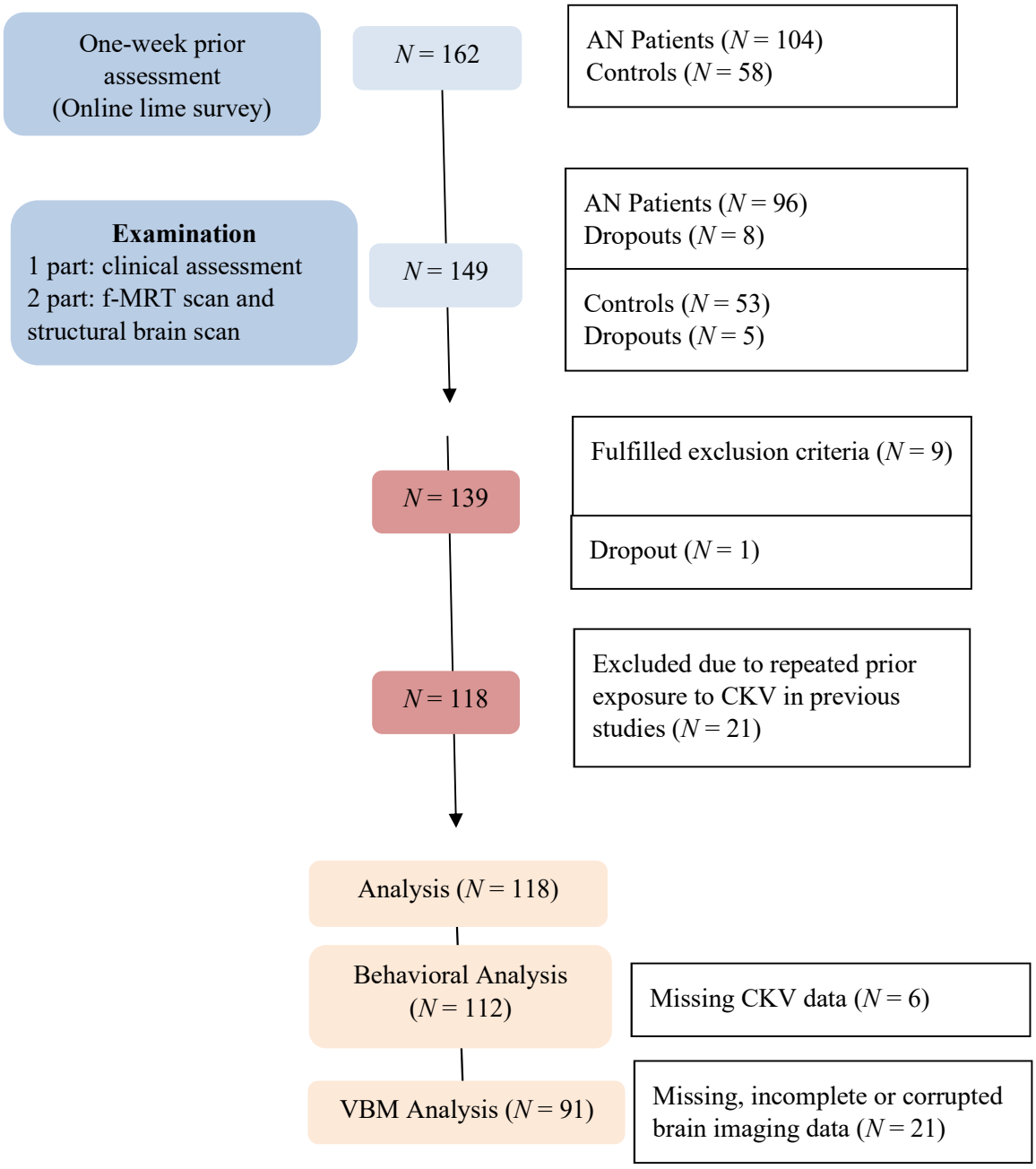
All interested participants completed an online questionnaire via Sosci Survey to verify whether they met the eligibility criteria. The AN participants additionally had to complete a short screening questionnaire about their current eating disorder symptoms. The screening questionnaire aimed to rule out eating disorders other than anorexia nervosa. For instance, the questionnaire included questions about whether the patient had a history of binge eating. The questionnaire also served to provide an initial indication of the AN illness stage group that the person was likely to be assigned. This assessment was done by asking specific questions from the German version of the Eating Disorder Examination interview from Hilbert et al. (2004). For instance, "Have you tried to lose weight in the last three months, or was it important for you not to gain weight?"

Participants eligible for the study received an examination appointment. One week before, they complete a one-hour online LimeSurvey containing demographic questions and multiple questionnaires (see figure 1). At about the same time, participants received a package with study information and consent forms, which they were asked to sign and bring with them to the examination.

The examination took place at the Department of Child and Adolescent Psychiatry at the University Hospital of Vienna. It was divided into two parts. The first part was a three-hour clinical assessment, conducted by a trained clinical psychologist or a trained psychology student. This assessment included weight and height measurements, neurological tests such as the "*Computergestütztes Kartensortierverfahren"* (CKV) from Drühe-Wienholt and Wienholt (2013) and clinical interviews using the German version of the Eating Disorder Examination interview (EDE) from Hilbert et al. (2004). Additionally, the structured diagnostic clinical interview (DIPS) from Margraf et al. (2017) was conducted to assess comorbid disorders in AN patients, as well as to screen the HC group for psychological disorders. The second part of the examination was a two-hour fMRI experiment. The final part was a 15-minute structural brain scan. The participants were asked to relax during these 15-minutes, and if needed, they were shown pictures of natural landscapes.

Figure 1

FLOW-diagram: Study design and exclusion of participants



Measurements

Eating Disorder Examination

The severity of anorexia nervosa and the current state of illness for the group classification were evaluated using the German version of the Eating Disorder Examination, a

semi-structured clinical interview developed by Hilbert et al. (2004). The EDE shows of a high interrater reliability (Hilbert et al., 2004). An example item is “Have you had a strong desire to lose weight in the last four weeks? If yes: How often per month?” (Hilbert et al., 2004). In total, it consists of 22 items across 4 subscales: restraint, eating concern, weight concern, and shape concern (Hilbert et al., 2004). For the total score, the items of the restraint subscale were added together and divided by 5 (Hilbert et al., 2004). A similar procedure was conducted for the subscales eating concern and weight concern (Hilbert et al., 2004). The items of the subscale shape concern were added together and divided by 8 (Hilbert et al., 2004). Then the scores of all subscales were added together and divided by 4 (Hilbert et al., 2004). This EDE score ranges from zero to six (Hilbert et al., 2004). Higher scores indicate greater eating disorder psychopathology (Hilbert et al., 2004).

Computergestütztes Kartensortierverfahren

Set shifting was measured using the “*Computergestütztes Kartensortierverfahren”* (CKV) from Drühe-Wienholt and Wienholt (2013). This is the German version of the modified Wisconsin Card Sorting Task (WCST) by Nelson (1976).

The “*Computergestütztes Kartensortierverfahren*” consists of four key cards: one with a red triangle, one with two green stars, one with three yellow crosses, and one with four blue circles (Drühe-Wienholt & Wienholt, 2013). The participant's task is to assign 96 stimulus cards to one of the four key cards without following any instructions (Wittek et al., 2025). The stimulus cards depict the symbols (circle, cross, star, triangle) in different colors (red, yellow, green, blue) and numbers (one to four) (Drühe-Wienholt & Wienholt, 2013). After each assignment, participants receive feedback stating whether their answer was correct or not, and they must use this information to figure out the sorting criteria (Wittek et al., 2025). The sorting criteria changes after 10 consecutive correct assignments (Drühe-Wienholt & Wienholt, 2013). Participants are not informed about this change and have to figure out the new criteria (Drühe-Wienholt & Wienholt, 2013).

The following outcome parameters were defined. Total responses, show the number of assignments done by the participant, up to a maximum of 96 (Drühe-Wienholt & Wienholt, 2013).

Total correct responses quantify the percentage of correct assignments (Drühe-Wienholt & Wienholt, 2013). This parameter is calculated by subtracting total response errors from total responses (Drühe-Wienholt & Wienholt, 2013).

Total response errors are the percentage of incorrect assignments (Drühe-Wienholt & Wienholt, 2013).

A perseverative error happens when the participant incorrectly assigns a card, by sticking to their previous assignment criteria, in spite of having received negative feedback (Drühe-Wienholt & Wienholt, 2013). Perseverative errors are associated with weaker set shifting abilities (Miles et al., 2021; Wittek et al., 2025).

Perseveration score is the percentage of perseveration errors relative to the total number of response errors (Drühe-Wienholt & Wienholt, 2013). The cut-off value for the perseveration score is 25 percent (Drühe-Wienholt & Wienholt, 2013). A perseveration score of less than 25 percent is within the normal range (Drühe-Wienholt & Wienholt, 2013). A score of 25 percent or above indicates impairments in concept comprehension and concept switching (Drühe-Wienholt & Wienholt, 2013).

A concept perseveration is registered when the participant makes at least two and up to 95 perseveration errors in a row (Drühe-Wienholt & Wienholt, 2013). Any correct assignment or non-perseverative error ends the span of that specific concept perseveration (Drühe-Wienholt & Wienholt, 2013). Registering one or several concept perseverations further evidence comprehension and switching impairments in participants with a perseveration score equal or higher than 25 (Drühe-Wienholt & Wienholt, 2013).

Non-perseverative errors were calculated as the percentage obtained by subtracting the perseveration errors from the total number of errors (Drühe-Wienholt & Wienholt, 2013).

A conceptual level response is registered when a participant assigns 3 or more cards in a row to the correct category (Drühe-Wienholt & Wienholt, 2013).

A failure to maintain set is recorded when the participant assigns from 3 to 9 cards correctly and then fails, not completing the sorting category (Drühe-Wienholt & Wienholt, 2013).

Another parameter were the number of trials to successful completion of the first sorting category (Drühe-Wienholt & Wienholt, 2013).

The "*Computergestütztes Kartensortierverfahren"* parameters have a split-half reliability between 0.90 and 0.95 (Drühe-Wienholt & Wienholt, 2013, as cited in Wittek et al., 2025).

Neuroimaging data

The neuroimaging data was collected using a 3T Siemens Prisma fit MRI scanner (Siemens Healthineers, Erlangen, Germany) with a 64-channel headcoil.

We captured the structural images using a magnetization-prepared two inversion time rapid gradient-echo (MP2RAGE) sequence (TE/TR = 2.98/5000 ms, flip angle = 4°/5°, voxel size = 1 x 1 x 1 mm, FOV = 256 x 216 x 160 mm).

The imaging data was preprocessed with Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, UCL, London, UK).

Use of AI

I used DeepL Write and ChatGPT to assist with language editing. They equipped me with synonyms and shortening suggestions as well as with improved phrasings.

ChatGPT supported the execution and interpretation of voxel-based morphometry analyses by providing additional explanations.

Data Analysis

Behavioral data

In this study, a Kruska Wallis test was conducted with SPSS Version 30.0.0.0 (172) to analyze the group differences in set shifting across the four groups. The parameters of the CKV were the dependent variables, while the four groups - AAN, PRAN, FRAN and healthy controls - were the independent variables. Post-hoc comparisons were performed using Bonferroni correction for multiple tests.

Voxel-based morphometry

All voxel-based morphometry analyses were conducted in MATLAB R2023b Update 10.

During the preprocessing stage, the data was converted from DICOM to NifTI format. Afterwards, it was segmented with CAT12 to generate separate gray and white matter files. Then, I smoothed the gray matter files using SPM 12 (6685) with the 8 mm setting.

In every voxel-based morphometry analysis, age was included as a covariate, and the correction of TIV was applied. The threshold masking was set to absolute (for VBM data) with a threshold of 0.1 at every step.

To answer hypothesis H2a, I conducted a full-factorial ANCOVA with group as a factor (four levels), controlled for age and TIV, using the SPM 12 (6685) and CAT12. The aim was to examine whole brain GMV differences by comparing the four groups pairwise. Positive direction indicated that the first group had increased GMV in the analyzed brain regions. Conversely, negative direction indicated that the first group had reduced GMV in the analyzed brain regions.

To answer hypothesis H2b, I conducted a multiple regression across all four groups, controlling for age and TIV, with concept perseveration included as a covariate. The analysis was performed using SPM 12 (6685) and CAT12. The goal was to test for associations between whole brain GMV differences and concept perseveration across all four groups. Positive direction indicated an association between higher concept perseveration scores and increased GMV in these brain regions across all groups. Negative direction indicated higher concept perseveration scores and reduced GMV in these brain regions across all groups.

To answer the hypothesis H2c, I conducted for each group a multiple regression, controlling for age and TIV, with concept perseveration as a covariate. The analysis was performed using SPM 12 (6685) and CAT12. The aim was to identify the brain regions in each group where GMV differences are associated with concept perseveration. Positive direction indicated an association between higher concept perseveration scores and increased GMV in these brain regions. Negative direction indicated higher concept perseveration scores and reduced GMV in these brain regions. Additionally, I conducted an exploratory two-sample t-test between AAN and PRAN, with concept perseveration as covariate and the group × concept perseveration interaction term. The analyses were performed using SPM 12 (6685) and CAT12. The goal was to identify in which voxels AAN and PRAN groups had similar associations between GMV and cognitive flexibility, and where these associations differed. Four separate contrasts were specified for this analysis. First, brain regions showing a positive association between concept perseveration and GMV in both groups. Second, brain regions showing a negative association between concept perseveration and GMV in both groups. Third, the associations between concept perseveration and GMV is stronger in PRAN than in AAN group. Fourth, the associations between concept perseveration and GMV is stronger in AAN than in PRAN group.

Results

Descriptive Variables

The demographic variables BMI and age of the four groups were shown in table 1. The HC group consisted 47 participants.

The AAN group consisted 28 participants. 27 (96.4%) have an anorexia nervosa diagnosis and 1 (3.6%) has an atypical anorexia nervosa diagnosis. A total of 25 (89.3%) have restrictive AN and 3 (10.7%) with bulimic symptoms (binge and purge). The mean age

of illness onset was 14.23 years (*SD* = 1.77, *N* = 22) and their mean duration of illness so far is 23.91 months (*SD* = 26.56, *N* = 22).

The PRAN group consisted 25 participants. 24 (96.0%) had an anorexia nervosa diagnosis and 1 (4.0%) had an atypical anorexia nervosa diagnosis. A total of 23 (92.0%) had restrictive AN and 2 (8.0%) with bulimic symptoms (binge and purge). The mean age of illness onset was 14.60 years (*SD* = 3.12, *N* = 25) and their mean duration of illness was 48.90 months (*SD* = 39.53, *N* = 20).

The FRAN group consisted 12 participants, who were diagnosed with anorexia nervosa at same point in their lives. A total of 11 (91.7%) had restrictive AN and 1 (8.3 %) with bulimic symptoms (binge/purge). The mean age of illness onset was 13.91 years (*SD* = 1.30, *N* = 11) and their mean duration of illness was 31.44 months (*SD* = 23.77, *N* = 8).

Table 1

Descriptive variables: demographics per group of age and BMI

Group	Age				BMI			
	N	*M*	*SD*	*Min*	*Max*	*M*	*SD*	*Min*	*Max*
HC	47	19.51	3.56	13	30	20.93	2.38	14.90	29,70
AAN	28	16.61	3.34	12	27	16.38	1.89	13.60	24.10
PRAN	25	21.08	3.62	15	27	21.09	2.80	15.70	26.90
FRAN	12	19.25	3.42	15	26	21.43	2.29	18.70	25.60

Note. total *N* = 112; *N* = sample size; *M* = mean; *SD* = standard deviation; *Min* = minimum; *Max* = maximum.

As expected, there was a significant effect of group on BMI, $F(3,108) = 27.47$, $p < .001$, $\eta^2 = .43$. The AAN group ($M = 16.38$, $SD = 1.86$) had a significant lower average BMI than HC group ($M = 20.93$, $SD = 2.38$), PRAN group ($M = 21.09$, $SD = 2.80$) and FRAN group ($M = 21.43$, $SD = 2.29$) (all $p < .001$). No significant differences in BMI were found between HC, PRAN and FRAN (all $p > .005$, see table 1).

Also, there was a significant effect of group on age, $F(3,108) = 7.62$, $p < .001$, $\eta^2 = .18$. AAN group ($M = 16.61$, $SD = 3.34$) were significantly younger than HC group ($M = 19.51$, $SD = 3.56$, $p = .004$) and PRAN group ($M = 21.08$, $SD = 3.62$, $p < .001$). No significant differences in age were found between AAN ($M = 16.61$, $SD = 3.34$) and FRAN ($M = 19.25$, $SD = 3.42$, $p = .133$). No significant differences in age were found between HC, PRAN and FRAN (all $p > .005$, see table 1).

In the context of the group assignment for anorexia nervosa illness stage, the acute AN group tended to be younger, as most of them are in the beginning of their illness. In contrast, those who are partially recovered are further along in the illness course and therefore typically older. This indicated a systematic age difference between the AN illness group. For this reason, I decided not to control for age in subsequent analyses, as doing so would risk partialling out meaningful variance between the groups.

Assumption Checks

Prior to conducting the ANOVA, the assumption of normal distribution was assessed for each group using the Shapiro–Wilk test. The results indicated a significant departure from normality (see table 2). Visual inspection of the data, histograms, and Q–Q plots, further confirmed this violation.

The homogeneity of variances was assessed using Levene's test. The results indicated that the assumption of homoscedasticity was violated for the dependent variable concept perseveration, $F(3, 108) = 3.06$, $p = .031$. For all other dependent variables, Levene's test was not significant (all $p > .05$), suggesting that the homogeneity of variances assumption was met.

Given the unequal group size, the small group size of the FRAN group ($N = 12$) as well as the violation of the normality assumption, I performed the non-parametric Kruskal–Wallis test as a robust variance of the ANOVA to ensure valid statistical inference.

The results of the Kruskal–Wallis test were inconsistent with the ANOVA.

Table 2

Shapiro-Wilk test of set shifting per group

	HC *(47)*		AAN *(28)*		PRAN *(25)*		FRAN *(12)*	
Variables								
	W	*p*	W	*p*	W	*p*	W	*p*
Set shifting (*N* = 112)								
Total Responses	.896	< .001**	.912	.022*	.921	.054	.926	.340
Total correct responses	.809	< .001**	.907	.017*	.884	.008*	.929	.367
Total response errors	.739	< .001**	.703	< .001**	.854	.002*	.736	.002*
Perseverative errors	.451	< .001**	.604	< .001**	.796	< .001**	.663	< .001**
Perseverative score	.816	< .001**	.780	< .001**	.909	.030*	.917	.264
Concept perseveration	.659	< .001**	.441	< .001**	.738	< .001**	.674	< .001**
Non-perseverative errors	.875	< .001**	.766	< .001**	.880	.007*	.875	.075
Conceptual Level Responses	.883	< .001**	.843	< .001**	.768	< .001**	.608	< .001**
Failure to maintain set	.765	< .001*	.803	< .001**	.633	< .001**	.608	< .001**
Trials to complete first category	.577	< .001*	.413	< .001**	.582	< .001**	.732	.002*

Note. total *N* = 112; W = Shapiro-Wilk test statistic; *p* = p-value; Significance level is .05; **p* < 05, Significance level is ***p* < 001.

Behavioral results: set shifting

Set shifting is a measurement of cognitive flexibility (Miles et al., 2020; Shott et al., 2012). Mean and standard deviation for each set shifting parameter per group (see table 11) and the intercorrelation matrix (see table 12, 13, 14, 15) are shown in the appendix. Median and mean ranks for each group are shown in table 3.

Table 3

Median and mean ranks of each set shifting parameter per group

Variables	HC *Mdn* (mean ranks)	AAN *Mdn* (mean ranks)	PRAN *Mdn* (mean ranks)	FRAN *Mdn* (mean ranks)
Set shifting (*N* = 112)				
Total Responses	77.00 (54.66)	78.00 (57.04)	81.00 (62.26)	50.46 (7.49)
Total correct responses	63.00 (59.91)	63.00 (55.70)	62.00 (49.78)	64.00 (59.00)
Total response errors	15.00 (53.17)	14.00 (54.59)	17.00 (66.80)	13.50 (52.54)
Perseverative errors	2.00 (55.67)	1.00 (47.63)	4.00 (69.88)	1.50 (49.75)
Perseverative score	14.30 (54.74)	10.55 (49.84)	24.00 (71.82)	13.25 (47.00)
Concept perseveration	0.00 (54.83)	0.00 (48.77)	1.00 (69.34)	0.00 (54.33)
Non-perseverative errors	11.00 (51.28)	12.00 (58.05)	14.00 (64.64)	11.00 (56.38)
Conceptual Level Responses	7.00 (59.78)	6.50 (57.79)	6.00 (46.82)	7.00 (60.83)
Failure to maintain set	1.00 (58.24)	1.00 (59.88)	0.00 (50.24)	1.00 (54.83)
Trials to complete first category	11.00 (55.65)	11.50 (57.61)	11.00 (55.38)	11.00 (59.58)

Note. df (HC, AAN, PRAN, FRAN) = 3; HC (*N* = 47), AAN (*N* = 28), PRAN (*N* =25), FRAN (*N* = 12); total *N* = 112; *Mdn* = median.

The Kruskal-Wallis test indicated that there was a significant difference in perseverative score across all four groups, χ^2 (3) = 7.94, p = .047 (see table 4). The mean ranks of perseverative score were 54.74 for HC, 49.84 for AAN, 71.82 for PRAN and 47.00 for FRAN (see table 4). Post-hoc comparisons using Bonferroni correction for multiple tests showed no significant group difference between HC, FRAN, PRAN and AAN, all $p > .005$.

However, there was also a significant difference in concept perseveration across all four groups, χ^2 (3) = 7.95, p = .047 (see table 4). The mean ranks of concept perseveration were 54.83 for HC, 48.77 for AAN, 69.34 for PRAN and 54.33 for FRAN. Post-hoc comparisons using Bonferroni correction for multiple tests indicated that the average of

concept perseveration scores of the PRAN group was significantly higher than of the AAN group, $p = .039$. However, no other significant group differences were observed, all $p > .05$.

Also, no significant group differences were found in total responses, total correct responses, total response errors, perseverative errors, non-perseverative errors, conceptual level responses, failure to maintain set and trials to complete the first category (see table 4).

Table 4

Results of set shifting in the Kruskal-Wallis test of an independent sample

Variables	*F*	*df*	*p*
Set shifting (*N* = 112)			
Total responses	1.366	3	.714
Total response errors	1.707	3	.635
Total response errors	3.296	3	.348
Perseverative errors	6.611	3	.085
Perseverative score	7.938	3	.047*
Concept perseveration	7.946	3	.047*
Non-perseverative errors	2.873	3	.412
Conceptual level responses	3.366	3	.339
Failure to maintain set	1.605	3	.658
Trials to complete first category	.219	3	.974

Note. Signific Nivea is .05; *$p < 05$.

Voxel-based morphometry analysis

GMV differences between AN stages and HC

To answer hypothesis 2a a full factorial ANCOVA was performed between groups, with age and TIV controlled for and the FWE correction was set to > .05 with a minimum cluster size of five.

VBM returned two significant clusters of voxels when comparing healthy controls (*N* = 35*)* with acute AN patients (*N* = 22), controlling for age and TIV. Healthy controls showed greater GMV in the Cerebellum Posterior Lobe, specifically in the Cerebellum_6_R (aal3v1), compared to patients with acute anorexia nervosa ($t = 5.99$, p corrected = 0.001, $k = 227$;

MNI x,y,z: 33, -69, -21). Additionally, healthy controls demonstrated greater GMV in the Cerebellum Posterior Lobe, specifically in the Cerebellar Tonsil, compared to acute AN patients (t = 5.66, p corrected = 0.003, k = 93; MNI x,y,z: 33, -51, -40).

Differences in GMV were found between healthy controls and partially remitted AN patients. The results are shown in table 5.

Table 5

VBM results showing differences in GMV between HC and PRAN patients controlled for age and TIV

Regions	Direction	Cluster size	p corrected	t	MNI coordinates		
					x	y	z
Parietal_Inf_L (aal3v1)	Positive	34	0.001	6.09	-50	-46	56
Putamen_L (aal3v1)	Positive	531	0.001	5.94	-32	-10	-2
Amygdala_L(aal3v1)	Positive		0.021	5.12	-24	-4	-12
Putamen_R (aal3v1)	Positive	894	0.001	5.92	27	2	-10
Putamen_R (aal3v1)	Positive		0.006	5.47	32	3	3
Cerebellum_Crus1_R (aal3v1)	Positive	180	0.003	5.65	44	-48	-27
Parietal Lobe	Positive	41	0.004	5.60	-38	-44	50
Parahippocampa Gyrus	Positive	48	0.005	5.50	26	-24	-24
Precentral Gyrus	Positive	62	0.007	5.45	56	-8	48
Middle Temporal Gyrus	Positive	78	0.010	5.33	64	-30	-8
Superior Temporal Gyrus	Positive	91	0.012	5.29	-45	3	-8
Inferior Temporal Gyrus	Positive	16	0.013	5.26	-56	-60	-12
Frontal_Mid_2_R (aal3v1)	Positive	15	0.014	5.24	27	46	28
Superior Temporal Gyrus	Positive	13	0.018	5.16	-58	-62	22
Inferior Parietal Lobule	Positive	9	0.019	5.16	-56	-50	42
Insula_R (aal3v1)	Positive	17	0.022	5.10	46	0	-3
Superior Temporal Gyrus	Positive	31	0.022	5.10	48	12	-9
Anterior Lobe	Positive	12	0.025	5.07	-45	-48	-27

Angular_R (aal3v1)	Positive	7	0.027	5.04	58	-64	27
Posterior Lobe	Positive	9	0.031	5.01	40	-44	-40

Note. HC (*N* = 35); PRAN (*N*= 24), MNI = Montreal Neurological Institute.

The results showed no altered GMV between healthy controls (*N* = 35) and fully remitted AN patients (*N* = 10) when controlled for age and TIV.

The comparison of partially remitted AN patients (*N* = 24) and acute AN patients (*N* = 22) revealed also no significant GMV differences when controlled for age and TIV.

VBM returned one significant cluster of voxels with two peaks when comparing fully remitted AN patients (*N* = 10) and acute AN patients (*N* = 22), controlling for age and TIV. Fully remitted AN patients showed increased GMV in the Fusiform Gyrus, specifically in the Fusiform_R (aal3v1), compared to acute AN patients (*t* = 5.68, *p* corrected = 0.003, *k* = 112; MNI x,y,z: 32, -68, -16). The second peak was in the Cerebellum Posterior Lobe (*t* = 4.97, *p* corrected = 0.035; MNI x,y,z: 34, -58, -15).

VBM returned two significant clusters of voxels when comparing fully remitted AN patients (*N* = 10) to partially remitted AN patients (*N* = 24), controlling for age and TIV. Fully remitted AN patients showed greater GMV in the Superior Temporal Gyrus, specifically in the Angular_L (aal3v1), compared to partially remitted AN patients (*t* = 5.46, *p* corrected = 0.001, *k* = 67; MNI x,y,z: -58, -62, 24). Additionally, fully remitted AN patients showed increased GMV in the Limbic Lobe - ACC_pre_L (aal3v1) compared to partially remitted AN patients (*t* = 5.26, *p* corrected = 0.013, *k* = 36; MNI x,y,z: -8, 44, -3).

Association between GMV and cognitive flexibility

In the analysis for hypothesis 2b GMV differences did not remain significant after applying the conservative FWE correction. Therefore, a more liberal statistical threshold was used. The uncorrected *p* value was set to 0.001 with a minimum cluster size of five.

The VBM analysis revealed negative correlations between GMV and concept perseveration across the four groups. Higher concept perseveration scores indicate weaker cognitive flexibility. The results of the VBM Regression between all groups (*N* = 91) with concept perseveration controlled for age and TIV are presented in table 6. The results are visualized in figure 2.

Table 6

VBM results of GMV x concept perseveration across all groups controlled for age and TIV

Regions	Direction	Cluster size	*p* uncorrected	*t*	MNI coordinates		
					x	y	z
Parietal_Inf_L (aal3v1)	Negative	849	0.000	4.67	-51	-46	52
Parietal_Inf_L (aal3v1)	Negative		0.000	4.12	-40	-45	44
Superior Temporal Gyrus	Negative	568	0.000	4.01	40	3	-24
Temporal_Pole_Sup_R (aal3v1)	Negative		0.000	3.59	58	14	-8
Temporal_Sup_R (aal3v1)	Negative		0.000	3.57	51	2	-9
Rectus_R (aal3v1)	Negative	489	0.000	3.92	3	18	-27
OFCmed_R (aal3v1)	Negative		0.000	3.55	15	14	-24
Precuneus_L (aal3v1)	Negative	171	0.000	3.89	-12	-48	50
Precentral_R (aal3v1)	Negative	109	0.000	3.88	44	-6	42
Temporal_Sup_R (aal3v1)	Negative	253	0.000	3.80	56	-57	22
Inferior Frontal Gyrus	Negative	536	0.000	3.78	-27	36	-24
OFCpost_L (aal3v1)	Negative		0.000	3.73	-28	22	-26
Orbital Gyrus	Negative		0.000	3.53	-20	39	-28
Angular_L (aal3v1) – Parietal Lobe	Negative	120	0.000	3.72	-48	-69	30
Temporal_Inf_L (aal3v1)	Negative	84	0.000	3.65	-54	-60	-9
Frontal_Mid_2_R (aal3v1)	Negative	7	0.000	3.56	38	66	-2
ParaHippocampal_R (aal3v1) - Cerebellum_4_5_R (aal3v1)	Negative	50	0.000	3.51	24	-22	-26

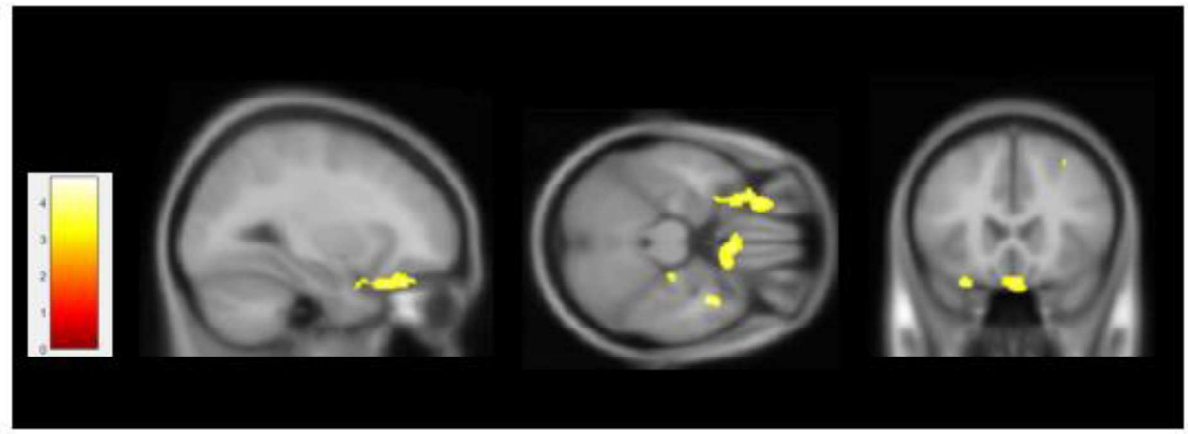
Rolandic_Oper_R (aal3v1)	Negative	69	0.000	3.50	48	-3	14
Precuneus_R (aal3v1)	Negative	30	0.000	3.49	10	-51	51
Lingual_L (aal3v1)	Negative	40	0.000	3.49	-14	-74	-3
Frontal_Sup_2_R (aal3v1)	Negative	19	0.000	3.44	26	4	70
Left Cerebellum	Negative	88	0.000	3.41	-9	-68	-50
Temporal_Inf_L (aal3v1)	Negative	8	0.000	3.41	-51	-40	-15
Rolandic_Oper_L (aal3v1)	Negative	24	0.001	3.39	-45	-8	21
Precuneus_R (aal3v1) – Parietal lobe	Negative	34	0.001	3.38	6	-54	42
Frontal Lobe	Negative	15	0.001	3.38	-2	33	-33
Heschl_R (aal3v1)	Negative	74	0.001	3.37	39	-26	9
Parietal_Inf_R (aal3v1)	Negative	37	0.001	3.37	46	-44	50
Temporal_Pole_Sup_L (aal3v1)	Negative	7	0.001	3.34	-18	9	-32
Fusiform_L (aal3v1)	Negative	6	0.001	3.34	-38	-58	-10
Putamen_R (aal3v1)	Negative	44	0.001	3.33	34	-4	-9
Inter-Hemispheric	Negative	5	0.001	3.32	3	52	-32
Cerebellum_8_R (aal3v1)	Negative	36	0.001	3.31	30	-39	-54
Frontal_Sup_2_R (aal3v1)	Negative	12	0.001	3.30	24	-10	57
Supp_Motor_Area_L (aal3v1)	Negative	17	0.001	3.30	-8	4	63
SupraMarginal_R (aal3v1) – Parietal Lobe	Negative	12	0.001	3.29	57	-16	20
Supp_Motor_Area_R (aal3v1)	Negative	9	0.001	3.29	4	2	51
Frontal_Mid_2_R (aal3v1)	Negative	10	0.001	3.28	32	22	50
Sub-lobar	Negative	15	0.001	3.27	-32	-6	-8
Temporal_Inf_L (aal3v1)	Negative	10	0.001	3.27	-51	-15	-33
Insula_R (aal3v1)	Negative	41	0.001	3.26	36	-2	9

Extra-Nuclear	Negative	14	0.001	3.26	38	-22	-3
Frontal_Mid_2_R (aal3v1)	Negative	5	0.001	3.25	44	0	58
Frontal_Inf_Tri_L (aal3v1)	Negative	5	0.001	3.25	-54	16	30
Cerebellum_8_R (aal3v1)	Negative	6	0.001	3.23	10	-63	-42

Note. (N = 91), MNI = Montreal Neurological Institute.

Figure 2

Statistical parametric maps: GMV x concept perseveration across all groups



Note. Structural templates were generated as an average from the combined sample across all groups. The first image shows a sagittal slice, the second a transverse slice, and the third a coronal slice. Cluster color indicates the statistical significance of GMV decrease, with t values represented by the color bar.

Different association between GMV and cognitive flexibility in AN stages and HC

In the analysis, to answer hypothesis 2c, GMV alterations did also not remain significant after applying the conservative FWE correction. Therefore, again a more liberal statistical threshold was used. The uncorrected p value was set to 0.001 with a minimum cluster size of five.

The VBM analysis revealed negative and positive correlation. Since higher concept perseveration scores indicate weaker cognitive flexibility, a negative correlation indicates that reduced GMV in the identified regions is associated with weaker cognitive flexibility and a positive correlation that increased GMV in the identified regions is associated with weaker cognitive flexibility.

Voxel-based morphometry results of the correlation between gray matter volume and concept perseveration controlled for age and TIV in the HC group (N = 35) are shown in table 7.

Table 7

VBM results of GMV x concept perseveration controlled for age and TIV in HC

Regions	Direction	Cluster size	*p* uncorrected	*t*	MNI coordinates		
					x	y	z
Cingulate_Mid_R (aal3v1)	Positive	122	0.000	4.45	12	22	39
Temporal_Inf_L (aal3v1)	Positive	23	0.000	3.99	-69	-40	-22
Superior Frontal Gyrus -	Positive	118	0.000	3.88	3	56	33
ACC_pre_R (aal3v1)	Positive		0.001	3.63	8	48	24
Inferior Frontal Gyrus	Positive	41	0.000	3.83	-57	18	0
Cingulate_Mid_R (aal3v1)	Positive	25	0.000	3.78	12	9	34
Inferior Frontal Gyrus	Positive	19	0.000	3.74	45	18	9
Temporal Lobe	Positive	12	0.000	3.66	-58	-34	-24
ACC_pre_R (aal3v1)	Positive	32	0.001	3.61	15	38	16
Limbic Lobe	Positive	14	0.001	3.60	18	-39	40
Parietal Lobe	Positive	13	0.001	3.59	50	-48	58
Cerebellum Posterior Lobe	Positive	11	0.001	3.51	48	-51	-26
Lingual_L (aal3v1)	Negative	11	0.000	3.79	-14	-74	-4

Note. N = 35, MNI = Montreal Neurological Institute.

Voxel-based morphometry results of the correlation between gray matter volume and concept perseveration controlled for age and TIV in the AAN group are shown in table 8. The results are visualized in figure 3.

Table 8

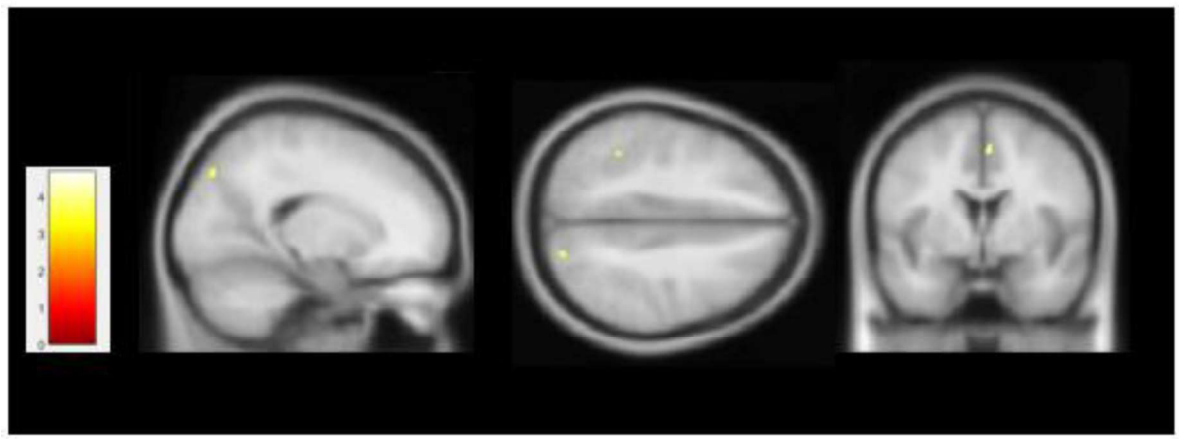
VBM results of GMV x concept perseveration controlled for age and TIV in AAN

Regions	Direction	Cluster size	*p* uncorrected	*t*	MNI coordinates		
					x	y	z
Temporal_Inf_L (aal3v1)	Negative	16	0.000	4.79	-42	-6	-36
OFClat_R (aal3v1)	Negative	8	0.000	4.41	45	30	-22
Supp_Motor_Area_R (aal3v1)	Negative	26	0.000	4.38	4	2	50
Precuneus_R (aal3v1)	Negative	21	0.000	4.29	14	-57	44
Frontal_Sup_2_R (aal3v1)	Negative	18	0.000	4.28	14	10	50
Precuneus_L (aal3v1)	Negative	22	0.000	4.11	-10	-42	46
Medial Frontal Gyrus	Negative	18	0.000	4.11	-58	-28	-33
Parietal_Inf_L (aal3v1)	Negative	33	0.000	4.05	-42	-45	44
Cerebrum - Cuneus_R (aal3v1)	Negative	14	0.001	3.84	20	-80	42
Middle Frontal Gyrus	Negative	17	0.001	3.74	-42	52	12

Note. N = 22, MNI = Montreal Neurological Institute.

Figure 3

Statistical parametric maps: GMV x concept perseveration in the AAN group



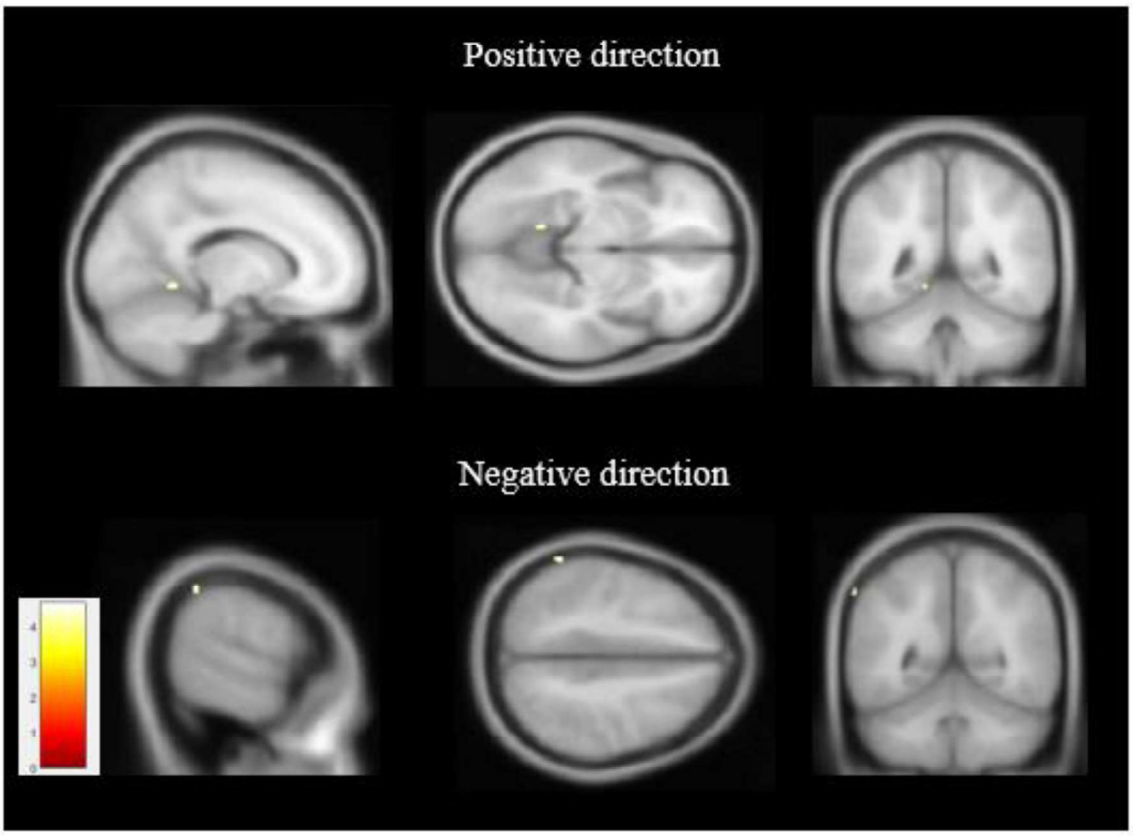
Note. Structural templates were generated as an average from the AAN group. The first image shows a sagittal slice, the second a transverse slice, and the third a coronal slice.

Cluster color indicates the statistical significance of GMV decrease, with t values represented by the color bar.

VBM returned four significant clusters of voxels for the correlation between gray matter volume and concept perseveration controlled for age and TIV in the PRAN group (N = 24) (see figure 4). Partially remitted AN patients showed an association between increased GMV in the Cerebellum Anterior Lobe, specifically in the Lingual_L (aal3v1), and higher concept perseveration scores (t = 4.14, p corrected = 0.000, k = 36; MNI x,y,z: -12, -51, -8). Partially remitted AN patients demonstrated an association between increased GMV in the Superior Frontal Gyrus and higher concept perseveration scores (t = 3.80, p corrected = 0.001, k = 7; MNI x,y,z: -36, 62, 20). Additionally, partially remitted AN patients demonstrated an association between increased GMV in the Middle Frontal Gyrus more specific in the Frontal_Mid_2_R (aal3v1) and higher concept perseveration scores (t = 3.76, p corrected = 0.001; k = 13; MNI x,y,z: 48, 14, 54). Partially remitted AN patients demonstrated an association between decreased GMV in the inferior parietal lobule and higher concept perseveration scores (t = 4.12, p corrected = 0.000; k = 25; MNI x,y,z: -63, 51, 48).

Figure 4

Statistical parametric maps: GMV x concept perseveration in the PRAN group



Note. Structural templates were generated as an average from the PRAN group. The first of the three images show a sagittal slice, the second a transverse slice, and the third a coronal slice of the positive direction, the second three of the negative direction of GMV x concept perseveration. Cluster color indicates the statistical significance of GMV decrease, with t values represented by the color bar.

Voxel-based morphometry results of the correlation between gray matter volume and concept perseveration controlled for age and TIV in the FRAN group are shown in table 9.

Table 9

VBM results of GMV x concept perseveration controlled for age and TIV in FRAN

Regions	Direction	Cluster size	*p* uncorrected	*t*	MNI coordinates		
					x	y	z
Temporal Lobe	Negative	16	0.000	10.38	36	-9	-28
Postcentral_L (aal3v1)	Negative	12	0.000	9.07	-58	-15	26
Superior Temporal Gyrus - Angular_R (aal3v1)	Negative	68	0.000	8.56	42	-52	22
Lingual_R (aal3v1)	Negative	12	0.000	7.45	9	-72	2
Rolandic_Oper_L (aal3v1)	Negative	14	0.000	6.87	-60	-2	8
Occipital Lobe	Negative	15	0.000	6.51	30	-93	28
Cerebellum Posterior Lobe	Negative	14	0.000	6.16	9	-75	-22
Cerebellum Posterior Lobe	Negative	13	0.000	6.12	-46	-51	-33
Cingulate Gyrus	Negative	6	0.001	5.64	10	-24	38
Inferior Frontal Gyrus	Negative	6	0.001	5.58	-57	3	15

Note. $N = 10$, MNI = Montreal Neurological Institute.

A positive association between concept perseveration and GMV showed the AAN and PRAN groups in the Cerebellum Anterior Lobe, specifically in the Lingual_L (aal3v1) (t = 3.69, p corrected = 0.000; k = 40; MNI x,y,z: -14, -50, -8). In the same groups, the results also showed a negative association with two peaks between concept perseveration and GMV. The first peak was in the Inferior Parietal Lobule, specifically in the Parietal_Inf_L (aal3v1) (t = 4.21, p corrected = 0.000; k = 174; MNI x,y,z: -62, -52, 46) and the second peak were in the brodmann area 40, specifically in the Parietal_Inf_L (aal3v1) (t = 4.00, p corrected = 0.000; MNI x,y,z: -54, -48, 51).

No brain regions were found where the association between concept perseveration and GMV is significantly stronger in PRAN than in the AAN group.

Brain regions where the association between concept perseveration and GMV is stronger in AAN than in PRAN are shown in table 10.

Table 10

VBM results were the association between concept perseveration and GMV is stronger in AAN group than in PRAN group

Regions	Cluster size	*p* uncorrected	*t*	MNI coordinates		
				x	y	z
Frontal_Mid_2_L (aal3v1)	74	0.000	3.99	-39	57	22
Frontal_Sup_2_L (aal3v1)		0.001	3.53	-32	56	26
Cuneus_R (aal3v1)	46	0.000	3.83	18	-80	44
Frontal_Mid_2_R (aal3v1)	38	0.000	3.83	44	8	38
OFClat_R (aal3v1)	14	0.001	3.54	50	28	-16
Middle Frontal Gyrus	20	0.001	3.44	36	16	63
Frontal_Mid_2_R (aal3v1)	32	0.001	3.42	48	10	52

Note. AAN (*N* = 22); PRAN (*N* = 24), MNI = Montreal Neurological Institute.

Discussion

Behavioral findings

This study examined differences in cognitive flexibility across illness stages of anorexia nervosa and healthy controls.

The hypothesis 1a, that participants with acute AN would demonstrate weaker cognitive flexibility than those in partial or full remission or healthy controls was not supported. On the contrary, acute AN patients demonstrated greater cognitive flexibility, as measured by concept perseveration, than AN patients in partial remission.

We did not find evidence of cognitive flexibility impairments in acute AN adolescents and young adults compared to healthy controls, contrary to several studies reporting such impairments in adults with acute AN (Miles et al., 2020; Roberts et al., 2010; Steinglass et al., 2006; Tchanturia et al., 2012) as well as in children and adolescents with acute AN (Lang

et al., 2015). However, our findings are consistent with prior work showing no significant differences in cognitive flexibility between acute AN adolescents and healthy controls (Fitzpatrick et al., 2012; Lang et al., 2014; Shott et al., 2012).

The absence of impaired cognitive flexibility in adolescents and young adults indicates that this impairment is unlikely to be an endophenotype for AN (Miles et al., 2020). Our findings are consistent with previous literature and suggest that the impairments observed in adults with AN may be a consequence of starvation, chronic illness, or longer illness duration (Fitzpatrick et al., 2012; Lang et al., 2014; Miles et al., 2020).

Additional support for this assumption comes from our only significant finding, showing that partially remitted AN patients exhibited significantly weaker cognitive flexibility, as measured by concept perseveration, than patients with acute AN. While this finding may seem counterintuitive, it can be explained by the longer illness duration in the partially remitted AN group rather than their remission status. This interpretation is consistent with a meta-analysis by Saure et al. (2020) which reported significant impairments in set shifting in AN patients compared to healthy controls with a mean illness duration of four until seven years and more. Our partially remitted AN group (mean illness duration = 4.08 years) falls within this range, while our acute AN group (mean illness duration = 1.99 years) does not. They researchers found no significant differences in cognitive flexibility between participants with AN and healthy controls with a mean illness duration under 4 years. Taken together, our findings provide further support for the illness-duration hypothesis and suggest two possible explanations for why longer illness duration may be associated with weaker cognitive flexibility (Saure et al., 2020; Treasure & Schmidt, 2013). Firstly, impaired cognitive flexibility could be a consequence of the anorexia nervosa illness itself, for example a result from long-term starvation (Treasure & Schmidt, 2013). Alternatively, individuals with weaker cognitive flexibility may be less likely to recover fully (Treasure & Schmidt, 2013). Future research is needed to clarify the causality of cognitive flexibility and anorexia nervosa illness duration.

An alternative explanation is that the impairments observed in cognitive flexibility in the acute AN group may be compensated for by other executive functions (Weinbach et al., 2019) that are enhanced during the acute stages of the AN illness (Hatch et al., 2010). Another possible compensatory executive function is working memory (Friedman & Miyake, 2017). According to the study by Dann et al. (2023) working memory scores are strong

independent predictors of WCST performance in individuals with a lifelong AN diagnosis. The researchers indicated that the ability to monitor or update working memory is necessary to follow the sorting rules of the WCST. Adolescents with acute AN showed superior working memory compared to healthy controls (Hatch et al., 2010). This superiority is specific to the younger AN population, as deficits in working memory have been found in adults with AN (Kemps et al., 2006). Therefore, working memory abilities could explain the missing cognitive inflexibility in studies of children and adolescents with AN, such as our own. Future research on cognitive flexibility in adolescents and young adults with AN should measure and control for working memory (Dann et al., 2023).

Another explanation for our not significant results is that acute AN participants may experience impairments in cognitive flexibility, specific to the food and exercise domains (Miles et al., 2020). These domains were not covered in the CKV, therefore these impairments might only be measurable through self-report and discussions with parents (Miles et al., 2020). This explanation is supported by previous studies which found self-reported weak cognitive flexibility in AN patients (Dann et al., 2023; Miles et al., 2020).

Another explanation for our findings in the acute AN group would be that only subgroups of AN patients have set shifting impairments (Talbot et al., 2015) as the study of Roberts et al. (2010) found a broad range and higher number of perseveration errors in AN group with bulimic symptoms (binge and purge). This subgroup is underrepresented in our sample with only 10.7% in the AAN group, 8.0% in the PRAN group and 8.3% in the FRAN group. However this hypothesis cannot completely explain our findings because Roberts et al. (2010) also found significantly more perseverative errors for only restrictive AN compared to healthy controls.

The hypothesis 1b, that participants with partially remitted AN would demonstrate weaker cognitive flexibility compared to those who are fully remitted or healthy controls must also be rejected. Furthermore, hypothesis 1c, that participants with fully remitted AN show weaker cognitive flexibility compared to healthy controls, could also not be confirmed.

Our findings did not provide evidence for impaired set shifting in adolescents and young adults with AN across illness stages, which contrast with several previous studies that reported significant difference in PRAN and FRAN adults with AN compared to healthy controls (Danner et al., 2012; Lindner et al., 2014; Talbot et al., 2015; Tchanturia et al., 2012) and in PRAN adolescents compared to healthy controls (Weinbach et al., 2019).

However, our results are in line with Tchanturia et al. (2011) for FRAN adults and in line with findings of Bohon et al. (2020) for PRAN adolescents.

Our findings are both consistent with and contradictory to the meta-analysis by Saure et al. (2020). They reported significant impairments in set shifting in AN patients compared to healthy controls, with an illness duration of at least four years. Our partially remitted AN group (mean illness duration = 4.08 years) falls within this range and should therefore have shown impairments compared to healthy controls. However, the researchers found no significant differences in cognitive flexibility between participants with AN and healthy controls with an illness duration of under four years as it was the case for our fully remitted AN group (mean illness duration = 2.62 years).

The absence of a significant difference between partially remitted AN patients and healthy controls in cognitive flexibility contradicts the illness duration hypothesis (Saure et al., 2020; Treasure & Schmidt, 2013). This may suggest that there is no association between AN illness duration and cognitive flexibility. An alternative explanation could be that our healthy control group was not fully representative, as siblings of AN patients were included. Previous studies already showed impairments in cognitive flexibility in unaffected sisters of AN patients (Holliday et al., 2005; Roberts et al., 2010). Further research is needed to clarify the differences in cognitive flexibility between patients with partially remitted AN and healthy controls. In future research it is important that relatives of patients with AN are excluded from the healthy control group.

The absence of impaired cognitive flexibility in adolescents and young adults across the AN illness stages is another indication that impaired cognitive flexibility is not an endophenotype (Miles et al., 2020), as an endophenotype needs to be largely independent of the current disease state (Gottesman & Gould, 2003).

Voxel-based-morphometry findings

The second aim of this study was to investigate whether cognitive flexibility is associated with structural brain differences across different stages of anorexia nervosa and healthy controls.

GMV differences between AN stages and HC

Our results support our hypothesis 2a, that participants with acute, partially remitted and fully remitted AN and healthy controls demonstrate altered GMV across the whole brain

compared to each other after controlling for age and TIV. All the results were also significant after FWE corrections.

GMV differences in acute AN. We detected reduction in the gray matter volume in acute AN patients compared to healthy controls. Our results of decreased GMV in acute AN patients compared to HC are in line with the majority of previous research (Castro-Fornieles et al., 2009; Seitz et al., 2016; Titova et al., 2013).

Moreover, we did not find any GMV increases in the AN groups compared to healthy controls which is also supported by previous findings (Friederich et al., 2012; Titova et al., 2013).

The GMV reductions between acute AN group compared to healthy controls were limited in our study to one region the Cerebellum, more specifically Cerebellum_6_R (aal3v1) and the Cerebellar Tonsil. The finding of reduced GMV in the cerebellum in acute AN patients compared to healthy controls are in line with previous research (Amianto et al., 2013; Boghi et al., 2011; Brooks et al., 2011).

The cerebellum is not only involved in motor coordination and somatic functions, but also in the control of feeding behavior, appetite and weight (Sader et al., 2023). There are neural pathways that link the cerebellum with several key regions for feeding, including the hypothalamus (Zhu & Wang, 2008). The direct cerebellohypothalamic projections allows the cerebellar outputs to reach the hypothalamus where they converge and are integrated with critical feeding signals (Zhu & Wang, 2008). Moreover, the cerebellum, via the cerebello-cerebral circuits and its direct and indirect connections to higher-order regions such as the amygdala and limbic system, may play a role in the sensory, affective, and cognitive aspects of feeding (Zhu & Wang, 2008). Through cognitive mechanisms of feeding behavior, the cerebellum may modulate altered appetite-related inputs, contributing to the formation of inflexible and recurrent food-related representations, memories, and expectations derived from previous experiences with food (Sader et al., 2023). Functional imaging studies support the connection of hunger and satiation with cerebellar activation (Zhu & Wang, 2008). Therefore reductions in cerebellar volume, which we found in acute AN, could enhance their ability to maintain a low weight and through this foster the maintenance of the AN illness (Brooks et al., 2011).

The reduced GMV in the cerebellum of acute AN patients could have multiple reasons (Seitz et al., 2016). It may reflect the consequences of starvation, which led to structural

'scars' in the brain (Seitz et al., 2016). Alternatively, it may also represent a pre-existing trait that contributes to the onset or chronic course of the illness (Seitz et al., 2016).

Our study failed to replicate the other overlapping GMV decreases found in comparison between AAN patients and HC in previous studies as the putamen (Friederich et al., 2012; Titova et al., 2013), left hippocampus (Amianto et al., 2013; Friederich et al., 2012) and the left SMA (Amianto et al., 2013; Boghi et al., 2011; Friederich et al., 2012).

One possible explanation for the absence of these reduced GMV regions in our findings could be differences in the inclusion criteria for the acute AAN group, including medication, illness duration, body mass index and comorbidity with other psychiatric disorders (Nickel et al., 2018).

GMV differences in partially remitted AN. In our study we also found no increases of GMV in partially remitted AN patients compared to healthy controls, similarly to Friederich et al. (2012).

In line with the previous studies we found reduced GMV in partially remitted AN patients compared to healthy controls (Seitz et al., 2016). However, only two brain areas in our results matched those found in previous literature on PRAN compared to HC. These overlapping areas are the parietal lobe, more specifically the left inferior parietal lobe, as well as the angular gyrus (Mainz et al., 2012). A previous study found that GMV was already reduced in the left inferior parietal lobe in an acute AN group compared to healthy controls (Titova et al., 2013).

The left inferior parietal lobe is one of the key regions that is connected to appetite and somatosensory perception, which are often observed to be abnormal in AN patients (Titova et al., 2013).

The angular gyrus lies in the posterior inferior parietal lobe (De Carvalho et al., 2024). It is connected to higher-order cognitive functions as concept of oneself and one’s body image (De Carvalho et al., 2024). Disturbance of one´s body image is an important characteristic of the anorexia nervosa illness (Glashouwer et al., 2019). The study by Glashouwer et al. (2019) found evidence indicating that there may be an association between body disturbance and illness duration in AN, which would align with our findings that this region demonstrated reduced GMV in the PRAN group.

Moreover, the PRAN group in our study showed GMV reductions that matched those of acute AN groups in previous literature. In line with the previous research of acute AN, we

found large clusters of GMV reduction in the cerebellum (Amianto et al., 2013; Boghi et al., 2011; Brooks et al., 2011), putamen (Friederich et al., 2012; Titova et al., 2013), right insula (Friederich et al., 2012), left amygdala (Burkert et al., 2019; Friederich et al., 2012) and the right precentral gyrus (Amianto et al., 2013).

Boghi et al. (2011) reported greater reduction in the GMV of the cerebellum in AN patients with longer disease duration. This may explain why we observed cerebellar GMV reductions in partially remitted AN patients.

The putamen is part of the reward process (Eddy et al., 2023; Keating et al., 2012). Also other neuropsychiatric and neurodegenerative disorders like developmental dyslexia and attention deficit hyperactivity disorder showed GMV reduction in the putamen (Luo et al., 2019).

The insula is a multisensory neural node of emotion, interoceptive awareness, cognition perception and gustation (S. Frank et al., 2013). The insula controls eating behavior top-down with projections to limbic structures independent of direct input of the hypothalamus (Azevedo et al., 2022; Livneh et al., 2017). Central gustatory processes are strongly linked to interoceptive awareness, which in the event of insula dysfunctions could manifest in reduced sensitivity to bodily signals such as absence of hunger signals, as reported by AN patients (S. Frank et al., 2013; Nunn et al., 2011). The insula is known to be the primary taste cortex and is part of a network, which control the appetite and regulates the energy balance by linking taste with memories of various foods (S. Frank et al., 2013; Nunn et al., 2011). Additionally, the insula participates in the reward system (S. Frank et al., 2013). Reduced insula activity could have a wide range of effects on patients with anorexia, such as impairing perception and leading to a distorted body image, an inability to connect thoughts and feelings, a higher pain threshold and relative insensitivity to pain, disrupted regulation of disgust, and reduced empathy during starvation (Nunn et al., 2011).

The amygdala plays an important role in the navigation of a wide range of inborn behaviors, including the regulation of appetite through its direct and indirect connection to the hypothalamus (Azevedo et al., 2022). The amygdala influences the hypothalamus by emotional regulation and assigning emotional responses to stimuli (Janak & Tye, 2015; Marcolini et al., 2024; Zheng et al., 2017). It does so by processing and transmitting primary sensory information about the positive or negative valence of stimuli (Janak & Tye, 2015). Moreover, it is involved in processing both threatening and rewarding environmental stimuli

(Janak & Tye, 2015). The influence of the amygdala on the hippocampus in emotional responses is being acknowledged with growing frequency in animal models (Zheng et al., 2017). The study of Burkert et al. (2019) with AN patients indicates that phobic anxiety and body image could be related to the volume of the amygdala.

The precentral gyrus is located in the primary motor cortex, which controls voluntary motor movements on the opposite side of the body (Banker & Tadi, 2023). Its role in eating disorders so far is unclear and more research is needed.

Our study failed to replicate the overlapping GMV decreases, which were found in previous studies between PRAN and HC as the SMA (Castro-Fornieles et al., 2009; Friederich et al., 2012; Mainz et al., 2012), paracentral lobule (Castro-Fornieles et al., 2009; Mainz et al., 2012) and the dorsal anterior cingulate cortex (Castro-Fornieles et al., 2009; Friederich et al., 2012).

One possible explanation for the missing reduced GMV findings between PRAN and HC could be the age of the PRAN group, duration of stable weight maintenance, differences in hormonal factors or premorbid group differences (Mainz et al., 2012).

GMV differences in fully remitted AN. As in previous research we could not find any significant GMV reduction between fully remitted AN women and healthy controls (Bang et al., 2016; Nickel et al., 2018; Seitz et al., 2016), which indicates that through full recovery the GMV decreases are reversible (Nickel et al., 2018).

GMV differences between AAN, PRAN and FRAN. We did not find any regions that showed greater GMV in acute AN compared to partially remitted AN patients. Our results are consistent with the study of Friederich et al. (2012). However, we did not find altered GMV between acute AN patients and partial remitted AN patients. These missing results are in conflict with the results of Friederich et al. (2012), who reported a reduction in GMV in the left amygdala, the putamen and the left inferior temporal cortex in acute AN patients compared to partially remitted AN patients.

Additionally, we found reduced GMV in the AAN group compared to FRAN group in the fusiform gyrus.

Lastly, we found reduced GMV in the PRAN group compared to the FRAN in the angular as well as the anterior cingulate cortex. Previous studies found GMV reduction in the dorsal anterior cingulate cortex in PRAN compared to HC (Castro-Fornieles et al., 2009; Friederich et al., 2012) as well as in the angular (Mainz et al., 2012).

Association between GMV and cognitive flexibility

Our findings support the hypothesis 2b, indicating that across groups, cognitive flexibility is associated with altered GMV across the whole brain after controlling for age and TIV. However, these GMV alterations did not remain significant after applying the conservative FWE correction. Therefore, we used a more liberal statistical threshold. The results should be interpreted with caution. However, this approach reduced the risk of false-negative results and enabled the identification of subtle GM abnormalities that would otherwise remain undetected (Mainz et al., 2012).

The VBM analysis revealed negative associations between GMV and concept perseveration across the groups. Given that higher concept perseveration scores indicate weaker cognitive flexibility, this pattern indicates that reduced GMV in the identified regions is connected to weaker cognitive flexibility.

Our study revealed largest GMV reductions associated with weaker cognitive flexibility are located in the inferior parietal lobule as well as in the rectus, superior temporal and inferior frontal gyri across all four groups.

The association between reductions of GMV in the regions of the frontal lobe and weaker cognitive flexibility align with previous literature (Haldane et al., 2008; Yuan & Raz, 2014). The meta-analysis by Yuan and Raz (2014) reported a positive association between prefrontal GMV and cognitive flexibility. In general, the frontal cortex has been suggested to play a key role in executive processes (Müller et al., 2015). Taken together, our results and the previous literature support the role of frontal lobe regions in cognitive flexibility and suggest that structural variability in GMV in this region may explain individual differences in cognitive flexibility.

Additionally, we identified an association between reduced GMV in the right insula and weaker cognitive flexibility. These results are similar to what Müller et al. (2015) report.

Furthermore, our study revealed an association between reduced GMV in the temporal cortex and weaker cognitive flexibility. This finding contrasts with the results of Zhu et al. (2019), who reported that decreased GMV in the temporal cortex was associated with greater cognitive flexibility. Further research is needed to clarify the direction of this relationship. Notably, these correlations in our study emerged only at the uncorrected level and should thus be interpreted with caution.

Inhibitory control is another executive function which could influence WCST performance (Friedman & Miyake, 2017; Weinbach et al., 2019). Haldane et al. (2008) examined the association between GMV and inhibitory control, using the Stroop Color-Word Task interference score, in healthy controls. Interestingly, the regions in which they reported reduced GMV associated with poorer inhibitory control overlapped with the regions we found to be associated with weaker cognitive flexibility. These regions included the right middle frontal gyrus, inferior frontal gyrus, left precuneus and right cerebellum. Our findings therefore extend previous results by showing that similar brain regions play a role in cognitive flexibility and inhibitory control in both clinical and non-clinical groups. This suggests that different executive functions may be based on shared brain structures, or that it is difficult to distinguish between executive functions in neurological tests. Further research will be needed to determine which interpretation is correct.

Different association between GMV and cognitive flexibility in AN stages and HC

The hypothesis 2c stating that the association between cognitive flexibility and GMV across the whole brain differed for acute, partially remitted, and fully remitted AN patients as well as healthy controls after controlling for age and TIV, can be considered confirmed. As in the previous analysis, the GMV alterations failed to reach significance after applying the conservative FWE correction. Therefore, we additionally examined the data using a more liberal statistical threshold.

With our results we could not support the positive correlation Friederich et al. (2012) found between cognitive flexibility and the right amygdala in AN patients (Friederich et al., 2012). It is important to note, that after corrections for multiple testing this correlation was also gone in their study (Friederich et al., 2012). Furthermore, our study identified an association between increased GMV in the right ACC and weaker cognitive flexibility in healthy controls. This association is in line with the negative correlation between cognitive flexibility performance and the right ACC volume in healthy controls found by Friederich et al. (2012). However, no other overlapping regions with previous research in each group could be identified. The following discussion will be restricted to the acute and partially remitted AN groups, since we only observed group differences between these two in cognitive flexibility in the CKV measured with concept preservation.

In the AAN group we identified an association between weaker cognitive flexibility and reduced GMV in the right supplementary motor area, left and right precuneus, inferior

parietal lobule, cerebrum as well as inferior temporal, right lateral orbital, superior frontal, medial frontal and middle frontal gyri.

The reduced GMV in the right supplementary motor area in the AAN group is in line with fMRI evidence showing decreased activation in sensorimotor regions during behavioral response shifting in AN patients compared to healthy controls (Zastrow et al., 2009). This suggests that structural and functional alterations in these supplementary motor areas may contribute to impaired cognitive flexibility.

In the PRAN group we identified an association between weaker cognitive flexibility and increased GMV in the cerebellum anterior lobe, superior and middle frontal gyri. Additionally, we found an association between weaker cognitive flexibility and decreased GMV in the inferior parietal lobule.

While we found reductions in GMV in the frontal cortex (superior frontal, medial frontal, and middle frontal gyri) associated with weaker cognitive flexibility in AAN patients, we identified increases in GMV in the frontal cortex (superior frontal and middle frontal gyri) that were associated with weaker cognitive flexibility in PRAN patients. The fMRI results regarding the frontal cortex are also contradictory (Sato et al., 2013; Zastrow et al., 2009). Sato et al. (2013) found reduced activation in the frontal cortex (right ventrolateral prefrontal cortex) by performing the WCST while undergoing fMRI in patients with AN compared to healthy controls. By contrast, an fMRI study by Zastrow et al. (2009) of AN patients showed greater activation in frontal brain regions during set shifting, among other regions. Overall, these findings suggest that both structural and functional alterations in the frontal cortex may contribute to cognitive flexibility. However, further research is required to disentangle the direction of functional activation and to determine whether stage-specific increases or decreases in GMV are reliably associated with AN.

We found an association between decreased GMV in the inferior parietal lobule and increased GMV in the cerebellum anterior lobe and weaker cognitive flexibility in the AAN and PRAN group.

We found a shared reduction in the GMV of the inferior parietal lobule in the AAN and PRAN group. Zastrow et al. (2009), found in a fMRI study increased activation in parietal regions during set shifting tasks in AN patients. Taken together, these findings indicate that GMV decreases and functional alterations in the parietal lobe may be involved in impairments in cognitive flexibility in AN patients. Notably, despite comparable GMV

reductions in acute ill and partially remitted AN patients, their behavioral performance on the cognitive flexibility task diverged significantly, highlighting that differences in these tasks cannot be only explained by brain regions abnormalities.

Another similarity between the AAN and PRAN groups was their common association between increased GMV in the cerebellum anterior lobe and weaker cognitive flexibility, which is in line with fMRI evidence showing reduced activation in the cerebellum in AN patients doing behavioral response shifting compared to healthy controls (Zastrow et al., 2009) as well as doing set shifting task compared to doing a control task (Castro-Fornieles et al., 2019). In Castro-Fornieles et al. (2019) study this previously significant difference failed to reach significance after six months of treatment and restoration of nutrition, however in our study we still found increases in GMV in cerebellum anterior lobe in PRAN group even after a period of restored nutrition. This pattern suggests that GMV increases and functional alterations in the cerebellum may contribute to impairments in cognitive flexibility in anorexia nervosa.

When comparing the PRAN to the AAN group, we found no brain regions where the association between cognitive flexibility and GMV was significantly stronger. This aligns with the behavioral findings from the CKV, where AAN patients showed significantly greater cognitive flexibility, measured with concept perseveration, than the PRAN patients.

Furthermore, we found that the association between concept perseveration and GMV was significantly stronger in the AAN compared to the PRAN group in the right cuneus as well as in the left and right middle frontal, left superior frontal and lateral orbital gyri.

The results in the frontal cortex, middle frontal and left superior frontal gyri, are interesting, as we found already a reduction in GMV in the frontal cortex associated with weaker cognitive flexibility in AAN patients as well as increases in GMV in the frontal cortex that were associated with weaker cognitive flexibility in PRAN patients. Furthermore, fMRI findings suggest that this region could play an important role in cognitive flexibility (Sato et al., 2013; Zastrow et al., 2009). This finding suggests that there are specific changes in the GMV of the frontal cortex at different anorexia nervosa stages associated with cognitive flexibility, but future research is needed to clarify this relationship.

Limitations

There are several limitations. The first limitation of our study is that our sample size is too small for identifying an association between brain structure and cognitive functions.

Identifying associations between brain structures and specific abilities, such as cognitive flexibility, requires a sample size of at least a thousand participants (Marek et al., 2022). Only then are replication rates and effect sizes acceptable (Marek et al., 2022). Using smaller sample sizes as in our study can lead to overestimation of findings and the discovery of irreproducible brain–phenotype associations (Marek et al., 2022).

The second limitation is the cross-sectional nature of our study (Friederich et al., 2012). Data comparing GMV between different stages of anorexia nervosa and healthy control participants should be interpreted with caution, as it is unclear whether the differences found actually reflect differences between disease stages or whether there are pre-existing differences independent of the disease stages in our sample (Friederich et al., 2012). Conducting a longitudinal study is also complicated by the long duration of illness until recovery from AN (Friederich et al., 2012).

Another limitation is the absence of comparison data for the modified version of the WCST used in this study (Drühe-Wienholt & Wienholt, 2013; Wittek et al., 2025). As most studies on cognitive flexibility use the unmodified English version of the WCST, the results can only be compared with those in the literature to a limited extent. It is particularly problematic that the concept perseveration parameter, for which significant results were found, only exists in the modified version, preventing any comparison.

The aim of our study was to close the research gap regarding cognitive flexibility, GMV, and the association between GMV and cognitive flexibility in adolescents and young adults. Another limitation is therefore that we included a broad age range from 12 to 30 years, which makes it difficult to make specific statements about AN in the early phase of life. This was done because the recruitment process for AN in different illness stages, especially fully remitted, is extremely difficult.

Lastly, a limitation of this study is that it was no exclusion criterion for the healthy control group to be a sibling of an anorexia nervosa patient. This could have been problematic for the results as previous studies already showed impairments in cognitive flexibility in unaffected sisters of AN patients (Holliday et al., 2005; Roberts et al., 2010). Further research should exclude relatives of AN patients for the HC group.

Conclusion and future directions

Together, our findings demonstrated that PRAN showed weaker cognitive flexibility compared to AAN. No other significant group difference was observed.

The voxel-based morphometry analysis revealed a reduction of GMV in the cerebellum of AAN patients compared to healthy controls. This reduction could affect the control of feeding behavior, appetite and weight in AAN (Sader et al., 2023). In partially remitted AN patient´s compared to HC, alteration in GMV were located in the left inferior parietal lobe, which is connected to appetite and somatosensory perception (Titova et al., 2013), as well as the angular gyrus, which is connected to the concept of oneself and one's body image (De Carvalho et al., 2024). No significant GMV reduction was found between the fully remitted AN group and healthy controls, indicating that GMV decreases are reversible upon full recovery (Nickel et al., 2018).

Using a more liberal statistical threshold, our study revealed that reduced GMV was associated with weaker cognitive flexibility, among other regions in the frontal lobe, across all groups. Previous literature (Haldane et al., 2008; Yuan & Raz, 2014) also support the role of the frontal lobe in cognitive flexibility.

Furthermore, with a more liberal statistical threshold our study revealed a reduced GMV associated with weaker cognitive flexibility in the AAN group in the right supplementary motor area, precuneus, inferior parietal lobule, cerebrum as well as inferior temporal, right lateral orbital, superior frontal, medial frontal and middle frontal gyri. In the PRAN group we identified an association between weaker cognitive flexibility and increased GMV in the cerebellum anterior lobe, superior frontal and middle frontal gyri and decreased GMV in the inferior parietal lobule We found an association between decreased GMV in the inferior parietal lobule and increased GMV in the cerebellum anterior lobe and weaker cognitive flexibility in the AAN and PRAN group. Furthermore, we found that the association between concept perseveration and GMV was significantly stronger in the AAN compared to the PRAN group in the right cuneus as well as left and right middle frontal, left superior frontal and lateral orbital gyri. The results in the frontal lobe further support that this region could play an important role in cognitive flexibility.

Future research should further explore the role of the frontal lobe in AN regarding cognitive flexibility. Moreover, voxel-based morphometry studies in unaffected siblings of AN patients are warranted to clarify whether abnormalities in GMV represent preexisting traits or consequences of the disorder (Seitz et al., 2016). Finally, longer-term follow-up studies are needed to determine whether fully remitted AN patients indeed show no persistent gray matter volume reductions (Seitz et al., 2016).

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Appendix

Abstract (EN)

Cognitive flexibility is often impaired in adults with acute anorexia nervosa (AN) and may reflect underlying brain differences. In adolescents with AN, neurocognitive profiles remain unknown. This study examined cognitive flexibility in acute AN (AAN), partially remitted AN (PRAN), and fully remitted AN (FRAN) compared with healthy controls (HC), and its associations with gray matter volume (GMV). A total of 112 adolescents and young adults completed the "Computergestütztes Kartensortierverfahren". The PRAN group showed significantly weaker cognitive flexibility than the AAN group. Voxel-based morphometry analyses were conducted on data from 91 participants. Group comparisons revealed reduced GMV in the cerebellum in the AAN group and in the parietal lobe in the PRAN group, compared to HC. No GMV differences emerged between the FRAN group and HC. Across all groups, weaker cognitive flexibility was associated with reduced GMV in the inferior parietal lobule, rectus gyrus, superior temporal gyrus, and inferior frontal gyrus. The association between cognitive flexibility and GMV differed across AAN, PRAN, and FRAN, and HC. In the AAN and PRAN groups, weaker cognitive flexibility was associated with decreased GMV in the inferior parietal lobule and increased GMV in the cerebellum. The associations between cognitive flexibility and GMV were significantly stronger in AAN than in PRAN. None of these GMV and cognitive flexibility associations remained significant after FWE corrections. Our findings suggest that cognitive flexibility is not impaired in adolescents with AN, whereas the impairments observed in PRAN indicate that weaker cognitive flexibility hinders recovery or may be a consequence of the illness.

Abstract (DE)

Kognitive Flexibilität ist bei Erwachsenen mit Anorexia nervosa (AN) häufig beeinträchtigt und könnte zugrunde liegende Unterschiede im Gehirn widerspiegeln. Bei Jugendlichen mit AN sind die neurokognitiven Profile weitgehend unbekannt. Diese Studie untersuchte die kognitive Flexibilität bei akuter AN (AAN), partiell remittierter AN (PRAN) und vollständig remittierter AN (FRAN) im Vergleich zu gesunden Kontrollen (HC) sowie im Zusammenhang mit dem Volumen der grauen Substanz (GMV). Insgesamt absolvierten 112 Jugendliche und junge Erwachsene das computergestützte Kartensortierverfahren. Die PRAN-Gruppe zeigte eine signifikant schwächere kognitive Flexibilität als die AAN-Gruppe. Die voxel-basierte Morphometrie wurde mit den Daten von 91 Probandinnen durchgeführt. Gruppenvergleiche ergaben ein reduziertes GMV im Cerebellum in der AAN Gruppe und im Parietallappen bei der PRAN Gruppe im Vergleich zu gesunden Kontrollen. Zwischen der FRAN Gruppe und HC zeigten sich keine GMV Unterschiede. Über alle Gruppen hinweg war eine schwächere kognitive Flexibilität mit reduziertem GMV im Lobulus parietalis inferior, Gyrus rectus, Gyrus temporalis superior und Gyrus frontalis inferior assoziiert. Der Zusammenhang zwischen kognitiver Flexibilität und GMV unterschied sich zwischen AAN, PRAN, FRAN und HC. In AAN und PRAN war eine schwächere kognitive Flexibilität mit verringerter GMV im Lobulus parietalis inferior sowie erhöhter GMV im Cerebellum verbunden. Diese Assoziationen waren in der AAN Gruppe signifikant stärker als in der PRAN Gruppe. Keiner dieser Zusammenhänge zwischen GMV und kognitiver Flexibilität blieb nach FWE-Korrektur signifikant. Unsere Ergebnisse deuten darauf hin, dass die kognitive Flexibilität bei Jugendlichen und jungen Erwachsenen mit AN nicht beeinträchtigt ist, während die in PRAN beobachteten Beeinträchtigungen darauf hinweisen, dass eine schwächere kognitive Flexibilität die Genesung erschweren könnte oder eine Folge der Erkrankung sein könnte.

Table 11

Mean and standard deviation of set shifting

Variables	HC *M* (*SD*)	FRAN *M* (*SD*)	PRAN *M* (*SD*)	AAN *M* (*SD*)
Set shifting (*N* = 112)				
Total Responses	80.45 (10.23)	78.42 (7.49)	82.40 (9.73)	80.75 (8.99)
Total correct responses	64.28 (7.30)	63.92 (3.32)	62.32 (6.46)	63.39 (7.70)
Total response errors	16.17 (10.28)	14.50 (5.73)	20.08 (11.68)	17.36 (11.91)
Perseverative errors	4.13 (7.99)	2.42 (3.26)	5.36 (5.39)	4.21 (7.28)
Perseverative score	17.75 (15.66)	13.53 (11.39)	25.02 (16.02)	18.53 (21.32)
Concept perseveration	0.45 (0.72)	0.42 (0.67)	1.16 (1.57)	0.68 (1.83)
Non-perseverative errors	12.04 (4.65)	12.08 (2 97)	14.72 (6.85)	13.14 (5.71)
Conceptual Level Responses	6.79 (1.28)	6.67 (0.49)	6.40 (1.26)	6.71 (0.98)
Failure to maintain set	1.06 (1.36)	0.67 (0.49)	0.80 (1.35)	1.11 (1.31)
Trials to complete first category	12.49 (3.58)	13.33 (4.08)	12.12 (2.40)	14.07 (9.10)

Note. HC (*N* = 47); FRAN (*N* = 12); PRAN (*N* =25); AAN (*N* = 28); total *N* = 112; *M* = mean; *SD* = standard deviation.

Table 12

Correlation matrix: HC

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Total Responses	-.15	.	.64**	.94**	.77**	.59**	.57**	.90**	.57**	.75**	.52**
2. Total correct responses	-.10	.64**	.	.43**	.24**	.09	.02	.53**	.88**	.79**	.36*
3. Total response errors	-.13	.94**	.43**	.	.87**	.69**	.59**	.38**	.57**	.57**	.45**
4. Perseverative errors	-.22	.77**	.24	.87**	.	.95**	.76**	.66**	.23	.41**	.76**
5. Perseverative score	-.26	.59**	.09	.69**	.95**	.	.77**	.41**	.11	.26	.14
6. Concept perseveration	-.35*	.51**	.02	.59**	.76**	.77**	.	.35*	-.03	.15	.15
7. Non-perseverative errors	-.06	.90**	.53**	.92**	.66**	.41**	.35*	.	.46**	.63**	.49**
8. Conceptual Level Responses	-.03	.57**	.88**	.38**	.23	.11	-.03	.46**	.	.89**	.45**
9. Failure to maintain set	-.01	.75**	.79**	.57**	.41**	.26**	.15	.63**	.89**	.	.52**
10. Trials to complete first category	.12	.45**	.36*	.46**	.30*	.14	.15	.49**	.45**	.51**	.

Note. $N = 47$, r = Correlation Coefficient, Signific Nivea is *$p < 05$; Signific Nivea is **$p < 001$

Table 13

Correlation matrix: AAN

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Total Responses	.02	.	.23	.80**	.75**	.66**	.62**	.73**	.37	.74**	.40*
2. Total correct responses	.05	.23	.	-.18	-.15	-.02	-.41*	-.24	.82**	.34	-.22
3. Total response errors	-.08	.81**	-.18	.	.82**	.64**	.66**	.93**	-.13	.30	.57**
4. Perseverative errors	.09	.75**	-.15	.82**	.	.90**	.69**	.62**	-.10	.33	.52**
5. Perseverative score	.03	.66**	-.02	.64**	.90**	.	.59**	.41*	-.01	.33	.35
6. Concept perseveration	.13	.62**	-.41*	.66**	.69**	.59**	.	.60**	-.24	.39*	.34
7. Non-perseverative errors	-.10	.73**	-.24	.93**	.62**	.41*	.60**	.	-.10	.30	.47*
8. Conceptual Level Responses	-.02	.37	.82**	-.13	-.10	-.01	-.24	-.10	.	.66**	-.28
9. Failure to maintain set	.02	.74**	.34	.30	.33	.33	.39+	.30	.66**	.	.05
10. Trials to complete first category	.10	.40*	-.22	.52**	.35	.47*	.34	.47*	-.28	.05	.

Note. $N = 28$, r = Correlation Coefficient, Signific Nivea is *$p < 05$; Signific Nivea is **$p < 001$.

Table 14

Correlation matrix: PRAN

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Total Responses	-.30	.	.19	.90**	.78**	.46*	.50*	.88**	.09	.60**	.05
2. Total correct responses	-.21	.19	.	-.13	-.19	-.19	-.25	-.09	.92**	.52**	.16
3. Total response errors	-.23	.90**	-.13	.	.88**	.62**	.58**	.94**	-.21	.32	-.07
4. Perseverative errors	-.40	.78**	-.19	.88**	.	.75**	.83**	.71**	-.26	.22	.01
5. Perseverative score	-.22	.46*	-.19	.62**	.75**	.	.76**	.40*	-.28	-.02	-.08
6. Concept perseveration	-.38	.50*	-.25	.58**	.83**	.76**	.	.36	-.32	.06	.01
7. Non-perseverative errors	-.16	.88**	-.09	.94**	.71**	.40*	.36	.	-.18	.36	-.12
8. Conceptual Level Responses	-.25	.09	.92**	-.21	-.26	-.28	-.32	-.18	.	.58**	.23
9. Failure to maintain set	-.15	.60**	.52**	.32	.22	-.02	.06	.36	.58**	.	.13
10. Trials to complete first category	-.17	.05	.16	-.07	.01	-.08	.01	-.12	.23	.13	.

Note. $N = 25$, r = Correlation Coefficient, Signific Nivea is *$p < 05$; Signific Nivea is **$p < 001$.

Table 15

Correlation matrix: FRAN

Variable	1	2	3	4	5	6	7	8	9	10	11
1. Total Responses	-.48	.	.80**	.94**	.56	.46	.74**	.94**	.82**	.82**	.32
2. Total correct responses	-.11	.80**	.	.64*	.09	-.02	.42	.75**	.83**	.82**	.10
3. Total response errors	-.65*	.94**	.64*	.	.65*	.56	.72**	.91**	.72**	.72**	.23
4. Perseverative errors	-.57	.60	.09	.65*	.	.98**	.79**	.40	.37	.37	.38
5. Perseverative score	-.57	.46	-.02	.56	.98**	.	.72**	.27	.31	.31	.47
6. Concept perseveration	-.57	.75**	.42	.72**	.79**	.72**	.	.57	.49	.49	.30
7. Non-perseverative errors	-.44	.94**	.75**	.91**	.40	.27	.76**	.	.76**	.76**	.17
8. Conceptual Level Responses	-.41	.82**	.83**	.72**	.37	.31	.49	.76**	.	.49	.44
9. Failure to maintain set	-.41	.82**	.83**	.72**	.37	.31	.49	.76**	1.00**	.	.44
10. Trials to complete first category	-.26	.32	.10	.23	.38	.47	.30	.17	.43	.43	.

Note. N =12, r = Correlation Coefficient, Signific Nivea is *p < 05; Signific Nivea is **p < 001.