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Alexithymia in adolescent Anorexia Nervosa patients and its neural substrates – a voxel-based morphometry (VBM) study

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## Theoretical Background

Anorexia Nervosa (AN) is a severe eating disorder (ED) which is characterized by deliberate weight loss which is induced or maintained by the patient. A commonly used guideline is a BMI less than 18.5 $kg/m^2$ or a rapid weight loss of more than 20% of total weight in less than 6 months. Patients with AN show behaviors that maintain or establish low body weight such as starving, purging or extensive exercising. Their self-evaluation is predominantly influenced by shape, weight and form of the body and this perception is often inaccurate (WHO, 2022). Global lifetime prevalence is 4% in women and 0.3% in men, notably a recent raise in prevalence in especially young women (< 15 years), but also men, has been found (Van Eeden et al., 2021). AN is one of the deadliest psychiatric conditions with the highest mortality rate (crude mortality rate = 5.1 per 1000 person years) out of all psychiatric disorders, with 1 in 5 deaths being caused by suicide (Arcelus et al., 2011; Smink et al., 2013) 20 to 30% of AN patients develop a severe and chronic form of AN (Steinhausen, 2002; Wonderlich et al., 2020). Especially chronic AN patients are difficult to treat successfully as their relationship with the disorder is paradoxical, giving psychological comfort and a sense of control, but also being a potentially fatal disorder (Starzomska et al., 2020). Less than 50% recover fully according to Steinhausen (2002); a number that has been replicated even 20 years later in research on modern therapy manuals for AN (Wittek et al., 2023) Those with an enduring or severe form of AN often develop organic problems such as liver dysfunction (Rosen et al., 2017), cardiovascular complications (Sachs et al., 2016) or decreased bone mass density leading to osteoporosis and a highly increased fracture risk (Misra & Klibanski, 2014).

Alexithymia, literally meaning “no words for feeling” (Sifneos, 1973), is a subclinical syndrome which describes the inability to recognize and describe feelings paired with a thinking style that is oriented towards the external world and its events rather than looking within (Preece et al., 2017). Generally, it is estimated that 10% of the population are alexithymic, with a higher prevalence in men than women (Mattila et al., 2006); a more recent study found a prevalence range of 4.4 – 9.8% in women and 7.8 – 16.6% in men (Mendia et al., 2024). In clinical populations, this prevalence is highly increased across multiple disorders such as EDs (Nowakowski et al., 2013), Post-traumatic stress disorder (Frewen et al., 2008), Autism (Kinnaird et al., 2019) or Schizophrenia (Xiao et al., 2024).

While alexithymia as a construct originally stems from psychodynamic theory that argued alexithymia serves as a defense mechanism to unconscious conflict (Wingbermühle et al., 2012), it has found its way into empirical psychology (Hollander et al., 1991, as cited in

Wingbermühle et al., 2012). The very first instrument to measure alexithymia, the Toronto Alexithymia Scale-26 (TAS-26), assessed four facets namely *Difficulties Identifying Feelings* (DIF), *Difficulties Describing Feelings* (DDF), *Externally Oriented Thinking* (EOT) and *Reduced Daydreaming* (RD) (Bagby et al., 1988). Bagby and collogues shortly realized that the RD subscale is inefficient and measures something other than alexithymia (contractionary to the observations by Sifneos, 1973), leading to a revised 3-factor questionnaire, the TAS-20 (Bagby et al., 1994). Nowadays the TAS-20 is the most widely used instrument to assess alexithymia. Initially, alexithymia was first was seen as a categorical variable (cutoff-score ≥ 61 on the TAS-20), but it is now established that alexithymia is a relatively stable personality trait in the general population that can be seen as a dimensional construct (e.g. Tolmunen et al., 2011). However, this stability is disputed in clinical populations (e.g. de Haan et al., 2012).

A second way to define alexithymia was proposed by Bermond and Vorst, which Preece et al. (2017) called the "*Amsterdam Model*" (as opposed to the *Toronto Model*), who introduced the BVAQ (Vorst & Bermond, 2001). They argue that the TAS-20 only measures a "cognitive alexithymia" which indeed exists but fails to cover the affective side of alexithymia: a damped emotional experiencing and a lack of fantasy and daydreams. In sound with the original psychodynamic idea of alexithymia they created a 5-factor model of alexithymia: *Identifying, Verbalizing* and *Analyzing*, which cover the 3 factors of the TAS-20 ($r = 0.80$; Müller et al., 2004) as a cognitive dimension and *Fantasizing* and *Emotionalizing* as an affective dimension. They differentiate between type II alexithymia which describes a condition in which only the cognitive aspects of emotion processing are impaired; this is the alexithymia measured by the TAS-20. Type I alexithymia refers to a lack of emotional experiencing and a reduced fantasizing which is then accompanied by an inability to process them cognitively (Wingbermuehle et al., 2012). Numerous of their studies have demonstrated the validity of the BVAQ (e.g. Bermond et al., 2006; Vorst & Bermond, 2001) but other studies have found the affective facets to measure something else than alexithymia (Bagby et al., 2009) which makes the Amsterdam model of alexithymia disputed (see Preece et al., 2017). The TAS-20 has also been criticized that it does not measure alexithymia but rather negative affect (Marchesi et al., 2014) psychological distress (Preece et al., 2024), physical neuroticism (Moriguchi & Komaki, 2013) or social shame (Suslow et al., 2000). Nevertheless, the three original factors DDF, DIF and EOT together have been generally accepted to measure alexithymia, even though the EOT-scale itself only has acceptable psychometric measures (e.g. Moriguchi et al., 2007; Preece et al., 2018; Torres et al., 2019).

**Relevance of Alexithymia to Anorexia Nervosa**

Oldershaw et al. (2019) provide a compelling overview about the history of AN: One of the very first descriptions of Anorexia Nervosa stems from Charles Lasègue in the 1870s who described a young woman with AN as a person "which suffers from some emotions she avows or conceals" (Lasègue, 1873, as cited in Oldershaw et al., 2019). Hilde Bruch (1962, as cited in Oldershaw et al., 2019) later postulated that AN is the consequence of a deficiency in identifying emotional states and responses, which sounds very similar to the syndrome we now call alexithymia. She proposes that the disorder itself is a way of regulating unidentified emotions, something that more recent theories on AN also propose. Oldershaw et al. (2019) for example argue that AN related behaviors emerge as a means to elicit control over potentially triggering emotions, and similar mechanisms have been postulated by other researchers as well (e.g. Speranza et al., 2005).

In fact, every modern theoretical model on AN (and EDs in general) proposes that difficulties in regulating emotions are a central part of disordered eating (Pennesi & Wade, 2016) and some of them explicitly name alexithymia as part of the model e.g. the Cognitive-Interpersonal Maintenance Model of Anorexia Nervosa (Treasure & Schmidt, 2013). Recent systematic reviews also point to the importance of researching alexithymia in AN more intensively to improve treatment (Arunagiri & Reilly, 2022; Gramaglia et al., 2020). Preece et al., (2017) have postulated integrating alexithymia in an *Attention-Appraisal-Model* as part of an *extended process model of emotion regulation* (Gross, 2015). An externally oriented thinking-style, in the sense of not looking within, can be understood as an impaired *attention* while the inability to identify and describe emotions are understood as an impairment of *appraisal*. Combining these approaches, an anorexic person high in alexithymia might avoid attending to their internal state. This leads to them not being able to identify and describe what they feel or want which ultimately results in maladaptive responses such as restricted eating behavior as a way of regulating emotions. This again can be seen as an impaired *response* in the *extended process model of emotion regulation*.

Empirical research has shown that emotion generation and regulation is highly impaired in patients with AN: A meta-analysis (Oldershaw et al., 2015) found large effect sizes for numerous variables concerning emotion generation and regulation in AN patients compared to healthy controls (HC) such as experiential avoidance ($d$ = 1.00), negative problem solving-style ($d$ = 1.06), external comparison ($d$ = 1.25) or alexithymia ($d$= 1.29). Regarding maladaptive schemata the study revealed effect sizes even up to $d$ = 2.81. A further meta-analysis explicitly investigating alexithymia in ED patients (Westwood et al., 2017)

came to very similar results ($d$ = 1.44). Concerning each facet of alexithymia, DIF evoked the largest effect size ($d$ = 1.57), followed by DDF ($d$ = 1.11) and EOT ($d$ = 0.48). If alexithymia is seen as a categorical variable, prevalence in AN populations is increased up to 77% (Nowakowski et al., 2013).

### *Treatment of Anorexia Nervosa*

Alexithymia is also relevant for treatment outcome in AN: Arunagiri and Reilly (2022) theorize that elevated alexithymia could interfere with treatment success as alexithymic patients tend to use fewer complex words to describe their internal state and recall less emotional events. Even Sifneos (1973) speculated fifty years ago that alexithymic patients would not benefit from psychodynamic therapy. Two studies have demonstrated that higher alexithymia predicted worse treatment outcome at treatment exit (Vrieze, 2018) and in a 3-year follow-up (Speranza et al., 2007). Further, the authors highlight that although alexithymia seems relatively stable in healthy populations, it can be successfully lowered in clinical populations in other disorders with psychological treatment (Cameron et al., 2014). In a systematic review, Gramaglia et al. (2020) investigated this specific question whether treatments for AN can lower alexithymia and found mixed results: out of ten studies, in three interventions could not lower alexithymia, while in five this seemed to be the case. Still the authors note that alexithymia levels remained higher than in healthy controls after treatment.

Of importance in this context is weight restoration (WR), as it is often used as the minimum criterion defined for treatment success in AN (Wonderlich et al., 2020). Evidence has shown that restoring weight reduced alexithymia scores using the TAS-20, but they remain higher than in healthy controls (Tchanturia et al., 2012). This result was also found in another study by Beadle et al, (2013): After weight restoration, TAS-20 scores were lower than at hospitalization, but they remained higher than control scores. Interestingly, when controlling for the change score in depression, the alexithymia reduction between hospitalization and weight restoration was not significant anymore. The authors conclude that the increased alexithymia is a trait feature of AN and does not recover with weight restoration, and depressive symptoms likely account for the increase during starvation. A similar result was shown in Sexton et al., (1998) who also found no difference between admission and discharge TAS-26 scores, after controlling for depression. The authors do not specify what treatment patients received, and patients were allowed for discharge when they reached adequate weight.

As WR goes along with restoration of body functions, e.g. menstruation (van Elburg et al., 2007) and digestion (West et al., 2021), these results seem reasonable. While acute AN

patients have less grey matter volume (GMV) and cortical thickness (e.g. Seitz et al., 2016; Titova et al., 2013; S. Zhang et al., 2018), brain size increases after weight restoration and normal global brain volumes return after long term recovery, albeit it is disputed whether it is a complete recovery (see Seitz et al., 2016). Depressive (e.g. Speranza et al., 2007) and more inconsistently also anxiety symptoms (Kezelman et al., 2015) decrease with weight restoration. Following weight restoration, it can thus be expected that areas of social cognition also improve in AN patients as seen in empathy (Oldershaw et al., 2010). Treasure and Schmidt (2013) argue that social functioning is decreased in AN due to a shrunken brain, as in most animal and bird kingdoms, brain size is associated with social complexity. Still there are numerous brain functions in WR AN patients that are still impaired compared to HCs, for example memory (Nikendei et al., 2011) or set shifting (Fuglset, 2019), indicating these are either permanently scarred domains or need treatment that extends beyond weight restoration.

To summarize, alexithymia seems to be a reasonable construct to consider in treatment for AN as emotion regulation difficulties have been central in recent theories of disordered eating. It is no surprise that novel treatment programs based on these theories such as MANTRA (Schmidt et al., 2014), CREST (Tchanturia et al., 2015) and SPEAKS (Oldershaw & Startup, 2024) lay more focus on emotion recognition and regulation skills than traditional treatment options such as standard CBT (Berkman et al., 2006). This seems even more relevant considering that a recent meta-analysis by Murray et al., (2019) found that there is no effective treatment for AN which is better than placebo. It should be noted that this study already included the first studies on MANTRA and CREST, while there is only one pilot study available for SPEAKS (Oldershaw & Startup, 2024). Both Arunagiri and Reily (2022) and Gramaglia et al. (2020) thus come to the conclusion that alexithymia seems more relevant than ever in AN research and should be studied more intensively to deepen the understanding of emotion processing in AN. It may interfere with treatment, but at the same time new findings could provide important information in order to optimize existing treatments. Arunagiri and Reily (2022) also highlight the importance of clarifying the overlap and distinction between related constructs with the most important one being depression.

### *The role of depression in Alexithymia and Anorexia Nervosa*

Depression and alexithymia correlate highly (e.g Espina Eizaguirre et al., 2004; for a meta-analysis see S. Li et al., 2015) and share similar theoretical constructs (see Torres et al., 2015). As stated above, there has been criticism that alexithymia could be in fact just measuring psychological distress (Preece et al., 2024) or negative affect (Marchesi et al., 2014), constructs closely related to depression (e.g. Dejonckheere et al., 2018). In AN, 50 %

of the patients report at least one mood disorder in their life (Treasure et al., 2020) and singular studies find prevalences up to 80% (Godart et al., 2015). Regarding its role in the relationship of alexithymia and AN, Arunagiri and Reily (2022) propose to always control for depression. A majority of studies have found controlling for depression diminishes the association (e.g. Bydlowski et al., 2005; Espina Eizaguirre et al., 2004), while there are studies which have found alexithymia to be still increased after controlling for depression (e.g. Bourke et al., 1992). In the study done by Beadle et al., (2013) change in depression scores accounted for the change in alexithymia following weight restoration, indicating that high alexithymia in acute patients is likely a state because of high depression, but there is a trait component as scores were still elevated after discharge. Torres et al., (2015) tested whether depression is a mediator and found it partially mediating the link between alexithymia and AN diagnosis, further underlining that there is both a trait and a state component to alexithymia in AN. This effect was mainly due to the DIF subscale of the TAS-20, but still the TAS could explain variation that depression did not account for.

In their meta-analysis, Westwood et. al (2017) came to a similar conclusion: 19 studies controlled for depression and eight remained significant when doing so. Of the 11 remaining studies some also controlled for anxiety or obsessive-compulsive-disorder symptoms, so it is unclear whether this was just the result of adjusting for depression. In the conclusion of their review which served as a foundation for Westwood et al. (2017), Nowakowski et al., (2013) state, that depression cannot fully explain alexithymia in EDs. Furthermore, they argue that alexithymia remained the same in an AN sample of patients high in depression and high in alexithymia who were treated with antidepressants (Schmidt et al., 1993). Lastly, there is also a genetic component to alexithymia that cannot be explained by depression (Picardi et al., 2011). In summary, there is an ongoing debate whether alexithymia is a trait in AN patients related to depression but has distinct features to it or if alexithymia is a state closely related to depression and alexithymia instruments might even be measuring parts of it. Additionally, a third perspective, to which Torres et al. (2015), Beadle et al. (2013) and Nowakowski et al. (2013) belong, exists: They argue that the presence of depressive symptoms can increase alexithymia, but there is a unique alexithymic personality trait in individuals suffering from AN and this is also to a lesser extend the case in remitted AN patients. Although researchers point to the limited relevance of a state-trait debate of alexithymia (Wingbermühle et al., 2012), this question appears to be more justified in the context of AN. Research ought to determine, to what extent alexithymia is a result of malnutrition and thus decreases with an initial weight restoration and to what extent alexithymia is psychological syndrome

independent of nutrition status, that needs psychological treatment to improve and how depressive symptoms might also interfere.

## Neuroscientific background

### *Anorexia Nervosa*

The neuropsychological functioning of the brain plays an important role regarding AN. More importantly, the changes in the brain might be a maintaining factor of AN: As malnutrition manifests, important brain functions shut down or are reduced such as set shifting, central coherence, interpreting social cues or interoceptive awareness (Treasure & Schmidt, 2013). According to the cognitive-interpersonal maintenance theory of AN (Treasure & Schmidt, 2013), both psychological predispositions, i.e. inflexibility and difficulties with emotions as well as negative social interactions with peers and in the family might lead to the onset of AN, meanwhile its maintenance is driven by a starved brain: the starvation leads to reduced high level brain functions which in turn aggravate the already existing psychological and social deficits. The disorder then becomes a vicious cycle as the consequence is a tunnel vision and ritualized behaviors which further promote caloric restriction. Breaking up this cycle becomes increasingly difficult as social symptoms (e.g. a mother trying to force their child to eat, leading to a worse relationship) and psychological symptoms (e.g. low self-confidence) manifest parallelly to a malnourished body and so do changes in the brain. In their updated version of the model, Treasure et al. (2020) postulate that not only interpersonal consequences, but also neuroadaptation, consolidated habit formation and chronic stress (and its neurobiological and psychological consequences) are key factors to the maintenance of AN. Neuroscientific research has become increasingly important to understand AN and numerous neurobiological theories have been postulated with a special interest in the insula in earlier theories (Kaye et al., 2009; Nunn et al., 2011). More recently, theories on altered reward processing and learning (Keating et al., 2012; Steinglass & Walsh, 2016) as well as attempts to summarize those have been published (Munro et al., 2017; Steinglass et al., 2019).

Regarding brain morphology, acutely anorexic patients have a reduced global GMV with an increase in cerebrospinal fluid (CSF) (e.g. Kappou et al., 2021; Seitz et al., 2016; Su et al., 2021; S. Zhang et al., 2018). Even more importantly, the GMV reduction is 2.5 times higher in adolescents than in adults (Seitz et al., 2016). Single studies investigating the structural changes in the brain offer little clarity as alterations are widespread and were found in virtually every area of the brain (for an overview of the studies, see S. Zhang et al., 2018). Coordinate-based meta-analysis offer a more nuanced answer grouping many AN patients

together. S. Zhang et al. (2018) identified reduced GMV in the bilateral middle cingulate cortex (MCC), posterior cingulate cortex (PCC), supplementary motor area (SMA), precuneus and cerebellum. Analyzing the studies with only adult patients revealed the right fusiform gyrus (FG) to have a decreased size as well, and analyzing the studies with pure AN patients (= no comorbid disorders) revealed a decrease in the left amygdala and anterior cingulate cortex (ACC) but not the cerebellum. As there were too few adolescent studies, there was no subgroup analysis for regional reductions in adolescents. A more recent meta-analysis by Su et al. (2021) investigating both brain morphology and resting state functional activity in AN patients validated these results: they observed GMV reductions in the bilateral cingulate cortex, the adjacent paracingulate parts, precuneus and in the left occipital cortex. Regarding resting state functional activity, they found an increase in subcortical and temporal regions and a decreased activity in the bilateral ACC and MCC.

Kappou et al., (2021) fill the gap by examining the GMV alterations in adolescents in a systematic review: They summarize that reductions are found in the parietal and temporal lobes, in the bilateral frontal gyrus, dorsolateral and medial frontal cortex, insular cortex, cerebellum and mesencephalon. Regarding subcortical structures, reductions were found in the amygdala, hippocampus and the cingulate cortex. The most recent and at the same time largest study investigating GMV differences in AN ($n$ = 103) with a multi-center paradigm (Tose et al., 2024) replicates most of these areas and finds even larger reductions: Decreases were found in the cerebellum, MCC, PCC, SMA and precuneus, but also in the anterior and posterior insula, a wide range of frontal lobe regions, in the parietal and temporal lobe and the thalamus. As meta-analyses usually do not use original data and cannot fix power issues of single studies per se, these results give additional insights into the brain alterations of AN patients and hint, that perhaps regional GMV reductions are even larger than expected.

Following weight restoration, study results have been mixed. While an increase in GMV following weight restoration is undisputed, there are studies in which GMV has normalized to the level of HCs (Bang et al., 2016; Lázaro et al., 2013; Nickel et al., 2018; Wagner et al., 2006), but in other studies GMV was still reduced either globally (e.g. Castro-Fornieles et al., 2009; Roberto et al., 2011) or in specific brain areas, for example the ACC (Friederich et al., 2012; Martin Monzon et al., 2017; Mühlau et al., 2007) or the amygdala and hippocampus (Martin Monzon et al., 2017).

In their meta-analysis, Seitz et al. (2016) distinguished between studies with short term recovered AN patients, on average 3 months, and long term recovered AN patients who were scanned at least 1.5 years later. After 3 months, total GMV was still reduced by 3.6 %

compared to HCs brains (compared to 4.6% during the acute phase), albeit especially adolescents' GMV recovered quickly from an 8.4% to a 3.7% reduction, which was not significantly different anymore to HCs. More importantly, in long-term recovered AN patients, the difference was only 0.4% and not significant anymore, indicating that in long term recovered patients, brain size returns to normal. Still, the authors hesitate to conclude that the brain fully recovers, as the trend to a reduction is still there, combined with studies in which single areas showed a decreased GMV even in long-term recovered patients (Friederich et al., 2012; King et al., 2015; Mühlau et al., 2007). To find such small differences with enough statistical power, huge samples would be needed (Steen et al., 2007). On top of that, these studies often exclude chronically ill and relapsed patients who might have a different brain physiology. Though, studies with a severe and enduring form of AN have shown similar results (Mishima et al., 2021).

The insula is an area which has been a central part of multiple neurobiological theories regarding AN as it is involved in a majority of the processes impaired in AN and has multiple unique functions that are relevant to AN such as disgust and gustatory functions (Kaye et al., 2009; Nunn et al., 2011). The insula is connected to the frontal, parietal and temporal cortex, including the SMA and also to subcortical structures such as the hippocampus, amygdala, thalamus and hypothalamus as well as the nucleus accumbens and striatum, serving as a bridge to allow better communication between millions of neurons (Nunn et al., 2008). Being hungry goes along with an increased insula activation as well as right before eating, while activation is decreased after eating (Nunn et al., 2011). Administering sucrose water to AN patients leads to a decreased insula activation compared to HCs (Oberndorfer et al., 2013; Wagner et al., 2008). Furthermore, the insula seems to be crucial for appropriate visceral interoception (Kerr et al., 2016) and whole-body evaluation (Craig, 2002). Critically, the insula has also gained attention as a neural substrate of alexithymia (see next section). The cingulate cortex, especially anterior and middle part, seems to be relevant in emotion processing and response production in AN which are strongly connected with limbic structures (Kaye et al., 2009). It is also involved in body perception (Lee et al., 2014) and alexithymia in AN (Miyake et al., 2009). Further, it is highly susceptible to GMV loss and needs an increased time to restore GMV or is scarred completely (McCormick et al., 2008; Mühlau et al., 2007).

Other important areas include the amygdala which is a key region for emotional processing and is disturbed in AN (for a review, see Marcolini et al., 2024) and areas related to planning and coordinating behavior such as the SMA and the cerebellum which could be a

neural representation of rigid behavior and impaired cognitive flexibility (S. Zhang et al., 2018). Additionally, the cerebellum is also involved with general visceral functions, feeding being one of them (Zhu & Wang, 2008). Recent studies also focus on the cerebellum's involvement in emotion regulation (Amianto et al., 2013; Zhong et al., 2023). Precuneus and PCC reductions are thought to be an impairment in the default mode network (DMN) (Lee et al., 2014). Finally, the frontal lobe regions are thought to be involved in habit learning, cognitive control and reward processing (see Steinglass et al., 2019). While the hippocampus has been found to be reduced in AN, only few studies found evidence for it being relevant to memory deficits in AN while others did not. Some studies found altered activation in the presence of food stimuli (for a review, see Keeler et al., 2020).

It is crucial to differentiate whether the GMV loss during the acute phase in specific areas is due to malnutrition of the brain in general or a specific aspect of AN pathophysiology. Some areas seem to be more susceptible to grey matter loss than others such as the ACC. Seitz et al. (2016) argue that these areas are highly susceptible to excessive cortisol and cortisol concentration is inversely related to GMV (Castro-Fornieles et al., 2009). Adolescents are more affected by GMV loss than adults which perhaps can be seen as an "overdone" pruning effect that happens during adolescents and is accelerated by starvation (Kappou et al., 2021). It is also noteworthy that certain areas are affected in adults but not in adolescents. The FG for example seems to be affected in adults, but not in adolescents (S. Zhang et al., 2018) while the hippocampus is affected in adolescents but not in adults (Kappou et al., 2021). When interpreting the results of studies regarding WR, caution is needed: Reduced GMV can be the consequence of AN, but they could have also been reduced before the prodromal phase of AN and might be a predisposition to develop AN. Lastly reduced volume can also be the neural substrate of a phase of missed learning, as especially chronic AN during adolescence interrupts normal brain development (Seitz et al., 2013).

In summary, AN goes in hand with a widespread reduction of GMV which is exacerbated during adolescence. WR leads to a GMV restoration although the exact magnitude is debated. Crucially, multiple brain areas that are relevant in the neuroscientific research of AN overlap with those relevant in the neuroscientific research of alexithymia.

### *Alexithymia*

Wingbermühle et al. (2012) gave a historical overview of the conceptualization of alexithymia tracing its development from a psychodynamic construct in the early 70s (Sifneos, 1973) through a developmental view, alexithymia as stagnation of the development in the concrete operational to formal stages of thinking in a Piagetian sense (Lane &

Schwartz, 1987), to its understanding of a disorder of social cognition, more specifically in the affective information processing which ultimately led to a neuroscientific interest in alexithymia (e.g. Lane et al., 1998) and research in disorders in which social cognition is impaired (e.g. Silani et al., 2008). Recent advancements include the demand to move away from studying alexithymia using the TAS and advocate for studying an affective side of Alexithymia too (Goerlich, 2018).

In the first neuroscientific studies of alexithymia, case studies based on lesions and early Positron Emission Tomography (PET) studies were used. Historically, there were two early neurobiological theories on alexithymia: first, a reduction in right-hemisphere activity and secondly an impairment of interhemispheric communication (Wingbermühle et al., 2012). The right hemisphere was thought to be responsible for the perception and coordination of emotions (Joseph, 1982). In one of the first PET studies on alexithymia, it was shown that there is less blood flow to the right hemisphere in alexithymic subjects compared to non-alexithymic subjects (Kano et al., 2003). The second theory conceptualized alexithymia as a corpus callosum impairment: Because the brain's interhemispheric communication is impaired, alexithymia emerges. This has been observed in split brain patients in several case studies (Hoppe & Bogen, 1977; TenHouten et al., 1986) and in a transcranial magnetic stimulation study (Romei et al., 2008).

More recent research focuses on the involvement of certain brain structures. Papez already hypothized in 1937 that the ACC is involved in emotion regulation (Papez, 1937, as cited in Wingbermühle et al. 2012). In 1998, Lane et al. were the first ones to demonstrate the involvement of the ACC in alexithymia. Participants with high alexithymia scores (using the Level of Emotional Awareness Scale, LEAS) showed abnormal ACC activity while watching emotional films which led to the theory that the ACC is responsible for alexithymia. While (functional) magnetic resonance imaging (MRI) studies investigating alexithymia were rather scarce when Wingbermühle et al. (2012) released their review, they have now become the dominating research paradigm in brain mapping research as they are safe, non-invasive and do not need any injections (compared to PET studies) (e.g. Kim & Kim, 2017).

A meta-analysis by Xu et al. (2018) investigated which brain areas are structurally associated with alexithymia: High alexithymia was associated with a smaller left insula, a smaller left amygdala, left orbitofrontal cortex (OFC) and left putamen and a smaller caudate nucleus in the right hemisphere. These results stand in contrast to the idea that alexithymia is a dysfunctional right hemisphere syndrome, at least on a structural level. The largest study investigating the neuroanatomy of Alexithymia today with a sample of $n$ = 1685 (Grabe et al.,

2014) found a reduced dorsal ACC (dACC) volume to be the neural substrate of Alexithymia. Importantly, this effect was not significant in the meta-analysis by Xu et al. (2018), as some of the other studies either found an increased ACC size (Gündel et al., 2004) or null effects (e.g. Heinzel et al., 2012). One possible explanation might be gender: decreased size was found in women (Borsci et al., 2009) but not in men (Heinzel et al., 2012). This difference was also found in another study (Goerlich-Dobre et al., 2015a) for some parts of the ACC. A second explanation can be offered by an functional MRI (fMRI) study done by Goerlich et al. (2017): Alexithymia was associated with a higher activation of subgenual and perigenual ACC during social reward anticipation using the social incentive delay task (Spreckelmeyer et al., 2009). These parts of the ACC might have an inhibitory function dampening the emotional experience of a reward as they are connected to the subcortical regions of the brain and are structurally different than the dACC (Palomero-Gallagher et al., 2015). Consequently, the mixed findings on the ACC in past studies might be the result of gender differences or inadequate distinguishing of the ACC.

The insula is involved in emotion processing (Craig, 2009), more specifically in the more cognitive parts of emotion processing such as emotion perception and awareness while the reduced amygdala volume is thought to be a reduced emotional response according to Xu et al. (2018). The reduced size in striatal areas and the OFC might be a neural substrate of a dysfunctional reward system: the OFC for the reward evaluation and the striatal areas for reward anticipation and reward associated emotional experience (Xu et al., 2018). These results are interesting, as both the reward system (Keating et al., 2012; Steinglass & Walsh, 2016) and the insula (Kaye et al., 2009; Nunn et al., 2011) have been postulated to play a key role in AN.

Regarding functionality, van der Velde et al., (2013) investigated the functional profile of alexithymia during emotional processing in a meta-analysis: In negative stimuli, lower activation was found in a wide range of brain areas including the bilateral FG, SMA, amygdala, the left dorsomedial prefrontal cortex, occipital gyrus, premotor cortex and superior parietal gyrus. For positive stimuli, this was observed in the bilateral precuneus, right insula and left superior temporal gyrus. Higher activation was found for both negative and positive stimuli in the ACC. These results highlight that the ACC is independently of valence involved in emotional processing and there is also evidence for the ACCs involvement in alexithymia in AN samples (Miyake et al., 2009, Miyake et al., 2012). Another interesting result was a decreased activation in the precuneus and insula during positive stimuli, which the authors speculate might underlie a reduced positive affect in alexithymic individuals. A

systematic review on this topic by Moriguchi and Komaki (2013) divided stimuli into external and internal stimuli and concluded a reduced activity across the cingulate cortex, the insula and amygdala for external emotional and social stimuli, but an increased activity for somatosensory and sensorimotor stimuli in the same areas highlighting the need for differentiation. An inverted U-shape activity in the ACC depending on stimuli complexity has been argued to explain this (van der Velde et al., 2013). Contrary to the mixed results of brain morphology, involvement of the ACC functionally in alexithymia is generally acknowledged. Taken together, alexithymia has gained a lot of attention in neuroscience and evidence shows that there are alterations in both structure and function of the alexithymic brain. Previous evidence shows that there is a large overlap between areas with altered size and activity – insula, amygdala, cingulate cortex and regions involved in reward processing - which are relevant to both AN and alexithymia. As alexithymia is highly increased in individuals suffering from AN and could play a significant role in the development and maintenance of the disorder, it seems reasonable to further investigate alexithymia in AN and its neural basis.

Only one study to date has looked at alexithymia and brain morphology in an ED sample (D'Agata et al., 2015). While they found a correlation between alexithymia and the GMV of the parietal lobe in a Bulimia Nervosa (BN) sample, they did not find any correlations between alexithymia and GMV in an AN sample. The authors have several speculations: First alexithymia in AN could be a byproduct of caloric restriction (BN-BMI = 22.0, AN-BMI =16.1) which would be supported by widespread atrophy in the brain areas related to alexithymia thus there not being enough variance in size to find meaningful differences. Secondly, Alexithymia might be a byproduct of general psychopathology, as people with AN might be able to identify and describe feelings, but this ability is overridden by constant anxiety, depressive symptoms or rumination. Part of the reason they did not find any correlations could also be their sample size, which was rather small: 21 women with AN, 19 with BN and 17 HCs. Furthermore, even though the TAS-20 is thought to be normally distributed, there has not been done an in-depth model diagnostic, and especially as the group size was lower than 30, which is the minimum sample size needed to assume normal distribution, this could lead to a null finding.

**Present study**

By addressing many of the mentioned issues, this study helps bridging various gaps existing literature: First it aims to replicate the findings regarding an increased alexithymia in acute AN patients (AAN), but also in WR AN patients compared to HCs in a cross-sectional design. While this was shown in longitudinal studies (e.g. Beadle et al., 2013), only few

studies investigated this in three groups cross-sectionally, as most either looked at ANN or WR AN patients, but not both. In the study done by Tchanturia et al. (2012) this linear increase from HCs to WR to AAN was shown, but with a sample of $n = 14$ in the WR patients' group, the results are not robust and lack power. Secondly, this study aims to replicate the partially mediating effect of depression by Torres et al. (2015) and add insights, how the association between alexithymia, depression and AN diagnosis changes when AN patients past the acute stage are considered. Beadle et al. (2013) found depression change scores to account for the difference in alexithymia in an AN sample at hospitalization and following WR and so did another study (Saxton et al., 1998). Thus, it is hypothesized that depression can fully explain the association between alexithymia and diagnosis when differentiating between WR and AAN patients, but only partially when comparing those to HCs, or no association at all if WR patients show very few depressive symptoms.

Only one study (D'Agata et al., 2015) has looked at neural substrates of alexithymia in AN patients and failed to find any significant correlations and no study has investigated this in WR subjects. This allows for a more holistic overview of the role in alexithymia in AN and its brain substrates. Additional insight is also provided into whether alexithymia is a temporary state caused by starvation or a persistent trait in AN patients that remains after weight restoration and is only exacerbated by starvation. Finally, this study also tries to add insights into the GMV of WR patients compared to AAN patients and controls in a cross-sectional design. There are multiple longitudinal studies, but results regarding GMV restoration have been mixed and especially studies concerning adolescent AN patients are few.

Several cross-sectional studies have looked into the GMV differences between all three groups (acute AN, WR & HC), but they found mixed results: Friederich et al. (2012) found no significant global difference in GMV between WR and HC but reduced GMV in the right ACC, operculum and SMA. Their sample consisted of adult AN patients and the WR group consisted of patients, who had a normal BMI for at least 12 months. King et al. (2015) also investigated differences between three groups with a sample with an age ranging from 12 to 28 years. WR patients were required to have a normal BMI and did not engage in ED related behavior for at least 6 months. While their research focus was on cortical thickness, which showed no differences between WR and HC, they also evaluated GMV in subcortical areas. Averaged over both hemispheres, they found reduced volume in the cerebellum and thalamus. Two more recent studies (Brodrick et al., 2021; Nickel et al., 2018) on the other hand, found no global and regional GMV differences between WR and HC with time criteria

of 1 year and 6 months respectively for WR. Similarly, novel studies with other methods such as cortical thickness or gyrification indices (Cascino et al., 2020; Miles et al., 2018) also do not find differences between WR AN subjects and HC.

While cross-sectional cannot track individual changes studies or offer causal explanations for structural changes, a greater sample size with more diverse age ranges and thus an increase in statistical power can be achieved. Especially regarding the period since weight recovery was achieved, precise criteria can be formulated, which can offer a more sophisticated understanding of the grey matter restoration process of the brain following starvation. Considering that Seitz et al. (2016) revealed that adolescent AN patients have more severe GMV reductions but also regain GMV more quickly, this study adds new insights: This sample consisted of mostly adolescents and WR patients are only required to have a normal BMI for at least 3 months, which was the average for the short-term recovery group in their meta-analysis, but less than in the previously mentioned studies. In the following parts, this WR AN subsample will be called partial remission (PR; see Methods for detailed group assignment criteria).

**Research Questions**

1) Does the level of alexithymia change regarding the severity of anorexia nervosa and how does it compare to healthy females?
2) What role do depressive symptoms play in the association between anorexia nervosa diagnosis and alexithymia?
3) How are differences in alexithymia and anorexia nervosa severity displayed in the grey matter of the brain?

***Hypotheses***

*H1: There is a difference between the groups HC, AAN and PR on the TAS-26.*

*H1a: There is a difference between the groups HC, AAN and PR on the TAS-26 subscale DIF.*

*H1b: There is a difference between the groups HC, AAN and PR on the TAS-26 subscale DDF.*

*H2: There is a linear increase observable regarding AN severity with HC having the lowest TAS-26 score followed by PR followed by AAN.*

*H3a: The association between alexithymia and diagnosis (HC / AAN) is partially mediated by depression.*

*H3b: The association between alexithymia and diagnosis (HC / PR) is either partially or not mediated by depression.*

*H3c: The association between alexithymia and diagnosis (PR / AAN) is fully mediated by depression.*

*H4: AAN has a reduced grey matter volume across various brain areas compared to HC/PR.*

*H5: A higher TAS-26 score is associated with altered grey matter volumes in the brain across all participants.*

*H6: The association between TAS-26 scores and GMV is different across the three groups.*

# Methods

## Research Project and Study Design

This master thesis is part of the AN-BEL project which is a collaborative project of the Medical University of Vienna and the University of Vienna focusing on reward processing in AN at different stages of the disease. For this, three groups of participants with AN are recruited (experimental group): acute AN (AAN), partial remission (PR) AN and fully remission (FR) AN. These are compared with a group of healthy control participants (HC). The primary goal of the study is to research a reward-based mechanistic model of AN in which *wanting* and *liking* is disturbed for both food and social rewards. To investigate this, a recently developed and validated experimental paradigm was used, in which participants can receive various food (i.e. different milks) or social (i.e. touch administration at different speed) stimuli during fMRI (see Chiappini et al., 2022). For more information on the project see: https://klinische-gesundheit-psy.univie.ac.at/forschung/arbeitsbereiche-und-arbeitsgruppen/clinical-social-neuroscience-unit/ongoing-projects/an-bel-projekt/

## Procedure

After a screening using Sosci-Survey (Leiner, 2024) to see whether participants are eligible for the study, participants were invited to be part of the study and to provide informed consent themselves or consent by their parents or legal guardian if they were below 18 years old.

The study consisted of three parts: 1) an online survey at home collecting data using various questionnaires using the platform Limesurvey, 2) a clinical interview at the Child and Adolescent Psychiatry Department, Medical University of Vienna and 3) an appointment at the Center of Excellence High-field MRI, Medical University of Vienna, where participants undergo an approximately 120-minute session in an MRI-scan. The MRI session is segregated into two parts: the experimental phase in which stimuli are administered (fMRI) and a second phase in which anatomical data is acquired using structural MRI (sMRI) and magnetic resonance spectroscopy. After the experiment, participants received a 70 € voucher as compensation along with a file of their brain scan with a corresponding manual. For this thesis, the fMRI data gathered from the task phase of the MRI session were not used and instead it focusses on data obtained from the sMRI regarding brain anatomy.

## Participants

Participants were female, required to be between 12 and 30 years old and fluent in German language. A large part of the participants of the experimental group were recruited

through the Department of Child and Adolescent Psychiatry at the Vienna General Hospital as either in- or outpatients. Furthermore, HC participants were recruited by the research team through the distribution of flyers, the promotion of the project on social media platforms including Instagram and Facebook and via presentations of the project at schools.

The goal sample size of the ANBEL project is $n = 30$ for each AN group and an equally large age-matched HC group resulting in a sample of $n = 90$ for the experimental group and $n = 90$ for the control group combined to a total target sample of n = 180. Individuals with an intellectual disability (IQ < 70), other severe psychiatric disorders such as bipolar disorder, psychotic disorder or other eating disorders were excluded. Pregnancy as well as severe physical diseases such as cardiovascular diseases, lung, neurological or metabolic conditions were also exclusion criteria. Moreover, HCs who have shown a severe history of fasting or ED related behavior were either excluded or invited to be part of the study in the experimental group.

For this master thesis, there were three relevant groups: AAN, PR and HC. Participants in the FR were included in the study design, but at the timing of this thesis, the sample size has been too small to be included in analysis. Furthermore, participants were removed from the sample if they had not completed the Limesurvey or did not complete the sMRI scan for various reasons.

**MRI Acquisition**

MRI examinations were performed on a 3 Tesla Siemens Prisma MRI scanner (Siemens Healthineers, Erlangen, Germany) with a 64-channel head-neck coil at the Center of Excellence High-field MRI of the Medical University of Vienna. Further, the participants head was supported with No Motion Correction pads within the head coil. Structural images are acquired with 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).

**Measures**

Participants were assigned to one of the three experimental groups using the German version of Eating Disorder Examination (EDE, Hilbert et al., 2004) by Fairburn and Cooper (1993). The EDE is a semi-structured interview and the gold standard to diagnose EDs. In the following, precise criteria for the conditions are given:

Criteria for ANN is a BMI beneath 18.5 $kg/m^2$ for above 18 years old participants and under the 10th percentile of weight distribution for under 18 years old participants (Criterion

A in DSM-5). Furthermore, every other criterion according to DSM-5 must be fulfilled: a pronounced fear of gaining weight (Criterion B1) or repeated behavior to prevent an increase in weight (Criterion B2) and a disturbed perception of body shape and weight and this perception is central to an individual's self-evaluation. (Criterion C).

Criteria for PR is a WR following a previous AN diagnosis: a BMI above 18.5 $kg/m^2$ for above 18 years old participants and above the 10th percentile of weight distribution for under 18 years old participants. Furthermore, patients must not show AN-related behaviors (purging, restricting or binge-eating) with regard to Criterion B1 and their EDE total score is within 2 standard deviations of the EDE mean in healthy samples (< 2.18 after Hilbert et al., 2004). Intense fear of gaining weight or disturbance of body perception may still persist (Criterion B2 and Criterion C) and this status has been upheld for at least 3 months. To avoid misunderstandings, this can essentially be seen a WR AN subsample in order to make comparisons to the existing literature.

Although not included in the sample, criteria for FR were WR (like PR), no AN-related behaviors, an EDE total score within 1.5 standard deviations of the EDE mean score in healthy samples (< 1.86), no intense fear of gaining weight or a disturbed body perception (Criteria B & C) and this status has been upheld for at least 12 months. This information is essential as this means there are no long-term weight recovered patients (or few but these still fulfill criteria B or C of DSM-5) in PR.

Alexithymia was measured with the German translation of the TAS-26 (Kupfer et al., 2001). This version only uses the 18 items of the subscales DIF, DDF and EOT as in the process of translation the RD subscale proved to be inefficient. Internal consistency from the German TAS-26 ranges from $\alpha = 0.67$ (EOT) to $\alpha = 0.84$. (DIF) with the total score having an internal consistency of $\alpha = 0.81$ which can be considered good. There are two aspects to consider: While the TAS-20 (Bagby et al., 1994) has established itself as the gold-standard to measure Alexithymia, the German translation of the TAS-20 (Bach et al., 1996) offers worse reliability than the English version and also worse reliability than the German version of the TAS-26 (Schiewer et al., 2022). To put this into perspective, the English version of the TAS-26 (with the RD subscale included) only has slightly worse internal consistency ($\alpha = 0.78$) than the TAS-20 ($\alpha = 0.85$) (Wise et al., 2000).

Secondly, the TAS-20 has been found to have a worse reliability (and thus validity) in a Portuguese AN sample (see Torres et al., 2019). Especially item 16 ("I prefer to watch 'light' entertainment shows rather than psychological dramas.") and item 20 ("Looking for hidden meanings in movies or plays distracts from my enjoyment.") seem to show poor performance

in an ED sample and contribute to the evidence in literature that EOT has the lowest internal consistency out of all three subscales and should be interpreted with caution, especially in clinical samples (e.g. Bressi et al., 1996; Moriguchi et al., 2007; D. Preece et al., 2018). Notably, both items have not been included in the 26-item version of the TAS which might have resulted in a more reliable measurement in this study. In the following, the abbreviation TAS is used for the TAS-26.

Depressive symptoms were measured using the German version of the Beck-Depression- Inventory II (BDI-II) by Kühner et al., (2007). The BDI-II is one of the most widely used questionnaires to measure depression. It offers great reliability with a Cronbach's $\alpha = .84$ in clinical samples and $\alpha = .89$ in non-clinical samples.

**Power**

Differences between AAN and HCs on the TAS-20 were $d = 1.44$ in the meta-analysis by Westwood et al. (2017). Regarding differences between AAN and weight restored AN patients, Tchanturia et al., (2012) found a difference with an effect size of $d = 1.0$. For WR and HC, effect sizes were consistently above $d = 0.8$, e.g. Parling et al. (2010) found an effect size of $d = 1.12$, and Tchanturia et al. (2012) an effect size of $d = 0.87$. According to Cohen (1992), to find a large effect ($d = 0.8$), sample size needs to be at least n = 21 per group for a 3-groups ANOVA or $n = 26$ for a t-test, if the goal is to achieve power = 0.80. As target sample size per group was at least $n = 30$, a sufficient power should have been achieved. Due to an unexpected high exclusion rate in the AAN group, power might have been slightly lower than expected (see *Results* section).

It should be noted that there have been studies in which WR and HC did not significantly differ among alexithymia (e.g., Oliva et al., 2020). Secondly, Cohen's benchmarks have been criticized for being arbitrary regarding effect size metric (e.g. Correll et al., 2020). When there are too few studies, as it is the case for the comparison with a WR group, sampling error might contribute to an underestimation of the true effect size. Still Cohen advocated, it is better to use any conventions that might be reasonable than none (Cohen, 1988, as cited in Schäfer & Schwarz, 2019).

Realistically, an effect size above d = 1.0 regarding between-subject differences can still be considered large. Lovakov & Agadullina (2021) estimated benchmarks based on empirical research results and conclude that Cohen's benchmarks overestimate effects in social psychology and a Cohen's $d$ of $d = .65$ can be considered large. Rubio-Aparicio et al. (2018) found a mean difference of $d = .75$ regarding within-subjects a $d = .43$ for between-subjects effect sizes when reviewing meta-analyses of treatment effectiveness in clinical

psychology. As this study is set in the field of clinical social neuroscience, it can be concluded that sufficient power was achieved.

Regarding MRI analysis, power calculations are scarce, as it proves to be difficult to calculate because of multiple comparison suggestions. Desmond and Glover (2002) recommend 12 participants per group for fMRI studies, Thirion et al., (2007) recommends group size to be at least $n = 20$ for adequate power. Other authors argue for at least $n = 40$ with seemingly open-end sample sizes (for an overview, see Grady et al., 2021). For sMRI data, authors recommend sample sizes as large as $n = 73$ per group in order to detect a 5 % difference in whole brain grey matter (Steen et al., 2007). As Szucs & Ioannidis (2020) state, few studies offer reasonable power calculations and the median of sMRI participants per group is $n = 24$. In that sense, this study had an above median sample size per group, as well as to my knowledge one of the largest WR AN patients sample comparing it to both AAN as well as HC subjects.

**Data Analysis**

Clinical data and absolute brain volumes were analyzed using JASP (Version 0.19.3) and the PROCESS application (Hayes, 2012) implemented in SPSS (Version 29, Chicago, IL, USA). For neuroimaging data, analysis was done in Matlab R2022b using SPM12 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, UCL, London, U). More precisely, CAT12 toolbox (Gaser et al., 2024) was used to preprocess data and xjview (https://www.alivelearn.net/xjview) was used to visualize results and gain anatomical information for relevant voxels and clusters.

***Clinical Data***

First, a descriptives table per group and correlation matrix was done with the relevant variables: Age, BMI, TAS, DDF, DIF, EOT and BDI scores. Differences were tested using analysis of variance (ANOVA) followed by post-hoc tests using Tukey if variance homogeneity was not harmed and Games-Downell if it was. Subscale analyses for DIF, DDF and EOT was done using ANOVA corrected for multiple comparisons using Benjamini-Hochberg correction with k = 3. A polynomial contrast was done to determine whether there is a trend regarding alexithymia in the three subsamples with a linear increase regarding AN severity.

Regarding model diagnostics for ANOVA, as group size was expected be > 30 for all three groups, normal distribution was expected (central limit theorem). Due to the small sample size in the AAN group, Shapiro-Wilk-test was performed to assess normal distribution

for each group regarding TAS and BDI scores. Levene's test was used to test for variance homogeneity. If variance was heterogeneous, Welch' correction was applied and reported. Analyses were not controlled for BMI like in previous studies, as a BMI criterion were necessary for group assignment which would have confounded the analysis. Associations can be observed descriptively and in the correlation matrix. Missing values did not happen as questionnaires were in an online forced choice format and participants who did not finish the questionnaires were excluded. Outliers were decided based on 3x centered leverage values regarding TAS-26 and BDI scores which was CLVmax = 0.1 The highest score was CLV = 0.015 in both variables, so no participant was excluded. Maximum cook-distance also indicated no outliers with the highest cook-distance (CD) being CD = 0.065 for TAS and CD = 0.074 for BDI.

Thereafter, a Mediation Model using PROCESS (Model 4) was done with BDI and TAS to determine whether alexithymia explained more variance than just depression or whether depressive symptoms could fully explain the association between alexithymia and AN. This follows the idea of Torres et al. (2015) who found a partial mediation between depression, alexithymia and diagnosis (AAN / HC) and extending this by adding a third group, PR. Precisely, the independent variable was alexithymia, depression the mediator and group membership (as a binary variable according to severity) the dependent variable. This was done for all three group comparisons (AAN-PR, AAN-HC, PR-HC) with 5000 bootstrap-samples.

***Neuroimaging data***

Voxel-based morphometry (VBM) analysis was performed using SPM 12. Preprocessing of the data was done using the *Segment* pipeline of the CAT12 toolbox. Pictures were checked on quality when IQR-Quality score was below 80% and individually decided, whether quality is sufficient to be included in data analysis (none were excluded). TIV and global brain volumes for the different tissues were extracted and data was smoothed with an accuracy of 8 mm.

As both AN and alexithymia combined have been shown to affect a large amount of different brain areas, whole brain (WB) analysis was employed. First an ANCOVA design controlling for TIV and age was done with the three groups AAN, PR, HC post-hoc tests using T-contrasts. Albeit age was associated with both group membership and alexithymia, controlling for age was necessary to consider individual brain development of a sample consisting majorly of adolescents. For group comparisons, a threshold of $p_{FWE} = 0.05$ at voxel-level and a minimum cluster size of $k = 10$ was used.

Secondly, alexithymia was correlated with GMV in the whole sample across all participants to find neural correlates of alexithymia independently of clinical status. Lastly, alexithymia was looked at in all three groups each. This allowed for a holistic approach to see how alexithymia was displayed at different stages of AN. For correlation analyses, a less strict threshold of $p_{unc} = 0.001$ at the voxel-level was used and a minimum cluster size of $k = 50$. Similarly, these analyses were controlled for age and TIV. Results are reported with cluster size, peak MNI coordinates and T-value and for FWE-corrected results with peak voxel *p*-value.

## Results

### Clinical Data

A total of $n = 90$ participants were included in the statistical analysis with $n = 24$ for AAN (restrictive subtype: $n = 23$, binge-purging subtype: $n = 1$), $n= 33$ for PR (restrictive subtype: $n = 31$, binge-purging subtype: $n = 2$) and $n = 33$ for HC. Notably, six participants in the AAN group did not complete the clinical questionnaires and another three did not complete the MRI session, while in the PR group, only two participants did not complete the MRI session, compromising the sample of the AAN group compared to the other groups. This also had an impact on power-related aspects.

Shapiro-Wilk-test was non-significant across all groups for both TAS (AN: $p = .123$, PR: $p = .238$, HC: $p = .312$) and BDI (AN: $p = .595$, PR: $p = .426$, HC: $p = .221$), indicating a normal distribution. Levene's Test was not significant for TAS ($p = .550$), but for BDI ($p < .001$) so Welch' correction was applied.

**Table 1**

*Descriptive Statistics of Participants: Mean (SD)*

| Variable | AAN ($n = 24$) | PR ($n = 33$) | HC ($n = 33$) | *F* | *p* | Tukey HSD post-hoc test |
|---|---|---|---|---|---|---|
| Age | 16.71 (2.87) | 20.36 (3.54) | 19.76 (3.35) | 9.33 | < .001 | AAN < PR, HC |
| BMI | 16.43 (2.06) | 20.50 (2.42) | 21.08 (2.22) | 33.35 | < .001 | AAN < PR, HC |
| BDI | 24.00 (9,78) | 17.18 (10.98) | 7.21 (4.76) | 36.30** | < .001** | AAN > PR > HC** |
| TAS | 50.83 (9.41) | 48.39 (9.36) | 40.61 (7.79) | 10.94 | < .001 | AAN, PR > HC |
| DIF | 20.08 (6.08) | 18.21 (5.33) | 13.82 (3.96) | 11.74 | < .001* | AAN, PR > HC |
| DDF | 15.58 (3.92) | 15.52 (3.84) | 12.64 (3.73) | 6.05 | .005* | AAN, PR > HC |
| EOT | 15.17 (4.07) | 14.67 (4.11) | 14.15 (2.94) | 0.53 | .593* | |

*Note.* AAN: acute AN patients, PR: partially remitted AN patients, HC: healthy controls, BMI: Body-mass-index, BDI: Beck-Depression-Inventory II, TAS: Toronto Alexithymia Scale 26, DIF: Difficulties Identifying Feelings, DDF: Difficulties Describing Feelings, EOT: Externally Oriented Thinking. *F* & *p*-value correspond to ANOVA results.
* : Benjamini Hochberg (BH) corrected *p*-value for k = 3 subscales
**: Welch' corrected *F* and *p*-value, post-hoc test with Games-Howell

Patients in the AAN group were significantly younger and had a lower BMI than PR (Age: $t$ (87) = 4.12, $p_{Tukey} < .001$, $d$ = 1.11; BMI: ($t$ (87) = 6.72, $p_{Tukey} < .001$, $d$ = 1.80) and HC (Age: $t$ (87) = 3.44, $p_{Tukey} = .003$, $d$ = 0.92; BMI: $t$ (87) = 7.67, $p_{Tukey} < .001$, $d$ = -2.06; for detailed descriptives, see Table 1). BDI was highest in the AAN group, followed by PR and then HC (AAN vsHC: $t$ (87) = 7.77, $p_{GH} < .001$, $d$ = 1.90; PR vs HC: $t$ (87) = 4.79, $p_{GH} < .001$, $d$ = 1.11; AAN vs PR: $t$ (87) = 2.47, $p_{GH} = .044$, $d$ = 0.77). In the total sample, TAS and BMI correlate highly ($r$= 0.60) which is largely the result of DIF ($r$= 0.56) and DDF ($r$= 0.55). Correlations can be observed in Table 2.

**Table 2**
*Correlation Matrix of Variables*

| Variable | BMI | Age | BDI | TAS | DIF | DDF |
|---|---|---|---|---|---|---|
| BMI | - | | | | | |
| Age | .45*** | - | | | | |
| BDI | -.45*** | -.40*** | - | | | |
| TAS | -.33** | -.18 | .60*** | - | | |
| DIF | -.33** | -.12 | .56*** | .83*** | - | |
| DDF | -.21* | -.15 | .55*** | .87*** | 0.64*** | - |
| EOT | -.15 | -.15 | .12 | .43*** | -.06 | .21* |

*Note*. BMI: Body-mass-index, BDI: Beck-Depression-Inventory II, TAS: Toronto Alexithymia Scale 26, DIF: Difficulties Identifying Feelings, DDF: Difficulties Describing Feelings, EOT: Externally Oriented Thinking
***: p < .001
**: p < .01
*: p < .05

There was a significant difference in TAS scores across the three groups and this result was robust, when controlling for age ($F$ (86,3) = 9.64, $p < .001$). Tukey HSD post-hoc tests revealed AAN having significantly higher scores than HC ($t$ (87) = 4.32, $p_{Tukey} < .001$, $d$ = 1.16) and PR also having significantly higher scores than HC ($t$ (87) = 3.58, $p_{Tukey} = .002$, $d$ = 0.88), but no difference between AAN and PR ($t$ (87) = 1.03, $p_{Tukey} = .56$, $d = 0.27$). Results did not differ when controlling for age (AAN vs HC: $t$ (86) = 3.70, $p_{Tukey} = .001$, $d = 1.05$; PR vs HC: $t$ (86) = 3.65, $p_{Tukey} = .001$, $d = 0.90$; AAN vs PR: $t$ (86) = 0.53, $p_{Tukey} = .859$, $d = 0.15$). Polynomial contrast indicated a significant linear trend ($t$ (87) = 4.32, $p < .001$) between the groups indicating that there is linear increase across the three groups. The quadratic term was not significant ($t$ (87) = -1.38, $p = .172$).

Similar results for the subscale analyses were observed: For both DIF and DDF significant results were found with Tukey HSD post-hoc tests showing significant differences regarding AAN vs HC (DIF: $t$(87)= 4.58, $p_{Tukey} < .001$, $d = 1.23$; DDF: $t$ (87)= 2.87, $p_{Tukey}$ = .014, $d = 0.77$) and PR vs HC (DIF: $t$ (87)= 3.50, $p_{Tukey} = .002$, $d = 0.86$; DDF: $t$ (87)= 3.05, $p_{Tukey} = .008$, $d = 0.75$). Between AAN and WR no significant differences were observed (DIF: $t$ (87) = 1.37, $p_{Tukey} = .362$; DDF: $t$ (87) = 0.06, $p_{Tukey} = .998$). As expected for EOT, there were no significant group differences.

***Mediation Analysis***

In all three group comparisons (HC – AAN, HC – PR & PR – AAN) depression fully mediated the association between alexithymia and group membership. Path models of the results are displayed in Figure 1 and a summary of the indirect effects in Table 3. In the model regarding PR - AAN, the second model (with both depression and alexithymia) did barely not reach significance ($p = .057$), but the 95% CI of the indirect effect did not include 0 which indicates a significant indirect small effect so these results should be interpreted with caution (see Table 3). For transparency reasons, a simple logistic regression with TAS-26 scores estimating group membership was calculated and was not significant ($\chi^2(1,55) = 0.97$, $p$ = .326) which is in line with the results of the ANOVA finding no difference between AAN and PR regarding alexithymia.

Due to the small sample and high correlations, the analysis in the HC – AAN subsample yielded non-convergence during bootstrapping, so a Monte-Carlo-Estimation was done in order to estimate the 95% CI which is recommended when bootstrap fails (see Preacher & Selig, 2010). Put into perspective, the variance explained in AN by alexithymia is accounted by depressive symptoms when comparing different stages of AN and HCs. This

effect was largest for the analysis regarding AAN – HC and smallest for the analysis in PR – AAN.

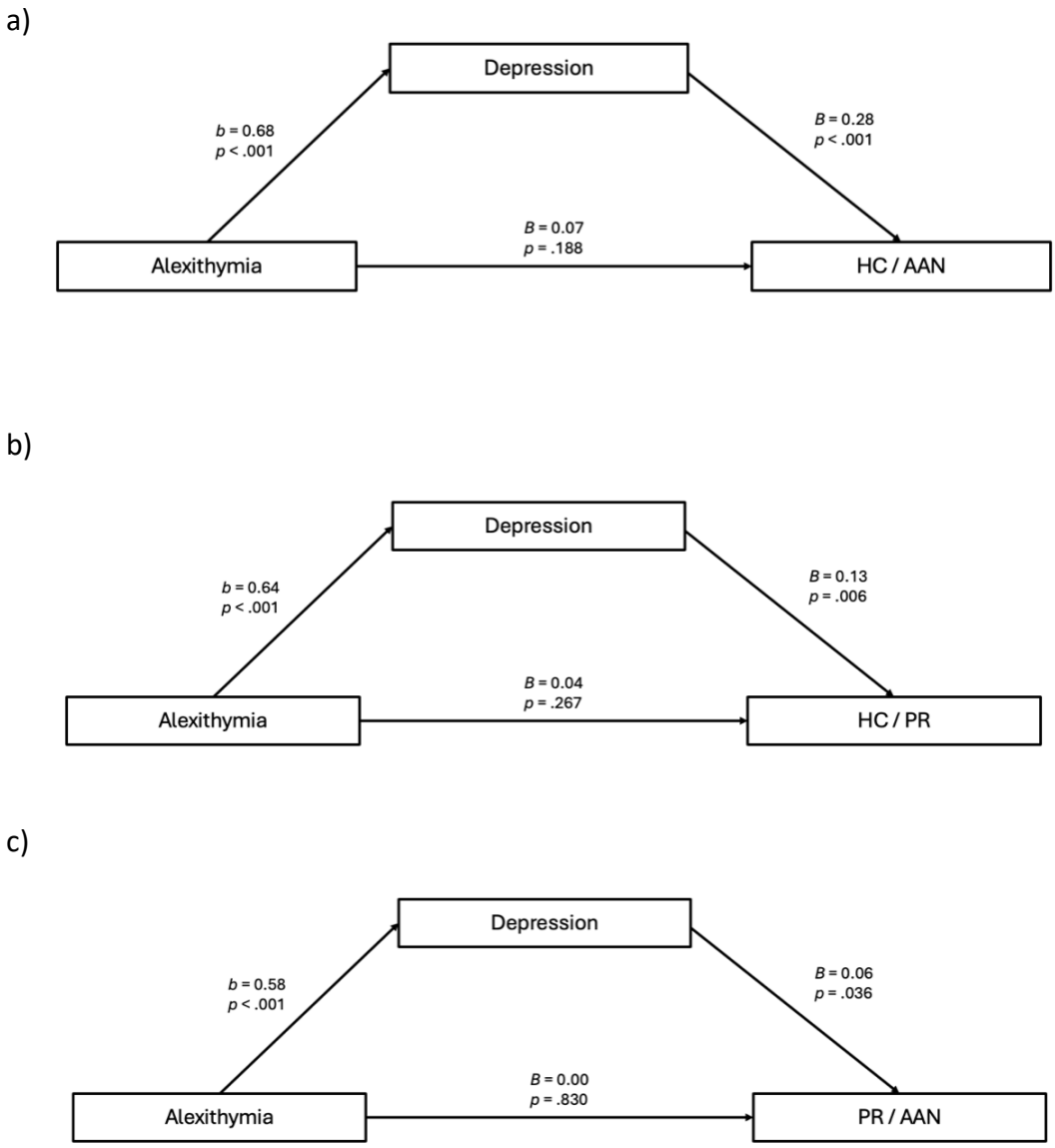
**Table 3**
*Summary of the Mediation Model Results*

| Model | Indirect Effect | Bootstrap SE | 95% LLCI | 95% ULCI |
|---|---|---|---|---|
| HC - AAN | .193 | 0.066* | .077* | .333* |
| HC - PR | .085 | 0.039 | .031 | .181 |
| PR - AAN | .038 | 0.023 | .003 | .091 |

*Note*. Model refers to the two groups included as the outcome variable with the first group being coded = 0 and second group = 1 (according to severity). Indirect effect is in log-odds metric. SE and 95 % CI are based on 5000 bootstrap samples.
*: Non-convergence during bootstrapping due to the differences in sample characteristics, even with 50000 bootstrap samples. Therefore, a Monte-Carlo Estimation based on 100000 draws using the path coefficients was calculated to estimate standard error and 95 % CI with the assistance of Open AI's ChatGPT.

**Figure 1**

*Mediation Analysis Results with a) HC - AAN b) HC - PR and c) PR - AAN*




*Note*. Group membership was coded as a dichotomous outcome regarding AN severity (0: less severe; 1: more severe of the two groups included in the analysis)

b: continuous unstandardized coefficient

B: log-odds coefficient

## Neuroimaging Data

### *Global Tissue Volumes*

Absolute global volumes for different tissues are displayed in Table 4. ANOVA showed significant differences across the three groups with AAN ($t$ (87) = 2.30, $p_{Tukey}$ = .061, $d$ = 0.62) and PR ($t$ (87) = 2.85, $p_{Tukey}$ = .015, $d$ = 0.70) having significantly lower GMV than HCs, but no difference between AAN and PR ($p_{Tukey}$ = .947) was found. For WMV, ANOVA was significant with PR having significantly lower WMV than HC ($t$ (87) = 2.74, $p_{Tukey}$ = .020, $d$ = 0.67). WMV in the AAN group did not differ from PR ($p_{Tukey}$ = .819) and from HC ($p_{Tukey}$ = .142). Regarding CSF, significant results were found with AAN having significantly higher CSF than HCs ($t$ (87) = 3.43, $p_{Tukey}$ = .003, $d$ = 0.92), but not for the other group comparisons (AAN vs. PR: $p_{Tukey}$ = .215; PR vs. HC: $p_{Tukey}$ = .145). Surprisingly, for TIV no significant result could be observed.

**Table 4**
*Global Brain Tissue Volumes: Mean (SD)*

| Variable | AAN | PR | HC | *F* | *P* | Tukey HSD post-hoc test |
|---|---|---|---|---|---|---|
| GMV | 697.67 (54.42) | 692.97 (54.81) | 732.17 (58.133) | 4.67 | .012 | HC > AAN, PR |
| WMV | 472.60 (39.90) | 465.83 (40.42) | 494.08 (44.67) | 4.02 | .021 | HC > PR |
| CSF | 277.60 (45.55) | 255.98 (49.65) | 233.66 (49.65) | 5.96 | .004 | AAN > HC |
| TIV | 1447.87 (97.33) | 1414.77 (95.38) | 1459.91 (95.38) | 1.164 | .200 | - |

*Note*. AAN: acute AN patients, PR: partially remitted AN patients, HC: healthy controls GMV: grey matter volume, WMV: White matter volume, CSF: Cerebrospinal fluid, TIV: Total intracranial volume; *F* & *p*-value correspond to ANOVA results.

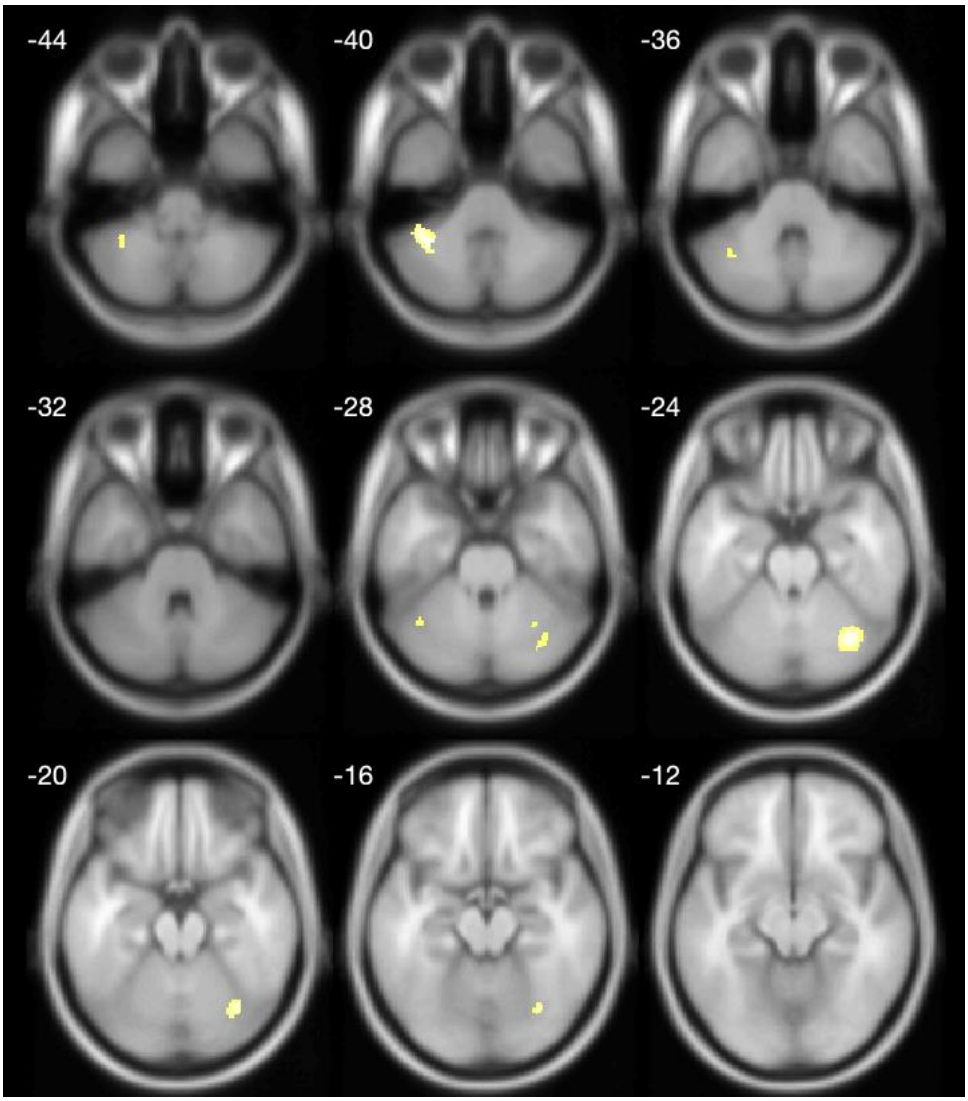
***Group Comparison***

***AAN vs. HC*** After FWE-correction, reduced GMV volume were found in the AAN group compared to HC in the bilateral cerebellum with one large cluster in the right and two in the left hemisphere (right: $k = 453$, x = 34, y = -68, z = -22, $p_{FWE} = .001$, left: $k = 233$; x = -33, y = -51, z = -40; $p_{FWE} = .001$ & $k = 30$; x = -40, y = -57, z = -27; $p_{FWE} = .024$; see Figure 2). Furthermore, one cluster was identified in the right middle frontal gyrus (MFG) ($k = 124$; x = 24, y= 27, z =43.5; $p_{FWE} = .005$, see Figure 3b) and a small cluster in the right middle temporal gyrus compromising Brodmann Area 22 ($k = 18$; x = 58, y= -33, z = 4; $p_{FWE} = .030$).

No increased regional GMV was found in AAN compared to HC.

**Figure 2**

*Axial Slice View of GMV Reductions in AAN Compared to HC.*



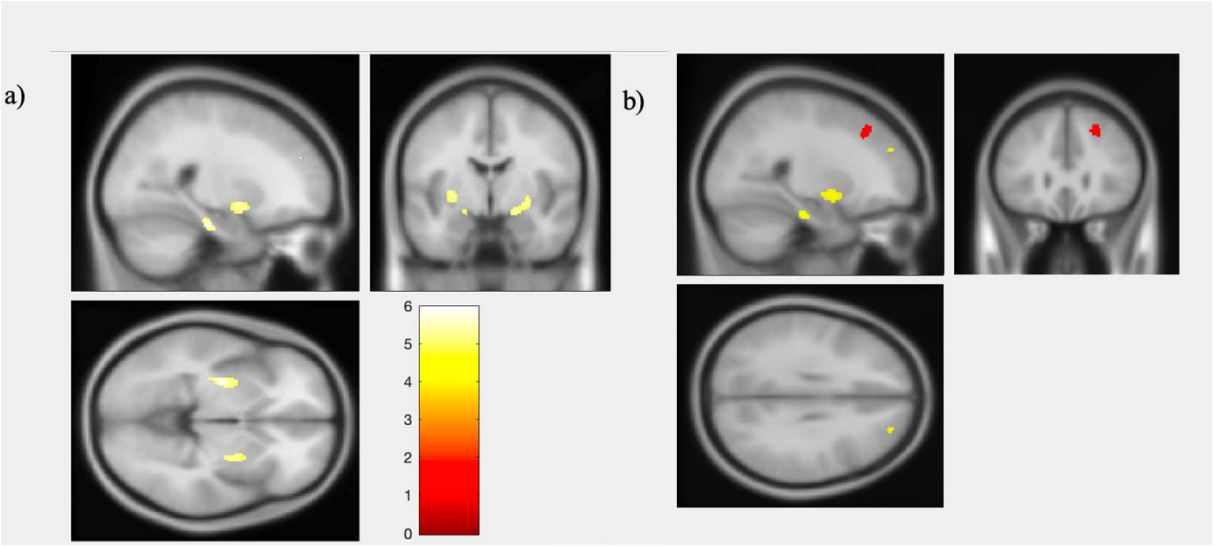
*Note.* Threshold: $p_{FWE}$ = .05 at voxel-level, cluster size $k$ = 10; brain slices in z-axis are shown. Yellow brain areas correspond to a reduced GMV. Clusters in the frontal gyrus and in the temporal gyri not pictured, see Figure 4b.

***PR vs HC*** In the PR group, two large clusters and one small cluster were found with GMV reductions in the bilateral putamen down to the bilateral amygdala (right: $k$ = 551, ; x = 27, y= 2, z = -9; $p_{FWE}$ = .005; amygdala: x = 20, y= 2, z = -12; $p_{FWE}$ = .008; left: $k$ = 371; x = -28, y = -14, z = -3; $p_{FWE}$ = .001; amygdala: $k$= 10; x = -18, y = -4, z = -14; $p_{FWE}$ = .035; see Figure 3a). Furthermore, a reduction was found in the right parahippocampal gyrus ($k$ = 96; x = 26, y = -22, z = -24; $p_{FWE}$ = .001) and two small clusters in the right middle frontal gyrus ($k$ =20; x = 27, y =46, z = 28; $p_{FWE}$ = .011) and the left inferior parietal lobule ($k$ =22; x = -38, y = -42, z = 48; $p_{FWE}$ = .013). Notably, the clusters in the AAN vs. HC and PR vs. HC in the right middle frontal gyrus do not overlap (see Figure 3b).

No increased regional GMV was found in PR compared to HC.

**Figure 3**

*a) GMV Reductions in PR Compared to HC b) GMV Reductions in the Right MFG in AN*




*Note.* AAN: acute AN patients, PR: partial remission AN patients, HC: healthy controls, MFG: medial frontal gyrus

a) MNI-Coordinates = [24, -4.5, -5]; Threshold: $p_{FWE}$ = .05 at voxel-level, cluster size $k$ = 10. Yellow brain areas correspond to a reduced GMV. Clusters in the frontal gyrus and parietal lobule not pictured.

b) MNI-Coordinates = [25, 28.5, 28.5]; Threshold: $p_{FWE}$ = .05 at voxel-level, cluster size $k$ = 10. Red indicates reductions in AAN vs. HC, yellow in PR vs. HC.

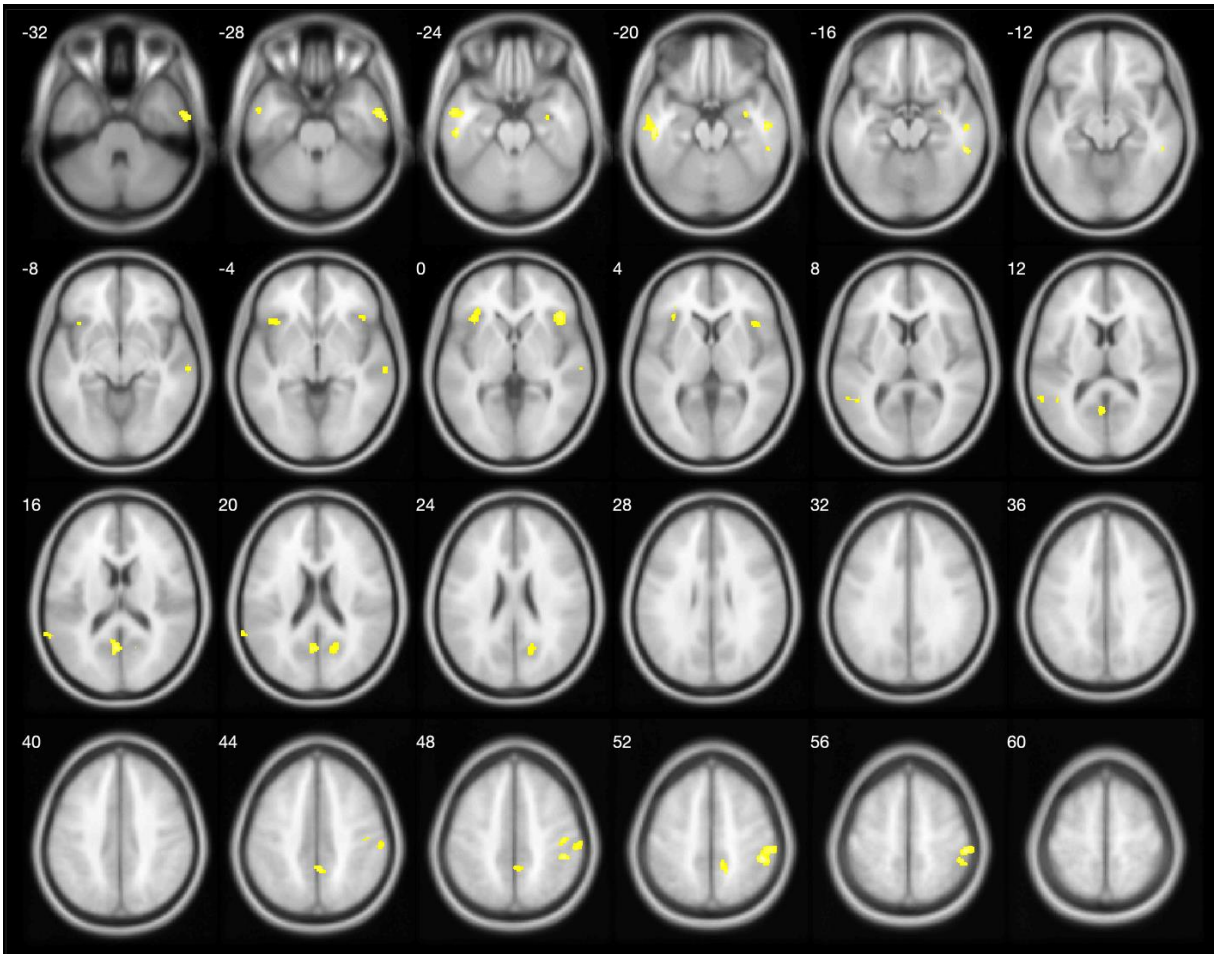
***AAN vs PR*** No regional GMV differences were observed.

### *Alexithymia*

Across the total sample, multiple areas correlated negatively with TAS-scores. Large clusters were identified in the bilateral precuneus, insula up to the inferior frontal gyrus (IFG), the right postcentral gyrus (PG), FG, hippocampus including the amygdala, as well as multiple small clusters across the bilateral temporal gyri including the bilateral Brodmann Area 20 (BA20) with a large cluster in the left inferior temporal gyrus (TG). Detailed statistics can be observed in Table 5 and axial slices in Figure 4.

**Figure 4**

*Axial Slices Displaying GMV Reductions that Correlate with TAS-26 Scores*




*Note.* Threshold: $p_{unc}$ = .001 at voxel-level, cluster size $k$ = 50; brain slices in z-axis are shown. Yellow brain areas correspond to a reduced GMV.

**Table 5**
*Brain Areas Correlating with TAS-26-Scores*

| Brain Area | Cluster size *k* | *t* | Peak MNI coordinates | | |
|---|---|---|---|---|---|
| | | | x | y | z |
| R Postcentral Gyrus / Supramarginal Gyrus | 639 | 4.62 | 46 | -38 | 51 |
| L Inferior / Middle TG | 365 | 4.87 | -51 | -21 | -21 |
| R IFG / Insula | 260 | 3.95 | 43.5 | 27 | 0 |
| L IFG / Insula | 232 | 3.57 | -36 | 24 | 0 |
| L Precuneus / PCC | 219 | 4.02 | -3 | -61.5 | 16.5 |
| R Precuneus | 202 | 4.00 | 15 | -50 | 51 |
| R Precuneus | 166 | 3.51 | 16.5 | -61.5 | 21 |
| R Fusiform Gyrus | 182 | 4.01 | 57 | -4.5 | -28.5 |
| L Superior TG | 156 | 3.58 | -43.5 | -51.5 | 10.5 |
| R Middle TG | 87 | 4.33 | 52.5 | -39 | -15 |
| R Middle / Inferior TG | 68 | 4.07 | 52.5 | -18 | -18 |
| R Middle TG | 67 | 3.56 | 63 | -22.5 | -6 |
| R Hippocampus / Amygdala | 60 | 3.60 | 31.5 | -6 | -21 |

*Note.* Threshold: $p_{unc}$ = .001 at voxel-level, cluster size $k$ = 50; L = left, R = right, TG = temporal gyrus, IFG = inferior frontal gyrus. Analysis was controlled for age and TIV

***Subgroup Analysis***

Subgroup analysis revealed different areas correlating with TAS-26 scores in each group. Within the AAN group, precentral gyrus was positively associated with alexithymia, which is the only positive association across all analyses. A reduced volume corresponded to TAS-scores in the right SMA and in the inferior TG (see Figure 5a).
In the PR group, higher alexithymia was associated with smaller right orbitofrontal cortex volume (Figure 5b) and a smaller medial temporal gyrus.

Finally, in the HC group, smaller left cerebellum was associated with higher alexithymia (Figure 5c). Furthermore, small clusters were found in the right inferior TG and in the left operculum. Noteworthy, a smaller precentral gyrus was associated with higher alexithymia scores which stands in contrast to the results of the AAN group and in general, most areas of the total sample did not replicate. Detailed results can be observed in Table 6.

**Table 6**

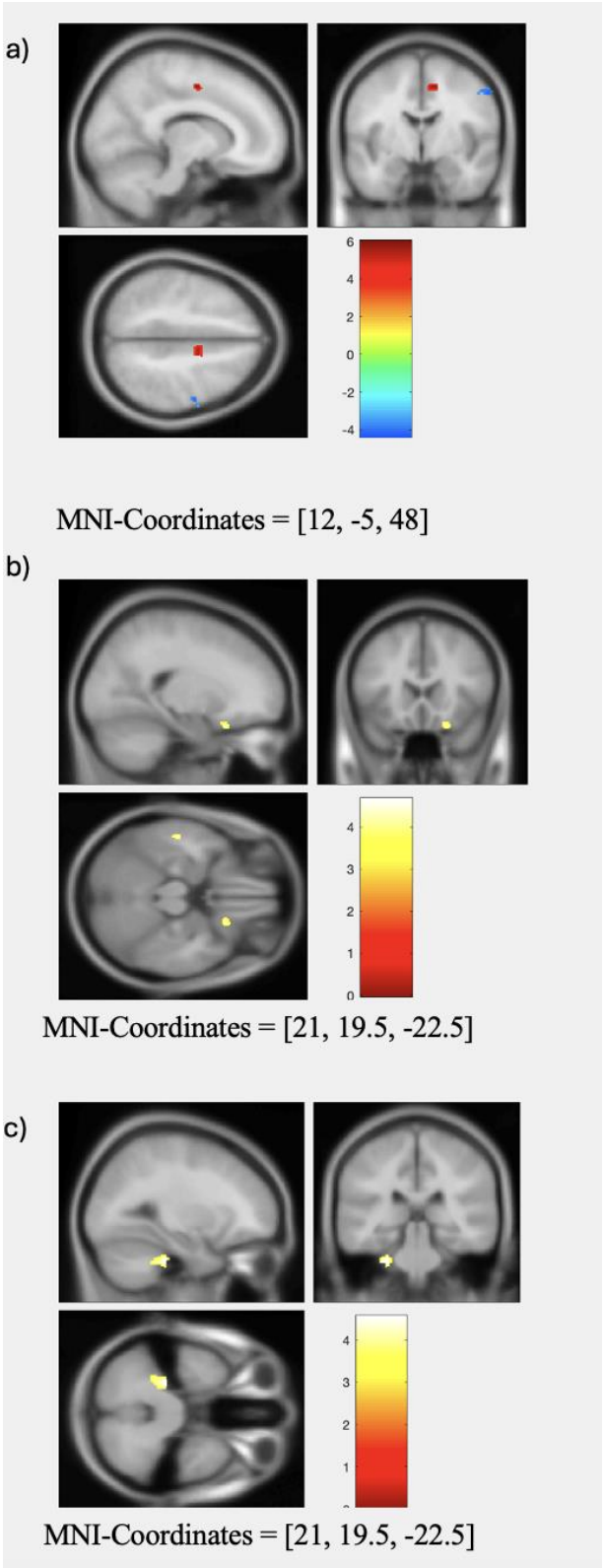
*Brain Areas Correlating with TAS-26-Scores within Subgroups*

| Brain area | Cluster size *k* | *t* | Peak MNI coordinates | | |
|---|---|---|---|---|---|
| | | | x | y | z |
| *AAN (negative)* | | | | | |
| R SMA | 89 | 6.01 | 13.5 | -6 | 49.5 |
| R ITG | 86 | 3.90 | 49.5 | -61.5 | -4.5 |
| *AAN (positive)* | | | | | |
| R Precentral Gyrus | 112 | -4.35 | 58.5 | -3 | 43.5 |
| *PR* | | | | | |
| R OFC | 59 | 4.11 | 21 | 19.5 | -22.5 |
| L MTG | 96 | 4.67 | -57 | -16.5 | -19.5 |
| *HC* | | | | | |
| L Cerebellum | 287 | 4.56 | -27 | -31.5 | -36 |
| R ITG | 71 | 4.15 | 54 | -39 | -15 |
| R ITG | 60 | 4.32 | 61.5 | -7.5 | -27 |
| L Operculum | 61 | 4.01 | -40 | 9 | 22.5 |
| R Precentral Gyrus | 50 | 3.96 | 61.5 | 7.5 | 39 |

*Note*. Threshold: $p_{unc}$ = .001 at voxel-level, cluster size $k$ = 50; L = left, R = right, SMA = supplementary motor area, ITG = inferior temporal gyrus, MTG = middle temporal gyrus, OFC = orbitofrontal cortex. AAN = acute AN, PR = partial remitted AN, HC = healthy control. Analysis was controlled for age and TIV. As negative correlations were expected, contrast was done by using -1, so *t*-values are inverted.

**Figure 5**

*GMV Alterations in a) AAN b) PR and c) HC*




*Note.* Threshold: $p_{unc}$ = .001 at voxel-level, cluster size $k$ = 50; a) AAN. Red area corresponds to a reduced GM & blue to an increased GMV; b): PR; c): HC. Yellow brain areas correspond to a reduced GMV.

## Discussion

This study investigated the differences in alexithymia using the TAS-26 in acutely ill AN patients as well as PR AN patients and HCs. Furthermore, the role of depression, more specifically whether it mediates the association between alexithymia and AN diagnosis, was investigated, and lastly, global and regional GMV differences regarding alexithymia and AN severity were analyzed using VBM.

Both AAN and PR exhibited significantly higher TAS scores than HC. Trend analysis indicated that there is a linear increase in alexithymia corresponding to AN-severity, but this difference between PR and AAN did not reach statistical significance in the post-hoc test. Contrary to the results of the previous study (Torres et al., 2015), depression levels fully explained the association between alexithymia and AN diagnosis or no diagnosis. In line with longitudinal research, depression differences explained the difference between AAN and PR. At least in this study, levels of alexithymia mirror depressive symptoms and did not account for additional variance in AN severity beyond that explained by depression.

Both AN groups showed a reduced volume in the right MFG which did not overlap. Additionally, AAN participants showed reduced bilateral cerebellum volumes, while PR had reduced GMV in the bilateral putamen and amygdala, as well as in the right parahippocampal gyrus. In the total sample, increased alexithymia was associated with reductions in the bilateral insula and precuneus. Furthermore, reductions were found in the bilateral temporal lobe, including the right fusiform gyrus, and a large cluster in the right postcentral gyrus. In the subgroup analysis, smaller motor areas were associated with alexithymia in AAN, while a smaller right OFC was associated with alexithymia in PR and in HC, cerebellum size was associated with alexithymia.

### Clinical Profile of Alexithymia

The results of the ANOVA are in line with the idea of alexithymia being a trait of AN. After partial remission, TAS scores were still elevated which means that starvation alone does not explain difficulties in emotion identification, but rather it being a psychological trait of AN patients. In line with previous results (e.g. D'Agata et al., 2015; Miyake et al., 2012; Parling et al., 2010), these differences were driven by the subscales DIF and DDF, but not EOT, although it should be mentioned that there are studies in which there is a difference in EOT (e.g. Adenzato et al., 2012) and this difference was significant in the meta-analysis from Westwood et al. (2017) albeit being the smallest effect.

The polynomial contrast confirmed the hypothesis of a linear increase depending on illness severity and this result give a hint that starvation aggravates emotional difficulties, but

this study did not find a significant difference between the groups in a post-hoc test. There are multiple possible explanations for this: First, the WR criterion for the PR group was only 3 months and the reverse of psychological starvation effects might need a prolonged time. Compared to HC, the PR group still showed a reduced global GMV which was similar to the AAN group supporting this explanation, but previous research showed a fast restoration of GMV in adolescents, while still reduced, not significantly different to HC anymore, in contrast to the results of this study (Seitz et al., 2016). On the other hand, psychopathology symptoms both regarding AN and comorbidities could still occur to be assigned to PR. This is also supported by the increased depressive symptoms compared to HC in this subsample. AN is a severe psychiatric condition which often needs a long period of treatment in to be fully remitted and WR is only the first step in treatment. Perhaps patients in the PR group were still high in alexithymia as treatment has only begun and subjects only reached initial stabilization through WR or treatment progress is slow, so patients had little improvements regarding emotional difficulties. Moreover, some individuals perhaps did not receive any treatment that went beyond WR. As stated before, improvements in alexithymia following treatment have shown mixed results (Gramaglia et al., 2020). In this context, one should also consider that is it impossible to disentangle whether the slightly reduced alexithymia in the PR sample is because of possible psychological treatment or solely a result of WR and increased nutrition of the brain.

Additionally, this could also be an effect of different measurement. Studies who found this effect (e.g. Beadle et al., 2013; Tchanturia et al., 2012) used the TAS-20, while we used the TAS-26 (without the RD subscale). Although small, the lower reliability of the TAS-26 (which on the other hand is not existent in the German language), could have led to either lower scores in the AAN group or higher sores in the PR group. Furthermore, recent research showed that the validity of the TAS in AN is improvable (Torres et al., 2019). Nevertheless, these results show that an increased difficulty in emotion identification and description is present in individuals with acute AN and in a stage of PR of AN.

However, these results should be interpreted with caution given that depressive symptoms fully explained the connection between alexithymia and AN diagnosis, which would contradict the conceptualization of alexithymia as a trait in AN as depressive symptoms mirror a state. It should be noted that the correlation of alexithymia and depression ($r$ = .60) in our study is higher than in the meta-analysis of (S. Li et al., 2015) with $r$ = .46 and in other studies concerning AN such as Espina Eizaguirre et al. (2004) who found a correlation of $r$ = .40. Furthermore, depression scores were high in both AAN and PR. In contrast to the study

done by Torres et al. (2015), solely the indirect path in the mediation model was significant for all three group comparisons. They used the Zung Self-Rating Depression Scale (SDS, Zung, 1965) as it also measures positive sides of affect, depression-absent items so to speak and has a lower literacy level, which might explain the discrepant results, but present research has shown very similar validity of SDS and BDI, at least in older adults (Jokelainen et al., 2019) which makes this explanation unlikely. For both the SDS (Müller et al., 2003) and the BDI (Honkalampi, 2001) previous studies found the questionnaires to load on separate factors and thus measure something different, however this was done in non-clinical samples and psychosomatic samples.

Still, given the conceptualization of alexithymia as an integral part of AN from a theoretical perspective (Oldershaw et al., 2019; Treasure & Schmidt, 2013), it raises questions given that from a purely statistical perspective, the variance than can be explained by alexithymia in AN can be accounted completely by depressive symptoms in this sample. On the other hand, this might simply mean that depressive symptoms distinguish between different stages of AN severity more effectively and that the conceptualization of alexithymia in the *Toronto* model is insufficient to capture the theoretical construct of alexithymia in AN and perhaps other ways i.e. the *Amsterdam* model (BVAQ, Bermond & Vorst, 2001) that also considers an affective side might be a more appropriate way to operationalize alexithymia in AN samples. This study adds to the body of research that alexithymia in AN populations is diminished by depressive symptoms (e.g. Bydlowski et al., 2005; see Westwood et al., 2017). This is the first study that tested a mediating role of depression across a WR subsample and provides both contrasting results to the results of Torres et al. (2015) and a more nuanced perspective on the association between alexithymia and AN at different stages which future research should aim to replicate. If this was to be true, alexithymia in AN might simply be an expression of a depressed mood that accompanies AN. As a majority of AN patients develop a mood disorder (Godart et al., 2015) further disentangling this association for example by comparing non-depressed AN subjects to AN patients with depressive symptoms will prove to be difficult.

## Brain Morphology

### *Anorexia Nervosa*

In this study, reduced regional GMV in both the AAN and the PR group was found. One interesting aspect in these results is that the smaller brain areas were distinct in each group. While in both groups, a reduced GMV in the right MFG was found, the exact locations

did not overlap. Secondly, more severe reductions in the PR group compared to HCs than in the AAN group compared to HCs were found. One plausible explanation is the reduced power in the AAN comparison as the sample size was nine participants less, which already leads to a reduced power in the analysis (Steen et al., 2007).

In AAN, a reduction in the bilateral cerebellum was found which is in line with the systematic review by Kappou et al. (2021) regarding adolescents and in line with key findings from meta-analyses regarding all age groups (Su et al., 2021; S. Zhang et al., 2018). The cerebellum is responsible for complex motor behavior and motor control (Manto et al., 2012) and is also heavily involved in feeding behavior (Zhu & Wang, 2008). It has intense bidirectional connections to the hypothalamus, the brain area responsible for body homeostasis, but also other parts of the limbic system. Furthermore, the cerebellum activates to hunger, satiation and thirst, underlining its importance in feeding control (for an overview, see Zhu & Wang, 2008). Recent developments in neuroscience also point to its potential importance in emotion regulation in AN (Amianto et al., 2013) and other disorders (e.g. Baldaçara et al., 2008). A recent meta-analysis regarding task-based fMRI studies in AN also showed that cerebellum activity is altered in AN for both emotion and food related tasks further underlining its importance (Zhong et al., 2023). Moreover, two studies (Milos et al., 2021; Seitz et al., 2015) found cerebellar volume to predict treatment success (in the form of weight gain) and one study found reduced cerebellar volume to be associated with longer illness duration (Boghi et al., 2011). GMV reductions in the cerebellum prove to be one of the most consistent findings across neurobiological research in AN, yet current neurobiological theories (see Munro et al., 2017; Steinglass et al., 2019) are yet to incorporate the cerebellum's role coherently in AN pathology.

In PR, GMV reductions in the bilateral putamen and amygdala were found. The putamen is part of the striatum which is involved in reward processing (Balleine et al., 2007; Delgado et al., 2003; Schultz, 1998) and studies have shown altered reward processing even in recovered AN patients (Cowdrey et al., 2011; Wagner et al., 2007). While reductions in the putamen have been shown multiple times in single studies regarding acute AN (e.g. Frank et al., 2013; Friederich et al., 2012) meta-analyses fail to find those reductions in striatal areas (S. Zhang et al., 2018). Interestingly, both the putamen and the amygdala were areas which were smaller in acute AN compared to HC and to WR AN patients in the study done by Friederich and colleagues (2012). While they conclude good reversibility of these two areas, one could argue that our results indicate the opposite or at least they need additional time to restore beyond 3 months of normal weight. AN is a disorder with a long average illness

duration of seven years (Fichter et al., 2017) and some studies found even longer durations (Dobrescu et al., 2020). While our sample is considerably younger and adolescents with AN have generally a more favorable outcome than adults (see Fichter et al., 2017), reduced putamen volume could indicate a prolonged time of altered reward processing. Noteworthy is that the putamen is also the part of the basal ganglia most involved in motor movement with most projections from the motor cortices ending in the putamen and it is activated in well-learned and repetitive behaviors (see Haber, 2016). Another plausible explanation thus might also be that this reduced size is a correlate of cognitive-behavioral inflexibility (e.g. Merwin et al., 2010). This reduction could thus perhaps mirror a brain dysfunction that led to the maintenance of AN as both reward processing and cognitive inflexibility have been postulated to play a central role in it (Steinglass et al., 2019; Steinglass & Walsh, 2016). This result underlines the need to further research reward processing in AN.

The amygdala is thought to play a role in emotion processing regarding food and other stimuli (e.g. Joos et al., 2011) and similarly, a reduced amygdala volume could be a neural correlate of an amygdala which was hyperactive to harmless stimuli for a prolonged time (see Marcolini et al., 2024). Alternatively, these structures lay deep within the brain, and they might need longer to recover to normal volume after weight restoration. Maybe both the amygdala and the putamen need further treatment in the form of psychotherapy to recover to normal size which was for example observed in PTSD-treatment (Laugharne et al., 2016)

The parahippocampal gyrus, lying between the hippocampus, responsible for memory formation, and higher order visual processing areas, seems to be involved in visuospatial processing and episodic memory (Amianto et al., 2013) and is prescribed the function of “contextual associative processing”, (Aminoff et al., 2013, p. 381). In AN patients, the parahippocampal gyrus is associated with viewing their own body (Vocks et al., 2010) and other studies also found GMV reductions in AN patients (e.g. Brooks et al., 2011), but no study has found this to be the case in WR (i.e. PR) patients. Brodrick et al. (2021) actually found an increased cortical thickness in the right parahippocampal gyrus in PR patients. As this part of the brain is involved in body perception, one plausible explanation might be that this reductions mirrors the disturbed body, weight and shape perception which was still persistent in the PR group. Another striking result found in a meta-analysis is an increased activation of the right parahippocampal gyrus to food stimuli in obese subjects compared to normal weight subjects (Brooks et al., 2013), indicating that it seems to play a role in a dysfunctional food evaluation.

Besides the right MFG, an area thought to be involved during attention (Fischer et al., 2021; Japee et al., 2015), reduction in the GMV were found in distinct areas. This could have multiple implications: Albeit being an observational study, this could hint to the idea that different areas are affected at different stages of AN and that there might be stages of GMV alterations similarly to recent theoretical work point to different stages of AN (Steinglass et al., 2020; Treasure et al., 2015). One could argue that these results point to a neuroprogessive model in which feeding behavior at a more fundamental level is impaired during the acute stage, while at a stage past full syndrome, both reward and emotional processing of emotional and food-related stimuli are impaired which can be considered a scarring after a prolonged time of altered feeding behavior. This study could thus add evidence to the idea of neuroprogression taking place during AN (Treasure et al., 2015), however exact illness duration at the time of scanning was not considered in this study and should be taken into account. Moreover, brain alterations might also be of reason that some achieve partial remission and then suffer a relapse compared to people who reach full remission and those who develop a severe and enduring form of AN (see Steinglass et al., 2020). Studies scanning AN patients at different phases would help inform such a model as this process would happen gradually similarly to how restrictive feeding behavior usually becomes more rewarding over time (and thus habits manifest), but at the same time most of acute AN subjects will receive treatment which would complicate such research.

From another interpretational standpoint, these findings might also just showcase that the cerebellum is the fastest brain area to lose GMV, but also rather quickly regains its original volume and similarly, subcortical structures such as the parahippocampus, putamen and amygdala are not directly affected during the acute stage of AN, but then as they also lose GMV might need an increased duration to restore its original size after WR and adequate nutrition. A recent study (Mishima et al., 2021) suggested that GMV loss in most areas is the result of global brain changes because of malnutrition and less area dependent. Yet as researchers we should still reflect whether the impact on some brain areas could contribute to the maintenance of a disorder. Given that theoretical frameworks conceptualize AN as a vicious cycle with paradoxical reward and emotional processing of food (Oldershaw et al., 2019; Treasure & Schmidt, 2013), it would make sense to contemplate a potential role of progressive morphological changes in this process. Accordingly, these morphological changes, if reliably replicable, could serve as biomarkers for different stages of AN and inform treatment options, e.g. reduced striatal areas as an indicator to implement reversal habit therapy techniques into the treatment of enduring AN (see Treasure et al., 2020).

### *Alexithymia*

Before discussing the results regarding alexithymia, it should be noted that the significance level of $p = .001$ was uncorrected which might lead to false positive effects. On the other hand, to find robust results when correlating brain morphology data with psychological variables, huge sample sizes are needed (Kharabian Masouleh et al., 2019). This is especially important for the discussion of the analyses in the subsamples. But notably, many of the results seem to be in line with previous research such as the insula, the precuneus and the FG.

In the total sample, a reduced GMV in the bilateral insula was associated with alexithymia which is in line with previous meta-analytic research for the left insula (Xu et al., 2018). The insula is a highly connected area and essential for emotional awareness (Gu et al., 2013a), general body perception (Craig, 2011) and the integration of cognition and emotion (Gu et al., 2013b). Notably, we found this association bilaterally for the Insula and we also found the right amygdala and hippocampus to be reduced instead of the left amygdala which is thought to be important in social cognition regarding emotions (e.g. Goerlich-Dobre et al., 2015a). Still, altered insula size and activity has emerged to be one of the most consistent result regarding alexithymia, and there also seems to be causal relationship between insula damage and level of alexithymia, even when accounted for ACC size (Hogeveen et al., 2016).

One plausible explanation regarding hemisphere differentiation perhaps can be found in related constructs to alexithymia such as empathy, which correlates negatively with alexithymia (Di Tella et al., 2024). Furthermore, a study by Goerlich-Dobre et al. (2015a) showed a shared neural substrate in the left amygdala in healthy participants and recent theoretical frameworks presume empathy deficits because of alexithymia both represented by insula pathology (Valdespino et al., 2017). The bilateral insula is active during empathy-tasks (Fan et al., 2011). While the left insula is involved in affective and cognitive empathy, the right insula was only involved in affective empathy. Similarly, in alexithymic subjects the right insula showed lower activation during positive stimuli (van der Velde et al., 2013), but the left insula is one of the key neural correlates regarding morphology. Contrary, one study also found increased right insula volume to be associated with cognitive alexithymia (Goerlich-Dobre et al., 2014). These results highlight that both insulae are involved during emotional awareness, but results regarding insula asymmetry are mixed and need further research.

For example, measuring an affective side of alexithymia similarly to empathy could help understanding this asymmetry. In several studies the anterior part of the MCC was associated

with affective alexithymia (Goerlich-Dobre et al., 2014; Goerlich-Dobre et al., 2015a; Goerlich-Dobre et al., 2015b), an area that (depending on brain area labeling) often coactivates with the insula (see Gu et al., 2013a). This is the first study to investigate alexithymia in mixed sample consisting of majorly AN patients during adolescence, a population with highly heterogenous brain development due to age, brain development, illness duration and severity, yet this association between alexithymia and insula size has been found, further strengthening insulae involvement in alexithymia. Noteworthy, both clusters in the analysis are more anterior ranging into the IFG. The IFG has a wide range of functions, and the most inferior parts have also been shown to be involved in empathy (Liakakis et al., 2011).

The precuneus was also bilaterally reduced in alexithymia, another highly connected area with diverse roles regarding complex cognitive functions. It is a central part of the default mode network (DMN) and plays an important role in memory and self-referential (Dadario & Sughrue, 2023). Recent research highlights the essential role of the DMN in social understanding (W. Li et al., 2014). More generally, the paracingulate networks including the precuneus "facilitate the integration of internal and external stimuli and link it with previous knowledge to guide subsequent behavior" (Dadario & Sughrue, 2023, p. 3603). Similarly to the insula, reduced activity to positive stimuli was observed in alexithymic individuals (Van der Velde et al., 2013) and reduced GMV volume has been observed in singular VBM studies (e.g. Borsci et al., 2009; Goerlich-Dobre et al., 2014), but not in meta-analytic research (Xu et al., 2018). Noteworthy, reduced precuneus volume appears to be one of the key results of structural studies regarding AN (Su et al., 2021) and 60% of this sample have a history of AN, but reduced precuneus size in the group comparisons was not observed.

Terasawa et al. (2013) showed functional connectivity of the precuneus and the insula during the evaluation of emotional states, and the precuneus is also involved in the mentalization of the emotions and thoughts of others (Arioli et al., 2021; Atique et al., 2011) with a stronger activation during the cognitive than the affective mentalization (Arioli et al., 2021). Recently, a hierarchical model of social cognition was postulated in which the precuneus is involved during the integration process of affective and cognitive information (Schurz et al., 2021). In summary, both areas seem to play an essential role during cognitive processing in which emotions are involved. One potential explanation could be that a reduced insulae volume represents a reduced ability to integrate feelings and cognition, while the reduced precuneus volume might mirror a decreased ability to offer context information to the sensations and feelings felt in one's body. It should be considered that both areas did not

replicate within the subgroup analysis, which can be seen as evidence that this might be the case independently of AN severity, but critically, also as a hint that they might be false positives. Alternatively, variance in the subgroups might have been too small, as in both AN groups higher alexithymia was observed and lower alexithymia in HCs leading to null results in the groups.

The FG is an area responsible for higher-level visual processing and is often linked with processing facial expressions (McCarthy et al., 1997), although this view is considered simplified in more recent research (Weiner & Grill-Spector, 2012). In the largest VBM-study on alexithymia (Grabe et al., 2014), the subscale DIF was explicitly correlated negatively with left FG volume, and in females, also the DDF subscale (in this study, it was the right FG). Moreover, a recent study found the FG to be increased in high alexithymic HCs and a reduced FG volume in alexithymic individuals suffering from MDD (Förster et al., 2020). Lower activation during emotion processing tasks in FG have been shown consistently (Van der Velde et al., 2013), even in studies investigating unconscious face processing (Duan et al., 2010). Alexithymic individuals have difficulties with looking at eyes during emotion recognition tasks (Fujiwara, 2018) and recent literature also suggests that alexithymic individuals have deficits in the automatic emotional processing of faces (Donges & Suslow, 2017). Consequently, the reduced volume of the right FG in high alexithymic individuals could mirror a reduced ability to process facial emotions at both a conscious and unconscious level.

Perhaps the most surprising result was that the largest cluster correlating negatively with alexithymia was found in the right PG up to the right supramarginal gyrus, an area usually not structurally associated with alexithymia. The PG incorporates the primary somatosensory cortex (SSA) of the brain, the areas in the brain responsible for receiving sensory information from the body (Kaas et al., 1979). Theoretically, it is thought that a perceiver mirrors sensations of the perceived in the brain in the somatosensory cortices, essentially internally simulating sensations and emotions they perceive (Adolphs, 2002) and recent literature also suggests an involvement of the SSA in emotion regulation (see Kropf et al., 2018). The postcentral gyrus also has extensive connections the posterior part of the insula (Cauda et al., 2011), the part more responsible for body interoception compared to the anterior parts (Craig, 2002; Uddin et al., 2017).

One study found reduced PG activity when alexithymic individuals were asked to suppress arising emotions (van der Velde et al., 2015) and Terasawa et al. (2021) found alexithymic individuals to have a “paradoxical” somatic processing: Alexithymic subjects had

an attenuated activity between the insula and the SSA when asked to interocept, but an increased activity between these areas when focusing on anxiety about pain. Similarly, in an earlier systematic review, Moriguchi and Komaki (2013) summarized that alexithymic individuals have increased activity across sensory and motor areas with regard to more "physical" stimuli which they interpret as an increased somatic experience during emotions. Potentially, this reduced volume in the PG could thus be a substrate of either directly an altered ability to process somatic information essential for emotions (e.g. pain) or indirectly a reduced ability to simulate somatic experiences associated with emotions, thus having an impaired emotional and somatic mirroring ability or the opposite, an increased somatic sensation in line with this paradoxical somatic processing.

Subgroup analysis revealed different areas correlating with alexithymia within each group and did not replicate any cluster besides the right inferior TG. Given that sample size is low, and significance threshold is liberal and thus power is low, one straightforward and rather unsatisfying answer would be to dismiss these results as false positives. Still, other possible explanations will be highlighted here, if these results were to be true. In the AAN group, we find alterations in the SMA, and the precentral gyrus related to alexithymia, both areas related to motor control: While the SMA seems to have a more complex planning and supporting role, the precentral gyrus incarnates the premotor cortex or M1, more involved in the execution of movements (Nachev et al., 2008). Both areas are reported to show decreased activity in alexithymia (van der Velde et al., 2013), which the authors of the meta-analysis speculate to be reflect poorer empathetic skills as part of internally simulating or mirroring motor actions involved in emotion recognition (see Valdespino et al., 2017). Interestingly, bilateral cerebellum was reduced in the AAN group, another brain area mainly responsible for motor coordination, but also involved in emotional processing in AN (Zhong et al., 2023). Following this narrative, reduced GMV in the acute stage of AN is found in primarily motor-related areas and additional regions are affected in AAN subjects with higher alexithymia. This could perhaps represent this impaired internal simulation, as well as an inflexibility in behavior along with an impairment in feeding control (Zhu & Wang, 2008), resulting in starving or purging during the acute phase of AN in response to amongst others things, potentially overwhelming emotions. In line with this would also be the finding of worse treatment outcome in AN patients with higher alexithymia (Speranza et al., 2007).

On the other hand, in PR, the right OFC volume correlated negatively with alexithymia. The left OFC is often found to be reduced in alexithymia (Xu et al., 2018) and is thought to represent the reward value of a stimuli (Padoa-Schioppa & Assad, 2006; Peters &

Büchel, 2009) and its pleasantness (Kringelbach, 2005) with studies showing a posterior-anterior gradient of different rewards (Y. Li et al., 2015). In line with this reward function of the OFC, putamen volume was also found to be reduced in PR, and so was the volume of the amygdala, an area that influences reward coding in the OFC (Rudebeck et al., 2013). One could argue, that in subjects at least partially in remission after the acute stage, reward and emotion processing in general seems to be altered, and within those individuals with more difficulties identifying and describing emotions, the evaluation of emotional value is impaired. So, subjects with a history of AN and high alexithymia might be worse at assessing how important an arising emotion is or correctly estimating the emotional significance of an external stimuli, as they have avoided their feelings for an extended period in their life (Oldershaw et al., 2019).

It is important to acknowledge the process of reverse inference (e.g. Poldrack, 2011) and that one area can have many different functions, and crucially this is even more important given that structural data was analyzed: A smaller volume of an area could both mean an impaired functioning and thus smaller or less neurons and supporting cells such as glia cells (Seitz et al., 2016) or more effective functioning and thus needing less or smaller neurons. The putamen for example also has a wide range of functions regarding motor control as discussed above, not just reward processing and learning, so these distinctions should not be read as fixed, but the opposite: different stages of one process in which initially areas related to motor control and feeding are affected, but as AN manifests the brains reward and learning networks change.

Supporting these ideas is the fact that this is not the first study to find the mentioned areas to be smaller in AN subjects. Additionally, this is the first study to investigate neural correlates of alexithymia at different stages of AN and thus should provide potential directions for future research. The potential mechanisms are broadly in line with the cognitive-interpersonal model of AN (Treasure & Schmidt, 2013) and its successor, the cognitive-interpersonal maintenance model of severe and enduring AN (Treasure et al., 2020). During the acute stage, brain nutrition decreases which leads to an increase in inflexibility and rigid behavior and in the socio-emotional domain, to a decreased ability to send and interpret social signals (all of them likely being more pronounced prodromal making individuals more vulnerable to AN). In the maintenance model, neuroadaptation takes place as the behaviors to induce weight loss are rewarding and positively reinforced (Treasure et al., 2020) which is mediated by frontostriatial circuits (see Steinglass & Walsh, 2016).

Again, it should be highlighted that these are purely speculative mechanism based on structural abnormalities in a cross-sectional sample of AN subjects and HCs. To address such mechanisms, functional imaging research is needed, ideally in a longitudinal design and functional-connectivity study designs could also help understanding these processes (e.g. Amianto et al., 2013). Furthermore, studies could implement tasks beyond emotion identifcation and include novel methods like ecological momentary assessment (EMA) which can help understanding the neuronal basis of emotion processing in AN outside of the scanner (see for example Seidel et al., 2018).

This study did not find any abnormalities in the anterior parts of the cingulate cortex for both AN and alexithymia. This adds to the findings that structurally the ACC seems to be unrelated to alexithymia (Xu et al., 2018). While S. Zhang et al. (2018) did not report ACC alterations, the latter meta-analysis by Su et al. (2021) found smaller ACC volume in AN patients. Earlier research demonstrated abnormalities in the ACC functionality regarding alexithymia (Lane et al., 1998) and later in its structure (Borsci et al., 2009; Grabe et al., 2014; Gündel et al., 2004; Heinzel et al., 2012), but a coherent picture is yet to be found (Xu et al., 2018). Functionally, altered activity is well documented (Van der Velde et al., 2013) independently of emotional stimuli valence and the authors further speculate, that ACC activity follows an inverted U-shape based on how much cognitive and affective effort is needed to process a stimuli. This sample is rather heterogenous with 60% having a history or current occurrence of AN and further highly diverse in brain development as subjects range between 12 and 27 years, which might explain null findings regarding neural substrates of alexithymia in the ACC.

The very same argument applies to AN: Initial studies highlight the importance of the ACC in AN (Mühlau et al., 2007; McCormick et al., 2008) but meta-analyses revealed unclear results (Su et al., 2021; S. Zhang et al., 2018). Notably, in this sample also posterior parts of the cingulate cortex did not present altered volumes. Similarly to alexithymia, age and different stages of brain development could be of reason, but previous research found cingulate cortices reductions also in purely adolescent samples (Castro-Fornieles et al., 2009; Martin Monzon et al., 2017). Lastly, the rather small sample size in the AAN group could have led to an underpowered analysis or a significance threshold too conservative to find these. Similarly, insulae volume also did not differ between HC and AN groups, although previous research found insula GMV reductions (Martin Monzon et al., 2017; Tose et al., 2024) and the insula also plays a crucial role in neurobiological theories of AN (Kaye et al., 2009; Nunn et al., 2011). Perhaps previous findings in AN samples in the insula mirrored

alexithymic traits as this study found the bilateral insula to correlate negatively with alexithymia in the total sample and higher alexithymia scores were observed in both AN groups, but then again these should have also been observable in the group comparisons. Accordingly, the absence of significant results related to the cingulate cortex remains unclear and needs further research.

## Limitations

Our sample consisted of three independent subsample, consequently potential mechanism and explanations regarding brain morphology, GMV alterations and recovery should be taken with caution. This is especially of concern, as none of the areas reduced in AAN and in PR overlapped. Furthermore, although the ANBEL-project aims to achieve an age-matched sample, the current sample consists of both a smaller and a younger AAN subsample. Although VBM-analysis was controlled for age and TIV in all analyses, the individual brain development of a subject cannot be completely controlled for. Both neuronal pruning during adolescence as well as the severity of AN are factors to consider, which ultimately make this sample heterogenous even though precise criteria for group assignment were formulated. Although most people who suffer from AN are female and so are the majority of samples used in studies regarding AN, one should also consider that these result do not necessarily transfer to male individuals suffering from AN. This also applies to the results with regard to alexithymia, especially since gender differences regarding brain structure and function are debated in the literature (see Theoretical Background).

Another limitation is the usage of the TAS-26: While still a reliable instrument to assess alexithymia, most of the research regarding alexithymia nowadays uses the revised version, the TAS-20 (Bagby et al., 1994), or other measurements such as the BVAQ (Vorst & Bermond, 2001) which also include an affective dimension of alexithymia. This could especially be of interest to assess whether starvation also leads to a dampened emotional life, which was the case for example in a study by Montebarocci et al. (2006). Ultimately, as previously mentioned the rather liberal threshold of VBM-analysis for alexithymia could have led to false positives. This is exacerbated in the subgroup analyses due to the smaller sample and variance and due to the rather heterogenous sample of young women and girls.

## Implications for Future Research

This study was able to show that alexithymia is increased in both acute AN individuals, as well as individuals who have reached PR. As in the ANBEL-project intended, future research should also look at fully remitted patients, to evaluate whether alexithymia is lower in these samples or whether therapy could lower alexithymia. For this concern, longitudinal research can be beneficial, and causal conclusions can be drawn. Furthermore, studying both atypical AN (Moskowitz & Weiselberg, 2017) and severe enduring AN (Wonderlich et al., 2020) might help understanding the influence of starvation and help understanding to what extent alexithymia is influenced by weight and brain nutrition. As

previously mentioned, future research could also benefit from measuring an affective side of alexithymia to clarify its existence and validity, especially in clinical samples this could provide important insights (Goerlich, 2018). This is especially of interest for neuroscientific research regarding alexithymia which has mainly been done with the TAS (Xu et al., 2018). Furthermore, the results of this study stand in contrast to Torres et al. (2015) and add to the research, in which alexithymia and depression are highly connected and depression diminishing the association between AN and alexithymia. Most people who suffer acutely from AN show depressive symptoms and in our sample, depressive symptoms were still high in PR with mean score in this group still being above the cut-off proposed for mild depression in the BDI-II (Dolle et al., 2012). Future research should thus investigate the relationship between these three variables further.

This is the first study to investigate neural correlates of Alexithymia in an anorectic sample at different stages. The sample was considerably bigger and more homogeneous (as only one disorder was included) than the sample of D'Agata et al. (2015), but they have also used a stricter threshold for correlation analyses of alexithymia, which might be the reason for their null findings. For VBM, especially correlational analyses, larger samples are always more favorable, multi-center studies for neuroimaging (Tose et al., 2024) could help addressing this issue. Albeit by using a liberal threshold, this study gives hints that different brain areas and thus perhaps different functions underlie difficulties in identifying and describing feelings in AN. Replicating these results with a larger and potentially more homogeneous sample is of need and so are functional neuroimaging studies. While using an adolescent sample provides higher external validity as the onset of AN is predominantly during adolescence, an adult sample of individuals with fully developed brains might provide clearer results as both development and pruning are finished.

Furthermore, these studies should implement task paradigms that go beyond emotion identifcation, such as applying emotion regulation strategies (see van der Velde et al., 2015) in AN samples and then also collect measures of alexithymia. Particularly interesting are translational approaches which connect brain activity measures with real-life measures: Seidel et al. (2018) showed that striatal activity during emotion regulation tasks could predict future rumination and negative affect in AN patients demonstrating the wide applicability of combining modern research techniques. Ultimately not just measuring alexithymia severity but also understanding how alexithymia is expressed in AN (and other clinical disorders) can help improving treatment options: Training not just emotion identification, but also communication of feelings to peers and (psychological) therapeutic practitioners, as well as

learning functional emotional regulation strategies and initializing adequate reactions to felt emotions. Neuroscientific evidence can influence these developments and perhaps also help developing techniques used in therapy, for example insula neurofeedback-training (see Y. Zhang et al., 2025) shows promising effects regarding improvements of self-regulation and could provide the basis for techniques suitable for clinical practice.

## Conclusion

This master thesis investigated alexithymia at different stages of AN in comparison to healthy women, the role of depression in this relationship and the neural substrates of AN and alexithymia in the brain by utilizing VBM. Alexithymia was elevated in both acute and partially remitted AN compared to HC, which allows the surmise of a trait character of alexithymia in AN. However, these differences could fully be explained differences in depressive symptoms, a state-dependent variable, which challenges the trait interpretation of alexithymia in AN.

Both AN groups showed reduced global and regional GMV compared to HC, but the areas were distinct and also no regional differences between the two AN groups were found: In AAN, cerebellum displayed smaller volume, while in PR putamen and amygdala volumes were reduced. Furthermore, both showed a slight reduction in the right medial frontal gyrus. Alexithymia was associated with smaller bilateral insula and precuneus volume, as well as a smaller left fusiform gyrus and postcentral gyrus. Within each subgroup, these associations were not replicated, but AAN showed alterations in motor areas, while PR showed a reduction in the right OFC in correspondence to alexithymia. These results demonstrate reduced brain volume during starvation and after starvation, and show that brain alterations differ across stages of AN. Further, they hint that either subcortical regions need an increased time to restore to normal GMV or that different functions of the brain are altered depending on stage of AN. These changes might also be related to alexithymia, which would also be in line with line with theoretical models and support staging models that postulate neuroprogression in AN.

Future research should investigate this using longitudinal designs, following AN patients from acute stages to recovery and take alexithymia and an affective side of it into account, which could help understanding causal relationships between AN, emotion regulation difficulties and neurobiology. As this study used an observational design investigating morphological changes, functional neuroimaging studies are needed to understand the mechanisms behind alexithymia in AN and particularly new developments in

research could help transferring neuroimaging data to real life experience of AN. Ultimately, insights into the neurobiology of both AN and emotion regulation difficulties have the potential to improve clinical treatment and consequently lead to a better quality of life of individuals suffering from AN.

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# Appendix

## English Abstract

Research has shown that alexithymia, a subclinical syndrome which characterizes difficulties in identifying and describing feelings, is increased in anorexia nervosa (AN) and more inconsistently also in partially remitted AN (PR) patients compared to healthy controls (HC). In this context, the role of depression in the relationship also remains unanswered. Though both alexithymia and AN have gained interest in neuroscience independently, only few studies explored alexithymia in AN neuroscientifically. In a sample of 90 female subjects (acute AN: $n = 24$, PR: $n = 33$, HC: $n = 33$) alexithymia and depression measures were collected and gray matter volume (GMV) was investigated using voxel-based-morphometry (VBM).

Both acute AN (AAN) and PR exhibited increased alexithymia, but differences were fully explained by depression. VBM revealed decreased GMV in the cerebellum in AAN and PR showed decreased GMV in the bilateral putamen and amygdala compared to HC, but no differences between the AN groups were found. Higher Alexithymia was associated with reduced GMV in the bilateral insula and precuneus in the total sample. Within each group distinct areas in motor areas correlated negatively with alexithymia in AAN, while in PR the orbitofrontal cortex size correlated with alexithymia. Results indicate that elevated alexithymia is present beyond the acute stage indicating a trait character in AN, but this is challenged by the finding that depressive symptoms can account for differences in alexithymia. AAN and PR show altered GMV in distinct brain regions suggesting differences in brain functioning depending on AN stage and alexithymia might contribute to this, which should be clarified by further research.

**German Abstract**

Forschungsergebnisse der letzten Jahre zeigten, dass Alexithymie, ein subklinisches Syndrom, welches Probleme bei der Identifikation und Beschreibung von Gefühlen beschreibt, stärker ausgeprägt ist bei Anorexie Nervosa (AN) und teilweise auch bei teilremittierten (TR) AN Patient*innen im Vergleich zu gesunden Kontrollen (HC). Die Rolle von Depression in diesem Kontext bislang ungeklärt. Obwohl AN und Alexithymie beide unabhängig vermehrt in den Neurowissenschaften erforscht werden, haben bisher wenige Studien Alexithymie bei AN neurowissenschaftlich untersucht. In einer Stichprobe von 90 Teilnehmerinnen (akute AN: $n = 24$, TR: $n = 33$, HC: $n = 33$) wurden Daten zu Alexithymie und Depressionen erhoben, sowie das graue Substanzvolumen (GSV) mithilfe von Voxel-basierter Morphemetrie (VBM) analysiert. Sowohl akute AN (AAN) als auch TR AN Teilnehmerinnen wiesen erhöhte Alexithymiewerte auf, aber diese Unterschiede konnten vollständig durch Depression erklärt werden. In der VBM zeigten sich reduziertes GSV im Cerebellum in AAN, sowie reduziertes GSV im bilateralen Putamen und der Aymgdala in TR. Alexithymie war in der gesamten Stichprobe mit dem bilateralen Insulae und Precuneus-Volumen negativ assoziiert. Innerhalb der Gruppen war Alexithymie in AAN mit Motorarealen assoziiert, sowie mit dem rechten orbitofrontalen Cortex in TR. Die Ergebnisse deuten darauf hin, dass eine ausgeprägte Alexithymie über die akute Phase von AN hinaus vorhanden ist, was auf ein Persönlichkeitsmerkmal hinweist, doch könnte dies infrage gestellt werden, da depressive Symptome Unterschiede in Alexithymie erklären können. AAN und TR zeigten eine veränderte GSV in verschiedenen Hirnregionen, was nahelegt, dass möglicherweise Unterschiede in der Hirnfunktion je nach AN-Stadium existieren und Alexithymie dabei eine Rolle spielen könnte. Dies sollte allerdings durch weitere Forschung geklärt werden.

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**List of Abbreviations**

AN: Anorexia Nervosa

AAN: Acute Anorexia Nervosa

ACC: Anterior cingulate cortex

BDI: Beck Depression Inventory II

BMI: Body-Mass-Index

BN: Bulimia Nervosa

BVAQ: Bermond Vorst Alexithymia Questionnaire

CSF: Cerebrospinal fluid

DDF: Difficulties Describing Feelings

DIF: Difficulties Identifying Feelings

ED: Eating disorder

EDE: Eating Disorder Examination

FG: fusiform gyrus / area

FR: full remission / fully remitted

fMRI: functional magnetic resonance imaging

EOT: Externally Oriented Thinking

GMV: Grey matter volume

HC: healthy control

IFG: Inferior frontal gyrus

ITG: Inferior temporal gyrus

MCC: Middle / Medial cingulate cortex

MRI: magnetic resonance imaging

OFC: Orbitofrontal cortex

PCC: Posterior cingulate cortex

PET: Positron Emission Tomography

PR: Partial remission / partially remissoned

PG: Postcentral gyrus

RD: Reduced Daydreaming

SMA: Supplementary motor area

sMRI: structural magnetic resonance imaging

SSA: Somatosensory area

TAS: Toronto Alexithymia Scale

TG: Temporal gyrus

TIV: Total intercranial volume

VBM: Voxel-Based-Morphometry

WB: whole-brain

WMV: White matter volume

WR: Weight restoration / weight restored