Thesis

Genetic Links of Implicit Learning in Anorexia Nervosa

submitted by

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Declaration of Academic Integrity

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Graz, 13.09.2023 *Markus Wiener m.p.*

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Abbreviations and definitions

2-AG	2-arachidonoylglycerol
5-HT	5-hydroxytryptamine, serotonin
AEA	N-arachidonoylethanolamine
AN	Anorexia nervosa
ANOVA	Analysis of variance
APA	American Psychiatric Association
ASD	Autism spectrum disorder
BDI	Beck Depression Inventory
BMI	Body mass index (kg/m^2)
CADM1	Cell adhesion molecule 1
CDH10	Cadherin-10
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAT-26	Eating Attitude Test with 26 items
EC	Endocannabinoids
EDE-Q	Eating Disorder Examination Questionnaire
EDNOS	Eating disorder, not otherwise specified
EDTA	Ethylene-diamine-tetra-acetic acid
FB	Feedback
FOXP1	Forkhead box protein 1
GWAS	Genome-wide association study
HAMD	Hamilton Depression Rating Scale

HC	Healthy controls
HGP	Human genome project
HPA	Hypothalamic-pituitary axis
ICD	International Classification of Diseases
IGF1	Insulin-like growth factor 1
IPAQ	International Physical Activity Questionnaire
LH	Luteinizing hormone
MANOVA	Multiple analysis of variance
MET	Multiples of the resting metabolic rate
MMST	Mini Mental Status Test
MRI	Magnetic resonance imaging
MTL	Medial Temporal Lobe
MWT-B	Multiple Choice Vocabulary Test
PA	Paired-associate
PET	Positron emission topography
PGC-ED	Psychiatric Genomic Consortium – Eating Disorders
SNP	Single-nucleotide polymorphism
SNRI	Serotonin and norepinephrine reuptake inhibitor
SPSS	Statistical Package for the Social Sciences
SSRI	Selective serotonin reuptake inhibitor
SSRT	Serial Reaction Time Task
THC	Tetrahydrocannabinol
WHO	World Health Organization
WPT	Weather Prediction Task

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Zusammenfassung

Einleitung: Veränderungen im ventralen Striatum sind bei Anorexia nervosa (AN) mit Störungen im impliziten Lernen assoziiert. Bisher wurden zwar verschiedene Theorien bezüglich der Entstehung dieser Veränderung angeregt, aber nicht weiterverfolgt. Gleichzeitig wurde im Jahr 2019 die erste große genomweite Assoziationsstudie (GWAS) für AN durchgeführt und neun genomweit signifikante Loci identifiziert. Ziel dieser Arbeit ist es zu erforschen, ob verschiedene Genotypen der Kandidatengene für AN mit der Leistung von Patient*innen bei impliziten Lerntests assoziiert sind.

Methodik: Im Rahmen einer Pilotstudie haben 25 Patient*innen mit AN und 56 gesunde Kontrollpersonen (HC) den Weather Prediction Task (WPT) absolviert. Dabei handelt es sich um einen impliziten Lerntest mit zwei Unterkategorien. Während der Bearbeitung der Feedback-Variante (FB) zeigt sich eine Aktivierung des ventralen Striatums, wobei beim Lösen der Paired-Associate-Variante (PA) der mediale Temporallappen (MTL) aktiviert wird. Mittels Varianzanalyse (ANOVA) wurden die Ergebnisse des WPT mit Genotypen von Single Nucleotide Polymorphismen (SNP) von Genen assoziiert, die im Vorfeld über die GWAS mit AN in Verbindung gebracht wurden. Die DNA-Isolierung wurde mittels QIAGEN's QIAsymphony SP Roboter durchgeführt, die Genotypisierung fand am Life & Brain Center Bonn mittels Illumina's Infinium Global Screening Array-24 v3.0 Kit statt. Die Genotypen wurden hypothesengeleitet mittels PLINK1.9 isoliert.

Ergebnisse: Patient*innen mit AN erzielten eine signifikant niedrigere Punktzahl im FB-Teil des WPT, sowohl im Vergleich zur HC-Gruppe ($p = .001$), als auch verglichen mit ihrer eigenen Punktzahl im PA-Teil ($p = .006$). Eine niedrige Punktzahl im FB-Teil war mit dem CT-Genotyp des SNP rs4307059 (*CDH10*-Gen) assoziiert ($p = .025$). Solch eine Assoziation zeigte sich nicht in der HC-Gruppe ($p = .334$).

Diskussion: Die Ergebnisse dieser Arbeit bestärken die Bedeutsamkeit von genetischen Faktoren in der Entstehung der AN und ihrer miteinhergehenden kognitiven Veränderungen. Cadherine und deren assoziierten Gene könnten durch ihre Rolle in der neuronalen Gewebsdifferenzierung und der Stabilisierung von synaptischer Signalübertragung zentral für die Degeneration des Striatums im Verlauf der Erkrankung sein. Diese Arbeit soll zu weiterer Forschung im Bereich der Anorexie-Kognitions-Genetik animieren und zu Studien auf polygener Ebene und mit größerem Stichprobenumfang inspirieren, um definitive Schlüsse zum Thema genetische Einflüsse auf Kognition bei AN ziehen zu können.

Abstract

Introduction: Fronto-striatal alterations are associated with difficulties in implicit learning in adults with anorexia nervosa (AN). Thus far, theories pertaining to this impairment's pathophysiology have been proposed but not further explored. Concurrently, the first large genome-wide association study (GWAS) for AN has emerged in 2019, confirming that a substantial genetic link is present in the disorder. The purpose of this thesis is to investigate whether different genotypes of newly discovered candidate genes of AN are associated with implicit learning task scores.

Methods: In a pilot-study, 25 patients with AN and 56 healthy controls (HC) completed the Weather Prediction Task (WPT), a probabilistic implicit learning task which shows activation of the ventral striatum during its feedback (FB) variant, and activation of the medial temporal lobe (MTL) during its paired-associate (PA) variant. Through analysis of variance (ANOVA), results of the WPT were then associated with different genotypes of single-nucleotide polymorphisms (SNP) that display association with genes related to AN. DNA isolation of blood samples was performed using QIAGEN's QIAsymphony SP robot, whereas genotyping occurred at the Life & Brain Center Bonn through use of Illumina's Infinium Global Screening Array-24 v3.0 Kit. Genotypes were extracted using PLINK1.9.

Results: AN patients scored significantly lower on the FB version of the WPT, both in comparison to the HC group ($p = .001$) and to their own performance on the PA version ($p = .006$). Low scores in the AN group were associated with the CT genotype of rs4307059 (*CDH10* gene) ($p = .025$). No such association was found in the HC group ($p = .334$).

Discussion: These results further reinforce the importance of genetics on the pathophysiology of AN and its dysfunctional brain circuits. Through mediation of tissue differentiation and synapse strength stabilization, cadherins and their related genes may play a crucial role in the striatal deterioration that AN patients are subject to. This thesis hopes to spark further research on genetic links of cognition in AN. In particular, a larger study population and analyses on a polygenic level would be needed to verify this thesis' results and draw definite conclusions on the topic.

1. Introduction

1.1 Anorexia nervosa

Anorexia nervosa (AN) is a heterogeneous eating disorder, characterized primarily by low bodyweight, a severe fear of weight gain and a disturbed body image. The condition most commonly develops during adolescence or early adulthood, typically following a stressful life event (World Health Organization, 2019). Prevalence of the condition is high, reported to be as much as 2.4% in women (Wade et al., 2006) and 0.29% in men (Bulik, C. M. et al., 2006). In spite of AN being this common, prognosis is still remarkably poor as full remission of AN is not achievable in a third of patients even ten years after onset (Nilsson, Hägglöf, 2005). Furthermore, AN continues to be the psychiatric disorder with the highest mortality rate, averaging a standardized mortality ratio (SMR) of 5.9 in the overall AN population (Arcelus et al., 2011), and an imposing SMR of 15.9 in AN inpatients who suffer from severe malnutrition (Guinhut et al., 2021). Causes for the poor outcome mainly lie in the condition's broad range of both psychiatric and somatic comorbidities, the lack of treatment adherence and the absence of pharmacological treatment options (Hay, 2020; Jagielska, Kacperska, 2017).

To classify a psychiatric disorder, there are usually two major classification systems being used to aid clinicians: The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), as well as the International Classification of Diseases (ICD-11).

1.1.1 Classification

The DSM-5 is a diagnostic manual specifically created for psychiatric diseases. It is published and regularly updated by the American Psychiatric Association (APA), and its fifth version is in effect since 2013 (American Psychiatric Association, 2013). In this update, a revision of the Feeding and Eating Disorders section was made, which significantly altered the definition of AN.

The modification process was aimed at clarifying and updating the diagnostic criteria to match the current state of research, and to reduce the number of patients diagnosed with not otherwise specified eating disorders (EDNOS) (Keel et al., 2011). In the case of AN, the perhaps most drastic change made was the removal of the amenorrhea criterion in the diagnostics of AN. In the old DSM-IV, amenorrhea was a core diagnostic criterion for AN,

but it was abolished in the new version as there were inconsistencies in applying it to male individuals, females before they reach menarche, as well as women receiving exogenous hormones (Zipfel et al., 2015). This change is further supported by a review from Attia & Roberto, showing that differences in patients with AN that menstruate, and those who do not, are largely based on nutritional status (Attia, Roberto, 2009). There are few psychological differences between the groups, suggesting that the two groups do not differ significantly in treatment outcome either. In fact, menstruating patients with AN show slightly higher severity of disease in eating disorder-related questionnaires compared to patients with amenorrhea (Attia, Roberto, 2009).

In addition to the removal of the amenorrhea criterion, there have also been several smaller changes. A comparison of diagnostic criteria for AN between the DSM-IV and the DSM-5 is displayed in **Table 1**.

Table 1: Key differences in the diagnostic criteria of anorexia nervosa between the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) (Own table, based on Zipfel et al., 2015)

	DSM-IV	**DSM-5**
A	A refusal to maintain bodyweight at or above a minimally normal weight for age and height (e.g., weight loss leading to a maintenance of bodyweight less than 85% of that expected, or failure to make expected weight gain during period of growth, leading to bodyweight less than 85% of that expected).	Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B	Intense fear of gaining weight or becoming fat, even though underweight.	Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.

C	Disturbance in the way in which one's bodyweight or shape is experienced, undue influence of bodyweight or shape on self-evaluation, or denial of the seriousness of the current low bodyweight.	Disturbance in the way in which one's bodyweight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low bodyweight.
D	In postmenarcheal females, amenorrhea - i.e., the absence of at least three or more consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone - e.g., estrogen administration).	Removed.

On the other hand, there is the ICD-11, a health statistics coding tool that is published and maintained by the WHO. Compared to the DSM-5, it not only covers psychiatric disorders but tries to quantify and standardize all health conditions that exist in humans. It is of particularly high interest as the updated version was only recently presented to the public in 2019 (The Lancet, 2019).

In its most recent revision, the ICD-11 adopted very similar changes as the DSM-5. Where DSM-5 and ICD-11 differ, however, is the weight criterion. While the new version of the DSM-5 doesn't list a weight requirement to diagnose AN, the ICD-11 now specifically lists a BMI of less than 18.5kg/m^2 as a diagnostic guideline for adult patients. It is important to note, however, that the ICD-11 also defines exceptions for this criterion in the form of rapid weight loss.

1.1.3 Etiology and pathogenesis

Anorexia nervosa is a condition of multifactorial origin. This means that there are multiple factors contributing to the development of the disorder, and no single cause can be determined. Possibly due to this circumstance, our understanding of the exact pathogenesis of AN is still limited. Nonetheless, significant progress has been made in recent years, particularly regarding the underlying molecular pathways of the disorder (Paolacci et al., 2020).

One theory that is often used to describe the pathogenesis of psychiatric disorders is the stress-vulnerability model, also called diathesis-stress model. According to this model, every individual's vulnerability towards the development of a disease is inherently different.

Depending on the amount of vulnerability one possesses, different intensity of stress is required to trigger the condition. When this theory first emerged in the 1960s, vulnerability was thought of as mostly biologically acquired (Broerman, 2017). This view, however, changed as time went by and vulnerability is now seen as a trait that is biologically, psychologically as well as socially acquired (Monroe, Simons, 1991).

Nowadays, this theory is mostly seen as an overly simplistic approach to understanding mental conditions and is used only as a building block to connect new scientific discoveries (Broerman, 2017).

1.1.3.1 Serotonin pathways

Serotonin (5-hydroxytryptamine:5-HT) is a neurotransmitter that is known best for its role in regulating mood, although it also plays an important part in controlling various aspects of feeding behavior. It is vital for regulating molecular substrates of survival, including those responsible for preventing depression-like states, gastro-intestinal peristalsis, and the regulation of food intake. This makes it probable that dysregulations in this system are partially at fault for causing the symptoms commonly seen in AN (Compan, 2017).

Studies in animals show that stimulation of the 5-HT_{1A} receptors in the dorsal raphe nuclei of the brainstem reduces the firing activity of 5-HT neurons and leads to hyperphagia, an increased sensation of hunger (Compan, 2013).

A similar behavior was observed in 5-HT receptors of the hypothalamus. Stimulation of hypothalamic 5-HT_{1B} and 5-HT_{2C} receptors led to hypophagia in mice, whereas stimulation of 5-HT_{1A} and 5-HT_{2B} caused exceptional hyperphagia (Yadav et al., 2009).

As a result of this strong connection between the serotonergic system and the sensation of hunger, 5-HT_4 receptors in particular have become a target of great interest in the development of pharmacological treatments for AN (Compan, 2017).

1.1.3.2 Opioid and dopamine pathways

Through mediation of the emotional response to food, opioids play a key role in the adaptation and regulation of the human energy intake (Hasan, Hasan, 2011). This reward-mediated system seems to be altered in individuals affected by AN. With positron emission topography (PET) imaging showing reduced opiate receptor availability in people affected by the condition, it is suspected that there is an increased opioid tone present, specifically in areas of the brain associated with reward and aversion (Galusca et al., 2020).

While the role of opioids in the pathogenesis of AN has only recently sparked the interest of researchers, it is well-established that affected individuals show signs of an altered dopamine pathway. Changes in the concentration of homovanillic acid, a major metabolite of dopamine, were first described in individuals with AN in 1984 (Kaye et al., 1984).

Similar to opioids, dopamine neurons are associated with reward-based behavior. Dopamine as a neurotransmitter is essential for establishing conditioned tendencies to re-approach stimuli that are associated with rewards (Wise, 2004). Recent research suggests that while dopamine levels in individuals affected by AN are indeed altered, it is possible that these changes stem from the nutritional deficit that goes along with the condition, rather than them being caused by an underlying abnormality of the brain. This would also explain why dopamine-related pharmacotherapy isn't effective in the treatment of AN, whereas normalization of eating habits generally results in a better survival outcome (Södersten et al., 2016).

1.1.3.3 Endocannabinoid pathways

The endocannabinoid system is another group of messenger molecules that is closely related to appetite and food intake (Paolacci et al., 2020). The physiologically most important endocannabinoids (EC) are N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG). AEA's concentration was shown to peak right before meals and to quickly decrease post-prandially, earning it the name of meal initiator (Gatta-Cherifi et al., 2012). EC also seem to play a crucial role in the fat metabolism, where their role is to maximize energy intake and to conserve as much energy as possible (Mazier et al., 2015). They achieve this through stimulating adipogenesis and increasing fat deposition in adipose tissue (Vettor, Pagano, 2009).

The concentration of EC is positively associated with physical activity, as well as stress and inflammation in the healthy population (Heyman et al., 2012; Sparling et al., 2003), whereas individuals suffering from AN show higher levels of EC throughout the course of their condition, and even after recovery (Tam et al., 2021).

The endocannabinoid system also seems to be connected to the opioid system, as naloxone, an opiate antagonist, was shown to be able to reduce the effectiveness of tetrahydrocannabinol (THC) on appetite (Trojniar, Wise, 1991). It may be the alterations in both the opioid and the endocannabinoid systems that enable individuals with AN to put up with their state of chronic hunger and dysphoria, caused by the severe restriction of food intake (Berry, Mechoulam, 2002).

Unfortunately, pharmacological treatment with synthetic endocannabinoid agonists, while well-tolerated, does not seem as promising as once anticipated. One study was able to show slight, but statistically significant weight gain under the synthetic endocannabinoid agonist dronabinol, compared to placebo. No significant changes in eating disorder-related questionnaires were observed, however (Andries et al., 2014).

1.1.3.4 Endocrine changes and vitamin D3 as a neurosteroid

AN brings with it a variety of endocrine changes, most notably a dysregulation in the hypothalamic-pituitary axis (HPA) and appetite-regulating hormones (Schorr, Miller, 2017).

Triggered by low food intake, alterations occur in the HPA. The pulsatile secretion of the luteinizing hormone (LH) gets altered, ranging from total absence of hormonal release to secretion patterns that are physiological only in females during early puberty (Boyar et al., 1974). The cause for this dysregulation may lie in leptin, a hormone produced mainly in adipocytes which is associated with reducing appetite and initiating a feeling of satiety. Leptin is believed to play an important part in the signaling cascade leading to the pulsatile secretion of gonadotropin-releasing hormone (GnRH) in the hypothalamus (Gottsch et al., 2004). For reference, leptin levels are known to be significantly lower in individuals suffering from AN, likely due to low body fat percentage (Grinspoon et al., 1996).

Another pituitary hormone that shows major alterations in AN is the growth hormone (GH). Daily pulsatile GH secretion was already shown to be significantly higher in AN back in 1999 (Støving et al., 1999) with subsequent studies indicating that a relative GH resistance

at the level of the liver might be present in individuals with AN. This can be deducted from the fact that while GH levels are significantly higher in AN, secretion of insulin-like growth factor 1 (IGF1) in the liver is significantly reduced (Støving et al., 2007). This is unusual because GH typically stimulates the secretion of IGF1 in the healthy population (Counts et al., 1992). This GH resistance is connected to bone growth retardation in male adolescents with AN (Modan-Moses et al., 2003), whereas studies in adolescent females show contradicting results (Modan-Moses et al., 2012; Prabhakaran et al., 2008).

The pathological bone metabolism that leads to osteoporosis and osteopenia in AN is also caused by severe vitamin D deficiency. A recent meta-analysis was able to show that vitamin D levels in individuals with AN are significantly lower than in the healthy population, even when vitamin D intake was reported to be similar in both groups (Veronese et al., 2015).

Besides its importance in bone metabolism, vitamin D also plays a crucial role as a neurosteroid. The molecule is known to be neuroprotective as it regulates the neurotrophic factors that support the growth and differentiation of neurons. It also modulates neurotransmission and contributes to synaptic plasticity, suggesting it plays a role in the pathogenesis of many mental disorders (Groves, McGrath & Burne, 2014). This claim is further supported by animal studies that show decreased exploration and maze performance in a state of vitamin D deficiency in rats (Altemus et al., 1987) and increased anxiety in genetically modified mice without vitamin D receptors (Kalueff et al., 2004).

1.2 Genetic links in anorexia nervosa

Ever since the launch of the Human Genome Project (HGP) more than three decades ago, genetic contributions to the etiology of diseases have been of large interest to researchers all over the world. This is particularly true for AN, where the hormonal, metabolic and neuro-cognitive changes that occur in the condition have been well-studied over the past decades, yet our understanding of why and how the disease develops remains limited. High hopes were placed in genetics to bridge this knowledge gap and to help bring all the previous findings together (de Jorge Martínez et al., 2022).

With the launch of the first large genetic studies with a population of AN patients, a strong genetic component was able to be confirmed in the disorder. Early twin-based studies showed genetic contributions of up to 75% (Klump et al., 2001) and an interview-based study with 152 AN patients found an eleven times increased risk to develop AN in female relatives of affected patients (Strober et al., 2000).

Most of the initial genetic research was performed through the use of linkage analysis and gene mapping, working successfully in disorders that follow Mendelian's rules. These conditions are called single-gene disorders, one primary example being cystic fibrosis (Chang, He & Cai, 2018). These simple genetic diseases tend to be rare and severe in effect, unlike complex diseases that are driven by many genes that have complex interactions with time and the environment such as AN (Uitterlinden, 2016).

Such common, yet complex conditions are oftentimes influenced by genetic variations that are very common in the general population, hence why these disorders occur so often in the first place. These genetic variations are commonly referred to as single-nucleotide polymorphisms (SNP). They are single base-pair changes in the DNA sequence that are very common in the human genome and have proven to be valuable genetic markers (Chang, He & Cai, 2018). The National Human Genome Institute GWAS Catalog provides a list of over 200.000 such SNPs that are associated with common diseases in humans (Buniello et al., 2019; Chang, He & Cai, 2018).

To analyze a large number of SNPs and to associate them with a disorder, a new study design besides the established linkage analysis was needed. This is why genome-wide association studies (GWAS) were developed. GWAS make use of the high-throughput genotyping technology that was developed in recent years to reveal connections between thousands of SNPs and disorders by using DNA samples of hundreds or even thousands of people (Chang,

He & Cai, 2018). Due to the large number of samples needed to conduct a GWAS, its advent caused the emergence of multiple global consortia and collaborations to make data collection feasible (Bulik, C. M. et al., 2019).

1.2.1 GWAS on anorexia nervosa

In the case of AN, the Eating Disorder Working Group of the Psychiatric Genomic Consortium (PGC-ED), as well as the Anorexia Nervosa Genetics Initiative (ANGI), were founded to identify genetic variants associated with AN (Bulik, Kennedy & Wade, 2020).

To date, several GWAS have been conducted on AN, with four of them being the most notable ones because of their large sample sizes (Boraska et al., 2014; Nakabayashi et al., 2009; Wang, K. et al., 2011; Watson, Hunna J. et al., 2019). Initial GWAS on AN were met with a lot of criticism. The very first GWAS from Nakabayashi et al. used a sample size of only 320 cases and 341 controls, making it severely statistically underpowered. In hindsight, it also suffered from a poor choice of methods, as it used DNA pooling and did not consider population stratification and false positives that occurred due to multiple testing (Nakabayashi et al., 2009). Follow-up studies by Wang et al. and Boraska et al. used much larger sample sizes of 1033 and 2907 cases respectively, yet neither of them was able to identify any genome-wide significant SNPs (Boraska et al., 2014; Wang, K. et al., 2011). Sign tests conducted by Boraska and colleagues in a replication sample, however, strongly hinted towards genome-wide significant loci being present in AN but requiring an increase in sample size to emerge (Zipfel et al., 2015).

This assumption turned out to be correct. In its first AN GWAS, the PGC was able to find one genome-wide significant locus in its sample of 3495 cases and 10.982 controls (Duncan et al., 2017), followed by a total 8 genome-wide significant loci in its second and most recent GWAS in 2019, using the DNA of a total of 16.992 AN cases and 55.525 controls (Watson, Hunna J. et al., 2019).

1.2.1.1 Genome-wide significant loci

As previously mentioned, the first-ever genome-wide significant locus associated with AN was found by Duncan et al. in 2017. It was SNP rs4622308 on chromosome 12, a region that it associated with a variety of genes, namely *ERBB3*, *IKZF4*, *PA2G4*, *RPS26*, *RPL41*, and *ZC3H10* (Duncan et al., 2017) – genes that are associated with a variety of other disorders as well (de Jorge Martínez et al., 2022). The significance of this locus couldn't be replicated in the second GWAS performed by the PGC but is expected to re-emerge in future higher-powered studies data sets (Watson, H. J. et al., 2021).

The largest AN GWAS conducted to date was the one created by Watson et al. in 2019. By utilizing data from the Anorexia Nervosa Genetics Initiative (ANGI), the PGC-ED as well as the UK biobank, an impressive sample of 16.992 cases and 55.525 controls was created. The study's results completely overturned the previous understanding of the disorder, now defining AN as a condition of metabo-psychiatric origin. A total of eight loci were identified, the four most significant ones being associated with the *CADM1*, *FOXP1*, *MGMT*, and *PTBP2* genes (Watson, Hunna J. et al., 2019).

All previously identified genome-wide significant SNPs as well as their corresponding genes are displayed in **Table 2.**

Table 2: Genome-wide significant single-nucleotide polymorphisms (SNPs) of anorexia nervosa with their corresponding genes and alleles, as identified in genome-wide association studies.

Chr	SNP	A1/A2	*P*-value	OR	Genes	Reference
12	rs4622308	T/C	4.252×10^{-9}	1.2	*ERBB3, IKZF4, PA2G4, RPL41, RPS26, ZC3H10*	(Duncan et al., 2017)
3	rs9821797	A/T	6.99×10^{-15}	1.17	*NCKIPSD*	(Watson, Hunna J. et al., 2019)
11	rs6589488	A/T	6.31×10^{-11}	1.14	*CADM1*	(Watson, Hunna J. et al., 2019)
2	rs2287348	T/C	5.62×10^{-9}	1.11	*ASB3, ERLEC1*	(Watson, Hunna J. et al., 2019)
10	rs2008387	A/G	1.73×10^{-8}	1.08	*MGMT*	(Watson, Hunna J. et al., 2019)
3	rs9874207	C/T	2.05×10^{-8}	1.08	*FOXP1*	(Watson, Hunna J. et al., 2019)
1	rs10747478	T/G	3.13×10^{-8}	1.08	*PTBP2*	(Watson, Hunna J. et al., 2019)
5	rs370838138	G/C	3.17×10^{-8}	1.08	*CDH10*	(Watson, Hunna J. et al., 2019)
3	rs13100344	T/A	4.21×10^{-8}	1.08	*NSUN3*	(Watson, Hunna J. et al., 2019)

1.2.2 Relevant genes associated with anorexia nervosa

Out of the 15 genes that are associated with AN, four of them seem suitable for analysis in this thesis as they are linked to cognition and neurodevelopment. These four genes are *CADM1* (Kitagishi et al., 2015), *CDH10* (Redies, C., Hertel & Hübner, 2012), *FOXP1* (Araujo et al., 2017), and *PTBP2* (Doan et al., 2016).

1.2.2.1 CADM1

CADM1 (Cell adhesion molecule 1) is a synaptic adhesion protein encoded by the *CADM1* gene that seems to be closely related to the development of autism spectrum disorder (ASD). *Cadm1*-knock-out mice show decreased cerebellar volume and a decreased number of Purkinje cell synapses, leading to the development of autism-like symptoms (Fujita et al., 2012). Recent studies also suggest some connections between *CADM1* and attention-deficit/hyperactivity disorder (ADHD). In their 2019 study, Jin et al. were able to provide preliminary evidence of *CADM1* impacting prefrontal brain activities in children with ADHD (Jin et al., 2019).

CADM1's effects are not limited to cognitive disorders, however. The expression of the gene in excitatory neurons is related to a reduction in leptin sensitivity and an increase in bone health and mineral content (Yan et al., 2018), as well as the pathogenesis of cancer (Saito et al., 2018), atopic dermatitis (Hagiyama et al., 2013), and more.

1.2.2.2 CDH10

CDH10 (Cadherin-10) is a gene that encodes for a single-pass transmembrane glycoprotein with the same name, responsible for the mediation of downstream signaling and cell adhesion. Typically, two types of cadherins are differentiated between, namely, type I cadherins and type II cadherins. Type I cadherins are characterized by a broad distribution pattern in human tissue, whereas type II cadherins are only present in very specific regions of the brain (Suzuki et al., 1997).

CDH10 specifically seems to be expressed mostly in the neocortex, including areas that play a role in the development of ASD (Bekirov et al., 2002). The way CDH10 functions may be related to the stabilization of excitatory and inhibitory synapse strength (E/I balance), a process that is assumed to be altered in many psychiatric disorders. A well-maintained E/I

balance is crucial for normal brain function and CDH10 may play an important role in keeping this balance active, specifically in cortical neurons. The transmembrane glycoprotein is present on both excitatory and inhibitory synapses and a reduction in CDH10 leads to an increase in inhibition and a reduction in excitation – a behavior that is in line with the theory of *CDH10* being an E/I-balancing gene (Smith, K. R. et al., 2017).

Besides their association with AN and ASD (Wang, K. et al., 2009), cadherins may also play a role in a variety of psychiatric diseases, most notably schizophrenia and bipolar disorder (Redies, C., Hertel & Hübner, 2012).

1.2.2.3 FOXP1

FOXP1 as a gene encodes for the forkhead box protein 1 which belongs to the family of forkhead transcription factors, known to play a vital role in the regulation of embryogenesis. It is assumed to contribute to the process of tissue differentiation, likely through a molecular process in which FOXP1 suppresses the transcription of proteins related to the process of differentiation (Carlsson, Mahlapuu, 2002). This way, mutations in the gene that reduce the expression of *FOXP1* could impact the development of multiple organ systems (Meerschaut et al., 2017).

The best-studied consequences of mutations in the *FOXP1* gene are cognition-related. Changes in the gene are common in individuals suffering from global developmental delay, speech defects and intellectual disability (Horn, 2012; Pariani et al., 2009). To a lesser extent, *FOXP1* also seems to be related to Schizophrenia (Bakshi et al., 2016), cancer (De Silva et al., 2019) and Huntington's disease (Louis Sam Titus et al., 2017), therefore establishing a strong link between the gene and neuropsychiatric disorders.

1.2.2.4 PTBP2

Polypyrimidine tract binding protein 2 is a key factor in the regulation of tissue-specific expression factors as its function is crucial for the process of differentiation and maturation of the brain. It is responsible for the splicing of transcripts for proteins essential for neuronal differentiation (Keppetipola et al., 2012). PTBP2 does this mostly by repressing the splicing of regulated exons, but it can also cause enhancement of the splicing process (Boutz et al., 2007).

While a lot of research has been done on the role of *PTBP2* on a molecular level, studies that associate the gene with human disorders are scarce. One study was able to link biallelic human accelerated region (HAR) mutations in active enhancers for the *PTBP2* gene to ASD (Doan et al., 2016) and another study showed connections to the etiology of progressive supranuclear palsy (Smith, P. Y. et al., 2011).

1.3 Neurocognition in anorexia nervosa

Alterations in neurocognition are plenty in AN, ranging from poor central coherence – the ability to focus on the bigger picture instead of getting lost in detail (Lang et al., 2014) – to worse performance in implicit learning (Shott et al., 2012) and set-shifting difficulty (Tchanturia et al., 2012). Besides neurocognitive changes, impairments in social cognition are present as well. A recent meta-analysis concluded that patients suffering from AN show poorer facial recognition, reduced facial communication, less agency and feel socially inferior compared to the healthy population (Caglar-Nazali et al., 2014).

Interestingly enough, many of these cognitive impairments were found to also be present in first-degree relatives of AN patients, even in those that have no history of AN. To some degree, these changes also seem to persist even after recovery (Kanakam, Treasure, 2013). One study was able to show that children of women with lifetime AN had significantly different neuropsychological profiles than children of healthy women, namely higher intelligence, increased working memory capacity and decreased attentional control (Kothari et al., 2013).

1.3.1 Human memory systems

The human memory system can roughly be divided into two parts: The declarative (explicit) and the nondeclarative (implicit) memory system (Batterink, Paller & Reber, 2019).

Declarative memory is majorly mediated by the medial temporal lobe (MTL) and various regions of the cortex, with its main function being the recall and recognition of facts and events (Squire, 2004). The nondeclarative memory system's main function is the process of implicit learning, defined as the learning of complex information in an incidental manner. This means that individuals acquire knowledge without awareness of what has been learned (Seger, 1994).

The process of implicit learning can be seen as a change in neuronal structure in exactly those processing areas of the brain that were activated during the initial learning process. These areas include the cerebellum for movement-based implicit learning processes, the basal ganglia and its structures for procedural learning, and the neocortex for perceptual learning. Implicit learning is a skill that is vital for humans as the recognition of patterns is central to our day-to-day lives, ranging from learning to understand language and acquiring motor skills like riding a bike, to simply finding enjoyment in music. (Reber, P. J., 2013; Squire, Zola, 1996).

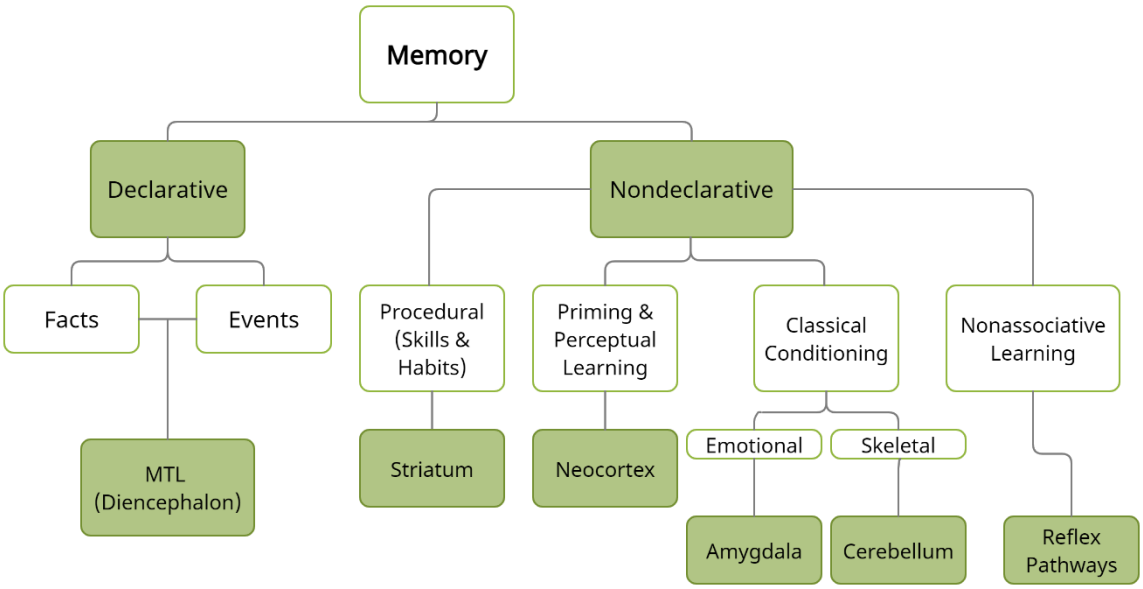

Figure 1: Taxonomy of the human memory system (Own figure, based on Squire, 2004)

It is important to note that these two memory systems are not in direct competition with each other. They operate independently and at the same time to support behavior. An aversive childhood event may lead to the creation of long-term declarative memory, but the same event could simultaneously also lead to the nondeclarative development of anxiety, demonstrating how both memory systems can be active at the same time (Squire, 2004).

When trying to quantify how well an individual can perform implicit learning, a variety of tests are frequently used. What they all have in common is that they introduce the participant to new items that aren't in direct reference to anything else that was previously learned by them. In addition, the acquisition of knowledge in these tests is generally assumed to be unconscious (Reber, A. S., 1989). The most popular tests to measure implicit learning

include the serial reaction time task (SRTT) for motor-based implicit learning (Nissen, Bullemer, 1987), the artificial grammar learning task (Reber, Arthur S., 1967), and the Weather Prediction Task for (WPT) for procedural learning (Knowlton, Squire & Gluck, 1994). The latter one will be the test of choice for this thesis, and an elaborate explanation of it will follow in the methods section.

1.3.2 Learning impairments in anorexia nervosa

When it comes to learning in AN, multiple theories have emerged in the last years in response to advances in cognitive neuroscience. Some researchers believe implicit learning processes to be crucial in the pathogenesis of the condition, stating that AN presents as a form of maladaptive habit that arises from continuous stimulus-response learning in regard to food restriction (Walsh, 2013). Habit strength was indeed found to be significantly higher in AN, correlating with disease severity according to the Eating Disorder Examination-Questionnaire (EDE-Q) (Davis et al., 2020).

It is possible that patients with AN are particularly prone to the formation of habits through a genetic vulnerability, and that the eating behavior they exhibit therefore very quickly becomes automated. This could explain why affected patients seemingly have so little difficulty maintaining their state of constant hunger and how difficult it is to let go of their eating habits, resulting in the generally poor prognosis that the condition has (Steinglass, Walsh, 2016). Additionally, there are strong hints that dopamine, which is involved in pathological pathways in AN, is associated with implicit learning (Karabanov et al., 2010).

On the topic of implicit learning in AN, previous studies have yielded interesting results. The first study to ever be conducted on the topic was by Shott et al. in 2012. They used an implicit learning task involving computer-generated Gabor patches to test perceptual implicit learning in a sample of 21 adult AN patients (Shott et al., 2012). What they found is that AN patients scored significantly lower on the Gabor patches task and that low scores correlated with high self-reported novelty-seeking scores as well as low sensitivity to punishment. A follow-up study from Sternheim et al. in 2021 used the same task on a group of 46 adolescent AN patients. They observed their patients performing significantly better on the implicit learning task compared to healthy controls. Seeing how, despite their low body mass index, the procedural memory function of juvenile patients seemed to be intact,

they suggested the impairment might stem from long-term malnourishment (Sternheim et al., 2021).

The exertion of procedural learning is mediated by the basal ganglia, a group of subcortical nuclei that are made up of the subthalamic nucleus, the substantia nigra, the globus pallidum, and the striatum (Alexander, DeLong & Strick, 1986; Squire, 2004). When using functional imaging, frontal circuits of the striatum in particular were shown to be active during the mediation of implicit learning processes (Hiebert et al., 2014), whereas dorsal circuits seem to contribute to decision-making only partially in these scenarios. Dorsal striatal circuits, however, seem to be vital for the regulation of compulsion and habits (Lipton, Gonzales & Citri, 2019). Furthermore, recent magnetic resonance imaging (MRI) studies were able to identify an organic correlate for this impairment in form of reduced volume and altered shape of the BG in adults affected with AN (Leppanen et al., 2020) as well as dysfunction of the fronto-striato-thalamic loop in adolescent patients (Firk et al., 2015).

Because this alteration seems to present clinically in long-term AN, it may be a key factor in understanding the neurological changes that occur in persisting AN, which may contribute to the gap in treatment outcomes between adolescents and adults with the condition. Determining which brain structures and circuits are responsible for the maintenance of AN has been named a key unmet challenge in the management of the disorder in a recent large review (Zipfel et al., 2015).

1.4 Hypothesis

The striatum is known to mediate probabilistic implicit feedback learning processes, and alterations in this brain region are associated with worse performance on implicit learning tasks. Such alterations occur in patients with AN but seem to only present clinically in adults, whereas adolescents with the condition merely show abnormalities in functional imaging. Performance on implicit learning tasks seems to be adequate in adolescents, but not in adults. It was proposed by some authors that this deficit may develop in response to long-term malnourishment, but no evidence of its pathophysiology exists thus far.

On the other hand, a strong link between the development of AN and genetics has recently been established. With the advent of GWAS, a total of nine genome-wide significant SNPs and their associated genes have been discovered in AN patients so far. Out of those genes, four of them encode proteins that are vital for the regulation of brain function, making them promising candidate genes to affect implicit learning processes and contribute to the development of this cognitive alteration in patients with AN. Because of the novelty of these genome-wide significant SNPs, little research has been performed thus far trying to correlate their genotypes with clinical parameters.

This is why with this thesis, I want to raise the following question: Do various genotypes of *CADM1, CDH10, FOXP1* and *PTBP2* differ in WPT FB accuracy scores in patients with AN in comparison to HC?

Hypothesis: There is a significant difference between the genotypes of *CADM1, CDH10, FOXP1* or *PTBP2* and the accuracy scores of AN patients on the FB variant of the WPT.

2 Methods

This diploma thesis is based on the data collected during the ILSD study, which was conducted at the Department of Psychiatry and Psychotherapeutic Medicine at the Medical University of Graz. When the study first launched in 2015, the initial aim was to research implicit learning in psychiatric disorders. In 2020 with the release of the so-far largest AN GWAS, however, the focus shifted with an amendment that resulted in the inclusion of genetic data into the study.

The ILSD study was permitted by the ethics committee of the Medical University of Graz in agreement with the Declaration of Helsinki (ICH Guidelines for Good Clinical Practice) with reference number 27-481 ex 14/15.

2.1 Participants

The sample for this thesis originally included data from 25 patients with AN and 56 healthy controls (HC). After excluding samples that failed to reach the required 95% call rate for all assays, the final sample included 25 AN patients and 55 controls, meaning a total of 80 participants.

Patients were gradually recruited over the course of two years from our hospital ward at the Department of Psychiatry and Psychotherapeutic Medicine at the Medical University of Graz. Participants from the AN group were diagnosed by experienced clinicians upon admission to the ward. Additionally, the diagnosis was confirmed by usage of the Eating Attitude Test (EAT-26) (Garner et al., 1982) and the Eating Disorder Examination Questionnaire (EDE-Q) (Fairburn, Beglin, 1994) at the time of enrollment in the study. The majority of participants from the HC group consisted of employees of the ward, researchers from other departments, medical students, as well as friends and family. Three controls were recruited using the online recruitment platform Probando GmbH.

Before partaking in the study, every participant was extensively informed about the study's procedure, exclusion and inclusion criteria as well as risks involved. Written consent had to be given before participation through the signing of the consent form, approved by the ethics committee. Data of participants were handled anonymously by assignment of a study code, saved on a protected USB flash drive. Participation was voluntary and could be revoked at any given time.

2.1.1 Inclusion criteria

Inclusion criteria for the AN group included:

- The participant meets the diagnostic criteria for AN in the ICD-10 (F.50.0).
- The participant's current BMI is below 17.5 kg/m^2.
- There is no family history of severe genetic diseases such as Huntington's Chorea, Alzheimer's disease, or chronic immunological disorders.
- There is an absence of neurological conditions, specifically learning impairments, mental retardation or dementia in the participant, demonstrated by a Mini-Mental-Status-Test score above 26.
- The participant is above the age of 18 at the time of partaking in the study.

Inclusion criteria for the HC group included:

- There is no history of psychiatric disorders in the patient.
- There is an all-time absence of axis-1 diagnoses in first-degree relatives.
- There is no family history of severe genetic diseases such as Huntington's Chorea, Alzheimer's disease, or chronic immunological disorders.
- There is an absence of neurological conditions, specifically learning impairments, mental retardation or dementia in the participant, demonstrated by a Mini-Mental-Status-Test score above 26.
- The participant is above the age of 18 at the time of partaking in the study.

All inclusion criteria were confirmed via a semi-structured interview before testing. Weight from AN patients was directly taken from their hospital chart, whereas weight from the HC was taken by asking the person to state their current weight.

2.2 Tests and questionnaires

Participation in the study required filling in multiple neuropsychiatric questionnaires. Some self-report questionnaires were given to participants prior to the scheduled implicit learning task and some interview-style questionnaires were conducted on the day of the implicit learning task.

The self-report questionnaires include:

Beck Depression Inventory (BDI)

The BDI is a questionnaire invented to measure the severity of depression in an individual. It includes a set of 21 questions concerning symptoms commonly associated with depression while offering four possible answers each. Answers are ranked in terms of severity, ranging from a complete absence of the symptom (awards zero points) to a severe manifestation (awards three points). A BDI score of zero to nine is considered to reflect an absence of depression, whereas 10 to 18 points indicate mild depression, 19 to 29 points moderate depression, and finally a score of 30 and above would be considered major depression (Beck et al., 1961). The BDI was included in this study to evaluate a possible influence of depressive comorbidity as a covariate on implicit learning accuracy scores.

Eating Attitude Test (EAT-26)

The EAT-26 is a self-report scale to measure the severity of eating disorders. It includes 26 statements concerning symptoms which are commonly exhibited in eating disorders and offers six possible answers for each of them: Always, usually, often, sometimes, rarely, and never. The participant is advised to choose the answer that most accurately describes how often they indulge in the stated behavior. Among others, behaviors listed in the EAT-26 include counting calories, anxiety regarding being overweight, or restriction of eating behavior. The options never, rarely, and sometimes award zero points, whereas often, usually, and always award one to three points respectively. A score of above 20 is generally assumed to be related to an eating disorder (Garner et al., 1982).

Eating Disorder Examination-Questionnaire (EDE-Q)

The EDE-Q is a commonly used tool to evaluate severity of eating disorders. It contains 28 items. Questions in the EDE-Q mainly revolve around how often the participant has recently indulged in behavior that is typically associated with eating disorders. The questions can be split into four different domains: Restraint, eating concern, weight concern and shape

concern, allowing a particularly nuanced analysis of the patient's eating behavior (Fairburn, Beglin, 1994). The average score per answer in patients with AN is 3.81 with a standard deviation of 1.43 (Hilbert et al., 2007).

International Physical Activity Questionnaire (IPAQ)

The IPAQ is a self-report questionnaire that aims to quantify the amount of physical activity an individual performs on a weekly basis. It involves 27 questions and is split into four major domains which include physical activity during work, activity for transportation, activity during housework, and activity during leisure time. The final score is then calculated as multiples of the resting metabolic rate (MET), multiplied by minutes per week (Craig et al., 2003).

Study participants were given all the above-mentioned questionnaires prior to the implicit learning task and were asked to bring the filled-in versions along on the day of their appointment. Their appointment at our research facilities included the following interviews:

Mini-Mental Status Test (MMST)

The Mini-Mental Status Test is a tool used to quickly evaluate the current cognitive state of an individual. It includes a variety of questions which concern one's orientation, memory, attention, and language. The maximum number of points achievable is 30 (Folstein, Folstein & McHugh, 1975). A minimum of 26 points were required to be eligible for further participation in the study as ruling out cognitive deficits before the implicit learning task was deemed crucial.

Hamilton Depression Rating Scale (HAMD)

The Hamilton Depression Rating Scale is similar to the previously mentioned BDI as it allows judgment about an individual's mood state. Unlike the BDI, the HAMD is conducted in an interview format. This means that in addition to the answers given by the patient, other factors such as body language can be taken into consideration by the interviewer. It also provides the additional benefit of allowing further exploration of the answers given by the patient, making it arguably superior to the BDI at the expense of more required time. The interview includes 21 questions that award either zero to two, or zero to four points. Patients that score zero to eight are generally viewed as not depressed, whereas nine to 16 points correlate with minor depression, 17 to 24 points with moderate depression, and 25 points and above with major depression (Hamilton, 1960).

Multiple Choice Vocabulary Test (MWT-B)

The MWT is a test that allows to gauge the participant's IQ based on their vocabulary knowledge. The proband is presented 37 lines containing five words each, of which only one word is spelled correctly. The participants are then advised to mark the correct word in each line without any time limit given to them. The complexity of words increases with each line and the total amount of obtainable points is 37 (Lehrl, Triebig & Fischer, 1995). Higher points on the MWT were previously shown to correlate with IQ values provided by popular IQ tests such as the HAWIE-R (Satzger, Fessmann & Engel, 2002), thus making the MWT a time-efficient tool to gauge someone's approximate IQ. The version used for this study was the updated MWT-B from Lehrl et al, 2005. It was included in the study to rule out any interferences of the IQ with accuracy scores on the WPT.

Mediterranean Diet Score (MDS)

The MDS is a tool to measure an individual's adherence to Mediterranean diet traditions, such as the consumption of an abundance of vegetables, fruits, and fish, as well as a general avoidance of red meat and sweet beverages (Willett et al., 1995). The MDS used in this study is an updated version from 2012 which includes a total of 14 items and was shown to have a strong inverse correlation with adiposity indexes (Martínez-González et al., 2012).

2.2.1 Weather Prediction Task

The WPT (Knowlton, Squire & Gluck, 1994) is a non-motor probabilistic learning task, used to assess implicit learning. It has previously been used in a variety of neuropsychiatric disorders, ranging from major depression (Mörkl et al., 2016), schizophrenia (Fernandez et al., 2021; Gomar et al., 2011; Karcher, Hua & Kerns, 2019) and bulimia nervosa (Labouliere et al., 2016) to attention-deficit hyperactivity disorder (ADHD) (Gabay, Goldfarb, 2017).

During the task, participants receive the instruction that they will learn how to forecast the weather in an imaginary scenario. They will do so based on four different tarot cards which serve as cues for one of two outcomes: either fine or rainy weather. A sequence of one to three of these cards is displayed at the center of the screen on each trial, thus making up for a total of 14 possible arrangements. When multiple cards are displayed, they influence each other's probabilities to sway the weather in one direction. Both weather outcomes occur in equal frequency throughout the test. Two out of the four cards are highly predictive as they are displayed on 75% of one outcome (i.e., fine, or rainy weather) and the other 25% of time on the opposite outcome. The remaining two cards are less predictive as they will be

displayed on merely 57% of trials with fine (or rainy) weather and on 43% of the opposite outcomes. The participant is instructed to find out, based on the cues the tarot cards provide them with, which cards correspond with which weather outcome.

In this study, every participant had to complete two versions of the WPT: one in which the weather forecast could be either hot or cold, and one in which the weather could be either fine or rainy. Furthermore, one of the tasks was set up to use a feedback learning variant (FB), whereas the leftover task assessed paired associate learning (PA). Which variant of the task participants had to complete first, and which of the two weather scenarios was connected to which learning task, was randomized. The randomization was performed to avoid potential bias in form of an attention decrease on the second of the two tasks, as well as personal bias towards one of the two visually different card sets. Additionally, it was ensured that the association of weather outcomes with the two learning tasks was of equal number throughout all participants. This means the same number of participants completed the PA version with fine/rainy weather and hot/cold weather. The different card patterns used for the WPT in this study are displayed in **Figure 2**.

The FB and the PA versions of the WPT each consist of 150 trials which are split into three blocks of 50. During the FB version of the WPT, participants are instructed to continuously guess the weather outcome based on the card combinations shown. They then immediately receive feedback on whether their decision was correct or not. During the PA version, however, participants are directly provided the information about which card combination corresponds with which weather outcome. After completing the 150 practice trials, participants then move on to the 42 test trials. During test trials, they are then asked to correctly predict the weather based on the cards on the screen. This time, no feedback about their choices will be given to participants.

Based on functional neuroimaging, the FB variant of the WPT and the feedback learning tied to it are thought to be mostly mediated by the striatum (Hiebert et al., 2014), whereas during paired-associate learning, the involvement of the MTL seems to be most distinct (Sperling et al., 2001; Zeineh et al., 2003).

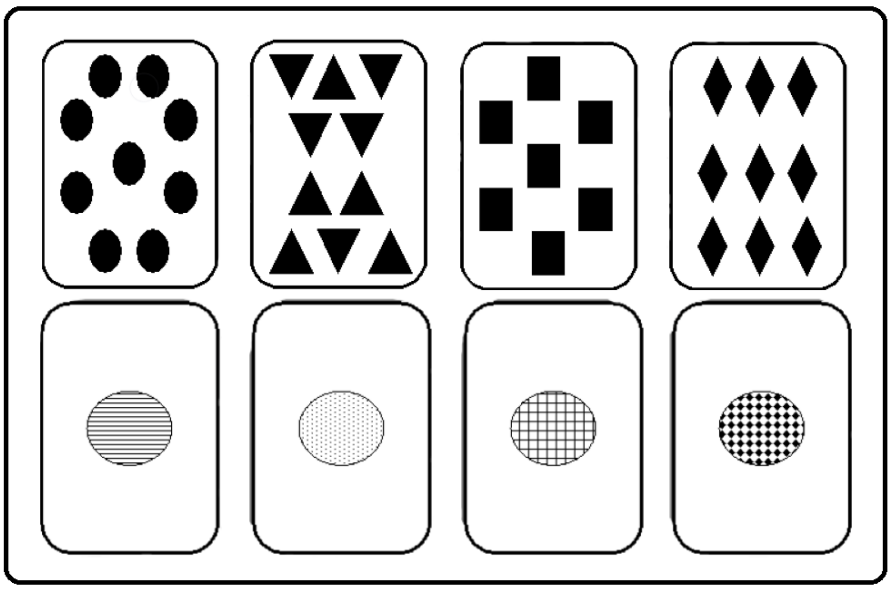

Figure 2: Card sets used during different scenarios of the Weather Prediction Task (WPT). Top row cards are displayed during the fine-rain scenario, bottom row cards are displayed during the hot-cold scenario. Assembled screenshots from the WPT (Knowlton, Squire & Gluck, 1994).

2.3 Genotyping

Blood samples were taken from study participants immediately prior to the implicit learning task, using ethylene-diamine-tetra-acetic-acid (EDTA) tubes. The blood samples were stored in freezers at -20°C until they were collectively transferred to the Institute of Human Genetics of the Medical University of Graz in October 2021 for DNA-extraction.

Extraction was performed using QIAGEN's QIAsymphony SP, a fully automated, high throughput device that allows the extraction of DNA in up to 96 samples simultaneously (Parham et al., 2012).

The samples were then sent to the Life & Brain Center in Bonn for genotyping, using Illumina's Infinium Global Screening Array-24 v3.0 Kit. Illumina's Infinium Global Screening Array-24 v3.0 is a classic microarray assay. The general principle behind assays is to attach specifically designed capture molecules, also called probing molecules, onto a solid support system. Probing molecules then bind to target molecules from the desired sample. In the case of DNA microarray assays, these types of probing molecules are DNA nucleotides, specifically nucleotides that are associated with SNPs and complementary to the nucleotides present in the sample. To later find out which target molecules reacted with

the probing molecules (e.g., which nucleotides are present in the sample), the target nucleotides are labelled using fluorescent molecules or other dyes (Dufva, 2009).

To provide an example: If we're looking to find out whether or not someone has the genotype TT of a target SNP, we would design AA probing nucleotides as they would match the TT nucleotides in the patient. If the patient has the TT genotype, the nucleotides will bind to our probes, and we would receive a fluorescent signal from this spot on the array. Modern microarrays typically test for hundreds of thousands of SNPs at the same time, allowing for a very quick process of genotyping.

Quality control checks were carried out prior to the extraction of genotypes. These measures include checks for data completeness, Hardy–Weinberg equilibrium, Mendelian incompatibilities, and familial correlations for quantitative traits. All classic quality control steps were performed with PLINK1.9 by our collaboration partners. The whole genome data analysis toolset Plink1.9 was then used for extracting the genotypes of selected SNPs from the dataset.

2.4 Statistical analysis

All statistical comparisons were performed using the Statistical Package for the Social Sciences (SPSS, Version 28.0). Prior to any calculations, participants who scored lower than 60% on any of the two WPT variants and those who failed to reach the required 95% call rate for all assays were removed from the sample.

To filter for potential covariates such as age, sex and years of education that could influence the participants' implicit learning scores, a Pearson correlation analysis was performed. This analysis was only done after ensuring normal distribution, lack of outliers and linear relationship between all tested variables were present. Participants from both groups were then matched based on demographic and clinical parameters for higher-quality comparison during the following ANOVAs.

To compare average implicit learning scores between AN and HC groups both in the practice trials as well as the test phase, multiple univariate analysis of variance (MANOVA) was performed. To analyze the effect variables on each other, a two-way ANOVA with "group" (AN patients vs. HC) as the between-groups factor and "task" (FB vs. PA) as the within-subject factor was calculated. Levene's test for equality of variances was performed prior to these calculations to confirm equal variance.

For genetic analyses, the non-matched sample was used. An ANOVA was performed to obtain information about the relationship between implicit learning scores (WPT) and genotypes of selected SNPs. The ANOVA was again preceded by Levene's test for equality of variances to confirm prerequisites are met. If the number of participants with a specific genotype was below 10, they were added to the other second least common genotype to ensure a representative statistical analysis. If, for example out of 30 patients, 3 of them had the genotype CC, 11 had the genotype TT, and 16 had the genotype CT, the CC genotype would get merged with the genotype TT.

3 Results

Prior studies reported a lack of motivation in participants when completing the WPT as a possible source of bias (Holl et al., 2012; Shohamy et al., 2004; Wilkinson et al., 2008). Therefore, an approach similar to other studies was adopted, and in a first step, all participants whose accuracy scores on the task were lower than 60% were excluded from further calculations. Through this measure, four out of 25 patients with AN (16%) and eight healthy controls (10.7%) were excluded from the trial, resulting in a total number of 69 eligible participants for calculations.

To filter for possible covariates, a Pearson correlation analysis was performed on the leftover sample of 69 participants. Using the Pearson correlation coefficient, no significant correlations were revealed between the WPT scores and demographic parameters. Matching of AN patients with controls based on demographic and clinical parameters was performed nonetheless for the sake of better statistical representation.

The final sample included 21 patients (20 female) with AN aged 18 to 54, and 21 HC (20 female) aged 19 to 61. As a consequence of the recruitment focusing exclusively on inpatients, BMI in the AN group was low, ranging from 11.9 to 16.9 (M =13.9). Out of the 21 AN patients, six received psychiatric medication at the time of testing. Four patients took a serotonin and norepinephrine reuptake inhibitor (SNRI), and two patients took a selective serotonin reuptake inhibitor (SSRI). None of the HC were taking any psychotropic medication at the time of the study.

The groups showed no significant differences in age and premorbid intelligence (ps > 0.05); however, they differed in years of education (p = .006). Patients in the AN group had a significantly lower BMI (M = 13.9, SD = 1.87, p < .001) and scored significantly higher on most clinical questionnaires, including the BDI (M = 25.44, SD = 12.64, p < .001), the HAMD (M = 16.9, SD = 6.16, p < .001) and the EDE-Q (M = 3.66, SD = 1.39, p < .001). On the IPAQ, AN patients reported lower activity levels (M = 2716, SD = 3379, p = .032) in comparison to HC. All participants scored 26 or above on the MMSE and had a normal-range or higher IQ. None of the HC presented with any signs of psychiatric disorders according to the BDI, HAMD, EAT-26, and EDE-Q. Detailed information about the demographic and clinical characteristics of AN patients and HC is portrayed in **Table 3.**

Table 3: Demographic and clinical characteristics for patients with anorexia nervosa (AN) and healthy controls (HC). A single asterisk indicates $p < 0.05$.

	AN **(n = 21)**	**HC** **(n = 21)**	***p***
	Mean (SD)	Mean (SD)	*t-Test*
Age (years)	24.14 (8.56)	26 (9.87)	*.519*
BMI (kg/m2)	13.9 (1.87)	21.7 (2.38)	*.001**
Education (years)	13.14 (2.29)	15 (1.82)	*.006**
Beck depression inventory (0-63)	25.44 (12.64)	3.67 (4.6)	*.001**
HAMD (0-66)	16.9 (6.16)	3.29 (2.72)	*.001**
EDE-Q (0-6)	3.66 (1.39)	0.87 (0.72)	*.001**
IPAQ (MET-minutes)	2716 (3379)	6631 (6908)	*.032**
Premorbid intelligence	108.1 (9.47)	112.86 (10.23)	*.064*
Duration of disease (months)	76.91 (114.45)		
Age at onset of disease (years)	17.9 (3.53)		

3.1 Weather Prediction Task

The two-way ANOVA showed no significant main effect for task [$F_{(1)} = 0.7$, $p = .41$] but did reveal a significant main effect for group [$F_{(1)} = 6.22$, $p = .017$] and a significant interaction between task and group [$F_{(1)} = 5.38$, $p = .026$].

During the FB test phase, the patient group had significantly lower scores ($M = 0.798$, $SD = 0.083$) than the controls ($M = 0.89$, $SD = 0.087$) [$t_{(40)} = -3.52$, $p = .001$], while no significant difference was found between the results of the PA test phase (patients $M = 0.86$, $SD = 0.07$; controls $M = 0.864$, $SD = 0.113$, [$t_{(31,45)} = -0.14$, $p = .89$]).

Within the patient group, there was a significant difference between performance on the FB and the PA task [$t_{(20)} = 3,1$, $p = .006$]. In the HC group, no such difference was present [$t_{(19)} = 0.85$, $p = .41$].

A comparison of the mean proportion of correct predictions between the two groups during the PA and FB test phases is displayed in **Figure 3.**

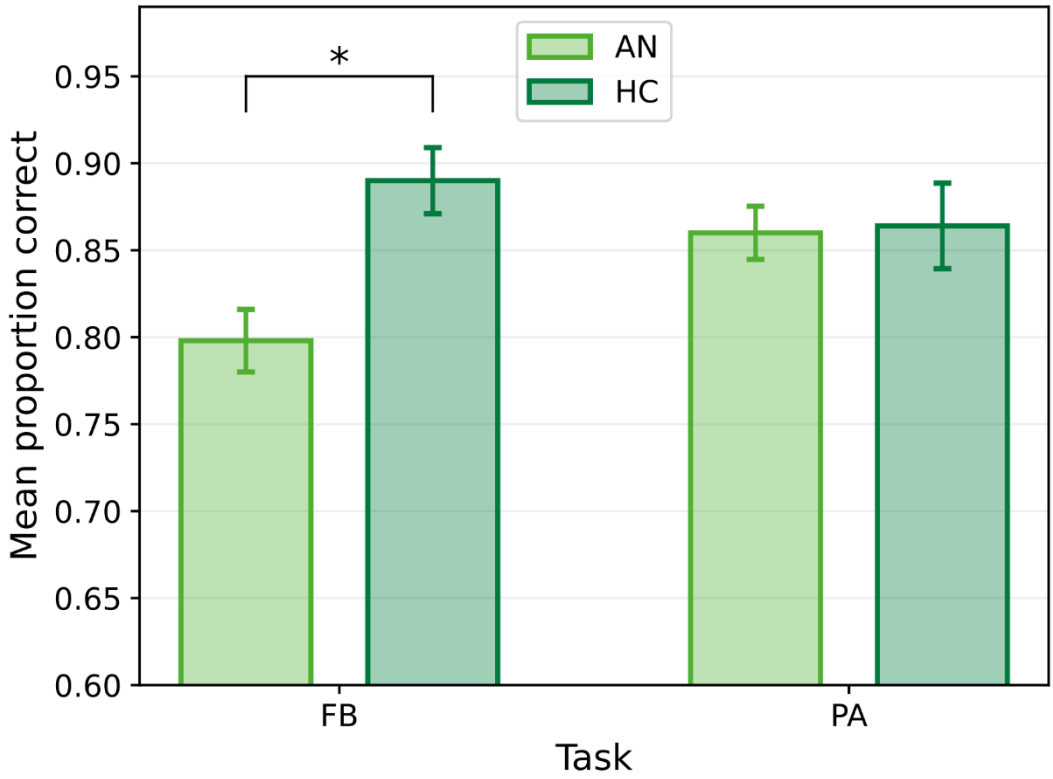

Figure 3: Mean proportion of correct predictions during the feedback (FB) and paired associate (PA) test phases of the Weather Prediction Task, plotted separately for patients with anorexia nervosa (AN) and healthy controls (HC). Error bars refer to standard errors. Statistically significant differences are marked with an asterisk.

WPT trial phase performance across blocks

A two-way ANOVA on mean proportion correct with blocks (trials 1-50, trials 51-100, trials 101-150) as the within-subjects factor, and group (AN vs. HC) as the between-groups factor was performed. This analysis resulted in a significant main effect of block [$F_{(2)} = 3.59$, $p = .032$] as the performance of both groups improved significantly over the 150 trials. Furthermore, a significant main effect of group [$F_{(1)} = 4{,}63$, $p = .037$] was found. This indicates that the AN group performed significantly worse than HC throughout the three trial blocks of the WPT FB variant. The group-block-interaction [$F_{(2)} = 0.825$, $p = .442$] yielded no significant result.

On trials 1-50, there was no significant difference in the mean proportion of correct answers between AN and HC groups ($M = 0.681$, $SD = 0.101$ for AN; $M = 0.702$, $SD = 0.772$ for HC; $p = .454$). HC improved comparatively more on trials 51-100, but still, no statistically significant difference between groups was found ($M = 0.685$, $SD = 0.125$ for AN; $M = 0.733$, $SD = 0.113$ for HC; $p = .263$). On the last block, consisting of trials 101-150, the HC ($M = 0.776$, $SD = 0.063$) differed significantly from the AN group ($M = 0.707$, $SD = 0.103$, $p = .013$). HC improved by an average of 7.5% over the course of the 150 trials, compared to AN patients who only improved by an average of 2.2%

The mean proportion of correct answers of the two groups across the three trial blocks of the WPT FB version is displayed in **Figure 4.**

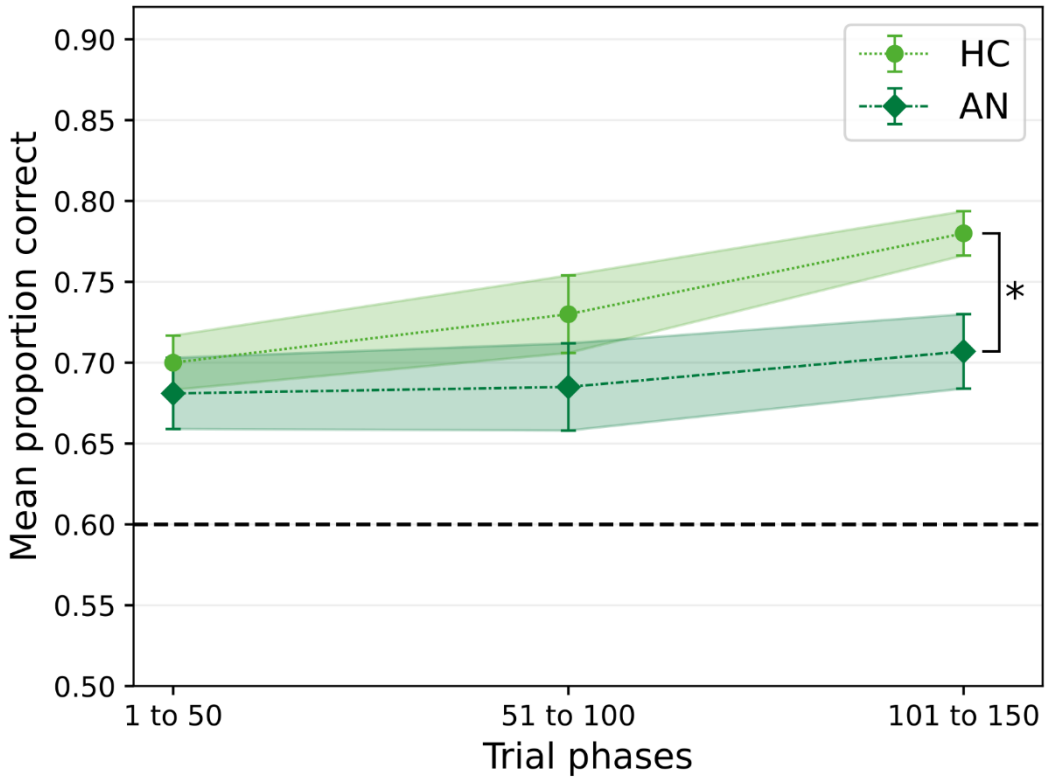

Figure 4: Mean proportion of correct predictions across three blocks of 50 trials during the Weather Prediction Task feedback variant, plotted separately for the patients with anorexia nervosa (AN) and healthy controls (HC). Error bars refer to standard errors. Statistically significant differences are marked with an asterisk.

To explore possible associations of the lower WPT FB scores within the group of AN patients, Pearson's *r* was calculated. Specifically, analyses on interactions between FB test phase scores and various clinical parameters available were run. These parameters include BMI, age of disease onset, duration of disease, BDI-, EDE-Q-, and IPAQ-scores, and scores on the restraint subscale of the EDE-Q as they are most closely related to habit strength. Assessing the results of the analysis through the use of a two-tailed significance test, no significant correlations between WPT FB test scores and clinical measures were found.

3.2 Genotypes

The sample used for this section includes a total of 69 participants, 21 of which had a current diagnosis of AN, with an age ranging from 18 to 54 ($M = 24.14$, $SD = 8.56$). Out of these 21 patients, 20 were female and one was male. The other 48 participants were part of the HC group, with an age ranging from 19 to 61 ($M = 29.98$, $SD = 9.19$). 47 of them were female, one was male. An overview of the participants' demographic and clinical data is displayed in **Table 4**.

Table 4: Demographic and clinical characteristics for patients with anorexia nervosa (AN) and healthy controls (HC) used for genetic calculations. A single asterisk indicates $p < 0.05$.

	AN (n = 21)	**HC (n = 54)**	
	Mean (SD)	Mean (SD)	*p*
Age (years)	24.14 (8.56)	28.98 (9.19)	*.044**
BMI (kg/m2)	13.9 (1.87)	22.12 (2.47)	*< .001**
Education (years)	13.14 (2.29)	17.17 (3.64)	*< .001**
Duration of disease (months)	76.9 (114.45)		
Age at onset of disease (years)	17.9 (3.53)		

Through the use of a one-way ANOVA, genotypes of rs4307059, a polymorphism of the *CDH10* gene, showed a significant difference in WPT FB scores in the AN group [$F_{(9, 11)}$ = 3,570, p = .025]. In particular, the CT genotype showed lower implicit learning scores (M = 0.78, SD = 0.099) in comparison with TT + CC genotypes (M = 0.817, SD = 0.062). Genotypes of other SNPs showed no significant differences ($p < 0.05$) or trends ($p < 0.1$) with WPT FB scores. All investigated SNPs and their statistical parameters based on the performed ANOVA are displayed in **Table 5**. WPT FB scores for different genotypes of rs4307059 are depicted in **Figure 5**.

Table 5: Results of analysis of variance (ANOVA) for comparison of mean Weather Prediction Task feedback scores and genetic polymorphisms in patients with anorexia nervosa (AN). Statistically significant results ($p < 0.05$) are marked with an asterisk.

Gene	**SNP**	**AN patients n = 21**			
		F	***df***	***ηp2***	***p***
CADM1	rs1048932	*0.524*	*9, 11*	*0,3*	*.830*
	rs9936385	*1.292*	*9, 11*	*0,513*	*.339*
	rs12286929	*0.331*	*8, 11*	*0,194*	*.936*
	rs17523342	*1.199*	*9, 11*	*0,495*	*.382*
CDH10	rs4307059	*3.579*	*9, 11*	*0,745*	*.025**
FOXP1	rs830622	*0.873*	*9, 11*	*0,416*	*.574*
	rs7640269	*0.914*	*9, 11*	*0,427*	*.546*
PTBP2	rs1555543	*1.023*	*9, 11*	*0,455*	*.478*
	rs2256459	*1.339*	*9, 11*	*0,522*	*.319*
	rs11165643	*1.023*	*9, 11*	*0,455*	*.487*

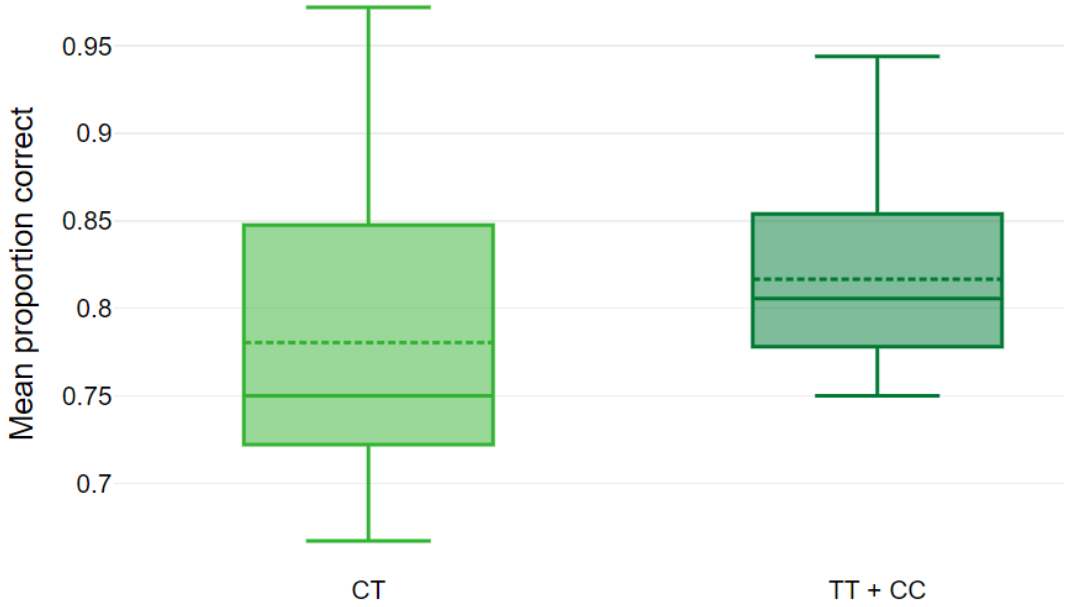

Figure 5: Genotypes of rs4307059 (*CDH10*) and mean proportion correct on the Weather Prediction Task feedback (FB) variant.

The same one-way ANOVA was also performed on the HC group, comparing WPT FB performance with genotypes of the previously selected 10 SNPs. Through this analysis, no significant differences ($p < 0.05$) or trends ($p < 0.1$) were found. All ANOVA results for the HC group are portrayed in **Table 6**.

Table 6: Results of analysis of variance (ANOVA) for comparison of mean Weather Prediction Task feedback scores and genetic polymorphisms in healthy controls.

Gene	SNP	HC group n = 48			
		F	***df***	***ηp2***	***p***
CADM1	rs1048932	*1.129*	*13, 34*	*0,301*	*.37*
	rs9936385	*0.626*	*13, 34*	*0,193*	*.816*
	rs12286929	*1.32*	*13, 30*	*0,363*	*.256*
	rs17523342	*1.145*	*13, 34*	*0,31*	*.36*
CDH10	rs4307059	*1.181*	*13, 34*	*0,311*	*.334*
FOXP1	rs830622	*1.529*	*13, 34*	*0,368*	*.157*
	rs7640269	*1.367*	*13, 34*	*0,343*	*.225*
PTBP2	rs1555543	*0.595*	*13, 34*	*0,185*	*.841*
	rs2256459	*0.506*	*13, 34*	*0,162*	*.905*
	rs11165643	*1.513*	*13, 34*	*0,366*	*.163*

4 Discussion

This thesis aimed to investigate whether various genotypes of patients with AN differ in striatal-based implicit learning performance. To achieve this, the WPT, a probabilistic implicit learning task, was used for the very first time on a group of AN patients, and its results were compared with novel genotypes that have recently been associated with AN by GWAS.

In the matched sample of 21 AN patients and 21 HC, I was able to confirm that a selective impairment on the striatal-based FB variant of the WPT is present in patients with the condition. AN patients scored significantly lower on the FB variant both when compared to the HC group and when compared to their own performance on the PA version of the task. Considering that previous authors who investigated this topic in experimental and fMRI studies came to similar conclusions, it seems highly likely that a deterioration of the striatum is a key pathophysiologic feature that occurs in chronic AN.

In a larger sample, the obtained implicit learning scores were then compared with different genotypes of loci that have previously been identified as genome-wide significant by published AN GWAS. Out of the ten investigated SNPs, SNP rs4307059 genotypes prove to significantly differ in striatal-based implicit learning scores. CT genotypes in particular showed significantly reduced scores on the WPT FB variant (M = 0.78, SD = 0.099) in comparison with TT + CC genotypes (M = 0.817, SD = 0.062, p = .025). In the HC group, genotypes of the same SNP showed no correlation with scores.

Rs4307059 is an intergenic SNP that is located between the encoding regions of the genes *CDH9* and *CDH10*, both encoding for proteins that are part of the cadherin family. The exact locus of the SNP is approximately 132 kb upstream of *CDH10* and 910 kb downstream of *CDH9* (St Pourcain et al., 2010). Despite not being encoding proteins, these intergenic SNPs are vital for regulating the expression of adjacent genes (Maurano et al., 2012). The SNP rs4307059 is best known for its significance in the development of ASD where it first emerged during a GWAS in 2009 (Wang, Kai et al., 2009) and was re-confirmed to be genome-wide significant during multiple follow-up GWAS with different study populations (Prandini et al., 2012; Wang, Ziqi et al., 2019). One study was also able to show a correlation between CC genotype and completed suicide (Chojnicka et al., 2012).

Cadherins seem to play a crucial role in the pathogenesis of many psychiatric diseases, the relevance of the *CDH10* subtype specifically has already been discussed in chapter **1.2.2.2**

CDH10. Broadly speaking, all cadherins are cell adhesion proteins that are vital for intracellular signaling by guiding tissue morphogenesis. In their most critical roles, they are essential for gray matter differentiation, the formation of neural circuits and synapses, and the process of remodeling (Hirano, Suzuki & Redies, 2003; Hirano, Takeichi, 2012; Takeichi, 2007). When it comes to gray matter differentiation, multiple cadherins are already expressed in neuro-epithelial tissue during the earliest stages of embryogenesis, including *CDH10*. Cadherins then guide early neuronal tissue to aggregate, whereby cells with the same expressed Cadherin subtype conglomerate in a process called homotypic adhesion. These aggregates later differentiate into complex gray matter structures such as the basal ganglia or the thalamus (Redies, Christoph, Hertel & Hübner, 2012). The striatum specifically displays distinct regional differences in the expression of cadherins, possibly reflecting subregions that operate functionally different (Hertel et al., 2008). Thus, cadherins possess special neurobiological features that predispose them toward an association with cognitive processes and psychiatric disorders.

As a result, it seems possible that different genotypes of the many cadherin proteins can influence the risk of developing AN and the subsequent cognitive impairments that occur in the condition. Previous theories have already proposed that individuals with AN possess a predisposition that causes the striatum to inadequately respond to triggers such as dieting (Bergh, Södersten, 1996). This predisposition may at least partially be genetic. Once triggered, it may set a process in motion that causes dysfunctional activity of the striatum and eventually leads to the deterioration of said brain region. This theory is in line with recent research in which pathological activation of the ventral striatum was shown to already be present even in adolescents with a short duration of disease (Fladung, A-K et al., 2013). These pathological striatal loops seem to become more apparent with a longer duration of disease (Fladung, Anne-Katharina et al., 2010) and may eventually lead to a macroscopically altered shape of the basal ganglia (Leppanen et al., 2020).

This circumstance could also explain why, unlike adults with AN, adolescents with the condition do not perform worse on implicit learning tasks. While these altered striatal circuits may already impact AN-characteristic thought patterns in the early stages of the disorder and contribute to the condition's progression and longevity, the deficits in implicit learning may not be clinically measurable until the deterioration reaches a critical point. This is a common theme in AN as adolescents with the condition consistently perform similarly or even better in most cognitive domains when set against healthy peers (Olivo, Gaudio &

Schiöth, 2019). One recent study even found that adolescents with AN have higher IQ in comparison to the healthy population (Schilder et al., 2017).

While genetics play an important role in the pathogenesis of AN and its changes in neurocognition, other factors should not be easily dismissed. Previous researchers have suggested an involvement of BMI and starvation as the trigger for neurodegenerative processes in AN. Some even believe that striatal dysfunction is something everyone can experience to a certain degree in the context of malnutrition and starvation and that patients with AN are merely more prone to its development and progression (Södersten et al., 2016).

This thesis' results do not reinforce this theory. Possibly because of the relatively small sample size in this study, correlations between BMI and implicit learning scores and correlations between duration of disease and implicit learning scores did not reach statistical significance. An important circumstance to consider is that periods of remission and normalization of body weight were not considered when calculating the duration of disease, making the metric used in this thesis not ideal.

Novel research also suggests an involvement of carotenoids in the cognitive impairments that AN patients experience (Lackner et al., 2019; Lackner et al., 2021). Carotenoids serve as a dietary precursor of vitamin A and retinoic acid, of which the latter has been linked to brain signaling and the development of affective disorders and cognitive disturbances (Bremner, McCaffery, 2008; Hu et al., 2020; Wołoszynowska-Fraser, Kouchmeshky & McCaffery, 2020). Thus, carotenoid metabolism is a promising field of research that could show major contributions to alterations of implicit learning in AN.

4.1 Limitations

While this thesis used a well-phenotyped sample, it still suffers from some limitations, most importantly the relatively small sample size, particularly in the AN group. The low number of participants is explicable by the strict matching and exclusion criteria concerning the 60% hurdle for the WPT. Furthermore, recruitment of AN patients was challenging as the implicit learning task required considerable amounts of sustained attention which many patients were not able to provide. As a result, several patients had to cancel the task and did not wish for a follow-up appointment.

Secondly, the AN group consisted of inpatients only, almost all of which suffered from the life-threatening severity of malnutrition. The study did not include outpatients, which is reflected by the comparably low BMI of a mean 13.9 kg/m^2 in the AN group. Previous studies used patient groups with higher average BMI, making the comparability of this study less ideal. Some of the patients were also receiving psychopharmacological treatment at the time of participation.

Lastly, the study did not analyze the learning strategies the participants used to solve the WPT. Very recently, a study came forward which analyzed the strategies patients used to solve the WPT, concluding that adolescents do not always use the previously assumed multi-cue strategy to solve the test (Bochud-Fragnière, Banta Lavenex & Lavenex, 2022). There is no evidence that adults use such deviating strategies, but it's a factor that should be considered in following trials.

4.2 Conclusions

In this thesis, I investigated implicit learning processes and their genetic links in patients with AN and HC. Through the use of the WPT, I was able to provide further evidence that functional alterations of the striatum in the form of implicit learning deficits are present in adults with the condition. Furthermore, for the very first time, statistically significant correlations with this impairment were found in form of the rs4307059 CT genotype. This SNP is related to the *CDH9* and *CDH10* genes which encode proteins that are part of the large cadherin family. Concerning the vital role that cadherins play in the process of neurodevelopment and cognition, not only a statistical but also a highly significant clinical correlation can be assumed between altered implicit learning and genes of the cadherin family in AN.

It is important to note, however, that this thesis only focused on singular alleles, even though their impact on the phenotypical features of an individual is usually rather slim. For this reason, while these results seem promising and should inspire future research, no definite conclusions about genetic links of implicit learning in AN should be drawn at this point. To provide more thorough evidence, further research should be conducted on a polygenic level, ideally through the use of polygenic risk scores.

Considering the multifactorial origin of AN, it is especially important to continue research in domains besides genetics as well. Based on this thesis' investigations, it seems unlikely

that striatal function in AN is influenced by disease severity and depressive comorbidities, but correlations with BMI and duration of disease showed trends that could yield promising results when explored further in a larger sample. Ideally, future research on this topic should consider the patient's history and the impact of disease severity at different stages, as well as periods of remission with normalized BMI on cognition. It seems plausible that even short periods of severe malnutrition could potentially leave long-lasting negative effects on neural structures.

In summary, this diploma thesis provides novel insights into the pathophysiology of cognitive impairments in AN and hopes to inspire further research on a polygenic level to explore the topic more thoroughly and hopefully pave the way for more effective screening and treatment methods for the condition that is AN.

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6 Appendix

6.1 Information about publications

Parts of this thesis, particularly contents of chapters **2.2 Tests and questionnaires, 3 Results, 3.1 Weather Prediction Task,** and **4 Discussion** are currently under review for publication in the International Journal of Eating Disorders. Consequently, no definite source can be cited as of now. Instead, a temporary source will be provided in the References section (Wiener et al., 2023), and a reference to this thesis will be added to the final published manuscript in accordance with the Standards for Good Scientific Practice of the Medical University Graz.