"Reshaping" the Brain – Longitudinal investigation of structural and functional brain alterations during weight gain in Anorexia nervosa

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Doctoral thesis

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Abstract

Anorexia nervosa (AN) is a life threatening and difficult-to-treat eating disorder with a high relapse rate and an often chronic course of illness. Despite various efforts, the etiopathogenesis of this disorder remains enigmatic. This work sets out to investigate structural and functional brain alterations in young women with AN and closely matched healthy control participants, to help clarify the role of neural changes in this challenging disorder. Its main aim is the temporal mapping of neural and behavioural changes in a longitudinal design with three measurement time points: from the acute phase of AN, with severe underweight, to a weight-restored phase.

To examine brain alterations during acute underweight, as well as restorative mechanisms induced by weight gain treatment, two longitudinal studies and a cross-sectional study were conducted. *Study I* provides insight into structural brain alterations of AN patients during acute underweight as well as longitudinal regenerative processes with weight restoration. The findings demonstrate strong global reductions of cortical and subcortical grey matter at the beginning of treatment and a partial reversibility over the course of treatment. Notably, these brain recovery processes were dependent on patients' age, potentially indicating decreases of brain plasticity across the lifespan.

Study II examines network changes of resting-state functional connectivity in patients with AN during acute underweight, as well as over the course of weight restoration treatment. With the help of network-based analyses a network of reduced functional connectivity was identified at the beginning of treatment comprising fronto-basal ganglia/limbic regions related to reward, learning, and cognitive-emotional integration. This network of reduced connectivity recovered with weight normalisation. The regeneration of functional connectivity within the network significantly correlated with changes in patients' psychopathology.

Study III is a cross-sectional investigation of structural connectivity at the beginning of treatment with a focus on the fornix, a tract of the limbic system connecting the mammillary bodies with the hippocampi. Findings

of reduced structural connectivity in previous studies had suggested the fornix as a key structure in the pathomechanism of AN. By integrating knowledge from Study I to investigate potential pitfalls in the investigation of structural connectivity in AN, Study III shows that previous results had been biased by enlarged ventricles of AN patients. The findings reveal that differences of structural connectivity in the fornix disappear, compared to healthy controls, when adequately controlling for effects of the enlarged ventricles. This suggests that microstructural alterations unlikely occurred in the fornix of AN patients.

Taken together, the findings of the present PhD thesis demonstrate a tremendous plasticity of young AN patients' brains and suggest that drastic alterations in the structural and functional realm are largely reversible with specific treatment and careful weight restoration. Remaining residual alterations both on a structural and functional level by the end of the weight normalisation treatment highlight the importance of sufficiently long and well-structured treatment programmes, including outpatient after-care, to further normalise and stabilise weight and eating behaviour, as well as to improve psychopathology. The complex nature of AN underscores the necessity in neuroimaging research to combine and carefully evaluate different sources of information to avoid erratic or premature conclusions about brain alterations.

Kurzfassung

Anorexia nervosa (AN) ist eine lebensbedrohliche und schwierig zu behandelnde Essstörung, mit einer hohen Rückfallrate und einem oft chronischen Krankheitsverlauf. Trotz vielseitiger Forschungsbemühungen bleibt die Äthiopathogenese dieser Krankheit bislang ein Rätsel. Die vorliegende Arbeit hat zum Ziel, strukturelle und funktionelle Gehirnveränderungen bei jungen Frauen mit AN, sowie gesunden Kontrollprobandinnen, zu untersuchen, um so die Rolle neuronaler Veränderungen bei dieser herausfordernden Krankheit zu beleuchten. Das Hauptziel der Arbeit ist die zeitliche Abbildung neuronaler und verhaltensbezogener Veränderungen in einem Länsschnittsdesign mit drei Messzeitpunkten: von der akuten Phase der AN mit schwerem Untergewicht, zu einer Phase der Gewichtsnormalisierung.

Um Gehirnveränderungen während des akuten Untergewichts, sowie Mechanismen der Hirnregeneration im Verlaufe des Gewichtsaufbaus zu untersuchen, wurden zwei Längsschnittstudien und eine Querschnittsstudie durchgeführt. *Studie I* liefert Einblicke in strukturelle Gehirnveränderungen bei Patientinnen mit AN, sowohl während akutem Untergewicht, als auch während des Gewichtsaufbaus. Die Ergebnisse zeigen eine starke globale Verminderung kortikaler und subkortikaler Grauer Substanz zu Beginn der Therapie, sowie eine unvollständige Erholung im Verlauf der Behandlung. Bemerkenswerterweise waren diese Erholungsprozesse abhängig vom Alter der Patientinnen, was auf die über die Lebensspanne hinweg abnehmende Hirnplastizität hinweisen könnte.

Studie II untersucht Netzwerkveränderungen funktioneller resting-state Konnektivität in Patientinnen mit AN während akutem Untergewicht, sowie über den Verlauf des Gewichtsaufbaus. Netzwerkanalysen identifizierten zu Beginn der Therapie ein Netzwerk mit reduzierter funktioneller Konnektivität in frontalen, basal gangliären und limbischen Regionen, die eine Rolle spielen bei Belohnung, Lernen und der Integration von Kognitionen und Emotionen. Dieses Netzwerk mit reduzierter Konnektivität erholte sich im Verlaufe der Gewichtsnormalisierung. Die Erholung der funktionellen Konnektivität innerhalb des Netzwerkes korrelierte

signifikant mit Veränderungen in der Psychopathologie der Patientinnen.

Studie III ist eine Querschnittsuntersuchung der strukturellen Konnektivität zu Beginn der Therapie, mit einem Fokus auf den Fornix, ein Fasertrakt des limbischen Systems, welcher die Mammillarkörper mit den Hippocampi verbindet. Ergebnisse vorheriger Studien zu reduzierter struktureller Konnektivität hatten den Fornix als eine Schlüsselstruktur im Pathomechanismus von AN suggeriert. Durch die Integration von Wissen gewonnen aus Studie I, zur Aufdeckung potentielle Fallstricke bei der Untersuchung struktureller Konnektivität in AN, konnte Studie III zeigen, dass vorherige Resultate verzerrt waren durch den Einfluss der vergrösserten Ventrikel der AN Patientinnen. Die Ergebnisse zeigen, dass Unterschiede in struktureller Konnektivität, im Vergleich von AN Patientinnen zu gesunden Kontrollprobanden, verschwinden, wenn für die Effekte der vergrösserten Ventrikel adäquat kontrolliert wird. Das weisst darauf hin, dass keine mikrostrukturellen Veränderungen im Fornix von AN Patientinnen vorliegen.

Zusammengefasst zeigen die Ergebnisse der vorliegenden Doktorarbeit eine enorme Plastizität der Gehirne junger AN Patientinnen und weissen darauf hin, dass sich drastische strukturelle und funktionelle Gehirnveränderungen mit spezifischer Behandlung und sorgfältigem Gewichtsaufbau weitgehend umkehren lassen. Die, nach der Gewichtsnormalisierung zurückbleibenden, strukturellen und funktionellen Gehirnveränderungen heben die Wichtigkeit eines ausreichend langen und gut strukturierten Behandlungsprogramms, mit anschliessender Nachbehandlung zur weiteren Normalisierung und Stabilisierung des Essverhaltens, sowie zur Verbesserung der Psychopathologie, hervor. Die komplexe Natur der AN unterstreicht für die Neurowissenschaften die Notwendigkeit verschiedene Informationsquellen zu kombinieren und sorgfältig auszuwerten, um keine fehlerhaften oder voreiligen Schlüsse bezüglich Gehirnveränderungen zu ziehen.

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List of Acronyms

A	Anterior
AAL	Automated anatomical labelling
AD	Axial diffusivity
AN	Anorexia nervosa
APA	American Psychiatric Association
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften
BDI	Becks Depression Inventory
BMI	Body mass index (kg/m^2)
CBT	Cognitive behavioural therapy
CSD	Constrained spherical deconvolution
CSF	Cortico-spinal fluid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion tensor imaging
EDE-Q	Eating Disorder Examination Questionnaire
EDI	Eating Disorder Inventory
EPI	Echo Planar Imaging
ERQ	Emotion Regulation Questionnaire
FA	Fractional anisotropy

FDR	False discovery rate
FDT	FMRIB's Diffusion Toolbox
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FPT	Focal psychodynamic therapy
GM	Grey matter
GWAS	Genome wide association study
HC	Healthy control
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICV	Inctra-cranial volume
MRI	Magnetic resonance imaging
NBS	Network based statistic
NICE	National Institute of Clinical Excellence
OCI	Obsessive Compulsive Inventory Revised
P	Posterior
PANAS	Positive and Negative Affective Schedule
PET	Positron emission tomography
PVE	Partial volume effects
RD	Radial diffusivity
ROI	Region of interest
rsFC	Resting-state functional connectivity
rsfMRI	Resting-state functional magnetic resonance imaging
SCID-I	Structured Clinical Interview for DSM-IV Axis I
SHAPS	Snaith-Hamilton-Pleasure Scale
STAI	State-Trait Anxiety Inventory

TCI	Temperament und Character Inventory
TE	Echo time
TFE	Turbo field echo
TMT	Trail Making Test
TP	Time point
TR	Repetition time
TRACULA	TRActs Constrained by UnderLying Anatomy
WGE	Weight gain estimation
WHO	World Health Organization
WM	White matter
WMT	Wiener Matritzen Test (Viennesse Matrices Test)
WST	Wortschatz-Test (Vocabulary Test)

CHAPTER 1

Introduction

Anorexia nervosa (AN) is a psychiatric disorder with initial manifestation often during puberty and adolescence (Zipfel, Giel, Bulik, Hay, and Schmidt, 2015). Current treatment options comprise psychotherapy along with nutritional counselling but treatment success is variable and often does not last. Relapse probabilities are high and up to half of the affected patients face a chronic course of illness (Herpertz-Dahlmann, Seitz, & Konrad, 2011; Kaye, 2009; Steinhausen, 2002). This may in part be attributable to our lack of a comprehensive understanding of the pathomechanisms underlying the disorder (Compan, Walsh, Kaye, & Geliebter, 2015; Herpertz-Dahlmann et al., 2011; Kaye, 2009). By means of magnet resonance imaging, the present thesis thus aims at providing a better understanding of the neural changes in AN during the phase of acute underweight, as well as during two distinct phases over the course of an inpatient weight restoration therapy.

The present thesis is structured into three parts: First, the theoretical background gives an overview of the clinical picture of AN, its treatment and its consequences. Epidemiological considerations and the current knowledge about the aetiology of AN will then serve as a theoretical basis for the present thesis. Second, in the empirical part, encompassing the aims and hypotheses, the general methods, and three empirical studies (Chapter 5-7), as well as an additional data exploration (Chapter 8), structural and functional brain alterations in young women with AN will be investigated. In the third and final part of the present thesis, key findings of the three studies, as well as the additional exploratory

data analyses, will be summarised briefly and integrated into a general discussion with respect to relationships between results. Furthermore, clinical and therapeutic implications of these findings, methodological considerations, and suggestions for future research will be outlined.

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CHAPTER 2

Background

This chapter gives an overview of the clinical picture of AN, its treatment, its consequences for the individual as well as for society. After a summary of the most important cornerstones in the history of the disease, current diagnostic criteria and treatment guidelines are outlined and supplemented with a short depiction of the economic burden of AN. Further, epidemiological aspects are highlighted and the current knowledge of predisposing and maintaining factors is summarised and assembled in an aetiological model of AN, which will serve as a theoretical basis for the present thesis.

2.1 Anorexia nervosa

2.1.1 Historical evolution of the concept of Anorexia nervosa

Etymologically the term *anorexia nervosa* originates from Greek *an-* ("without") and *órexis*, ("appetite, desire"), and Latin *nervosa* ("nervous"), thus translating to "nervous absence of appetite" (Stevenson, 2010). However, the syndrome was described long before the medical term anorexia nervosa had been coined. First reports that are now suspected to be early cases of AN stem from cases of religious fasting (Bemporad, 1997; Fox, 1987). From the Hellenistic era (323 BC - 330 AD) until the Middle Ages there have been numerous accounts of self-starvation, often in the name of religion with the aim of spiritual purification (Pearce, 2004; Vandereycken & Van Deth, 1994b). The death of a young woman following the precepts of Saint Jerome in 383 AD is probably the first

record of such a case (Bemporad, 1997; Fox, 1987). Whether these historical accounts of fasting women were cases of AN as we see them today, or merely showed analogous symptoms cannot be determined conclusively (Vandereycken & Van Deth, 1994a).

These early anecdotes were followed by a medical description of the anorexic condition by the English physician Richard Morton in 1689 (Morton, 1720). He described two independent cases of a girl and a boy, who both started fasting at the age of 16. Shortly after the girl sought help from Dr Morton because of her frequent fainting fits, the unsuccessful treatment resulted in her death at the age of 18. The male patient, "Son of the Reverend Minister Steele", "recovered his Health in a great Measure" when he adhered to the "Milk Diet" (Morton, 1720, p.10) and abandoned his studies as Morton had prescribed (Morton, 1720). With Morton's work, AN was the first eating disorder to be recognised as a clinical condition (American Psychiatric Association [APA], 1952; Morton, 1720; Pearce, 2004). This marks the beginning of a change in perception of the ascetic fasting in earlier centuries (Fox, 1987).

Two centuries later, Sir William Gull, a famous British physician, furthered the medicalisation of self-starvation as he described the emaciated condition in young women in his address to the British Medical Association in Oxford (Gull, 1868). Independently, the French neuropsychiatrist Ernest Charles Lasègue published a similar description in a paper in 1873 with the title "*De l'anorexie hystérique [On hysterical anorexia]*" (Lasègue, 1873). While both men used the term "Anorexia", Gull is generally credited with coining the term "Anorexia nervosa" (Gull, 1874, p.22) in his seminal work "*Anorexia nervosa (Apepsia Hysterica, Anorexia Hysterica)*" (Gull, 1874; Pearce, 2004). He stated that the onset of the condition is chiefly during adolescence and affects mostly females (Gull, 1868, 1874), observations that hold true until today (Treasure, Cardi, Leppanen, & Turton, 2015). Further, he notes that there is no primary medical lesion to be observed, that the origin of the condition seems to be "central" (brain) rather than "peripheral" (stomach) (Gull, 1874, , p.24) and that patients are often restless and in constant motion. Additionally, he points out that the causes for the condition are unknown

(Gull, 1874), a circumstance that sadly also still applies (Woerwag-Mehta & Treasure, 2008). Comparing Gull's (1868, 1874) description to today's diagnostic criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (American Psychiatric Association [APA], 2013), demonstrates that presentation and concept of AN have remained relatively stable over a long period of time. While Gull (1868) defined many of the core features of AN we know today, there are aspects he did not mention, like shape concerns and the fear of gaining weight. Whether these symptoms were not mentioned or observed by Gull, or not present in the patients he encountered, remains unclear (Moncrieff-Boyd, 2016). Notably though, his work laid the foundation for the understanding and the research of AN conducted today (Gianini et al., 2016; Guarda, Schreyer, Boersma, Tamashiro, & Moran, 2015).

2.1.2 Symptomatology and diagnostic criteria today

With the latest version of the DSM-5 (APA, 2013), AN is placed in the "Feeding and Eating Disorders" chapter and characterised by the following diagnostic criteria: (A) restricted nutritional "intake relative to requirements, leading to a significantly lower body weight", (B) "fear of gaining weight . . . , or persistent behaviour that interferes with weight gain" despite significant underweight, (C) distorted body image, "undue influence of body weight or shape on self-evaluation" (APA, 2013, pp. 338-9), or enduring denial of the severity of the low weight (APA, 2013). The previously in the DSM-IV-TR included criterion (D) requiring amenorrhoea, or the absence of at least three menstrual cycles (APA, 2000), was deleted from the DSM-5 (APA, 2013) as it inherently only applied to post-menarcheal and pre-menopausal women. Furthermore, criterion (A) was changed to no longer contain the word "refusal" in regard to weight maintenance, as to avoid the inappropriate implication of intentional behaviour (American Psychiatric Association Division of Research, 2014).

Two different subgroups of AN can be distinguished as reflected in the diagnoses of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) (World Health Organization [WHO], 2009): a restrictive and a binge-purge subtype.

While both subtypes are characterised by a highly restrictive eating pattern, the binge-purge subtype also displays "episodes of binge-eating or purging behaviour" (APA, 2013, pp. 338-9), such as vomiting or abuse of laxatives (WHO, 2009). In addition to the specific diagnosis, the DSM-5 (APA, 2013) offers an estimation of the current severity of the disorder according to the Body Mass Index (BMI, calculated as kg/m^2) of a patient as mild (BMI $\geq$ 17), moderate (BMI 16-16.99), severe (BMI 15-15.99), and extreme (BMI $<$ 15).

2.1.3 Somatic complications

AN is associated with several somatic problems due to the emaciation of the body. Often times, patients are not immediately aware of the severity of these issues but only become aware of them when the situation is progressed and physical signs become more obvious and urgent (Katz & Vollenhoven, 2000). While most of these symptoms are reversible with weight restoration, some, e.g. osteoporosis, can cause permanent damage even when remission is achieved, e.g. bone fractures or the need for artificial joints (Fairburn & Harrison, 2003).

Nearly all organ systems are affected by the severe malnutrition (see Figure 2.1 for a summary) (Zipfel et al., 2015). Physical signs include heightened sensitivity to low temperatures (Wakeling & Russell, 1970), low body temperature (Zipfel et al., 2015), sleep disturbances (Kim et al., 2010; Lauer & Krieg, 2004), gastrointestinal problems (e.g. obstipation) (McCallum et al., 1985), dizziness and fainting (Sharp & Freeman, 1993), as well as reduced libido (Gold et al., 1986; Katz & Vollenhoven, 2000). Furthermore, dermatological alterations such as dryness of the skin and a gradual skin yellowing can be observed, along with loss of scalp hair, the development of fine hair covering the body (i.e. lanugo hair), and oedema (Strumia, 2005).

The malnutrition also causes disturbances of the neuroendocrine system, such as decreased luteinising hormone, follicle stimulating hormone, and oestrogen, leading to amenorrhoea and thus infertility in post-menarcheal women (Katz & Vollenhoven, 2000). In men, reduced

testosterone levels can be observed, which instigate hypogonadism (Katz & Vollenhoven, 2000). In children with pre-pubertal onset of AN, puberty onset may be significantly delayed (Pugliese, Lifshitz, Grad, Fort, & Marks-Katz, 1983) and body growth reduced (Fairburn & Harrison, 2003). Some of these alterations improve upon weight restoration others, however, persist (Katz & Vollenhoven, 2000; Meczekalski, Podfigurna-Stopa, & Katulski, 2013). For example, while body growth in pre-pubertal AN patients has been reported to accelerate upon re-nutrition, body height remains stunted even after weight normalisation (Lantzouni, Frank, Golden, & Shenker, 2002).

Additionally, AN can be accompanied by abnormal electrolyte levels (Mitchell & Crow, 2006; Sharp & Freeman, 1993). Hypokalaemia, hypomagnesaemia, and imbalances of the acid-base metabolism influence bowel motility (Fairburn & Harrison, 2003), and cause renal dysfunction (Stheneur, Bergeron, & Lapeyraque, 2014). Other severe consequences of the electrolyte disturbances include impaired cardiovascular functioning such as bradycardia, hypotension, and arrhythmia (Cooke et al., 1994; Mont et al., 2003). These symptoms are potentially life threatening (Sharp & Freeman, 1993), thus electrolyte levels need close monitoring during therapy (Winston, 2012). Cardiovascular complications and infections represent the most common medical cause of death among AN patients (Papadopoulos, Ekbom, Brandt, & Ekselius, 2009). Particularly the diagnosis of the latter is often critically delayed, due to the absence of febrile temperatures and inflammatory markers in most AN patients (Brown, Bartrop, Beumont, & Birmingham, 2005).

Among the irreversible or difficult to treat somatic problems, osteoporosis is one of the most important (Fairburn & Harrison, 2003). Puberty is the critical phase for bone structure configuration, where maximal bone mineral density is reached in healthy adolescents (Theintz et al., 1992). Illness onset of AN typically happens around the same time, causing insufficient bone density build up in affected individuals (Misra & Klibanski, 2007). Almost half of adolescent AN patients are reported to suffer from osteopenia, a reduction in mineral density, and 11% from osteoporosis, where bone strength is severely reduced (Castro, Lázaro,

Pons, Halperin, & Toro, 2000; Castro, Toro, Lázaro, Pons, & Halperin, 2002; Misra et al., 2004). In adults, the proportion of osteoporosis goes up to 40% and normal bone mineral density is found in only 11% of patients (Milos et al., 2005). These changes in bone metabolism become irreversible with a proceeding malnutrition of the body (Milos et al., 2007), causing an elevated risk for fractures already at a young age (Faje et al., 2014; Lucas, Melton, Crowson, & O'Fallon, 1999).

2.1.4 Comorbid mental conditions

AN often comes with other comorbid diagnoses such as depressive and anxiety disorders (Bühren et al., 2014; Hudson, Hiripi, Pope, & Kessler, 2007; O'Brien & Vincent, 2003). Furthermore, an increased occurrence of personality disorders, especially cluster B (borderline, histrionic, and narcissistic) and C (avoidant, dependent, and obsessive compulsive) personality disorders, have been reported (Cassin & von Ranson, 2005; Spindler & Milos, 2007). Other psychological features present in patients with AN comprise perfectionism (Bastiani, Rao, Weltzin, & Kaye, 1995; Halmi et al., 2000; Lloyd, Yiend, Schmidt, & Tchanturia, 2014), heightened impulsivity and impulse-control problems, alcohol and drug abuse, the latter of which are mainly reported in individuals exhibiting the binge-purge subtype of AN (DaCosta & Halmi, 1992; Garner, Garner, & Rosen, 1993; Rosval et al., 2006). In the realm of affect, recent studies suggest altered emotional processing in AN patients, such as heightened harm avoidance (Cassin & von Ranson, 2005), anhedonia (Davis & Woodside, 2002; Tchanturia et al., 2012), alexithymia (Bourke, Taylor, Parker, & Bagby, 1992; Tchanturia et al., 2012), and impaired emotion regulation skills (Lavender et al., 2015). The heritability of these traits (Bevilacqua & Goldman, 2011; Jørgensen, Zachariae, Skytthe, & Kyvik, 2007) suggests a potential genetic component contributing to a heightened vulnerability for AN, similar to other mental disorders (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Schürhoff et al., 2003). Depending on the severity, these comorbid disorders and psychological features may have a significant influence on therapy outcome and need to be considered for treatment planning (Kask et al., 2016; Milos, Spindler,

Organ systems or organ	Pathological findings	Leading systems
Central nervous system	Morphological and functional cerebral changes; volume reduction in vertebral grey and white matter	Cognitive deficits
Dental system and parotid glands	Impaired dental status, dental caries, increased serum amylase	Dental caries, enlargement of the parotid glands
Endocrine system and reproductive function	Hypothalamus-pituitary-gonadal-axis, low T3 syndrome, hypercortisol	Amenorrhoea in women, symptoms of hypothyroidism, depression, elevated stress levels
Cardiovascular system	Hypotension, bradycardia, arrhythmia	Syncope
Gastrointestinal tract	Impaired gastric emptying, gastric dilation, gastroduodenal ulcers	Anaemia, (bacterial) infections, compromised immune competence
Renal tract	Hypokalaemia, hypophosphatemia, hypernatremia	Nephrolithiasis, oedema, syncope
Bone	Reduced bone density (osteopenia) or osteoporosis	Bone fractures and concomitant pain, spinal compression

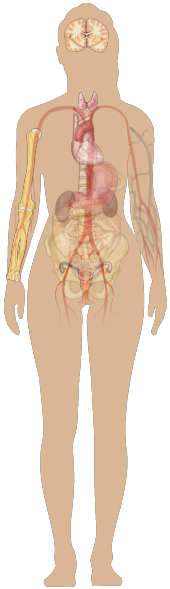

Figure 2.1. Organs and organ sytems affected by AN (adapted after Zipfel et al., 2015). Figure on the right adapted from "Female shadow with organs", by M. Häggström, 2011 (`https://commons.wikimedia.org/wiki/File:Female_shadow_with_organs.png`) via Wikimedia Commons. Used under Creative Commons Attribution CC0 1.0 Universal Public Domain Dedication.

Buddeberg, & Crameri, 2003). Due to the complexity of the disorder and the illness onset in late adolescence (see Section 2.3), AN can have serious consequences for the education and later career of a patient. In sum, this causes significant direct and indirect costs.

2.1.5 Economic burden

Considering the treatment costs and productivity losses, the annual expenses for AN sum up to a substantial economic burden (Simon, Schmidt, & Pilling, 2005). A recent cost-of-care study by Guarda et al. (2017) has estimated the cost of weight restoration in an inpatient treatment for a single patient in the *Johns Hopkins Eating Disorder Program* to vary between approximately 75'000 and 300'000 Euro per stay, depending on the speed of weight gain, with faster weight gain inducing lower costs. The authors suggest that on top of reduced costs, faster weight gain increases the likelihood of a full weight restoration (Guarda et al., 2017). However, the situation is more complex as a higher weight gain target per week not only seems to make it less likely for the patients to achieve a healthy BMI during treatment but additionally might make patients less likely to maintain the gained weight in the long-run (Herzog, Zeeck, Hartmann, & Nickel, 2004).

Broadening the focus beyond purely treatment related costs, a cost-of-illness study conducted in Germany suggests a total of direct and indirect costs of 195 million Euro per year due to AN (Krauth, Buser, & Vogel, 2002), excluding outpatient treatment, medication, and secondary costs, such as losses of productivity among caretakers of under-age patients. The bulk of the costs (67% of the overall costs) does not stem from immediate expenses due to necessary treatments but rather from indirect costs such as inability to work or premature death (Krauth et al., 2002). The significant indirect costs due to premature death (63% of the overall costs) are related to the young age of the patient population, where a fatal disease trajectory corresponds to several decades of potential gainful employment (Krauth et al., 2002). These numbers underline the potential gains of a successful treatment and the prevention of a chronic course of AN, not only for the individual patient but also for society.

2.2 Therapeutic treatment

Incorporating the available research results and suggestions, the German Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) published evidence-based (S3) guidelines regarding the diagnostic and treatment of eating disorders in 2011 (Zeeck et al., 2011). These guidelines were the first German guidelines for eating disorders and amended the evidence-based guidelines by the National Institute of Clinical Excellence (NICE, 2004) and the APA (APA, 2006). Striving to support practitioners with informed recommendations regarding treatment strategies and diagnostics, these guidelines integrate findings from basic research, systematically collected expert knowledge, and results from randomized controlled trials.

The primary treatment targets for AN as recommended by the S3-guidelines are restoration of a normal body weight, normalisation of eating behaviour, and treatment of psychological and somatic issues. The recommended approach to achieve these therapy aims comprises specialised psychotherapy, accompanied by nutrition counselling, as well as close monitoring and treatment of somatic issues (Zeeck et al., 2011). In the following, the main psychotherapeutic approaches will be characterised briefly.

2.2.1 Cognitive behavioural therapy

In the A-B-C triad of psychology, cognitive behavioural therapy (CBT) addresses the latter two elements behaviour (B) and cognition (C) to influence the patients' condition and affect (A) (Pike, Carter, & Olmsted, 2010). During therapy, individuals learn to identify dysfunctional beliefs, attitudes, and behaviours and to replace them with more appropriate cognitions and behaviour (Garner, Vitousek, & Pike, 1997). A core element of CBT for AN is a tailored psychoeducation regarding the importance of a healthy body weight, the association of hunger and eating disorder symptoms like binge eating, the somatic consequences of the disorder, as well as the identification and handling of sociocultural influences such as media images of an ideal body (Garner et al., 1997). Additionally, a problem analysis is typically conducted to identify predisposing and maintaining conditions for disordered eating behaviours and to develop response alternatives (Pike et al., 2010). Food and weight management represent a central component throughout the treatment, with regular meals to reach weight normalisation and stabilisation, and eventually a reduction of the "forbidden foods list" that most patients have (Pike et al., 2010). Finally, the identification and treatment of underlying problems, as well as work on a potential body dysmorphic disorder are important in CBT for AN (Pike et al., 2010). In sum, the underlying model of AN in CBT is one of dysfunctional cognitions (over-valuation of weight and shape) and behaviours (avoidance of high caloric food, excessive physical activity), developed to cope with stressful life experiences, that are targeted in therapy and aimed to be replace with more appropriate ones (Vitousek, 2002). CBT for AN does not focus on aetiological factors, however its theory recognises a multifactorial origin of the disorder (Pike et al., 2010) and views the need for self-control (Fairburn, Cowen, & Harrison, 1999), low self-esteem, mood intolerance, interpersonal problems, and high perfectionism as important aspects in the maintenance of AN (Fairburn & Harrison, 2003).

2.2.2 Psychodynamic therapy

In contrast to CBT, psychodynamic therapy for AN focusses predominantly on the meaning of the eating disorder symptomatology within the life on an individual and in the context of important relationships (Zeeck et al., 2011). The constitution of self, self-image, and self-esteem form a core process in the psychodynamic model of AN (Zerbe, 2010). Repetitive neurotic, interpersonal behaviour patterns, the role of food and eating, and the conflict of autonomy and dependence are viewed as central to AN and are targeted by means of psychoeducative components as well as genuine psychotherapeutic strategies such as conflict repetition within the therapeutic relationship (Zerbe, 2010). In an effort to standardise this otherwise rather broad and diverse therapy approach, a treatment manual for focal psychodynamic therapy (FPT) has been developed, to allow for comparisons with other treatments in an outpatient setting (Wild et al., 2009). At the beginning of FPT, a diagnostic interview is conducted to identify psychodynamic conflicts (Arbeitskreis OPD, 2006). FPT then follows three phases, the first of which is dedicated to exploring the disordered eating behaviour, related beliefs, and the self-esteem of an individual. The second phase looks at interpersonal relationships in the context of AN. The last phase is used to prepare the transfer to everyday life and the end of therapy (Schauenburg, Friederich, Wild, Zipfel, & Herzog, 2009). In the context of FPT, AN is interpreted as an attempt to gain control over the body and to form an identity, as well as to avoid anxiety. Main aetiological factors are seen in the interaction of biological, sociocultural and family aspects (Schauenburg et al., 2009).

2.2.3 Family therapy

Due to the onset of AN during adolescence, different forms of therapy have been developed that specifically consider the family system in the treatment of the individual. Two main groups of approaches can be distinguished: (1) structural and (2) strategic family therapy (Dare, Gerald, Szmukler, Grange, & Dodge, 2011). While structural family therapy views the family as a causative factor of the disease and concentrates

on improving the dysfunctional family dynamic, strategic family therapy focuses on using the family as resource to improve the individual's behaviour (Dare et al., 2011). More recently, family-based therapy was developed as a combination of the earlier variants of family-therapeutic approaches and represents to most widely implemented family therapy today (Dare et al., 2011). Its view is agnostic regarding the pathogenesis of AN and treatment generally consists of three stages (Lock & le Grange, 2005). In the first stage, the focus is put on weight restoration and parents are given authority over their child's eating behaviour until a healthy weight is reached and a normal eating pattern is established. During family meals, the therapist helps to identify behaviours of family members that may hinder refeeding. In the second stage, the patient gradually takes back on responsibility for the eating behaviour. In the last stage of family-based therapy, the focus is widened to general topics such as challenges in the family dynamic during adolescence (Lock & le Grange, 2005).

2.2.4 Therapy settings

Regarding the question whether treatment should be delivered in an in- or outpatient setting, there is not enough empirical data available to date to favour one setting over the other. However, weight gain seems to be faster during inpatient treatment (Hartmann, Weber, Herpertz, & Zeeck, 2011). Furthermore, due to the need for intensive interdisciplinary treatment, inpatient therapy often becomes necessary with increasing severity of the disorder (Zeeck et al., 2011).

2.2.5 Pharmacotherapy

Pharmacological agents have not proven to be effective in the treatment of AN. The body of evidence for the efficacy of pharmacotherapy in AN is unsatisfactory, and the quality of studies – often conducted in small samples – is questionable (Claudino et al., 2006; Court, Mulder, Hetrick, Purcell, & McGorry, 2008). In case of enduring rumination and anxiety related to eating and body shape, or intense physical hyperactivity, off-label use of low dosed neuroleptics might be justified (Brewerton, 2012).

For the treatment of comorbid depressive symptoms antidepressants are occasionally being used (Zeeck et al., 2011). However, no beneficial effects for the treatment of AN have been reported (Brewerton, 2012).

2.2.6 Treatment conclusions

The evidence base for particular psychotherapeutic approaches is very limited. While all sufficiently examined eating-disorder specific treatments described above seem to be partly effective, findings suggest that none of the available approaches is superior (Hay et al., 2003; Zeeck et al., 2011; Zipfel et al., 2014). A recent randomised controlled trial comparing outpatient CBT, FPT, and treatment as usual (outpatient psychotherapy and care from a family doctor) for adult patients suggests that over the course of treatment, as well as after a follow-up period of 3 and 10 months, all three treatment approaches performed equally well regarding BMI improvement (Zipfel et al., 2014). An exception to this equal effectiveness may be the treatment of adolescents. A recent meta-analysis suggests that while immediate treatment outcomes are the same, there may be positive long-term effects of family-based therapy that exceeds the impact of individual treatment for adolescents (Couturier, Kimber, & Szatmari, 2013). A possible explanation for this might be that younger patients are not yet able to fully understand the implications of the disorder, thus the involvement of parents or close relatives is important (Jäger, Herpertz, Salbach-Andrae, Hagenah, & Tuschen-Caffier, 2011).

A common goal of the summarised psychotherapeutic approaches represents the normalisation of eating behaviours, body weight, and the treatment of problems associated with AN (Jäger et al., 2011). Furthermore, two approaches acknowledge a multifactorial aetiological model of AN (CBT and FPT), while one is agnostic with regard to its causes (family-based therapy). Independent of the specific psychotherapeutic approach, there is evidence that treatment should be started as soon as possible to reduce the risk for a chronic course of the disorder (Steinhausen, 2002; Zeeck et al., 2011). Additionally, as the somatic risks of the disorder require intensive interdisciplinary collaboration of health care

providers, treatment should take place in institutions and with therapists that have expertise and training with eating disorders (Jäger et al., 2011).

2.3 Epidemiology

While eating disorders in general affect 5.3% of women and 1.3% of men, AN affects 1.2–1.9% (DSM-IV vs. DSM-5) of women and 0.2% of men in Switzerland (Mohler-Kuo, Schnyder, Dermota, Wei, & Milos, 2016). These lifetime prevalences of AN are comparable to those of other European countries[1], where the lifetime prevalence amounts to 0.9% in females and 0% in males, (Preti et al., 2009) and the United States, where 0.9% of females and 0.3% of males are affected by AN (Hudson et al., 2007). Although the prevalence of AN may appear low, the numbers are very similar compared with the prevalence of other serious psychiatric disorders affecting young adults, such as schizophrenia (prevalence rate of 1%; McGrath, Saha, Chant, & Welham, 2008; Simeone, Ward, Rotella, Collins, & Windisch, 2015).

To measure time trends, the incidence rate is a more suitable measure than prevalence. The incidence describes the occurrence of new cases within a defined time frame, in the following the incidence per year will be reported. Several studies have suggested that the incidence of AN in industrialised countries may have risen over the last decades (Hoek, 2006; Hoek & Van Hoeken, 2003; Milos et al., 2004). However, recent reviews have concluded that the overall incidence of AN in these countries has remained stable at 4.7 to 7 per 100,000 person-years after a rise of incidence up to the 1970s (Fombonne, 1995; Pike, Hoek, & Dunne, 2014; Smink, Van Hoeken, & Hoek, 2012). It might be that increases between the 1930s and 1970s reflect a true rise of incidence of AN, it is also possible that raising numbers are attributable to a heightened awareness and improvements in diagnostics during that time (Fombonne, 1995).

AN is the eating disorder with the lowest age of onset (Smink et

1 Belgium, France, Germany, Italy, the Netherlands and Spain

al., 2012). The incidence peak of AN lies in late adolescence, between 16-18 years of age, although early-onsets have been reported from age 10 (Hudson et al., 2007; Mohler-Kuo et al., 2016). As underweight and emaciation affect the whole body (see Section 2.1.3), AN holds the unedifying record of the highest mortality rate amongst mental disorders with a crude mortality rate of 5-10% (Chesney, Goodwin, & Fazel, 2014; Steinhausen, 2002). Of the surviving patients, less than 50% achieve a full recovery after a follow-up time of more than four years, while 30% show some improvement in clinical symptoms, and roughly 20% of AN patients face a chronic course of illness (Steinhausen, 2002). A more positive outcome has been associated with younger age at illness onset, a shorter duration of symptoms before treatment, as well as features of a histrionic personality (Steinhausen, 2002). Negative prognoses have been linked to binge-purging behaviour, a longer duration or chronic course of illness, and symptoms of an obsessive-compulsive personality (Steinhausen, 2002). Thus, although there are specialised guidelines and treatments available (see Section 2.2), the long-term prognosis of AN is not yet satisfactory.

2.4 Aetiology

The long history of AN has been accompanied by assumptions and speculations about the causes and contributing factors that lead to the disorder. Early research saw the family environment, namely conflict-avoiding interactions between patients and their parents and an overprotective parenting style, as a key influence (Katz, Mazer, & Litt, 1985; Kog & Vandereycken, 1985). These assumptions quickly formed the basis for stigmatisation of the parents and patients (Herpertz-Dahlmann et al., 2011). Continued investigation of the disorder however challenged this perception. Today, numerous predisposing and maintaining factors are considered to be relevant for the aetiology of AN. After a short clarification of terminology, the main aetiological factors will be described and summarised in a neuropsychiatric model of the disease.

2.4.1 Aetiological terminology

When talking about aetiological factors of a disorder, it is useful to distinguish predisposing and maintaining factors. The main difference between the two is the temporal precedence of occurrence. A predisposing factor, also called risk factor, occurs first and prospectively predicts the subsequent symptomatic. A maintaining factor on the other hand predicts the symptom persistence or remission in affected individuals over time (Kraemer, 1997). Risk factors are commonly targeted with preventive programmes, maintaining factors on the other hand are targeted with treatment intervention designs.

It is evident that the temporal succession of risk factors, disorder, and maintaining factors gives a causal attribute to the former. To establish causality, randomized controlled trials are a useful instrument. However, due to the nature of the risk factors, randomised experiments often cannot be performed to establish causality (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). In that case, it is not possible to separate causal and proxy risk factors, the latter of which show a prospective correlation with the disorder due to a concealed correlation with a causal risk factor (Kraemer et al., 2001). Due to a lack of randomised prospective studies, this important differentiation is difficult to make when it comes to the aetiology of AN. Thus, in the following the term risk factor will be used to describe factors which may contribute causally to the disorder, as well as factors which may be associated with AN in a more indirect way.

2.4.2 Sociocultural and developmental factors

Regarding cultural factors, looking at reports of lower prevalence rates of AN in Africa and Latin-America the question arose whether increased exposure to Western lifestyle with its eating habits and thin body ideal leads to increasing prevalence rates (Smink et al., 2012). This fits with findings of body dissatisfaction as a risk factor for eating disorders in general (Stice, Marti, & Durant, 2011). However, to date there is no solid empirical evidence of sociocultural pressure for women to be slim as a risk factor for AN (Zipfel et al., 2015). Furthermore, AN can also be

found in countries where the culture does not promote a thin body ideal, such as Iran (Nobakht & Dezhkam, 2000) or Kenya (Njenga & Kangethe, 2004) and there are reports of AN cases with confirmed non-exposure to Western influences from India (Chandra et al., 1995; Gandhi, Appaya, & Machado, 1991), Pakistan (Yager & Smith, 1993), and the United Arab Emirates (Abou-Saleh, Younis, & Karim, 1998). Recognising the possible impact of this factor, it is possible that Western influences facilitate the onset of eating disorders in vulnerable individuals by promoting strict dieting or extreme exercising behaviour.

Common developmental factors that may promote such vulnerability include adverse experiences in infancy such as prematurity, dysmaturity, as well as feeding and sleeping difficulties (Jacobi, Hayward, de Zwaan, Kraemer, & Agras, 2004; Tenconi, Santonastaso, Monaco, & Favaro, 2015). Furthermore, developmental disorders from the autism spectrum as well as the development of personality traits related to obsessionality, anxiety, depression, and perfectionism have been frequently reported in AN (Jacobi et al., 2004).

2.4.3 Genetic factors

Female sex has been consistently reported to be a risk factor for AN as it is unchangeable for the affected patients. It is unclear, how much of this correlation can be ascribed to biological factors rather than sociocultural factors. However, genetic factors have become increasingly important in the quest for the etiopathology of this challenging disorder. While family studies have reported heterogeneous findings regarding the familial element of AN (Steinhausen, Jakobsen, Helenius, Munk-Jørgensen, & Strober, 2015; Strober, 2000), twin-studies have repeatedly pointed to a strong heritable component in AN, with explained phenotypic variance ranging from 48–74% (Yilmaz, Hardaway, & Bulik, 2015). To further explore the heritable biological features, several genetic studies have been conducted. Progress in genotyping technologies has made it possible to genotype genetic markers on a much larger scale than before and most recent efforts focus on genome-wide association studies (GWAS). Three of these studies have been published on AN (Boraska et al., 2014;

Nakabayashi et al., 2009; Wang et al., 2011), all of which were unable to reach enough power to detect genome-wide significant loci. However, a very recent unpublished study by Duncan et al. (2016), comparing 3'495 cases with AN to 10'982 controls, was able to identify a first robust genome-wide locus in a region including six genes. The authors note that functional data will be necessary to draw more specific conclusions about the role of these variants in the aetiology of AN. However, they state that the identified genes have been suspected to play a role in growth regulation, in calcium signalling, postsynaptic density of patients with schizophrenia, as well as in diabetes type 1 and rheumatoid arthritis. Further analyses of the study revealed positive genetic correlations between AN and a range of other phenotypes, including neuroticism and schizophrenia. Significant negative correlations were found with regard to weight-related phenotypes such as BMI and obesity (Duncan et al., 2016). These promising results support a biopsychosocial model of AN as well as they underline the complexity of the disorder.

2.4.4 Neurobiological factors

Together with genetic research, neurobiological studies may help elucidate mechanisms associated with brain pathophysiology that drive and maintain disordered eating habits. Impaired brain development due to complications during pregnancy and delivery, as well as neonatal complications have been suggested to play an important role in the development of AN (Favaro, Tenconi, & Santonastaso, 2006; Tenconi et al., 2015). The brain uses approximately 20% of the body's metabolic energy at rest (Attwell & Laughlin, 2001), which makes it the main energy consumer and renders it particularly vulnerable to effects of malnourishment. As brain functioning depends on glucose metabolism, poor nutrition affects brain development as well as general brain functioning (Mergenthaler, Lindauer, Dienel, & Meisel, 2013). This is of particular importance in the case of AN, as the disorder emerges during a crucial period for brain maturation and reorganisation (Giedd et al., 1999).

A variety of neuroimaging techniques are available to study the human brain *in vivo*. T1-weighted magnet resonance imaging (MRI) is used to

examine brain structure, diffusion tensor imaging (DTI) allows studying water diffusion in white matter tracts and thus inspect fibre integrity (Mori & Zhang, 2006), functional MRI (fMRI) maps blood flow and is used as a proxy for brain activity, and positron emission tomography (PET) assesses the distribution of neurotransmitter receptors (Raichle & Mintun, 2006). The main findings of these approaches with regard to the understanding of AN will be summarised below.

2.4.4.1 Findings from structural neuroimaging

In AN with severe underweight, MRI studies have largely demonstrated reduced grey matter volumes of a distributed set of brain regions, most consistently of limbic/paralimbic areas and the cortex (Seitz et al., 2016; Eynde et al., 2012). Findings of reduced white matter volume have been less consistent. While some studies reported decreased white matter volume (e.g., Seitz et al., 2015; Via et al., 2014), others report no significant differences (Fonville, Giampietro, Williams, Simmons, & Tchanturia, 2014; Roberto et al., 2011). In cross-sectional studies with long-term recovered AN patients, the broad impact of starvation-induced shrinkage was found to be no longer present (Favaro, Tenconi, Degortes, Manara, & Santonastaso, 2015; Frank, Shott, Hagman, & Yang, 2013; Friederich et al., 2012; Joos et al., 2011; Wagner et al., 2006). A recent meta-analysis supports these results (Seitz et al., 2016). However, persisting local grey matter decreases in the precuneus were reported in a study with a small sample of AN patients after a remission period of more than 5 years (Joos et al., 2011). Longitudinal studies in adolescent AN patients report normalisation of grey matter loss after a brief period of weight restoration (Bernardoni et al., 2016; Bomba et al., 2015; Mainz, Schulte-Rüther, Fink, Herpertz-Dahlmann, & Konrad, 2012). For adult AN patients there is a lack of longitudinal studies. The two existing studies examined only global volumes of grey and white matter before and after treatment without performing a detailed regional analyses (Roberto et al., 2011; Swayze et al., 2003), thus a thorough understanding of mechanisms of grey matter reduction and recovery in AN is still lacking.

To date, five studies have used DTI in a cross-sectional design to

more specifically measure structural connectivity in adults with acute AN (Frieling et al., 2012; Hayes et al., 2015; Kazlouski et al., 2011; Nagahara et al., 2014; Via et al., 2014). The main results of these studies point to reduced fractional anisotropy (FA, a measure of fibre directedness), which is commonly interpreted as white matter integrity (Mori & Zhang, 2006). Only three studies were conducted on adolescents with acute AN, reporting decreased (Frank, Shott, Hagman, & Yang, 2013; Travis et al., 2015), as well as increased FA measures (Travis et al., 2015; Vogel et al., 2016). Possible explanations for these mixed findings might be developmental factors, interacting with the nutritional challenges of starvation (Vogel et al., 2016), in addition to longer duration of illness and higher chronicity in adult patients (Steinhausen, 2002).

2.4.4.2 Findings from functional neuroimaging

Examining brain function, fMRI studies in AN have investigated activation patterns at rest, as well as during a variety of tasks. Given the reduced grey matter volume in the limbic/paralimbic system (Seitz et al., 2016), structures of the "salience" resting-state network such as the anterior insula and the anterior cingulate cortex, along with subcortical structures are of particular interest in AN research (Seeley et al., 2007). Indeed, the majority of resting-state studies conducted in acute AN have reported brain regions with impaired hemodynamic activation located in cortico-limbic circuits (Gaudio, Wiemerslage, Brooks, & Schiöth, 2016). However, the heterogeneity in analysis approaches with varying *a priori* assumptions makes the comparison of results difficult and studies investigating the same networks (i.e. default mode and visual networks) show diverging results (Boehm et al., 2014; Favaro et al., 2012; Phillipou et al., 2016). Hence to date no consensus regarding alterations in the acute stage of AN has been reached. Furthermore, the reversibility of these diverging alterations over the course of treatment has yet to be examined. First evidence of a cross-sectional study on weight-recovered AN patients suggests that reduced resting-state functional connectivity (rsFC) in visual and auditory resting-state networks (Scaife, Godier, Filippini, Harmer, & Park, 2017) and increased rsFC in the default mode

network (Cowdrey, Filippini, Park, Smith, & McCabe, 2014) remain even after weight recovery. As a recent review on resting-state fMRI (rsfMRI) in AN points out, there is a need for longitudinal investigation of rsFC in AN employing whole-brain analysis, to elucidate potential causative neurobiological mechanisms and possible subsequent damage due to the disorder (Gaudio et al., 2016).

Task-based fMRI research has used a number of different paradigms to examine the effect of disease related conditions on brain activation, such as exposure to body, food, and emotional stimuli (Zhu et al., 2012). Overall, the results of the fMRI studies point to increased activation in reaction to food and body stimuli in regions associated with emotions (caudate nucleus, insula, uncus, frontal cortex, temporal cortex) and a decreased hemodynamic response in parietal regions. Results with regard to emotional stimuli have been inconclusive (Zhu et al., 2012). In this context, the anticipation of stimuli seems to play a role as well, as decreased response sensitivity to expected salient stimuli was reported in limbic/paralimbic regions and heightened sensitivity during the occurrence of unexpected, although salient, stimuli (Treasure et al., 2015).

Assessing the functional availability of neurotransmitter receptors in the brain, PET studies have mainly focused on the dopaminergic and serotonergic system of the brain (Kaye, Wierenga, Bailer, Simmons, & Bischoff-Grethe, 2013; Treasure et al., 2015). Playing an important role in learning, motivation and reward processes, the dopamine D2 receptors of recovered AN patients have been found to demonstrate increased binding, while no differences were found in acutely ill patients (Broft et al., 2015; Gérard, Pieters, Goffin, Bormans, & Van Laere, 2011). Serotonin receptors (5-HT1A and 5-HT2A), involved in anxiety and eating regulation, have been found to exhibit increased binding properties in acute as well as in recovered patients (Bailer et al., 2005; Bailer et al., 2007; Galusca et al., 2008). The interpretation of these altered binding properties is not straight forward, as increased binding may reflect either a neuroadaptation to increased transmission of dopamine or serotonin, or a genuine hypofunction of the neurotransmitter signalling (Broft et al., 2015; Laruelle, Slifstein, & Huang, 2003). It remains to be determined whether

these alterations are apparent before illness onset (thus represent a risk factor), or whether they are influenced by malnutrition and represent a consequence of the illness (Treasure et al., 2015).

2.4.4.3 Neuroendocrinology

Besides the brain alterations summarised above, another neurobiological factor is of importance: The underweight in AN leads to significant endocrine alterations. Altered levels of hormones involved in appetite regulation, such as leptin and ghrelin, altered thyroid function, as well as decreased gonadal hormone levels have most frequently been reported (Lawson & Klibanski, 2008; Misra & Klibanski, 2014). Most of these hormone alterations can be seen as physiological adaptations to starvation and seem to normalise with weight recovery, however, some persist even after recovery and may pose a risk factor for future relapse (Lawson & Klibanski, 2008; Misra & Klibanski, 2014; Schorr & Miller, 2016).

2.4.5 An aetiological model of Anorexia nervosa and its challenges

In conclusion, there are multiple risk and maintaining factors associated with AN, which have led to a multifactorial model of the disorder. Integrating the interaction of risk and maintaining factors with respect to their occurrence during human development, Fig. 2.2 illustrates the neuropsychiatric aetiological model of AN (Herpertz-Dahlmann et al., 2011; Kaye, 2009). This model represents a diathesis-stress model of the disorder and will serve as a theoretical framework of the present thesis. It is based on the available empirical evidence summarised above and considers the interplay of psychosocial processes and biological mechanisms, as well as stressful life events as prompting the illness onset (Herpertz-Dahlmann et al., 2011; Kaye, 2009): Based on factors that originated prenatal or emerged during childhood (such as genetic predispositions, developmental characteristics and personality traits), cultural factors and developmental influences (puberty) facilitate initial dieting behaviour and elicit weight loss. In combination with neurobiological alterations, vulnerable individuals may find themselves in a vicious cycle that reinforces restrictive eating to counter negative emotionality, thus leading to further weight loss and neurobiological alterations, which worsen the dysphoric mood. In 20-50% of cases this leads to a chronic course of AN (Steinhausen, 2002). To what extend individual factors, such as endocrine

or brain circuit alterations, interact and influence behaviour of patients with AN has yet to be explored (Treasure et al., 2015). However, the contribution of brain alterations observed in AN are likely to facilitate the abnormal food intake and high anxiety, and in interaction with endocrine alterations, traits and environmental factors, determine the course of the illness (Herpertz-Dahlmann et al., 2011; Kaye, 2009).

A main challenge in AN research poses the differentiation between primary and secondary effects of starvation (e.g. effects of acute underweight vs. irreversible neural alterations due to malnourishment), affecting neurobiological factors and behaviour, and primary mechanisms driving the disorder (Frank, Shott, Hagman, & Yang, 2013). Regarding neuroimaging studies, this issue has yet to be resolved. The clear majority of studies summarised above has either been conducted on currently ill or already recovered patients. Longitudinal assessments are needed to enhance the understanding of the restorative neural mechanisms in AN.

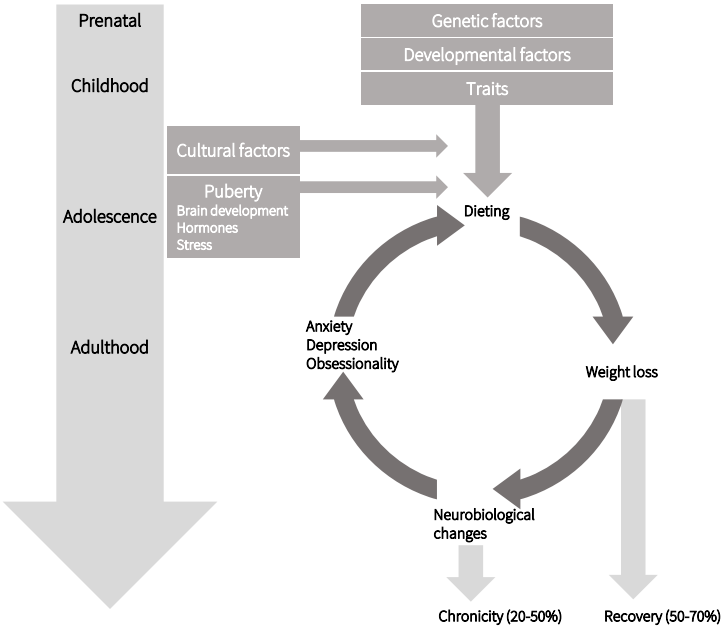

Figure 2.2. Aetiological model of Anorexia nervosa (adapted after Herpertz-Dahlmann et al., 2011; Kaye et al., 2009; Steinhausen, 2002).

CHAPTER 3

Aims and hypotheses

In the previous chapter, current knowledge about AN was summarised and an aetiological model presented. The relationship between neural alterations and AN are of particular importance to this thesis. The differentiation between premorbid, potentially causative, neurobiological alterations and post-morbid consequences of AN, as well as the effect of starvation on neurobiological systems represents a key challenge in AN research due to the lack of prospective longitudinal studies (see Section 2.4.4). Furthermore, the majority of neurobiological studies has been conducted cross-sectionally with either currently ill or already recovered patients, thus processes of recovery are poorly understood. Given the young age of potential subjects and the rarity of the disorder, prospective longitudinal studies on the neurobiology of AN are difficult to conduct. However, reorganisation processes during weight recovery are feasible to investigate in a longitudinal design with acutely ill patients. The current thesis therefore focusses on brain alterations in the acute phase of AN and mechanisms of plasticity and gradual reorganisation during weight recovery. Its main aim is the temporal mapping of neural and behavioural changes induced by weight gain, to help elucidate restorative mechanisms and identify potential residual brain alterations. In the following, the aims and hypotheses of the empirical part of this thesis project will be outlined.

3.1 Empirical work I – Structural brain morphometry over the course of treatment

As outlined above, the majority of brain imaging studies in AN have been conducted with currently ill or recovered patients, capturing either state-related consequences of malnourishment or so-called "scarring" (Herpertz-Dahlmann et al., 2011; Joos et al., 2011; Uher et al., 2003). The aim of the first empirical work thus was to examine structural brain changes in the cerebrum and subcortical regions by using a novel surface-based analysis approach. Morphometric alterations in AN patients were investigated at three time points in AN patients: (TP1) at the beginning of treatment with severe underweight, (TP2) during therapy after initial weight gain, (TP3) at the end of therapy with a close to healthy BMI. In accordance with previous studies, it was hypothesised that cortical thickness and subcortical brain volumes of AN patients would be decreased at the beginning of treatment compared to healthy control women (HC). The AN group was predicted to show at least a partial recovery with weight restoration, while no changes in the HC group were expected. Furthermore, correlations between structural brain alterations in AN patients and parameters of illness history, changes in eating disorder severity, and age were explored.

3.2 Empirical work II – Resting-state functional connectivity over the course of treatment

Investigation of resting-state functional connectivity (rsFC) networks offers a task-independent tool to gain insight into biased information processing underlying AN (Fox & Greicius, 2010; Gaudio et al., 2016). There is a lack of longitudinal examination of rsFC in AN patients and as a recent review points out, longitudinal whole-brain studies are required to identify neurobiological mechanisms (Gaudio et al., 2016). Thus, the second study aims at investigating rsFC in AN in a longitudinal design, to elucidate potential network alterations and recovery processes. We used resting-state fMRI to examine global network deviations and local differences in neural synchrony at three time points in AN patients: (TP1)

at the beginning of treatment with severe underweight, (TP2) during therapy after initial weight gain, (TP3) at the end of therapy with a close to healthy BMI. Based on the existing literature, it was hypothesized that functional connectivity in AN patients is reduced at TP1, compared to HC. With weight restoration, processes of recovery were expected in the AN group. Additionally, correlations with clinical parameters were explored.

3.3 Empirical work III – Cross-sectional investigation of biased diffusion indices in the fornix due to structural alterations in Anorexia nervosa

Acute AN is characterized by reduced brain mass and increased cerebrospinal fluid (CSF) in the ventricles and the subarachnoid space (Seitz et al., 2014; Titova, Hjorth, Schiöth, & Brooks, 2013). Although the underlying pathophysiology of AN is little understood, recent diffusion imaging studies have repeatedly suggested the fornix as a key structure with impaired fibre integrity in AN (Frank, 2015; Frank, Shott, Hagman, & Yang, 2013; Hayes et al., 2015; Kazlouski et al., 2011; Nagahara et al., 2014; Via et al., 2014). The aim of the third study thus was to combine insights from structural MRI and DTI to investigate the identified alterations of diffusion indices in the fornix with advanced analysis techniques, considering CSF as potential confounder of diffusion imaging. It was hypothesised that impaired forniceal fibre integrity in AN, as measured by aberrant fractional anisotropy (FA), is dependent on ventricular volumes and biased by partial volume effects (PVE). Previously found differences in the fornix of AN patients were expected to diminish when appropriately controlling for the PVE.

CHAPTER 4

Methods

This chapter will give an overview of the process and criteria of participant recruitment, the design of the project, as well as utilised measurements pertaining all three empirical studies of the present work.

4.1 Participants

4.1.1 Recruitment

Women diagnosed with current AN were recruited at the inpatient unit, Centre for Eating Disorders, Department of Psychiatry and Psychotherapy, University Hospital Zurich, Zurich, Switzerland. At the Centre, all patients participated in an interdisciplinary, multimodal inpatient program that offers structured and specific treatment for severely eating-disordered patients (Department of Psychiatry and Psychotherapy, 2016). For the duration of data acquisition of the current project, patients were either presently participating in the inpatient programme or had completed their inpatient treatment within four weeks prior to data acquisition. A group of healthy control women was recruited using flyers and email advertisements. Both groups were closely matched with respect to age, handedness, intelligence, and education. Participant characteristics are summarised in Table 4.1.

4.1.2 Inclusion and exclusion criteria

General inclusion criteria comprised being female, aged between 18 and 35 years, and having good command of standard or Swiss German.

Furthermore, AN patients were deemed eligible when diagnosed with current AN (as assessed by the Structured Clinical Interview for DSM-IV Axis I, SCID-I; Wittchen, Zaudig, and Fydrich, 1997), with a BMI $\leq$ 15.5 (severe AN), and a duration of illness of at least 1 year. Healthy controls were required to have a BMI between 18 and 23, no current or past eating disorders or other psychiatric disorders (screened with the SCID-I; Wittchen et al., 1997), no current diet, and no life-time medication affecting the central nervous system.

General exclusion criteria included current or past neurological disorders, current or past diagnosis of a psychotic disorder or psychoactive substance dependence, abuse of alcohol/nicotine/caffeine, current pregnancy, high debility of sight (wearing glasses with no possibility of wearing contact lenses), professional knowledge about nutrition (e.g., cook or dietician), and general contraindications against MRI procedures.

Table 4.1

Project participants' characteristics assessed at TP1, per time point sample

	Group (time point)										AN1	AN1	AN1
	AN1		AN2		AN3		HC1		HC3		vs. AN2	vs. AN3	vs. HC1
Measure	$n = 41$		$n = 30$		$n = 20$		$n = 28$		$n = 22$		p	p	p
Age (*M, SD*)	22.3	4.3	22.1	4.4	22.4	4.4	23.6	3.3	23.7	3.4	.85	.93	.182
Age of illness onset (*M, SD*)	15.7	2.4	15.8	2.3	16.2	2.5					.86	.45	
Duration of illness (*M, SD*)	6.4	4.3	5.9	4.0	6.2	4.4					.62	.87	
Education (*M, SD*)	12.9	3	13.1	3.1	13.8	2.7	14.7	4.4	14.1	4.8	.79	.26	.057[a]
Spatial perception (*M, SD*)	9.6	0.8					9.5	1.0					.652
BMI (*M, SD*)	13.8	1.3	16.3	1.1	18.3	0.6	20.9	1.8	20.6	1.5	<.001	<.001	<.001
AN subtype (*n*, %)													
Restrictive	35	85.4	26	86.7	17	85	0	0	0	0	.88	.97	<.001
Binge-purge	6	14.6	4	13.3	3	15	0	0	0	0	.88	.97	.036
Comorbid diagnoses (*n*, %)													
- Depressive disorders	14	34.1	11	36.7	8	40	0	0	0	0	.82	.65	<.001
- Depression and Panic disorder	1	2.4	1	3.3	0	0	0	0	0	0	.82	.49	.412
- Depression and social phobia	2	4.9	2	6.7	2	10	0	0	0	0	.75	.45	.238
- Dysthymia	1	2.4	1	3.3	0	0	0	0	0	0	.82	.49	.412
- Dysthymia, PTSD, and nonorganic psychosis	1	2.4	0	0.0	0	0	0	0	0	0	.38	.49	.412
- Total	19	46.3	14	46.7	10	50	0	0	0	0	.97	.79	<.001

Note. Age, age of illness onset, duration, and education in years; spatial perception measured as correct responses to the Number location test (Warrington & James, 1991); BMI = body mass index; PTSD = post-traumatic stress disorder. *Upper part*: *p*-values correspond to 2-tailed t-tests; AN1 vs. AN2 and AN1 vs. AN3, for paired groups; AN1 vs. HC1, for independent groups. *Lower part*: *p*-values correspond to chi-square tests. [a]Equal variances not given (Levene's test), Welch's t-test used instead (Welch, 1947).

4.2 Design

4.2.1 Project design

The project for the present thesis had a prospective longitudinal and cross-sectional comparative design, with two groups. A group of AN patients was assessed at three time points (TP1, TP2, TP3) to closely capture potential weight-related brain changes over the course of an in-patient programme at the University Hospital of Zurich, Switzerland (Klinik für Psychiatrie und Psychotherapie, 2016). Measurements of the AN group were scheduled according to patient's BMI and were taken at the beginning (TP1: BMI ≤ 15.5), in the middle (TP2: $15.5 <$ BMI < 17.5), and at the end of treatment with a (close to) healthy BMI ≥ 17.5 (TP3). A group of HC was assessed at two time points (TP1 and TP3). The interval between TP1 and TP3 for both groups was 4-6 months after TP1 (Table 4.2). Data acquisition started in April 2014 and is ongoing to this date, the last datasets considered for the present work were acquired in February 2017. Total counts of participants per time point are summarised in Fig. 4.1.

4.2.2 Study design

Of the three empirical studies included into this work, two were longitudinal and cross-sectional comparative in design and included all three time points (Study I and II, see Chapter 5 and 6). Study III was designed in a comparative cross-sectional design and focused on data from TP1 (see Chapter 7). Participant counts per study are summarised in Fig. 4.1.

Table 4.2

Project design and procedures for each time point

Group	Measures	TP1	TP2	TP3
AN	BMI	$\leq$15.5	15.5 < BMI < 17.5	$\geq$ 17.5
	Time after TP1		1-3 months	4-6 months
	Inclusion/ exclusion criteria	×	×	×
	Diagnostic interview (SCID-I)	×		
	Informed consent	×		
	Neuropsychological tests	×		
	MRI	×	×	×
	Questionnaires	×	×	×
HC	BMI	18.0 – 23.0		18.0 – 23.0
	Time after TP1			4-6 months
	Inclusion / exclusion criteria	×		×
	Diagnostic interview (SCID-I)	×		
	Informed consent	×		
	Neuropsychological tests	×		
	MRI	×		×
	Questionnaires	×		×

Note. AN=Anorexia nervosa; BMI=Body mass index (kg/m^2); HC=Healthy controls; MRI=Magnetic resonance imaging; SCID-I=Structured Clinical Interview for DSM-IV, Axis I; TP=Time point.

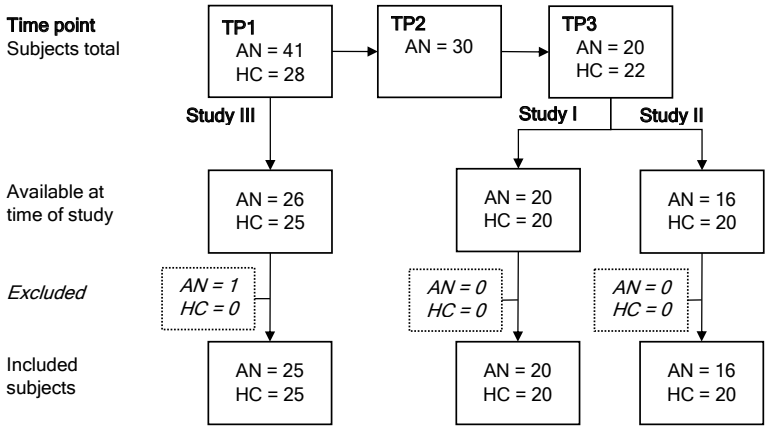

Figure 4.1. Overview of participant recruitment over time, with separate participant counts per study.

4.3 Procedures

For the AN group, data for the first measurement time-points (TP1) were collected after a minimum hospitalisation time of 2 weeks with a fixed meal plan and extensive somatic checks, to exclude biases due to acute malnutrition and dehydration. To avoid effects of short-term hormone dependent effects on functional or structural brain measures in HC (Hagemann et al., 2011; Petersen, Kilpatrick, Goharzad, & Cahill, 2014), both scans were scheduled in the folicular phase of the women, within the first 10 days of their cycle. Inpatients with AN had their meals at 7.30 a.m., 11.45 a.m., and 5.45 p.m. each day. MRI measurements took place between 3 p.m. and 4.30 p.m., corresponding to a fasting time of about 3-4 hours and an intermediate hunger-satiety state during MRI (Uher et al., 2003; Uher et al., 2004). Healthy subjects were instructed to have a proper meal at noon.

4.4 Measures

In this section, the specific properties of the collected measures will be summarised. The first subsection describes the interview and questionnaires assessed throughout the project, the second subsection describes neuropsychological tests administered at TP1. A broad overview of the time line of the measures assessed within this project is displayed in Table 4.2.

4.4.1 Interview and questionnaires

Apart from establishing BMI, socio-demographic data, and medical history by semi-structured interviews, validated German versions of psychometric instruments were used to assess the following constructs.

4.4.1.1 Diagnostic interview

The Structured Clinical Interview for DSM-IV Axis I (SCID-I; Wittchen et al., 1997) was used to validate patients' diagnosis, to assess any comorbid psychiatric disorders, and to confirm the absence of any diagnosis

in the HC group. The SCID-I is a well-established diagnostic interview for the assessment of Axis I mental disorders according to DSM-IV-TR (APA, 2000) with fair to excellent inter-rater reliability (Lobbestael, Leurgans, & Arntz, 2011; Zanarini & Frankenburg, 2001). The SCID-I was administered at TP1 of the present thesis project. Comprehensive interviews with patients were conducted face-to-face, screening for diagnosis with HC were conducted via telephone by well-trained interviewers. Telephone-based screenings are comparable to diagnostic information from face-to-face assessments (Rohde, Lewinsohn, & Seeley, 1997).

4.4.1.2 Eating disorder symptoms

The severity of eating disorder symptoms was measured with the Eating Disorder Examination Questionnaire (EDE-Q; Hilbert & Tuschen-Caffier, 2006) and the Eating Disorder Inventory (EDI; Garner, Olmstead, & Polivy, 1983; Paul & Thiel, 2005).

The EDE-Q is a standardised self-report questionnaire, based on the Eating Disorder Examination interview (Cooper & Fairburn, 1987), to assess the eating disorder pathology within the past 28 days. Twenty-two items are rated from 0 to 6 and form the four subscales eating concern, restraint eating, shape concern, and weight concern. Additionally, a global score can be calculated with a maximum value of 6, higher scores indicating greater eating disorder severity. The optimal cut-off score to discriminate between patients and controls on the global score is 2.5 (Rø, Reas, & Stedal, 2015). Six additional items capture the frequency of eating disorder-related behaviours, such as binging or purging, within the same time frame of 28 days. Cronbach's alpha (α) of the German version ranges between .85 and .97 and the test-test reliability of the total score is .88 (Hilbert, Tuschen-Caffier, Karwautz, Niederhofer, & Munsch, 2007). Within the present thesis project the EDE-Q was administered at all three time points. In the sample of the present thesis, Cronbach's alpha of the AN group was .64 at TP1, .88 at TP2, .86 at TP3, and of the HC group .88 at TP1, .91 at TP3, indicating overall good to excellent internal reliability. The low internal reliability of the AN group at TP1 needs to be understood within the context of a low variance of response scores

of the patients, which directly influences the calculation of Cronbach's alpha (α; Cronbach, 1951).

The EDI (Garner et al., 1983; Paul & Thiel, 2005) is a multidimensional self-report questionnaire to assess pathological eating behaviours with a 6-point Likert scale format ranging from 1 to 6. It consists of 64 items, which constitute the following 8 subscales: drive for thinness, interoceptive awareness, body dissatisfaction, maturity fears, perfectionism, interpersonal distrust, as well as a total score. Scale scores are the sum of all relevant items, thus the maximum possible total score is 384. The EDI has good ($\alpha > .80$) to excellent ($\alpha > .90$) internal consistency scores for AN patients (Garner et al., 1983; Paul & Thiel, 2005) and shows good test-retest reliability (Thiel & Paul, 2006). The EDI was administered at TP1 and TP3 of the present thesis project. In the sample of present thesis, Cronbach's alpha of the AN group was .95 at TP1, .96 at TP3, and of the HC group .94 at TP1, .93 at TP3, indicating excellent internal reliability.

4.4.1.3 Depression

The Beck Depression Inventory (BDI; Beck & Steer, 1984; Hautzinger, Bailer, Worall, & Keller, 1994) is a widely used 21-item self-rating questionnaire to assess depression severity. Participants are being asked to rate how they felt during the past week on a Likert-scale ranging from 0 to 3, with a maximum possible sum score of 63. The clinically meaningful cut-off score is 18, higher values indicating a higher depression severity. The BDI has an internal consistency between .74 and .92 for psychiatric and non-clinical samples respectively and shows good test-retest reliability (Hautzinger et al., 1994). The BDI was administered at all three time points of this thesis project. For this thesis, Cronbach's alpha of the AN group was .90 at TP1, .88 at TP2, .86 at TP3, and of the HC group .82 at TP1, .64 at TP3, indicating overall good to excellent internal reliability. As mentioned above, low variance of response scores directly influences the calculation of Cronbach's alpha (Cronbach, 1951), the low internal reliability for the HC group at TP3 falls in this category.

4.4.1.4 Hedonic capacity / anhedonia

The Snaith-Hamilton-Pleasure Scale (SHAPS; Franz et al., 1998; Snaith et al., 1995) is a self-report questionnaire capturing the ability to experience pleasure (hedonic capacity) with 14 items. Answers range from 1 to 4 to indicate agreement, and are dichotomised for the total score to 0 and 1, with 1 indicating disagreement (response value 1 or 2). The total score is calculated as sum of the dichotomised answers, leading to a maximum score of 14, with greater values indicating higher levels of anhedonia. A cut-off score of 2 discriminates between normal and abnormal levels of hedonic tone (Snaith et al., 1995). The SHAPS has demonstrated good to excellent internal consistency in clinical (Franken, Rassin, & Muris, 2007; Franz et al., 1998) as well as healthy samples (Franken et al., 2007). The SHAPS was administered at all three time points of the present thesis project. In the sample of present thesis, Cronbach's alpha of the AN group was .90 at TP1, .89 at TP2, .87 at TP3, and of the HC group .86 at TP1, .84 at TP3, indicating good to excellent internal reliability.

4.4.1.5 Handedness

To match patients and healthy controls for handedness, all participants filled out a short form of the Edinburgh Handedness Inventory (Veale, 2014). This scale comprises 4-items and captures lateralised behaviour along a continuum (from left-handed -100 to +100 right-handed). Participants with a laterality score between -60 and +60 are classified as mixed-handers. The scale shows very good internal consistency (α=.93) and correlates highly with the long form of this questionnaire (r=.94) (Oldfield, 1971). In the sample of the present thesis, Cronbach's alpha was .90 at TP1 for both groups.

4.4.2 Neuropsychological tests

To assess the cognitive abilities of the participants, a number of neuropsychological tests were used at TP1. All computer-based tests

were administered within the Hogrefe Test System (Hänsgen & Merten, 2001).

4.4.2.1 Spatial neglect

To exclude brain lesions, laterality in spatial perception was assessed using the well-established number location test from the validated Visual Object and Space Perception Battery (Rapport, Millis, & Bonello, 1998; Warrington & James, 1991). Cards with two squares each are presented to the participant; the upper square presents a random selection of numbers and the bottom square contains a single black dot. During 10 trials, participants identify the number in the upper square that corresponds to the position of the dot in the bottom square (Warrington & James, 1991). The test has been reported to have good specificity and an internal consistency of .84 (Bonello, Rapport, & Millis, 1997), indicating a good internal reliability. For the present sample, answers to individual items were recorded as a sum score, thus individual item values could not be analysed for internal consistency.

4.4.2.2 Intelligence

In addition, two scales were used to assess intelligence. Results of these intelligence measures can be found in the sample descriptions of the respective empirical work (see Table 5.1, 6.1, and 7.1). Fluid intelligence was captured with the Wiener Matrizen-Test (WMT), a Rasch-scaled language-free inventory (Formann & Piswanger, 1979). The original test consists of 24 items, each presenting an array of abstract geometric figures in a specific order. The participant is asked to choose for each item one of eight possible answers to continue the array with the same logical rule. For the present project, the updated shorter version with 18 items was used (Formann, Waldherr, & Piswanger, 2011). The internal consistency of the computer version lies between .76 and .81 (Formann et al., 2011).

To estimate verbal intelligence, a digital version of the Wortschatztest (WST) was chosen (Schmidt & Metzler, 1992). The test presents six words, only one of which actually exists. The participants are requested

to identify the existing word. Besides verbal intelligence and language understanding, this test allows for an estimation of the premorbid intelligence level in case of mild to moderate brain impairments. The internal consistency of the test is .94 (Schmidt & Metzler, 1992), indicating excellent internal reliability. For the present sample, answers to individual items of both performance tests (WMT and WST) were recorded as a sum score, thus individual item values were not analysed for internal reliability.

4.5 Magnetic resonance imaging

For MRI data acquisition of the present thesis, a 3.0 Tesla whole-body MRI system (Ingenia, Philips, Best, The Netherlands) was used, equipped with a 32-channel head coil. The scans were conducted at the Division of Neuroradiology, University Hospital Zurich. For all participants, T1-weighted structural images were inspected by a trained neuroradiologist for any relevant pathology. All scans comprised the following sequences:

4.5.1 T1-weighted images (structural MRI)

3D T1-weighted structural images were acquired using a three-dimensional turbo field echo (TFE) sequence with echo time (TE)=3.8 ms, repetition time (TR)=8.3 ms, field of view (FOV)=240×240 mm^2, acquisition matrix=240×240, 160 sagittal slices, isotropic voxel size=$1 \times 1 \times 1$ mm^3, flip angle=8°, and TFE factor=240.

4.5.2 Resting-state functional MRI

Resting-state functional images (rsfMRI) were acquired with eyes closed using a gradient-echo T2*-weighted echo planar imaging (EPI) sequence with TE=30 ms, TR=2.3s, flip angle=78°, FOV=220×220 mm^2, isotropic voxel size=$3 \times 3 \times 3$ mm^3, 40 axial slices, and 210 volumes with a scan duration of ∼8 min. Subjects were instructed to close their eyes, to lie quietly in the scanner, to relax, and to let their mind wander.

4.5.3 Diffusion weighted images

Structural diffusion weighted images were acquired for 64 non-colinear diffusion gradient directions and one non-diffusion-weighted b0 reference volume, with a b-value of 1000 s/mm^2, TE=90 ms, TR=9.8 s, flip angle=90°, FOV=224 × 224 mm^2, SENSE factor 2 (Pruessmann, Weiger, Scheidegger, & Boesiger, 1999), EPI factor 55 (Mansfield, 1977)), isotropic voxel size=2×2×2 mm^3, 75 slices and a scan duration of 14 min. Additionally, a T1-weighted fast-field echo sequence was acquired to map the B0 field in order to correct the DTI data for echo planar imaging related geometrical distortions (Jones & Cercignani, 2010) with TE=4.4 ms, TR=4.0 s, flip angle=45°, FOV=256 × 256 mm^2, isotropic voxel size=2×2×2 mm^3, 77 slices and a scan duration of $\sim$ 2 min. During DTI acquisition, subjects were instructed to lie still and had the option to either watch a video or to close their eyes and relax.

4.5.4 Cardiopulmonary data

For each MRI sequence, the heart rate was concurrently recorded at 500 Hz using an MRI compatible electrocardiograph (InVivo International, Best, The Netherlands). The scanner software automatically detected the maximum of the cardiac signal (R-peak) and registered their occurrences in a logfile.

4.6 Ethics

Permission to conduct this research was granted by the Ethics Committee of Zurich, Switzerland (see Appendix C). The study protocol complied with the Declaration of Helsinki and all participants provided written informed consent prior to participation (see Appendix C).

CHAPTER 5

Empirical Work - Study I: Longitudinal investigation of brain plasticity and the influence of age on structural brain recovery in anorexia nervosa

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5.1 Abstract

Background: Neuroimaging studies on anorexia nervosa (AN) have consistently reported globally reduced grey matter in AN patients with acute underweight. While some studies on recovered patients provide evidence for the reversibility of these impairments, longitudinal studies investigating temporal patterns of recovery processes are scarce and factors associated with brain restitution are poorly understood.

Methods: We report a structural magnetic resonance imaging study using surface-based morphometry to analyse high resolution T1-weighted images from a sample of 20 adult patients with severe AN and 20 closely matched healthy controls (HC). The longitudinal design comprised three time points, capturing the course of weight restoration therapy in AN patients at distinct stages of weight gain.

Results: Linear-mixed effect models revealed reversibility of globally reduced cortical thickness and reduced subcortical volumes observed in AN patients at the beginning of treatment, with significant residual differences remaining in parietal and frontal brain regions even after weight restoration. Interestingly, the broad restoration of cortical thickness in AN patients showed a strong negative association with age.

Conclusions: Temporal patterns of structural brain recovery in adult AN patients suggest partial restoration of cortical thickness with patients' age as a strong predictor of brain restitution, potentially indicating decreases of brain plasticity across the lifespan. These results may be of value to provide evidence for treatment decisions towards early weight restoration therapy and a sufficient period of weight stabilisation at the end of treatment.

5.2 Introduction

Anorexia nervosa (AN) is a severe and enduring psychiatric disorder, characterised by significantly reduced body weight (APA, 2013) and associated reduced brain volume (Seitz et al., 2016; Titova et al., 2013). Results from early computed tomographic (CT) studies provided first evidence for enlarged ventricles and sulci in AN patients with acute underweight (Artmann, Grau, Adelmann, & Schleiffer, 1985; Dolan, Mitchell, & Wakeling, 1988; Krieg, Backmund, & Pirke, 1986). Later magnetic resonance imaging (MRI) studies supported these findings and further suggested grey and white matter reductions (Golden et al., 1996; Katzman et al., 1996; Kingston, Szmukler, Andrewes, Tress, & Desmond, 1996).

Recent studies have largely demonstrated reduced grey matter volume in AN with severe underweight, in a globally distributed set of brain regions, affecting almost the whole cortex (for reviews see Seitz et al., 2016; Eynde et al., 2012). Reports on reduced white matter volumes have been less consistent, with some studies reporting decreased volume (e.g., Seitz et al., 2015; Via et al., 2014), while others did not find significant changes (Fonville et al., 2014; Roberto et al., 2011). These reductions are generally interpreted as consequences of patients' malnutrition and have been largely found to be absent in long-term recovered adult AN patients (Favaro et al., 2015; Frank, Shott, Hagman, & Yang, 2013; Friederich et al., 2012; Joos et al., 2011; Wagner et al., 2006). In a voxel-based morphometric study, an adult sample of long-term recovered AN patients displayed grey and white matter values similar to HC after a remission period of more than one year (Wagner et al., 2006). However, a more recent study on five AN patients with a remission period of more than 5 years found some indication of persevering grey matter decreases (Joos et al., 2011).

In adolescent AN patients, three longitudinal studies exist reporting complete normalisation of grey matter loss after a brief period of weight restoration (Bernardoni et al., 2016; Bomba et al., 2015; Mainz et al., 2012). For adult AN patients there is a lack of longitudinal studies. The

two existing studies only examined overall volumes of grey and white matter before and after treatment and failed to perform detailed regional analyses (Roberto et al., 2011; Swayze et al., 2003).

In the present longitudinal study, we used a well-validated surface-based approach to analyse structural MRI scans from female patients with AN, acquired at three time points: (1) at the beginning of treatment with acute underweight, (2) during therapy after initial weight gain, and (3) at the end of therapy with a close to healthy BMI. The aim was to identify brain structural alterations in the phase of acute underweight and monitor their development over the course of treatment to better understand regional processes of disease-specific brain changes with weight restoration. Specifically, we hypothesised in accordance with previous studies (Seitz et al., 2016; Eynde et al., 2012) that cortical and subcortical brain structures of AN patients would show decreases in thickness or volume, respectively, at the beginning of treatment compared to healthy control women (HC). With respect to the temporal development of these impairments we predicted at least a partial recovery with weight restoration. Additionally, we examined whether structural brain alterations in AN patients were related to parameters of eating disorder severity and patients' age at the time of the study. We hypothesised that patients' initial cortical thickness would be associated with lower BMI, longer illness history, and greater eating disorder pathology. As patients with an early onset of AN have been reported to have a more favourable outcome (Steinhausen, 2002), increasing cortical thickness over the course of treatment was expected to be more pronounced in younger patients.

5.3 Methods and materials

5.3.1 Participants

Women diagnosed with severe AN (BMI $\leq$ 15.5) according to DSM-IV criteria (APA, 2000) and a group of HC were assessed with the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I, First, Spitzer, Gibbon, & Williams, 2002). Groups were matched for sex, age, handedness, intelligence and education. All women were strongly right-handed, except for one left-handed woman in each group, as assessed with the Edinburgh inventory (Oldfield, 1971).

Patients with AN participated in an eating disorder-specific inpatient programme at the University Hospital of Zurich, Switzerland (Department of Psychiatry and Psychotherapy, 2016), with a target BMI $\geq$ 18.5. Thirty-five patients completed the baseline time point (TP1) of this study, 20 of which were eligible for participation in all three time points (see study design). Two patients' data was not available at TP1 due to technical difficulties. Nine patients were given comorbid diagnoses besides AN: major depressive disorder (n=7) and depression and social phobia (n=2). Seven patients (38.9%) were medicated: SSRI (n=4) and SSRI and atypical antipsychotics/anxiolytics (n=3). Medication was stable for 3 weeks prior to TP1 and patients were instructed to continue taking it as normal.

Inclusion criteria for HC were a BMI of 18.5-23.0, not having a history of any mental illness, not having first-degree relatives with a lifetime diagnosis of an eating disorder, and not be taking any medication, including hormonal contraceptives. Twenty-two controls participated in TP1, two of whom had to be excluded from the second time point due to somatic complaints. Thus, the final sample for the statistical analyses consisted of 20 AN patients and 20 HC. The study was approved by the local ethics committee and the study protocol complied with the Declaration of Helsinki. All participants gave their written informed consent prior to study enrolment.

5.3.2 Study design

Over the course of the inpatient programme (Department of Psychiatry and Psychotherapy, 2016), measurements of the AN group were taken at three time points: at the beginning (TP1, BMI $\leq$ 15.5), in the middle (TP2: 15.5 $<$ BMI $<$ 17.5), and at the end of treatment with a close to healthy BMI of $\geq$ 17.5 (TP3). To calculate the BMI, patients' height was measured at the beginning of treatment, weight measures were obtained twice per week before breakfast, within the regular treatment scheme by trained hospital nurses. The HC group participated in the same procedure at two time points (TP1 and TP3). The interval between TP1 and TP3 for both groups was 4-6 months after TP1. The first time point of AN patients was scheduled after a hospitalization time of 2 weeks with a fixed meal plan and extensive somatic checks, to exclude biases due to acute malnutrition and dehydration. To avoid effects of short-term hormone dependent structural changes in HC (Hagemann et al., 2011), both scans were scheduled in the folicular phase of the women, within the first 10 days of their cycle. Scans for all participants were performed between 3 p.m. and 4.30 p.m.

5.3.3 Behavioural and psychometric assessment

Validated German versions of the following psychometric tests were used in this study: The Viennese Matrices Test (WMT) for non-verbal intelligence (Formann & Piswanger, 1979) and the Vocabulary test (WST) for verbal intelligence (Schmidt & Metzler, 1992). Eating disorder severity was assessed with the Eating Disorder Examination Questionnaire (EDE-Q) (Hilbert & Tuschen-Caffier, 2006), depression severity was captured with the Beck Depression Inventory (BDI, Hautzinger et al., 1994), and anhedonia was assessed with the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995).

5.3.4 MRI data acquisition

Brain images were acquired with a 3.0 Tesla whole-body magnetic resonance imaging (MRI) system (Ingenia, Philips, Best, The Netherlands),

equipped with a 32-channel head coil. Whole-brain 3D T1-weighted structural images were acquired using a three-dimensional turbo field echo (TFE) sequence with echo time (TE)=3.8 ms, repetition time (TR)=8.3 ms, field of view (FOV)=240 × 240 mm^2, acquisition matrix=240 × 240, 160 sagittal slices, isotropic voxel size=1×1×1 mm^3, flip angle=8°, and TFE factor=240. For all subjects, T1-weighted images were checked for relevant clinical pathology or anomalies by a trained neuroradiologist.

5.3.5 MRI data pre-processing

Structural T1-weighted images were processed with the FreeSurfer software suite version 6.0 (surfer.nmr.mgh.harvard.edu). This automated analysis procedure has been widely used and its processing steps have been described in detail elsewhere (Dale, Fischl, & Sereno, 1999). In brief, T1-weighted images in stereotactic space are segmented into different tissue types, considering a priori anatomical information and each voxel's intensity value. To reliably estimate cortical thickness and subcortical volumes, images were processed with FreeSurfer's longitudinal stream (Reuter, Schmansky, Rosas, & Fischl, 2012). For each subject, an unbiased median template image was created (Reuter & Fischl, 2011) using robust, inverse consistent registration between each time point of a subject (Reuter, Rosas, & Fischl, 2010). Data for each subject were then resampled to the respective template and pre-processed by (1) registration to Talairach space, (2) construction of brain mask and skull stripping, (3) normalisation and registration to the probabilistic atlas (Fischl et al., 2002; Fischl et al., 2004), (4) segmentation of subcortical regions, (5) creation of spherical surface maps, registration to cortical atlas, and parcellation, initialised with common information from the within-subject template to improve statistical power and reliability (Reuter et al., 2012). For each time point, cortical thickness maps for both hemispheres were then extracted and smoothed with a 15 mm full-width at half-maximum Gaussian kernel. Additionally, the following subcortical structures provided by the FreeSurfer stream were segmented and extracted for both hemispheres: nucleus accumbens, amygdala, caudate nucleus, hippocampus, globus pallidus, putamen, and thalamus. To assure data quality, all pre-

processed images were visually inspected and checked with the FreeSurfer QA tools 1.1 (surfer.nmr.mgh.harvard.edu/fswiki/QATools). All subjects had sufficient data quality.

5.3.6 MRI data analyses

Cross-sectional whole-brain differences of cortical thickness between groups at TP1 and TP3 were analysed using vertex-wise general linear models with group as independent and cortical thickness as dependent variable. Subcortical volumes and global brain measures (cortical grey matter, cortical white matter, cerebellar grey matter, cerebellar white matter, cortico-spinal fluid [CSF], intracranial volume) were compared using t-test for independent samples, corrected for multiple comparisons using false discovery rate (FDR) correction (Benjamini & Hochberg, 1995; Yekutieli & Benjamini, 1999).

The longitudinal analyses of the data were performed with linear-mixed effects (LME) models, more specifically with the spatiotemporal extension for mass-univariate data as implemented in FreeSurfer (Bernal-Rusiel, Greve, Reuter, Fischl, & Sabuncu, 2013; Bernal-Rusiel, Reuter, Greve, Fischl, & Sabuncu, 2013). LME models offer a powerful and versatile approach for the analysis of longitudinal data, with the advantage of differentiating between-subject and within-subject sources of variance and handling unequal numbers of time points (Bernal-Rusiel, Greve, et al., 2013). Visual inspection of mean trajectories revealed a linear trend over time, thus the spatio-temporal model was fitted with the intercept as random effect. For each tested contrast (main effect group, main effect time, interaction effect group $\times$ time), significance maps were created and FDR corrected at level 0.05 within FreeSurfer using an adaptive linear two-stage procedure (Benjamini, Krieger, & Yekutieli, 2006) to control for multiple comparisons.

5.3.7 Additional statistical analyses

Within- and between-group comparisons of demographic and psychometric measures were performed using t-tests for paired and independent

samples, respectively. Associations between brain measures and eating disorder symptoms were calculated with Pearson's correlations. These tests were performed using IBM SPSS Statistics 23.0 (SPSS Inc, an IBM company, Armonk, NY) and subsequently corrected for multiple comparisons with FDR correction (Benjamini & Hochberg, 1995; Yekutieli & Benjamini, 1999). If not otherwise stated, two-tailed p-values are reported.

5.4 Results

5.4.1 Demographic and psychometric measures

Group comparisons of demographic data at baseline (TP1) revealed no significant differences between AN patients an HC with respect to age, intelligence and education (ps $> .17$, see Table 5.1). As expected, AN patients had significantly lower BMIs and higher eating disorder severity (EDE-Q), depression (BDI), and anhedonia (SHAPS) scores compared to HC. These scores improved significantly over the course of therapy within the AN group, but stayed significantly elevated even at the end of treatment (Table 5.1).

5.4.2 Brain alterations during severe underweight

Global brain volumes at TP1 showed significantly reduced cortical and subcortical grey matter, reduced cerebellar white matter, and heightened CSF in AN patients compared to HC (Table 5.2). No differences were observed with respect to intracranial volume, excluding overall smaller skulls in AN patients as explanation for the observed differences ($p >.95$). Furthermore, volumes of cerebral white matter did not differ between groups ($p >.56$, Table 5.2).

Cross-sectional group comparisons of cortical thickness at TP1 demonstrated that global volumetric grey matter differences reported above were largely driven by differences in cortical thickness. Compared to HC,

Table 5.1

Group characteristics Study I

	TP1				TP2		TP3						
	AN1 $n = 18$		HC1 $n = 20$		AN2 $n = 18$		AN3 $n = 18$		HC3 $n = 20$		AN1 vs. HC1	AN3 vs. HC3	AN1 vs. AN3
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p*	*p*	*p*
Age	22.17	4.55	24	3.32							0.17		
Age of illness onset	16.04	2.65											
Duration of illness	6.12	4.45											
Education	13.72	2.70	14.20	4.99							0.72		
BMI	13.66	1.20	21.06	2.00	16.30	1.28	18.16	1.0	20.56	1.49	<.001	<.001	<.001
BMI increase per week					0.31	0.18	0.21	0.1					
Time after TP1 (weeks)					9.69	3.13	19.83	7.67	25.91	10.01		0.044	
EDE-Q total	3.18	1.32	0.65	0.56	1.86	1.01	1.64[a]	1.08	0.60	0.52	<.001	<.001	<.001
EDE-Q eating concern	3.09	1.49	0.22	0.49	1.56	0.94	1.24[a]	0.94	0.32	0.46	<.001	<.001	<.001
EDE-Q restraint	3.24	1.72	0.41	0.44	1.14	1.07	1.11[a]	0.95	0.29	0.35	<.001	<.001	<.001
EDE-Q shape concern	3.53	1.29	1.07	0.93	2.83	1.50	2.45[a]	1.68	1.01	0.75	<.001	<.001	<.001
EDE-Q weight concern	2.87	1.26	0.92	0.81	1.92	1.18	1.75[a]	1.38	0.77	0.82	<.001	0.003	<.001
BDI	21.39	9.51	3.95	3.97	16.28	9.21	11.31[a]	8.1	2.75	2.63	<.001	<.001	<.001
SHAPS	33.33	3.11	0.35	0.93	2.28	2.37	1.75[a]	2.32	0.30	0.73	<.001	0.024	0.019
WMT	125.59[b]	17.49	127.6	15.75							0.76		
WST	104.18[b]	8.56	106.7	11.28							0.46		

Notes. Age, age of illness onset, duration, and education in years; BMI = body mass index; BDI = Becks Depression Inventory total score; EDE-Q = Eating Disorder Examination Questionnaire score; SHAPS = Snaith-Hamilton Pleasure Scale total score; WMT = Viennese Matrices Test; WST = Multiple Choice Vocabulary Test. [a]Data available only for AN = 16 subjects; [b]AN = 17.

Table 5.2

Comparison of global brain measures between groups at TP1

	Group					
	AN (n = 18)		HC (n = 20)			
Measure	*M*	*SD*	*M*	*SD*	*t*	*p*
Grey matter (cortex)	453.6	31.1	483.2	32.9	−2.8	.018
Grey matter (subcortical)	56.9	3.9	60.4	3.7	−2.8	.011
White matter	432.9	33.6	440.6	53.5	−0.5	.605
CSF	1.5	0.5	1.2	0.2	3.1	.020
Intracranial volume	1554.1	139.6	1517.2	176.6	0.7	.604

Notes. Mean volumes represent absolute values (cm^3). Comparisons were corrected for false positives with FDR (Benjamini & Hochberg, 1995; Yekutieli & Benjamini, 1999). CSF = cortico-spinal fluid.

AN patients showed considerable bilateral atrophy in clusters covering large parts of both hemispheres (Fig. 5.1), sparing only parts of the sensorimotor cortex.

In accordance with the overall reduced subcortical volume, separate analyses of the individual subcortical structures yielded significant group differences at TP1 with reduced bilateral volumes in AN patients of nucleus accumbens, caudate nucleus, hippocampus, putamen, and thalamus, as well as the amygdala of the right hemisphere and the left hemispheric pallidum (Table 5.3).

5.4.3 Recovery processes with weight restoration

LME analyses yielded a significant interaction of group × time, revealing patterns of cortical thickness restoration in AN patients over the course of treatment (Fig. 5.3A), controlled for multiple comparisons at $p < 0.05$ with FDR correction across both hemispheres. Within-group analysis demonstrated significant improvements of cortical thickness during both treatment phases (Fig. 5.2). Restoration processes took place

Table 5.3

Subcortical volumes per group and time point

	TP1				TP2		TP3					
	AN1		HC1		AN2		AN3		HC3		AN1	AN3
	(n = 18)		(n = 20)		(n = 18)		(n = 18)		(n = 20)		vs. HC1	vs. HC3
Region	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	p^a	p^a
Accumbens ncl. L	0.31	0.10	0.37	0.09	0.28	0.09	0.28	0.11	0.36	0.10	.048	n.s.
Amygdala L	1.38	0.13	1.47	0.13	1.41*	0.12	1.40	0.13	1.47	0.12	n.s.	n.s.
Caudate ncl. L	3.48	0.43	3.81	0.39	3.56*	0.43	3.61	0.47	3.72	0.37	.027	n.s.
Hippocampus L	4.09	0.43	4.44	0.33	4.22**	0.42	4.25	0.42	4.47	0.36	.014	n.s.
Pallidum L	2.00	0.16	2.10	0.20	1.99	0.15	2.00	0.14	2.12	0.20	.048	n.s.
Putamen L	4.76	0.39	5.05	0.52	4.81	0.41	4.83	0.50	5.01	0.52	.048	n.s.
Thalamus L	7.71	0.58	8.23	0.62	7.90**	0.59	8.04**	0.62	8.20	0.59	.028	n.s.
Accumbens ncl. R	0.51	0.08	0.58	0.07	0.50	0.09	0.51	0.09	0.57	0.07	.028	n.s.
Amygdala R	1.72	0.17	1.83	0.11	1.75*	0.16	1.74	0.17	1.83	0.12	.048	n.s.
Caudate ncl. R	3.66	0.44	3.99	0.39	3.77*	0.43	3.79	0.47	3.95	0.39	.028	n.s.
Hippocampus R	4.10	0.43	4.42	0.35	4.22**	0.44	4.28	0.44	4.44	0.40	.027	n.s.
Pallidum R	1.96	0.16	2.03	0.21	1.95	0.15	1.95	0.13	2.05	0.20	n.s.	n.s.
Putamen R	4.85	0.42	5.28	0.46	4.93	0.48	4.93	0.52	5.26	0.48	.027	n.s.
Thalamus R	6.99	0.45	7.34	0.60	7.18**	0.51	7.28*	0.51	7.31	0.57	.048	n.s.

Notes. Mean values represent absolute values (cm^3). Significant differences within the patient group are marked with $*p < .05$, $**p < .001$ in column AN2 (AN1 vs. AN2) and column AN3 (AN2 vs. AN3). All comparisons were performed with mean values controlled for total intra-cranial volume and [a]corrected for false positives with FDR (Benjamini & Hochberg, 1995; Yekutieli & Benjamini, 1999). L = left hemisphere; ncl. = nucleus; n.s. = not significant; R = right hemisphere.

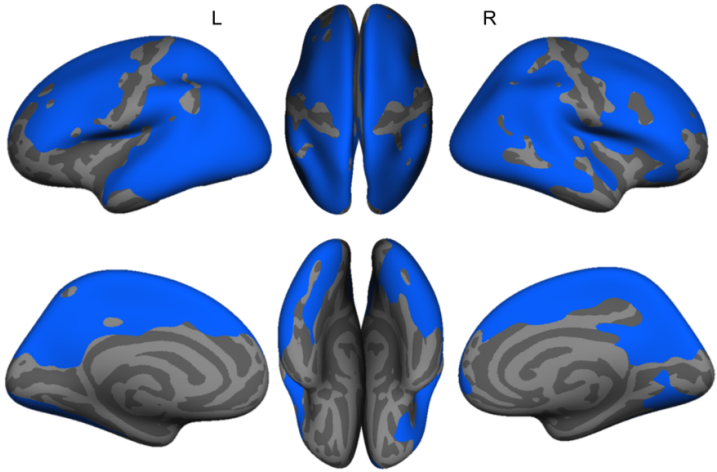

Figure 5.1. Cross-sectional comparisons of cortical thickness between groups at TP1. Significant clusters (blue) were projected onto inflated brain surfaces (grey), after correcting for multiple comparisons using Monte-Carlo simulations (5'000 permutations).

globally in both hemispheres during the first (TP1-TP2: mean increase left=0.09mm ± 0.06, $t(17)$=-6.6, $p < .001$; mean increase right=0.08mm ± 0.06, $t(17)$=-6.1, $p < .001$) and second treatment phase (TP2-TP3: mean increase left=0.03mm ± 0.06, $t(19)$=-2.1, p=.051; mean increase right=0.03mm ± 0.06, $t(19)$=-2.1, p=.045), with a notably stronger regeneration during the first phase.

Despite the significant global restoration of cortical thickness over the course of treatment (Fig. 5.3A), whole-brain group comparisons at TP3 yielded clusters of significant residual cortical thinning in AN patients compared to HC in frontal and parietal regions (Fig. 5.3B).

With regard to subcortical structures, mean volumes of the amygdala, caudate nucleus, hippocampus, and thalamus of both hemispheres

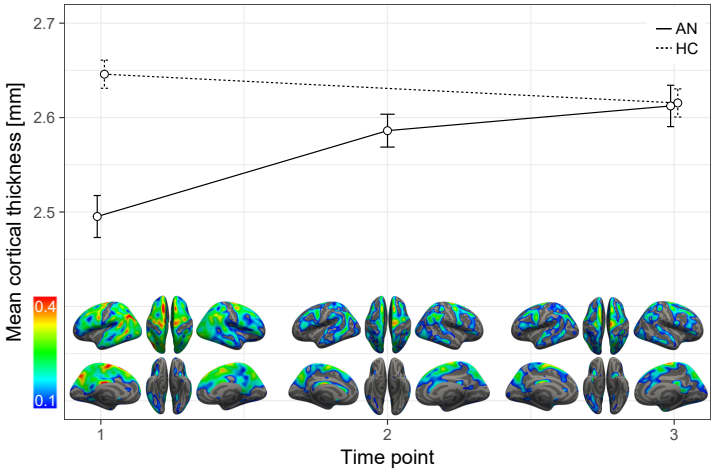

Figure 5.2. Mean cortical thickness per time point. *Top*: Global cortical thickness (mm) per group, left hemisphere displayed (similar trajectory for right hemisphere, not displayed). Error bars represent 95 % within-subject confidence intervals (Morey, 2008). *Bottom*: Local differences in cortical thickness [mm] between groups (HC-AN) per time point, projected onto inflated brain surfaces. HC values were averaged over time before differences to AN patients were calculated.

significantly increased in AN patients over the course of treatment (see Table 5.3). Although mean values of the bilateral amygdala, pallidum, and putamen did not increase significantly, group comparisons no longer yielded significant differences at TP3 (Table 5.3). Interestingly, volumes of the nucleus accumbens and the pallidum of both hemispheres did not increase between TP1 and TP3, although the difference to HC was no longer significant at TP3 (Table 5.3).

5.4.4 Correlations with clinical and demographic parameters

Within the group of AN patients, hemispheric mean cortical thickness at TP1 was positively correlated with lower body weight, as measured

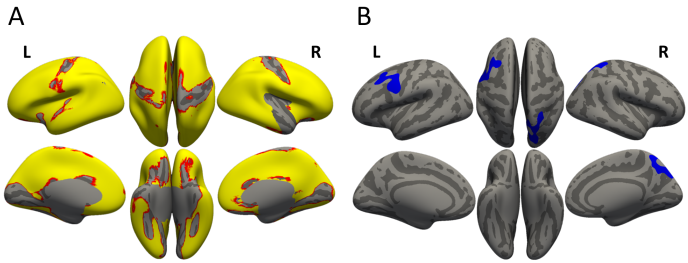

Figure 5.3. Cortical thickness. (*A*) Interaction of group × time, significant increase with weight restoration in AN patients. Red, $p < .05$; yellow, $p < .01$, controlled for multiple comparisons with FDR correction. (*B*) Cross-sectional comparisons of cortical thickness AN vs. HC, significant cluster at the end of treatment (TP3), corrected for multiple comparisons using Monte-Carlo simulation (5'000 permutations).

by BMI (left hemisphere, r=.41, p=.046, one-tailed; right hemisphere, r=.40, p=.048, one-tailed). Similarly, reduced subcortical tissue of the left caudate nucleus (r=.42, p=.041) and the right amygdala (r=.41, p=.047) were associated with poorer BMI values. Considering the high homogeneity of BMI within the AN patient group, resulting in low intra-individual variance and making it less likely to find significant correlations, these associations underline the strong influence of BMI on brain structural measures. The observed cortical thickness differences were independent of age at AN onset and duration of illness (ps > .15).

To explore potential influence variables on recovery of cortical thickness, correlations between change in cortical thickness and eating disorder severity (EDE-Q), as well as the individuals' age were computed. Due to the massive global reductions of cortical thickness in both hemispheres, mean cortical thickness per hemisphere was used for analyses. While changes in cortical thickness did not predict improved eating disorder severity (as measured with the EDE-Q; ps > .16), they were negatively associated with age of AN patients. More specifically, recovery of cortical thickness proceeded independently of age during initial weight restora-

tion, however, changes over the second half of treatment were strongly associated with patients' age, suggesting that younger patients' cortical thickness recovered to a larger degree than older patients' (Fig. 5.4). Of note, this relationship persisted even when controlling for the BMI level at TP3 (left hemisphere, r=-.64, p=.004; right hemisphere, r=-.65, p=.003). Similarly, the individual values of cortical thickness within the residual clusters remaining at TP3 were significantly correlated with the patients' age (left hemisphere, r=-.552, p=.012; right hemisphere, r=-.584, p=.007).

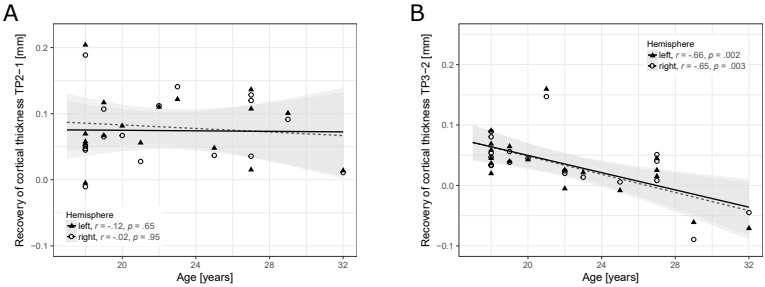

Figure 5.4. Correlation between age and recovery of cortical thickness in AN patients. *Left*: No significant correlation between age and changes in cortical thickness between TP1 and TP2. *Right*: Significant correlations between age and changes in cortical thickness of both hemispheres between TP2 and TP3; left hemisphere R^2=0.43, right hemisphere R^2=0.42.

5.4.5 Medication effects

Structural brain measures are susceptible to psychotropic medication, with atypical antipsychotics being associated with significant shrinkage of brain volume (Dorph-Petersen et al., 2005; Lieberman, 2005). To assess whether morphology of AN patients with medication differed from patients without medication with regard to cortical thickness and subcortical volumes, AN patients were divided into two subgroups. Mean values of cortical thickness (ps $\geq$ .68) and subcortical volumes (ps $>$ .19) did not differ between these subgroups, suggesting our findings of

differences between AN patients and HC at TP1 and TP3 were not driven by current medication at the time of scanning.

5.5 Discussion

This study investigated temporal patterns of cortical and subcortical recovery during weight restoration therapy in adult patients with severe AN. To the best of our knowledge, this is the first longitudinal study on AN patients using three distinct time points to assess brain restorative processes during multiple stages of weight recovery. Our longitudinal analyses revealed reduced cortical thickness as well as diminished subcortical volumes which regenerated (partially) with weight restoration. Specifically, during the early phase of treatment (TP1-2, BMI increase of 19% compared to baseline), patients' mean cortical thickness increased markedly by 0.08-0.09mm. During the later phase of treatment (TP2-3, BMI increase of 33% compared to baseline), further restitution of mean cortical thickness by 0.03mm was observed. However, significant residual differences remained in a left hemispheric frontal and a right hemispheric parietal cluster. Closer examination of associated factors revealed a strong negative association between restoration of cortical thickness and age, suggesting that younger patients were more likely to restore cortical thickness and potentially indicating decreases of brain plasticity across the lifespan (Pascual-Leone et al., 2011).

The reversibility of cortical and subcortical reductions is in agreement with overall findings of longitudinal studies in adolescent AN patients after a brief period of weight restoration in an inpatient setting (Bernardoni et al., 2016; Bomba et al., 2015). In adolescents, BMI increases of at least 10% were accompanied by an average restitution of cortical thickness of 0.16 mm after a mean treatment duration of 12 weeks (Bernardoni et al., 2016). In contrast, the mean increases of cortical thickness in our sample ranged from 0.11–0.12 mm (right and left hemisphere, respectively) after a total treatment duration of 20 weeks. At TP2, 10 weeks after baseline and approximately 12 weeks after the beginning of treatment, our adult sample had regained only 0.09 mm of cortical thickness. Recovery

processes in adolescent AN patients thus might happen at a faster rate compared to adult patients.

Additionally, cross-sectional comparisons at TP3 demonstrated remaining decreases of cortical thickness in frontal and parietal regions. These residual reductions where strongly negatively correlated with age, further supporting our hypothesis of a slower or incomplete recovery in "older" AN patients. The residual grey matter reductions are in line with another study on weight restored adult AN patients who reported persisting reductions after recovering 90% of their ideal body weight (Roberto et al., 2011). However, the authors of the study did not separately analyse the influence of patients' age (Roberto et al., 2011). A study on long-term (1.6 years) recovered AN patients (18 to 42 years) with a similar age range as our study (18 to 32 years) reported no significant association between age and residual alterations in the cingulate cortex (Mühlau et al., 2007). Similarly, Wagner et al. (2006) found grey matter volume to be independent of patients' age after mean recovery length of 3 years. This could indicate that recovery in older patients is slower, rather than incomplete compared to younger patients. However, further research including a wider age range beyond young adults is needed to clarify the long-term influence of age in this context.

At baseline, volumes of the subcortical structures (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen, and thalamus) were significantly reduced compared to HC, even after controlling for multiple comparisons. After weight restoration at TP3, most of these impairments had improved and were no longer significantly different form HC, indicating a substantial restoration of subcortical structures. Average volumes of nucleus accumbens and pallidum in both hemispheres stayed largely unchanged, although differences compared to HC were no longer significant at TP3. These results are in accordance with longitudinal results from a study on adolescents, where volumes of subcortical regions also increased with weight restoration, except for the pallidum where a decrease was observed (Bernardoni et al., 2016).

5.5.1 Underlying biology

Several biological mechanisms have been discussed but did not prevail as possible explanations for the observed grey matter reduction and recovery in AN patients, such as dehydration (Frank, 2015; Frank, Shott, Hagman, & Mittal, 2013; Via et al., 2014), or programmed cell death (apoptosis) of neurons or glia cells (Ehrlich, Burghardt, et al., 2008; Ehrlich, Salbach-Andrae, et al., 2008). A recent study investigating an animal model of activity-based anorexia (ABA) strongly supports the hypothesis of glia cells playing a key role in AN. In a chronic model of ABA, the study on female rats by Frintrop et al. (2017) observed massive decreases of astrocyte counts in the cerebrum and corpus callosum of up to 39%, using glial fibrillary acid protein as marker, and reductions of total cortical surface area covered by astrocytes of up to 83%. No alterations in neuron or oligodendrocyte count were detected (Frintrop et al., 2017), suggesting that severe sub-/cortical alterations in AN are selectively linked to processes of astroglia. Astrocytes come in different forms and exist both in the white and in the grey matter of the brain, closely connected with surrounding neurons (Nedergaard, Ransom, & Goldman, 2003; Oberheim, Wang, Goldman, & Nedergaard, 2006). The authors presume these strong effects may be owed to reduced glia cell proliferation, as demonstrated in an acute model of activity-based AN (Barbarich-Marsteller et al., 2013). Reduced astrocyte density has previously been implicated in a study on dehydration-induced anorexia and forced food restriction in rats (Reyes-Haro, Labrada-Moncada, Miledi, & Martínez-Torres, 2015).

5.5.2 Brain plasticity and age

While the number of glia cells seems to stay relatively stable during healthy ageing (Weissleder et al., 2016), the notion of diminished astrocyte proliferation (Barbarich-Marsteller et al., 2013) could offer an intriguing explanation for the slower recovery of cortical thickness as marked by the strong correlation of age and recovery during the second treatment phase of our study. Importantly, the observed influence of age persisted even after controlling for the BMI level at TP3, suggesting

that individual BMI levels were not mediating this association. Altered astrocyte function has been implicated in the pathological processes related to both neurodegenerative diseases as well as normal brain ageing (for a review see Chen & Swanson, 2003). Recent evidence suggests that particularly the senescence of astrocytic cells, a protective response which permanently prevents cell proliferation (Campisi, 2001; Collado & Serrano, 2010), increases with age (Chinta et al., 2015). The correlation between patients' age and the reduced recovery of cortical thickness thus might be influenced by ageing processes of glia cells, in particular reduced astrocyte proliferation (Chinta et al., 2015; Frintrop et al., 2017). Younger AN patients potentially have a capacity for full restoration of cortical thickness. This is in line with research on prognostic factors in AN, reporting better outcome with illness onset at younger age (Steinhausen, 2002). In that respect, age may pose a risk factor for persisting brain impairments and a chronic illness trajectory.

5.5.3 Cortical regions unaffected by starvation

The broad reductions of cortical thickness in both hemispheres raises the question why some regions, namely the sensorimotor cortices (Fig. 5.1), were spared from weight-related shrinkage processes. Two distinctive features of these regions stand out. First, the affected regions are known to be myelinated very late in brain maturation, partly adolescence, whereas the unaffected regions are myelinated early on in brain maturation (Lenroot & Giedd, 2006). There may be protective mechanisms in place, shielding primary brain regions essential to survival (Lenroot & Giedd, 2006). Second, the unaffected regions, namely the motor cortex, might be protected by high activation due to excessive physical activity (hyperactivity) in AN patients (Gümmer et al., 2015).

Apart from the unaffected grey matter regions, cortical white matter volume was another region unchanged by the severe underweight of AN patients at baseline, compared to healthy controls (Table 5.2). While this is well in line with previous morphometric studies on adult AN patients (Fonville et al., 2014; Friederich et al., 2012; Joos et al., 2011; Roberto et al., 2011), two voxel-based morphometry studies reported reduced cortical

white matter volumes (Boghi et al., 2011; Via et al., 2014). Furthermore, preliminary findings of diffusion tensor imaging studies in adolescent AN patients indicate potential alterations in a number of white matter tracts (Travis et al., 2015; Vogel et al., 2016), thus warrant further exploration of potentially undetected white matter alterations employing other MRI modalities.

5.5.4 Clinical implications

Overall, the findings of the present study provide encouraging evidence for weight restoration as an effective intervention to ameliorate damages of cortical and subcortical brain structures. Reductions of brain measures in AN patients at baseline were independent parameters of patients' illness history, such as duration of illness and age at illness onset. However, the strong correlation of age and recovery of cortical thickness in the later treatment phase may indicate that younger patients have a better chance for complete cortical restitution. Age-dependent decreases in brain plasticity potentially aggravate the detrimental effects of malnutrition on the brain. This has important clinical implications. Regarding therapy start, these findings point out the benefit of weight restoration treatment at an early stage of the disease when patients are younger. Moreover, with regard to treatment planning and the question of treatment duration, a phase of continued (guided) stabilisation of a healthy BMI ($\geq$18.5) seems vital to give all patients enough time to adjust and recover internally, on a psychological as well as on a neural level. In fact, longer weight maintenance before hospital discharge has previously been found to be predictive of a longer time period before rehospitalisation (Lay, Jennen-Steinmetz, Reinhard, & Schmidt, 2002).

5.5.5 Limitations

The strict weight criteria of the current study posed a challenge for patient recruitment and thus resulted in a medium sample size. Nevertheless, our results are based on modern and powerful analyses approaches and are in line with previous structural studies of adult AN patients (Seitz

et al., 2016). Furthermore, the longitudinal measurement of both AN patients and age-matched HC allowed to account for potential age-related decreases of brain structures in HC (Lemaitre et al., 2012; Salat et al., 2004; Tamnes et al., 2010) and supports the reliability of the findings.

Dehydration may lead to reduced measures of brain morphology by affecting astrocyte density as findings in rats have demonstrated (Reyes-Haro et al., 2015). Hydration status of the current AN sample was not assessed separately, thus effects of dehydration cannot be ruled out completely. However, the baseline scans of AN patients were acquired after a minimum hospitalisation of 2 weeks to facilitate rehydration and to avoid effects of acute starvation in patients. Furthermore, a recent study (Bernardoni et al., 2016) gauging hydration status in AN patients by specific gravity of urine samples suggests dehydration is unlikely to be the main cause of the observed reductions in brain measures.

At the end of treatment, scanning took place after a restoration of at least 85% of the ideal body weight (BMI > 17.5). Although at TP3 the mean BMI of our sample was close to the recommended minimal BMI of 18.5 (18.2 ± 1.0), the question whether the residual clusters of altered cortical thickness will completely be reversible with full weight restoration cannot be answered with the current data set. Future studies should address this question by implementing an additional follow-up time point after a period of weight stabilisation at BMI > 18.5.

5.5.6 Conclusion

Temporal patterns of structural brain recovery in adult AN patients suggest (partial) reversibility of cortical thickness and volumes of subcortical structures. Patients' age seems to have a notable influence on brain restitution, potentially indicating decreases of brain plasticity across the lifespan. Further longitudinal studies including an additional follow-up time point after a period of weight stabilisation will allow us to advance our understanding of the pathophysiological mechanism and elucidate potential mediating factors of successful brain recovery in AN patients.

5.6 Acknowledgements

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CHAPTER 6

Empirical Work - Study II: Longitudinal investigation of resting-state functional connectivity in women with anorexia nervosa before, during, and after weight restoration

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6.1 Abstract

Background: While treatment of anorexia nervosa (AN) is often focused on reducing the strong fear of gaining weight, the neuropathological underpinnings of such changes remain unclear. AN patients with acute underweight were repeatedly reported to have altered functional connectivity. The aim of this study was to elucidate alterations of functional connectivity in AN patients over the course of a standardised multimodal inpatient treatment and to investigate potential associations with changes in eating disorder pathology such as excessive weight concerns.

Methods: In a longitudinal study with three time points, each reflecting a distinct stage of the treatment process, we performed resting state functional magnetic resonance imaging and conducted a whole-brain analysis in 16 women with AN and 20 closely matched healthy controls. Using network-based statistics, we analysed functional connectivity on the whole-brain level. Correlations between functional connectivity and clinical variables were assessed.

Results: Compared to healthy controls, AN patients showed reduced functional connectivity in a fronto-basal ganglia/limbic network in the stage of severe underweight. This network of reduced connectivity recovered with weight normalisation. Network changes significantly correlated with changes in patients' weight concerns.

Conclusions: Weight restoration therapy has the potential to elicit normalisation processes in a network related to reward, learning, and cognitive-emotional integration, associated with improvements of eating disorder symptoms. Potential residual alterations need additional investigation.

6.2 Introduction

Anorexia nervosa (AN) is a severe and enduring psychiatric disorder, characterised by a fear of gaining weight despite low body weight (APA, 2013). The main goals in treatment of AN is to restore and maintain a healthy body weight (NICE, 2004; Watson & Bulik, 2013), though long-term treatment results are often not satisfactory (Steinhausen, 2002). This may be in part due to an incomplete understanding of the mechanisms underlying and driving the etiopathology of AN (Zipfel et al., 2015).

Neuroimaging techniques have increasingly been employed to further elucidate the neurobiology of AN and resting-state functional magnetic resonance imaging (rsfMRI) studies have revealed a number of alterations in functional connectivity in the acute phase of AN, with partially converging findings of reduced resting-state functional connectivity (rsFC) in cortico-limbic circuits (Gaudio et al., 2016; Phillipou, Rossell, & Castle, 2014). However, varying a priori assumptions and heterogeneous analysis approaches impede comparisons and even studies investigating the same networks (i.e. default mode and visual networks) show diverging results (Boehm et al., 2014; Favaro et al., 2012; Phillipou et al., 2016). Thus, no definite consensus regarding alterations in the acute stage of AN has been reached. Whether these diverging alterations remain stable over the course of treatment or whether recovery processes on a functional level take place is yet unclear. First evidence in weight recovered AN patients suggests that reduced rsFC in visual and auditory resting-state networks (Scaife et al., 2017) and increased rsFC in the default mode network (Cowdrey et al., 2014) persist after a recovery time of one year.

Resting-state functional connectivity is thought to reflect the intrinsic connectivity of the brain(van den Heuvel & Hulshoff Pol, 2010). It is based on the degree of inter-regional coherence of the spontaneous rsfMRI signal changes (Biswal, Van Kylen, & Hyde, 1997). Investigation of rsFC has great potential to elucidate dysfunctional network-related mechanisms in psychiatric disorders (Greicius, 2008). Its minimal requirements of lying quietly in the scanner without any particular cognitive performance can be easily achieved by participants and thus it is not affected by po-

tential attentional biases that task-based measurements might experience in patients with AN due to impaired cognitive performance (Weider, Indredavik, Lydersen, & Hestad, 2015) or avoidance of stimuli (Giel et al., 2011).

Studies so far have predominantly used a region-specific approach to examine rsFC in AN, employing seed-based analysis or independent component analysis in networks of interest. Identified alterations in AN comprised increased as well as decreased rsFC in a number of different regions (Amianto et al., 2013; Biezonski, Cha, Steinglass, & Posner, 2016; Boehm et al., 2014; Collantoni et al., 2016; Favaro et al., 2012; Favaro et al., 2013; Lee et al., 2014; Phillipou et al., 2016), including the prefrontal cortex (Biezonski et al., 2016; Boehm et al., 2014; Collantoni et al., 2016) and the insula (Amianto et al., 2013; Boehm et al., 2014). One study reported decreased rsFC between the executive control network and the anterior cingulate cortex after a whole-brain independent component analysis (Gaudio et al., 2015). More recently, the available analysis approaches have been complemented with a network-based approach on the whole-brain level (Zalesky, Fornito, & Bullmore, 2010), allowing data-driven investigations of connections between multiple brain regions. Network-based statistic (NBS) offers the advantage of representing the underlying neural architecture of the brain on a global connectivity level by conceptualising the brain as a complex network (Fornito, Zalesky, & Breakspear, 2015; Zalesky, Fornito, & Bullmore, 2010). Two cross-sectional studies have used this approach so far in AN research and reported decreased connectivity of a thalamo-insular network in mixed samples of adolescent and adult patients with AN compared to controls (Ehrlich et al., 2015; Lord et al., 2016).

To date, there is no agreement regarding dysfunctional networks impaired in acute underweight in AN patients and a lack of longitudinal examinations of functional connectivity. As a recent review on rsfMRI in AN points out, there is a need for longitudinal investigation of rsFC in AN employing whole-brain analysis, to elucidate potential causative neurobiological mechanisms and possible subsequent damage due to the disorder (Gaudio et al., 2016). Thus, the present study investigated rsFC

in AN in a longitudinal design, aiming at elucidating potential network alterations and recovery processes in a sample of adult AN patients and closely matched healthy controls (HC). In addition, associations of rsFC and symptom improvements were explored. We used rsfMRI to examine global network deviations and local differences in neural synchrony at three time points in AN patients: (TP1) at the beginning of treatment with severe underweight, (TP2) during therapy after initial weight gain of approximately 2 BMI points, and (TP3) at the end of therapy with a close to healthy body mass index (BMI, kg/m^2). Based on the existing literature, we hypothesized that rsFC between regions related to reward, learning, and cognitive-emotional integration, such as the prefrontal/orbitofrontal cortex and basal ganglia is reduced in AN patients at TP1, compared to HC, and recovers with weight restoration.

6.3 Methods and materials

6.3.1 Participants

Thirty-two women with severe AN (BMI $\leq$ 15.5) and 22 HC participated in the baseline assessment (TP1). Patients were enrolled in an interdisciplinary multimodal inpatient programme at the University Hospital of Zurich, Switzerland, (Department of Psychiatry and Psychotherapy, 2016), with a target BMI $\geq$ 18.5. The nutritional program consist in balanced structured fixed meals adequate to the severe underweight situation of the patients, in order to avoid refeeding problems. Sixteen patients did not sufficiently gain weight to participate in the second and third measurement (see study design), two HC were not able to participate in the second measurement due to somatic complaints and were excluded from the analysis. Thus, the final sample completing all required measurements consisted of 16 patients with AN and 20 HC.

Healthy controls were required to have no history of any mental illness, no first-degree relatives with a lifetime diagnosis of an eating disorder, and not be taking any medications, including hormonal contraceptives. Patients with AN who received medication were instructed to continue with these as prescribed. Six patients (37.5%) were taking psychotropic

medications: selective serotonin reuptake inhibitors (SSRI; 3), SSRI and atypical antipsychotics/anxiolytics (3). The Structured Clinical Interview for DSM-IV-TR (First et al., 2002, SCID-I) was used to assess axis I psychiatric disorders according to the DSM-IV-TR (APA, 2000). Comorbid diagnoses included major depressive disorder (6) and depression plus social phobia (1).

Groups were matched for age, handedness, and intelligence. All participants were female and strongly right handed, except for one patient and one matched HC, as assessed with the Edinburgh handedness inventory (Oldfield, 1971). The study protocol complied with the Declaration of Helsinki and was approved by the local ethics review board. All participants provided written informed consent prior to participation.

6.3.2 Study design

Brain images and psychometric parameters of the patients were acquired at the beginning of treatment when severely underweight (TP1), after an initial weight gain (TP2: $15.5 < \text{BMI} < 17.5$), and at the end of treatment with a (close to) healthy BMI ≥ 17.5 (TP3) 4-6 months after TP1. To avoid effects of acute malnutrition and dehydration, the patients' first visit (TP1) was scheduled after a minimal hospitalization time of 2 weeks with a fixed meal plan and extensive somatic checks. At the beginning of treatment, all patients were amenorrhoic.

Healthy controls underwent the same procedure at two time points (TP1 and TP3) with an interval of 4-6 months. As rsFC is influenced by alterations of sex hormones across the menstrual cycle (Petersen et al., 2014), all HC women were scanned in the follicular phase within the first 10 days of their cycle, to exclude modulation of rsFC. All participants were asked to refrain from caffeine or alcohol consumption 24 hours prior to scanning. Scanning took place between 3 p.m. and 4.30 p.m.

6.3.3 MRI data acquisition

A 3.0 Tesla whole-body magnetic resonance imaging (MRI) system (Ingenia, Philips Healthcare, Best, The Netherlands) equipped with a 32-

channels receive phased array head coil was used for data acquisition. 3D T1-weighted structural images were acquired using a three-dimensional turbo field echo (TFE) sequence with echo time (TE)=3.8 ms, repetition time (TR)=8.3 ms, field of view (FOV)=240 x 240 mm^2, acquisition matrix=240 x 240, 160 sagittal slices, isotropic voxel size=1×1×1 mm^3, flip angle=8°, and TFE factor=240.

Resting-state functional images were acquired with eyes closed using a gradient-echo T2*-weighted echo planar imaging (EPI) sequence with TE=30 ms, TR=2.3 s, flip angle=78°, FOV=220 x 220 mm^2, isotropic voxel size=3×3×3 mm^3, 40 axial slices, EPI factor=41, and 210 volumes with a scan duration of 8 min. For all subjects, T1-weighted and resting-state images were acquired and inspected by a trained neuroradiologist for any relevant pathology.

6.3.4 MRI data preprocessing

Functional MRI data were preprocessed with the DPARSFA toolbox (version 4.1) as part of DPABI (version 2.1, http://rfmri.org/dpabi Yan, Wang, Zuo, & Zang, 2016) with functions of SPM 12 (www.fil.ion.ucl.ac.uk/spm/software/spm12), comprising the following steps: 1) slice timing correction, 2) realignment and extraction of mean frame-wise displacement values (Vinet & Zhedanov, 2010), 3) coregistering the mean rsfMRI with the T1-weighted image, segmenting and normalizing the T1-weighted image to MNI152 structural (T1-weighted) space using linear and non-linear transformation, and storing the transformations, 4) applying the transformations from step 3 to the rsfMRI data and voxel re-sampling to 2 x 2 x 2 mm^3, 5) smoothing with an isotropic Gaussian kernel of 4 mm full width at half maximum, 6) detrending, 7) band-pass filtering between 0.01-0.08 Hz, and 8) regressing out the variance of the six parameters from head motion correction (three translation and three rotation parameters), their first temporal derivatives and the 12 corresponding squared items (24-parameter model; Friston, Williams, Howard, Frackowiak, & Turner, 1996), as well as the mean signals of cerebrospinal fluid and white matter. To prevent spurious correlations due to head motion (Power et al., 2014; Power, Schlaggar, &

Petersen, 2015), group-level correction for mean frame-wise displacement (FD; Vinet & Zhedanov, 2010) was used as recommended by Yan et al. (2013). Global signal was not regressed out, as this step has been shown to lower test-retest reliability (Yan et al., 2013) and is known to increase anti-correlations and distance-dependent artefacts (Jo et al., 2013), which are problematic for network-based analyses. To ensure the robustness of our findings, all analysis steps were repeated with motion correction at individual-level instead of group-level, using spike regression to identify time points with FD > 0.2 mm and modelling each time point and their 1 back and 2 forward neighbours as separate regressors (Vinet & Zhedanov, 2010; Power et al., 2014, see Fig. A.2, Appendix A). Functional scans were checked for excessive head motion (FD >3 mm Power, Barnes, Snyder, Schlaggar, & Petersen, 2012); no participants had to be excluded (mean FD=0.12 mm; max FD=0.31 mm; no significant group difference, p=.73).

An adapted version of the automated anatomical labelling (AAL) atlas with 94 ROIs was used to define the network nodes (Tzourio-Mazoyer et al., 2002). The nucleus accumbens (derived from the Harvard-Oxford subcortical atlas; Desikan et al., 2006) was added for both hemispheres, as this structure is of interest in AN research due to its involvement in reward processes (Sesack & Grace, 2010). Further, the insular cortex was divided into anterior and posterior parts, as it has been shown that the two regions are associated with distinct brain functions and are involved in dissociable resting-state networks (Cauda et al., 2011). Functional segmentation of the insula in its anterior and posterior parts based on rsfMRI data of an independent sample was performed in a previous study of our group and is described in detail elsewhere (Baur, Hänggi, Langer, & Jäncke, 2013).

The connectivity matrices calculated with DPARSFA captured the strength of functional connectivity as Pearson correlation coefficients between the time series of two nodes, standardised with Fisher's r-to-Z-transformation. To test whether the network of disrupted rsFC in AN patients could be explained by local reductions in neuronal synchrony, intra-nodal (regional) homogeneity within nodes was extracted for group

comparisons. Regional homogeneity of intrinsic brain activity was calculated as Kendall's coefficient of concordance of the time series of a given voxel with those of its 26 nearest neighbouring voxels (Zang, Jiang, Lu, He, & Tian, 2004).

6.3.5 Network-based analyses

The network-based statistic (NBS) tool (Zalesky, Fornito, & Bullmore, 2010) and MATLAB (version R2016a, http://www.mathworks.com/) were used for the network analyses to test for altered connections. With the AAL parcellation scheme of 94 ROIs, our network consisted of 4371 (94 $\times$ 93 / 2; as connections are undirected) possible connections (edges). When testing each of these edges, NBS offers a non-parametric method to control the family-wise error rate of the large number of comparisons. Network-based statistics translates the basic principles of conventional cluster-based thresholding of statistical parametric maps (Hayasaka & Nichols, 2004; Nichols & Holmes, 2002) to a graph. In brief, it applies a chosen sensitivity threshold to the test statistic calculated for each edge. Existing interconnected structures above that threshold are thus identified, before assigning a family-wise error corrected p-value to each of these so-called components through permutation testing (Zalesky, Fornito, & Bullmore, 2010).

Functional connectomes were compared cross-sectionally between groups at TP1, as well as with a longitudinal interaction analysis, calculated for the factor group (AN / HC) and time point (TP1 / TP3; TP2 was not included into the interaction analysis as it was not assessed for HC). To examine possible recovery processes within networks, the longitudinal analysis was first performed focusing on the component identified at TP1. Second, to investigate potential differences emerging during therapy, a whole-brain interaction analysis was performed independent of the initial alterations at TP1. To elucidate differences between groups at the end of treatment, we conducted group comparisons at TP3 for the network initially altered (at TP1) as well as for the whole-brain.

Group comparisons were performed for both contrasts (AN $<$ HC and

AN > HC) and all analyses were done with the total number of connections as measure of component size, controlled for multiple comparisons using 5'000 permutations at $p < .05$, as implemented in NBS. The primary sensitivity threshold for the cross-sectional analysis at TP1 and TP3 was set to t=3.5, the threshold for the longitudinal interaction analysis was set to F=0.5. As the sensitivity threshold for the analyses must be determined in an explorative way, these thresholds were chosen striving for a network of interpretable edge count. To demonstrate the robustness of the network over a broader range of thresholds, additional results are reported in the supplementary. For further analysis, the mean correlation (functional connectivity) of the network was extracted and examined for significant within-group changes over time, using t-tests for dependent samples.

6.3.6 Psychometric assessment

Eating disorder psychopathology was assessed at all time points with the validated German version of the Eating Disorder Examination Questionnaire (EDE-Q; Hilbert & Tuschen-Caffier, 2006), comprising four subscales to restrained eating, concerns regarding eating, shape, and weight. Becks Depression Inventory (BDI; Hautzinger et al., 1994) was used to quantify depressive symptoms and the Snaith-Hamilton Pleasure Scale (SHAPS) was employed to measure anhedonia (Franz et al., 1998). Intelligence was estimated using the following two scales: Viennese Matrices Test (WMT) for fluid intelligence (Formann & Piswanger, 1979); Vocabulary test (WST) for verbal intelligence (Schmidt & Metzler, 1992).

6.3.7 Additional statistical analyses

Demographic and psychometric measures were compared between groups using t-tests for independent samples. Pearson correlations were calculated to test associations between mean functional connectivity and demographic or psychometric parameters, as well as between functional connectivity and regional homogeneity measures. These tests were performed using R (R Core Team, 2016) and IBM SPSS Statistics 23.0 (SPSS

Inc, an IBM company, Armonk, NY). If not otherwise stated, two-tailed p-values are reported.

6.4 Results

6.4.1 Demographic and psychometric measures

We observed no significant differences between patients and HC in age, education, and intelligence (Table 6.1). In AN patients, the psychopathology scores for eating disorder severity, anhedonia and depression were significantly higher at baseline compared to HC. These differences decreased over the course of therapy, but remained significant even at the end of treatment (Table 6.1).

6.4.2 Functional connectivity in the phase of severe underweight

Whole-brain analyses of rsFC yielded a significant network of decreased functional connectivity in patients with AN compared to HC (p=.018, corrected for multiple comparisons). The network comprised 20 edges distributed over 14 nodes in mainly fronto-basal ganglia/limbic regions, including the anterior insula, fusiform gyrus, hippocampus, nucleus caudatus, nucleus accumbens, putamen, as well as frontal areas (Fig. 6.1 and Table A.1, Appendix A). Decreased rsFC of this network was independent of age and education within the groups (ps $> .18$) and independent of age of illness onset and duration of illness within the patient group (ps $> .31$).

6.4.3 Weight dependent changes in rsFC over the course of treatment

The interaction analysis (group x time) of the network identified at baseline showed a significant change of rsFC in 18 of the 20 edges over time (p=.006, corrected). Follow-up analysis of the direction of change revealed an increase in mean rsFC in the patient group, most notably between TP1 and TP2 (mean difference=0.08, SD=0.11, $t(16)$=2.803, p=.013, d=.95), indicating that the network identified to be altered in the

Table 6.1

Group characteristics

	Group (time point)												
	AN1 $n = 16$		AN2 $n = 16$		AN3 $n = 16$		HC1 $n = 20$		HC3 $n = 20$		AN1 vs. HC1	AN3 vs. HC3	AN1 vs. AN3
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*p*	*p*	*p*
Age	22.69	4.57					24	3.32			.33		
Age of illness onset	16.28	2.7											
Duration of illness	6.41	4.64											
Education	13.94	2.79					14.2	4.99			.85		
BMI	13.56	1.24	16.34	1.35	18.28	0.64	21.06	2.00	20.56	1.49	<.001	<.001	
BMI increase per week			0.30	0.16	0.20	0.10							
Time after TP1 (weeks)			9.9	2.84	20.12	8.01			25.91	10.01		.07	
EDE-Q total	3.03	1.31	1.86	1	1.68a	1.1	0.65	0.56	0.6	0.52	<.001	<.01	.14
EDE-Q eating concern	2.98	1.48	1.54	0.94	1.23[a]	0.97	0.22	0.49	0.32	0.46	<.001	<.01	.002
EDE-Q restraint	3.05	1.73	1.2	1.12	1.16[a]	0.97	0.41	0.44	0.29	0.35	<.001	<.01	<.001
EDE-Q shape concern	3.35	1.24	2.82	1.47	2.51[a]	1.72	1.07	0.93	1.01	0.75	<.001	<.01	.06
EDE-Q weight concern	2.73	1.22	1.88	1.12	1.84[a]	1.38	0.92	0.81	0.77	0.82	<.001	.014	.01
BDI	20.63	9.8	15.06	8.87	10.33[a]	7.34	3.95	3.97	2.75	2.63	<.001	<.01	<.001
SHAPS	3.19	0.35	2.13	2.13	1.75[a]	2.32	0.35	0.93	0.3	0.73	.003	.03	.03
WMT	125.56	18.07					127.60	15.75			.72		
WST	104.50	8.76					106.70	11.28			.53		

Note. Age, age of illness onset, duration, and education in years. BMI = body mass index; BDI = Becks Depression Inventory total score (maximum score: 63, clinically meaningful cut-off: 18); EDE-Q = Eating Disorder Examination Questionnaire score (maximum total score: 6); SHAPS = Snaith-Hamilton Pleasure Scale total score (maximum score: 14); WMT = Viennese Matrices Test; WST = Multiple Choice Vocabulary Test. [a]Data available only for AN = 15 subjects.

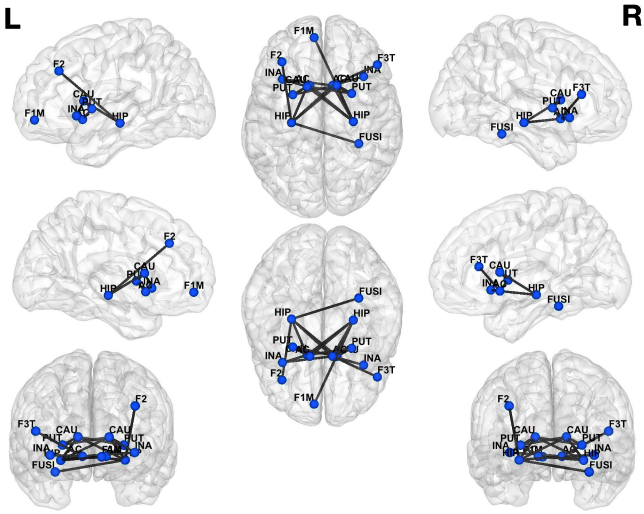

Figure 6.1. Network of hypoconnectivity in AN compared to HC at TP1. Network-based statistics were applied to compare whole-brain functional connectivity between the groups. The network consists of 14 nodes (blue spheres, 7 per hemishpere) and 20 edges (dark grey lines) that survived a statistical threshold (p=.05), corrected for multiple comparisons using family-wise error correction. *Left column* (top to bottom): Lateral and medial view of left hemisphere, anterior view. *Middle*: Top and bottom view. *Right column*: Lateral and medial view of right hemisphere, posterior view. AC=Accumbens; CAU=Caudate nucleus; F1MO=Superior frontal gyrus, medial orbital; F2=Middle frontal gyrus; F3T=Inferior frontal gyrus, triangular; FUSI=Fusiform gyrus; HIP=Hippocampus; INA=Insula anterior; PUT=Putamen. Network visualised using BrainNet Viewer (Xia, Wang, & He, 2013).

acute phase at TP1 recovered at least partially with weight restoration. Between TP2 and TP3, mean rsFC in AN remained largely unchanged (mean difference=0.004, SD=0.11, $t(16)$=0.158, p=.88). Within the HC group, a medium decrease in mean connectivity was significant (mean difference=-0.05, SD=0.08, $t(19)$=-2.793, p=.012, d=-0.53).

Group comparison of the network affected at TP1 no longer reach significance at TP3. Furthermore, a whole-brain comparison of groups at TP3 did not reveal additional networks with altered connectivity. However, a residual reduction of functional connectivity in AN patients seems to remain even after weight restoration (BMI $\geq$ 17.5), as not all edges significantly changed between TP1 and TP3 in the specific interaction analysis and the mean level of rsFC did not reach the same level as in HC (compare Fig. 6.2). Comparing both groups in a whole-brain interaction analysis (group x time) yielded no significant network components, suggesting that no significant additional group differences occurred over the course of therapy.

6.4.4 Correlations with clinical and demographic parameters

To explore whether individual differences in eating disorder symptomatology would explain additional variance in connectivity, correlations between the mean rsFC of the network and the EDE-Q (total score and subscale for weight concerns) were calculated within groups for values at TP1 and change scores between TP1 and TP2, as well as between TP2 and TP3. There were no significant relationships in either group with respect to the total score. Within the patient group, increases in rsFC were correlated with a significant reduction in weight concerns between TP1 and TP2 (EDE-Q; Fig. 6.3A), this negative association did not reach statistical significance in the second half of therapy between TP2 and TP3 (Fig. 6.3B).

6.4.5 Intra-nodal homogeneity

Groups comparisons of intra-nodal homogeneity showed no significant differences between groups at TP1. Furthermore, exploratory

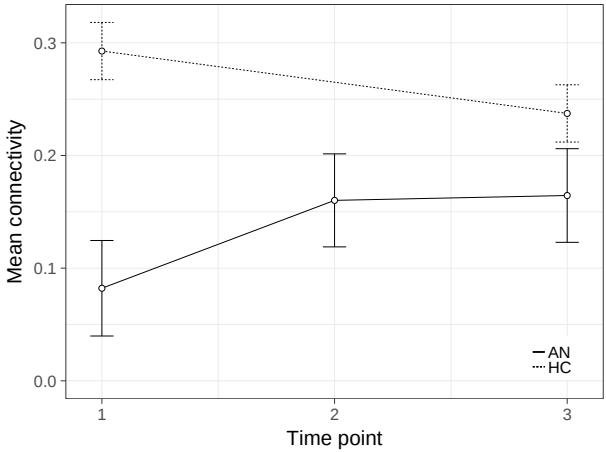

Figure 6.2. Trajectory of functional connectivity (standardised with Fisher's r-to-Z-transformation) per group within the network identified at TP1. Error bars represent 95 % within-subject confidence intervals (Morey, 2008).

group comparisons of correlations between intra-nodal homogeneity and inter-regional connectivity yielded no significant differences in correlations, except for the left putamen (for further details see Table A.2, Appendix A).

6.4.6 Medication effects

Six patients of the AN group were on psychotropic medication at the time of scanning. As this might alter functional brain connectivity (McCabe & Mishor, 2011; van Wingen et al., 2014), we compared mean connectivity within the network at TP1 of patients with and without medication. There were no differences between patients receiving medication (M=0.079, SD=0.080) and patients without medication (M=0.083, SD=0.052; $t(14)$=0.13, p=.90), suggesting that group differences between AN and HC were not driven by extreme values of medicated patients (see

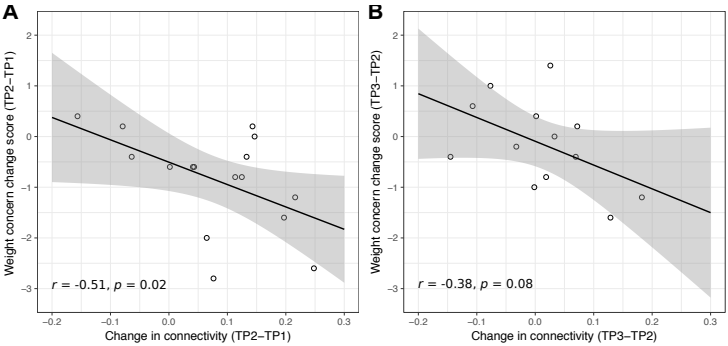

Figure 6.3. Correlations between changes in connectivity within the network and changes in weight concern scores in patients with Anorexia nervosa. *A*: time point 2 – time point 1; one-tailed comparison. *B*: time point 3 – time point 2; one-tailed comparison. Confidence intervals of the mean at 95 % are displayed in grey.

also Fig. A.4, Appendix A).

6.5 Discussion

Using a longitudinal design with three time points, this is the first study to examine rsFC in women with AN over the course of weight-recovery therapy, compared to closely matched HC. At the initial phase of treatment, rsFC was disrupted in a fronto-basal ganglia/limbic network in patients with AN. More specifically, using network-based analysis we observed reductions of rsFC, which were (partially) reversible with weight normalisation during a multimodal inpatient treatment. Critically, the extent of normalization of rsFC at the first half of the therapy correlated with the extent of clinical amelioration.

Alterations of rsFC in AN have been previously reported in a number of cross-sectional resting-state studies using whole-brain approaches, spanning samples in the acute stage (Ehrlich et al., 2015; Gaudio et al., 2015; Geisler et al., 2016; Scaife et al., 2017) as well as samples recovered from AN (Cowdrey et al., 2014; Scaife et al., 2017). The present longitudinal investigation of functional connectivity during weight gain for the first time extends these findings by examining their evolution over the course of treatment. Measurements of a homogeneous sample of adult AN patients with similar age, undergoing the same standardised treatment, were obtained at three time points to capture their dynamic over the different stages of weight gain. With the design of our study it is for the first time possible to examine trajectories of early vs. late normalisation of rsFC during therapy.

rsfMRI is an established and reliable method to investigate brain activation at rest (Shehzad et al., 2009). To take account for its known sensitivity to natural fluctuations of anxiety during MRI scans (Dennis, Gotlib, Thompson, & Thomason, 2011), measurements of the HC group were collected at two time points. This allowed for a robust assessment of rsFC over time in both groups, as state anxiety between first-time scans and follow-up sessions has been found to decrease substantially due to habituation (Chapman, Bernier, & Rusak, 2010). Another strength of the present study is the use of a reliable data-driven analysis method (Zalesky, Fornito, & Bullmore, 2010) examining the whole brain without

a priori restrictions to specific brain regions.

6.5.1 Stage of severe underweight (TP1)

In the stage of severe underweight, our results suggest a distinctive network of functional hypoconnectivity in AN. The almost symmetric network comprised bilateral nodes of the basal ganglia (caudate nucleus; putamen), the limbic system (hippocampus; nucleus accumbens), the anterior insular cortex, unilateral frontal areas (left middle frontal gyrus; left medial orbitofrontal cortex; right inferior frontal gyrus, pars triangularis), and the right fusiform gyrus. Except for the left putamen, the inter-regional network of disrupted connectivity was not explained by reductions in intra-nodal signal homogeneity. This result is in line with a previous study in which alterations in functional connectivity were unrelated to local neuronal synchrony of AN patients (Ehrlich et al., 2015).

The basal ganglia are not only highly interconnected but also project to frontal regions and are chiefly involved in reward processes of the brain (Sesack & Grace, 2010). Decreased connectivity among these regions in AN may be in line with findings of altered dopaminergic neurotransmission observed in the reward system of recovered AN patients (Bailer et al., 2012; Frank et al., 2005). The basal ganglia are closely connected to the identified limbic regions (Sesack & Grace, 2010), which play an important role in reward-dependent decision making, as well as in higher mental functions such as memory formation and habit-learning (Rolls, 2015). Alterations in these regions are in accordance with a number of different task-based studies in AN patients, implicating the mesolimbic reward system as central to AN. A study on the perception of female bodies of varying weight categories observed strong differences in brain activation between AN patients and HC in the ventral striatum (Fladung et al., 2010). Food-related tasks, using pictures (Cowdrey, Park, Harmer, & McCabe, 2011) or sugar solution as stimuli (Frank & Kaye, 2012), have reported markedly elevated activation in the nucleus accumbens as well as the orbitofrontal cortex. Tasks with monetary reward observed aberrant

striatal activation in acute (Decker, Figner, & Steinglass, 2015) and recovered AN patients (Wagner et al., 2007).

Further nodes of the affected network were the anterior insular cortex, critical for interoception (Adolfi et al., 2017), the fusiform gyrus, associated with body recognition (Peelen & Downing, 2007), as well as frontal regions, related to divers cognitive, affective, and volitional brain functions. These results extend prior findings of cross-sectional NBS studies, reporting networks of reduced connectivity in a sample of adolescents and young adults affected by AN (Ehrlich et al., 2015; Lord et al., 2016). Of note, using a similar parcellation scheme, there was an overlap in nodes with our network in the left and right putamen as well as the right fusiform gyrus. Contrasting our findings, Ehrlich et al. (2015) found reduced connectivity of the left amygdala and thalamus, and the posterior insula. These deviations are possibly due to the differences in sample composition (e.g. a mixed sample of adolescents and adults vs. adults only in our study), as processes of brain development continue throughout adolescence and lead to substantial alterations in brain measures (Semple, Blomgren, Gimlin, Ferriero, & Noble-Haeusslein, 2013). There are two other cross-sectional whole-brain rsFC studies with adult samples, the most recently published used independent component analysis and found decreased insular connectivity (anterior and posterior parts were not differentiated) in AN patients (Scaife et al., 2017). The other study by Kullmann et al. (2014), used degree centrality and effective connectivity as measures in a graph-theoretical analysis approach. Their results suggested increased connectivity of the insula (anterior and posterior parts were not differentiated) to the inferior frontal gyrus and decreased connectivity from the orbitofrontal gyrus to the inferior frontal gyrus, as well as decreased connectivity from the inferior frontal gyrus to the midcingulate cortex (Kullmann et al., 2014), underlining the potential importance of the connectivity between these regions in the pathomechanisms of AN. Given the known involvements of the nodes identified in our study, these regions form a network of reduced connectivity in AN that might underlie symptoms central to AN, such as a dissatisfaction with body and body weight, a desire to fast, and avoidance of food despite

low body weight (APA, 2013).

6.5.2 Stages of weight restoration (TP2 and TP3)

Over the course of weight restoration, connectivity within the weakened network of AN patients normalised at least partially. Notably, this increase happened mainly within the first half of treatment (1-10 weeks after TP1) during an improvement of eating disorder severity from severe to moderate (estimated by BMI: APA, 2013). Furthermore, recovery of connectivity during this period was predictive of ameliorated eating disorder symptomatology, as expressed by a reduction of weight concerns (EDE-Q). Weight restoration during the second half of treatment (11-20 weeks after TP1) seemed to have a lesser influence on connectivity as there was no substantial increase in mean connectivity of the network. The lack of connectivity changes was paralleled by a diminished improvement of weight concerns, suggesting that the initial phase of therapy might be of particular importance to successful recovery processes. Group comparisons at the end of treatment no longer revealed any differences, indicating an effective treatment and reversibility of the initial brain alterations. However, as the mean connectivity was still slightly weaker in the AN group, subthreshold alterations cannot be ruled out. Indeed, when using a more liberal significance level (p=.10, corrected), there were still edges of reduced connectivity (see Fig. A.1, Appendix A). The hypothesis of residual brain alterations is further supported by the elevated scores of eating disorder pathology at the end of inpatient therapy and points to the importance of continued treatment in an outpatient setting. Whether the potential residuals of brain alterations represent 'neural scars' or whether they are reversible with a continued treatment and a prolonged weight stabilisation remains to be investigated.

6.5.3 Limitations

There are some limitations to the present study. There is no consensus regarding an accepted method to find the optimal test statistic threshold in NBS for a given data set (Zalesky, Fornito, Harding, et al., 2010).

Thus, the set thresholds were arbitrarily chosen and the results are not independent of the distinct primary threshold. However, as the core of initial network remained intact over threshold changes of $\pm$ 0.5, we are confident that the chosen threshold did not selectively shape the composition of the identified network (for results see Fig. A.3, Appendix A).

Studies have shown that the degree of brain parcellation used to calculate the connectivity matrices influences the identified networks (Lord et al., 2016; Zalesky, Fornito, Harding, et al., 2010). The current results thus might be contingent on the implemented parcellation scheme. However, the anatomical atlas was chosen because of its wide usage in the field (e.g. Bomba et al., 2015; Friederich et al., 2012; Zalesky, Fornito, Harding, et al., 2010) to enable comparisons with other studies and variability between different parcellation schemes is rather small with respect to the subcortical structures such as the putamen and the caudate nucleus, important nodes in the present study.

The longitudinal design of the current study led to a relatively small number of patients being eligible for participation due to insufficient weight gain. Although our results are highly significant and fit the established literature, future studies using data-driven approaches should replicate the findings with larger sample sizes to further investigate group differences after weight restoration and to gain further insight into subsequent neurobiological damage after weight recovery.

6.5.4 Conclusion

This is the first longitudinal study to demonstrate the functional connectivity reduction in a fronto-basal ganglia/limbic network and its recovery in adult patients with severe AN who gained weight during treatment. Interdisciplinary multimodal inpatient treatment has the potential to elicit normalisation processes in a distinct network of weakened connectivity that are accompanied by improvements of eating disorder symptoms. These findings support the reversibility of disrupted functional connectivity during weight restoration therapy.

6.6 Acknowledgements

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CHAPTER 7

Empirical Work - Study III: Fornix under water? Ventricular enlargement biases forniceal diffusion MRI indices in anorexia nervosa

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7.1 Abstract

Background: Acute anorexia nervosa (AN) is characterized by reduced brain mass and corresponding increased sulcal and ventricular cerebrospinal fluid (CSF). Recent studies of white matter (WM) using diffusion tensor imaging (DTI) consistently identified alterations in the fornix, such as reduced fractional anisotropy (FA). However, because the fornix penetrates the ventricles, it is prone to CSF-induced partial volume effects that interfere with a valid assessment of FA. Here, we investigated the hypothesis that in the acute stage of AN, FA of the fornix is markedly affected by ventricular volumes.

Methods: First, using DTI data we established the inverse associations between forniceal FA and volumes of the third and lateral ventricles in a pre-study with 32 healthy subjects to demonstrate the strength of ventricular influence on forniceal FA independent of AN. Second, we investigated a sample of 25 acute AN patients and 25 healthy controls.

Results: Using ventricular volumes as covariates markedly reduced the group effect of forniceal FA, even with tract-based spatial statistics focusing only on the centre of the fornix. Further, after correcting for free-water on voxel-level, the group differences in forniceal FA between AN patients and controls disappeared completely.

Conclusion: It is unlikely that microstructural changes affecting FA occurred in the fornix of AN patients. Previously identified alterations in acute AN may have been biased by partial volume effects and the proposed central role of this structure in the pathophysiology may need to be reconsidered. Future studies on WM alterations in AN should carefully deal with partial volume effects.

7.2 Introduction

Anorexia nervosa (AN) is a serious and potentially life-threatening mental illness, often with poor long-term outcomes (Berkman, Lohr, & Bulik, 2007; Papadopoulos et al., 2009). Despite various efforts to identify the underlying causes and pathomechanisms of AN (Polivy & Herman, 2002), the current understanding of this condition remains unsatisfactory. Acute AN is characterized by reduced brain mass and corresponding increased cerebrospinal fluid (CSF) in the sulci and ventricles (Seitz et al., 2014; Titova et al., 2013). Recent neuroimaging studies have investigated regional white matter (WM) alterations in AN using diffusion-tensor imaging (DTI) (Moseley et al., 1990). The most common DTI derived measure is fractional anisotropy (FA) (Chenevert, Brunberg, & Pipe, 1990), which measures the directionality of water diffusion, and is thought to be affected by WM structural properties such as axonal integrity and fibre coherence. Five DTI studies on acute AN were published to date, all of which have reported alterations of diffusion parameters in the fornix, both in adult (Hayes et al., 2015; Kazlouski et al., 2011; Nagahara et al., 2014; Via et al., 2014) and adolescent patients with AN (Frank, Shott, Hagman, & Yang, 2013). In a recent review (Frank, 2015), fornix alterations have thus been suggested to play a central role in the pathophysiology of AN and, because of comparable alterations in bulimia nervosa, in eating disorders in general.

The fornix is part of the limbic system connecting the mammillary bodies with the hippocampi in two C-shaped bundles of WM fibres. Joined in the middle, its body runs above the third ventricle, parting into the fornix crus in its posterior segment where it is enclosed by the lateral ventricles (Fig. 7.1). Due to its position between the CSF-filled ventricles, the diffusion indices of the fornix are severely susceptible to bias by partial volume effects (PVE) (Concha, Livy, Beaulieu, Wheatley, & Gross, 2010; Jones & Cercignani, 2010; Pasternak, Sochen, Gur, Intrator, & Assaf, 2009). PVE occur when voxels contain heterogeneous tissue types, which in the case of the fornix are WM tissue and CSF. A larger amount of CSF within a voxel means greater liberty for molecules to move in all

directions, hence lesser anisotropy. Subsequently, PVE will result in an underestimation of FA (Alexander, Hasan, Lazar, Tsuruda, & Parker, 2001).

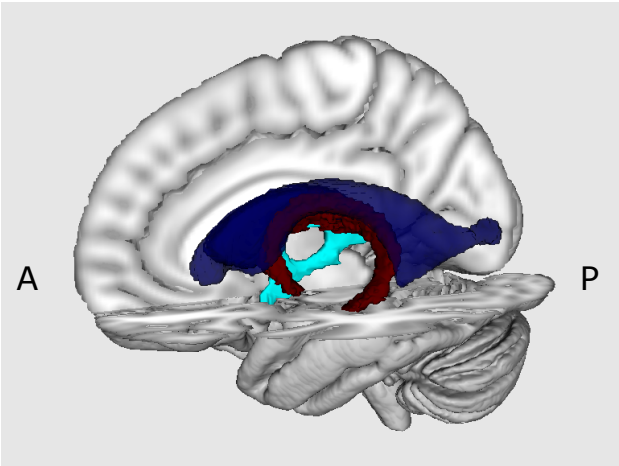

Figure 7.1. Location of the fornix (red) surrounded by lateral ventricles (dark blue) and third ventricle (light blue) in sagittal view. A=anterior, P=posterior.

Given (i) the proneness of forniceal diffusion indices for PVE and (ii) the increased volume of CSF-filled ventricles in acute AN (Seitz et al., 2014; Titova et al., 2013), the consistently reported fornix alterations in acute AN warrant further investigation. It is of note that studies with recovered AN patients (Frieling et al., 2012; Yau et al., 2013), where CSF volumes largely returns to normal values, did not indicate alterations in forniceal diffusivity metrics (Wagner et al., 2006). Furthermore, studies investigating samples with ventricular volume increase due to other factors like ageing processes (Metzler-Baddeley, O'Sullivan, Bells, Pasternak, & Jones, 2012) demonstrated an increase of CSF contamination in forniceal diffusivity measures. This underlines the importance of considering biases in PVE-prone samples such as patients with acute AN.

Tissue volume and shape can modulate PVE (Vos, Jones, Viergever, & Leemans, 2011). Modern neuroimaging data analysis pipelines like FreeSurfer (surfer.nmr.mgh.harvard.edu) allow volumetric assessment of CSF-filled spaces with a high regional specificity, which thus could facilitate a proxy measure of the extent to which ventricular volumes influence adjacent WM. However, the relation between ventricular volumes and fornix FA has not been established so far. To support the hypothesis that increased volumes of the third and lateral ventricles are influencing PVE in the fornix, we first examined the association between these volumes and forniceal FA in an independent sample of healthy subjects. This was followed by the main analysis of acute AN patients and age-matched healthy controls. Here we first considered ventricular volumes as covariates to control for the increased CSF in AN patients. However, the relationship between ventricular volumes and PVE might not be captured best in a linear relationship (Metzler-Baddeley et al., 2012). To account for a possibly irregular association and to acknowledge the potential co-occurrence of increased ventricular volume and decreased WM integrity we further removed PVE in a second step by employing a free-water elimination approach (Pasternak et al., 2009), modelling and removing the amount of PVE from the diffusion tensor at voxel level. We hypothesized that a putative group difference (i.e., aberrant forniceal FA in AN) depends on ventricular volumes, so that previously found effects in the fornix might be, to some extent, biased by PVE and do not entirely represent a "true" group difference.

7.3 Methods and materials

7.3.1 Participants (pre-study)

To examine the influence of PVE independent of AN, we first examined the relationship between ventricular volumes and forniceal FA in a pre-study with healthy subjects of similar age as the samples of the main study. Thirty-four healthy subjects free of neurological and psychiatric disorders were recruited. Two subjects had to be excluded due to aberrant volumes of the third and lateral ventricles ($> 3\times$ interquartile range),

so the final sample consisted of n=32 subjects (17 females, 15 males; mean ± standard deviation, (SD) age: 25.06 ± 4.56 years). Details of subjects' recruitment have been reported elsewhere (Baur, Hänggi, & Jäncke, 2012).

7.3.2 Participants (main-study)

Twenty-six women diagnosed with AN were recruited from the inpatient unit of the Center for Eating Disorders, Department of Psychiatry and Psychotherapy, University Hospital Zurich, Switzerland. Inclusion criteria were a minimum duration of illness of one year and a body-mass-index (BMI) $\leq$ 15.5. To avoid effects of acute malnutrition and dehydration, patients were recruited after a hospitalisation time of 2 weeks with a fixed meal plan and extensive somatic checks. A trained neurologist checked the anatomical images for possible anomalies. One patient had to be excluded due to temporal lobe abnormalities (arachnoid cyst) and atrophy beyond the normal range. Thus, the final sample consisted of n=25 patients with AN, eleven of which (40.74 %) were taking psychotropic medication (serotonergic and/or noradrenergic antidepressants: 5, atypical antipsychotics: 3, both: 3). Separately from the pre-study sample, healthy control women (HC; n=25) were recruited via notice boards and mailing lists. None of the controls had current or past psychiatric disorders.

Additional exclusion criteria for both groups were: current or past neurological disorders, substance abuse or addiction, as well as contraindications to MRI. To evaluate general and eating disorder-specific psychopathology, all participants were assessed using the German versions of the Structured Clinical Interview for DSM-IV (SCID; Wittchen et al., 1997) and the eating disorder inventory (EDI-2; Paul & Thiel, 2005). Fluid IQ was measured using the Vienesse Matrices Test, verbal IQ was assessed with the Multiple Choice Vocabulary Test (WST; Schmidt & Metzler, 1992). Groups were matched for age and IQ (see Table 7.1). All participants were right handed, except for one AN and one HC subject who were left handed, as measured with the Edinburgh Handedness Inventory short form (Veale, 2014). Further group characteristics are

summarized in Table 7.1. The study was approved by the ethics committee of the Canton of Zurich, Switzerland. Written informed consent was obtained from all participants prior to study enrolment.

Table 7.1

Group characteristics of main study sample

	Group					
	AN $n = 25$		HC $n = 25$			
	M	*SD*	*M*	*SD*	*t*	*p*
Age	22.84	4.75	23.36	3.35	−1.0	.66
Age of illness onset	16.04	2.63				
Duration of illness	6.8	4.92				
BMI	13.83	1.33	21.07	1.93	−15.35	<.001
Heart rate	56.59	9.03	64.63	10.14	−2.96	.005
EDI-2 total	224.52	44.53	147.46	34.36	6.66	<.001
WMT	122.75	20.22	126.12	15.57	−0.66	.52
WST	102.79	10.16	105.72	11.53	−0.94	.35

Notes. Groups were compared with two-tailed t-tests. Age, age of illness onset, and duration in years; BMI = body mass index; Heart rate recorded during DTI sequence (beats per minute); EDI-2 = Eating Disorder Inventory-2; WMT = Viennese Matrices Test; WST = Multiple Choice Vocabulary Test.

7.3.3 MRI data acquisition and pre-processing (pre-study)

For data acquisition, a 3 Tesla whole-body magnetic resonance imaging (MRI) system (Ingenia, Philips, Best, The Netherlands) was used, equipped with a 15-channel head coil. One high-resolution T1-weighted scan (voxel size: 0.94 x 0.94 x 1 mm^3) and one diffusion-weighted (DTI) data set (voxel size: 2 x 2 x 2 mm^3, 64 diffusion-weighted gradients with a b-value of 1000 s/mm^2, one non-diffusion-weighted b0 reference volume) per subject were obtained. Preprocessing was performed with FMRIB Software Library (FSL) Version 4.1.8 (www.fmrib.ox.ac.uk/fsl). Further details have been described elsewhere (Baur et al., 2012).

7.3.4 MRI data acquisition and pre-processing (main study)

For data acquisition, a 3 Tesla whole-body magnetic resonance imaging (MRI) system (Ingenia, Philips, Best, The Netherlands) was used, equipped with a 32-channel head coil. One high-resolution 3D T1-weighted scan (voxel size: 1 x 1 x 1 mm^3) and one DTI data set (voxel size: 2 x 2 x 2 mm^3, 64 diffusion-weighted gradients with a b-value of 1000 s/mm^2, one non-diffusion-weighted b0 reference volume, echo time (TE): 90 ms, repetition time (TR): 9.8 s, SENSE factor 2 (Pruessmann et al., 1999), EPI factor 55 (Mansfield, 1977)) per subject were obtained. In addition, a T1-weighted fast-field echo sequence was used to map the B0 field in order to correct the DTI data for echo planar imaging related geometrical distortions (Jones & Cercignani, 2010, ; see Appendix B for further details). During DTI acquisition, the heart rate was concurrently recorded at 500 Hz using an MRI compatible electrocardiograph (InVivo International, Best, The Netherlands). The scanner software automatically detected the maximum of the cardiac signal (R-peak) and registered their occurrences in a logfile.

T1-weighted images were processed with the FreeSurfer software suite version 5.3 (surfer.nmr.mgh.harvard.edu). FreeSurfer offers an automated analysis procedure which has been used widely and its processing steps have been described in detail elsewhere (e.g. Dale et al., 1999). In brief, FreeSurfer segments the individual raw T1-weighted image into different tissue classes, based on intensity values of each voxel and a priori information of anatomical atlases in stereotactic space. Data quality and processed images were checked using the FreeSurfer QA tools 1.1 (surfer.nmr.mgh.harvard.edu/fswiki/QATools). For the present study, volumes of interest from the FreeSurfer “aseg” analysis stream (Fischl et al., 2002) were: total GM, total WM, total CSF, total intra-cranial (ICV), third ventricle, and left and right lateral ventricle volume. Volumes of the inferior lateral ventricles were left out, since these are anatomically too distant to influence forniceal diffusion measures. Furthermore, volumes of the lateral ventricles were summed up to obtain a single value, as we did not expect hemispheric differences. At the individual level, ventricular

volumes were normalized by dividing by total ICV. DTI volumes were (pre-)processed with scripts and tools of the FMRIB Software Library 5.0 (FSL; fsl.fmrib.ox.ac.uk/fsl/fslwiki; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). This comprised brain extraction (Jenkinson, Pechaud, & Smith, 2005), eddy current (eddy_correct) and head movement correction, implicit adjustment of diffusion directions according to the head movement correction parameters using FMRIB's Diffusion Toolbox (FDT; Behrens et al., 2003), unwarping geometrical distortions due to magnetic field inhomogeneities using the B0 map and FSL's fugue tool (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fugue), and voxel-wise fitting of diffusion tensors along with the computation of FA using FDT.

To explicitly model the potential influence of head movement onto diffusion parameters, we separately ran the image quality assessment step of the TRACULA (TRActs Constrained by UnderLying Anatomy) stream embedded into FreeSurfer (Yendiki, 2011). TRACULA is a tool for automated probabilistic reconstruction of major white-matter pathways from DTI images, whose processing stream allows the extraction of motion parameters (i.e. translation, rotation, proportion of slices with drop-out, drop-out score) (Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2014). There were no group differences in movement during DTI as indicated by the four motion parameters (all $p > .13$).

7.3.5 Free-water correction, spatial normalisation / skeletonisation of diffusivity maps and of fornix a priori masks (pre- and main study)

To compute the free-water corrected FA maps, a bi-tensor model was fitted to the diffusion data as described in Pasternak et al. (2009). In brief, the attenuated signal is modelled by two compartments on a voxel-level: a tissue compartment and an isotropic free-water compartment, incorporating the diffusivity of water at body temperature (3 x 10^{-3} mm^2/s). The free-water compartment accounts for any contribution of CSF. The tissue compartment is then used for further analysis, allowing for a PVE free evaluation of diffusivity measures. This model-based approach overcomes the drawbacks of acquisition based PVE elimination techniques, such as low signal-to-noise ratio and prolonged acquisition time in fluid-attenuated inversion recovery (Cheng, Chung, Chen, & Chou, 2011; Papadakis et al., 2002). It has been used previously to improve the sensitivity of the resulted DTI measures in a number of studies (Bergamino, Pasternak, Farmer, Shenton, & Paul Hamilton, 2016; Metzler-Baddeley, Baddeley, Jones, Aggleton, & O'Sullivan, 2013; Metzler-Baddeley et al., 2012; Steventon, Trueman, Rosser, & Jones, 2016). The uncorrected FA maps were estimated following an identical preprocssing pipeline as the free-water corrected FA maps, with tensors estimated using the least squares method. Both, uncorrected and free-water corrected FA maps were further processed with FSL scripts for tract-based spatial statistics (TBSS) (Smith et al., 2006). This comprised: 1) optimisation of image quality (tbss_1_preproc) and visual inspection of images, 2) non-linear registration onto the FMRIB58_FA high-resolution (1 x 1 x 1 mm^3) template in standard-space (MNI), 3) creation of mean FA image across all subjects, and creation of skeletonised FA maps of uncorrected maps, 4) representing the centres of WM tracts, including only those voxels with FA > 0.2 (Smith et al., 2006).

The a priori mask of the fornix was derived from the probability map of the Juelich histological atlas embedded into FSL viewer (fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) (Eickhoff et al., 2005). A threshold of 20 % probability of belonging to the fornix was applied to each voxel,

before creating the final binarised mask (denoted "$\text{fornix}_{\text{broad}}$"). Additionally, for the analysis of WM centres the binary fornix mask was multiplied (logical AND) with the binary skeleton mask image derived from TBSS (see above), resulting in a new mask image covering a small section of the skeleton within the fornix (denoted "$\text{fornix}_{\text{centre}}$"). For $\text{fornix}_{\text{broad}}$ the same mask was used for the participants of both studies, whereas the $\text{fornix}_{\text{centre}}$ mask was adapted to the study specific skeletons, thus, different masks were used for pre- and main-study. To ensure proper alignment of the masks with the fornix location, visual inspection was performed and revealed a good fit of the masks for all participants.

7.3.6 Statistical analysis (pre-study)

Mask-based mean values of FA maps (both for $\text{fornix}_{\text{broad}}$ and $\text{fornix}_{\text{centre}}$) were extracted per subject using fslstats as part of FSL. To examine associations with ventricular volumes, these FA values were subjected to partial correlation analyses, using age and sex as covariates of no interest (SPSS® version 23, IBM® SPSS Statistics Inc., Armonk, NY).

7.3.7 Statistical analysis (main study)

To assess group differences in global brain anatomical measures and ventricular volumes, we applied five analyses of covariance (ANCOVA) with age as covariate of no interest, correcting for multiple comparisons using a false discovery rate correction (Benjamini & Hochberg, 1995; Yekutieli & Benjamini, 1999). Next, we focused according to our hypothesis on the fornix and extracted mask-based forniceal mean FA values per subject (for $\text{fornix}_{\text{broad}}$ as well as for $\text{fornix}_{\text{centre}}$) per subject using fslstats within FSL. To gain deeper insight into between-group differences with respect to diffusivity measures and to statistically control for covariates, these values were subjected to ANCOVAs. For mean FA values of $\text{fornix}_{\text{broad}}$ and $\text{fornix}_{\text{centre}}$ two separate analyses were performed, with age, mean heart rate, and the four head motion parameters as covariates of no interest (Yendiki et al., 2014). Similar analyses were done with

regard to radial and axial diffusivity (results shown in Supplementary material). Lastly, the enlarged ventricles of AN patients were considered. First, to determine whether ventricular size can be used to sufficiently account for the impact of increased CSF in AN, volumes of third and lateral ventricles were added as additional covariates to the group comparisons. Second, the ANCOVAs described above were conducted without ventricular volumes as covariates, using free-water corrected values of $\text{fornix}_{\text{broad}}$ and $\text{fornix}_{\text{centre}}$. All group comparisons were calculated using SPSS® (version 23, IBM® SPSS Statistics Inc., Armonk, NY).

7.4 Results

7.4.1 Pre-study

The volume of the third ventricle and the volume of the lateral ventricles negatively correlated with uncorrected mean FA of $\text{fornix}_{\text{broad}}$, as well as $\text{fornix}_{\text{centre}}$ (Fig. 7.2). These results establish a direct quantitative link between ventricular volumes and fornix FA independent of AN. Forniceal FA means and standard deviations of the pre-study sample are presented in Appendix B.

7.4.2 Main study

7.4.2.1 Volumetric and heart rate group differences

Table 7.2 summarizes the values of heart rate, ventricular and whole-brain tissue volumes, including group comparisons. As expected, patients with AN showed significantly enlarged ventricles compared to HC, along with increased CSF and reduced GM.

7.4.2.2 Group comparison of FA

Reproducing previously reported differences in forniceal FA, ANCOVAs with uncorrected values of $\text{fornix}_{\text{broad}}$ confirmed the significant reduction in AN patients (Table 7.3). To gain new insight, the main

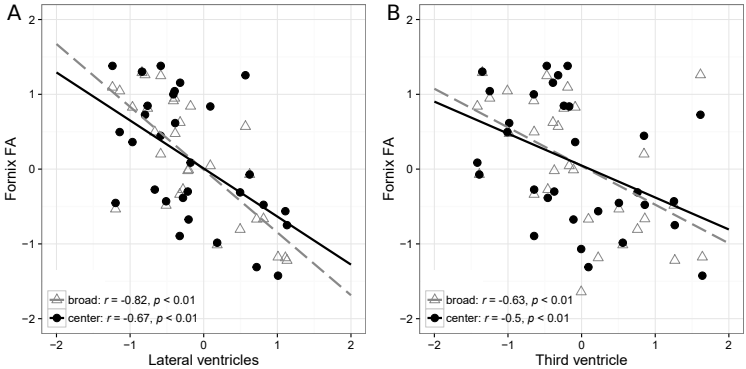

Figure 7.2. Pearson correlations between Z-scores of (A) lateral and (B) third ventricle volumes with Z-scores of fractional anisotropy (FA) of the fornix in an independent healthy sample (n=32), controlled for sex and age. Strong negative correlations with ventricular volumes can be observed for both $\text{fornix}_{\text{broad}}$ and $\text{fornix}_{\text{centre}}$.

goal of the current study was to consider the effect of increased ventricular CSF of AN patients on the analysis. We thus added volumes of the third and the lateral ventricles as covariates to the group comparisons. Incorporating ventricular CSF reduced the variance explained by group (FA_{broad}, $F[1, 40]=4.67$, $p=.04$, ${\eta_p}^2=0.11$; $\text{FA}_{\text{centre}}$, $F[1, 40]=4.37$, $p=.04$, ${\eta_p}^2=0.10$) , indicating a strong influence of ventricular volumes on FA values. Nevertheless, the group differences remained statistically significant.

As ventricular volume might be an incomplete measure of PVE, we further sought to control for the influence of CSF by correcting for free-water (Pasternak et al., 2009) to prevent residual confounding. Using the free-water corrected FA values, group comparisons no longer showed differences between patients and controls (Table 7.3), pointing out the strong bias of PVE in the uncorrected results reported above (Fig. 7.3). Additional group comparisons for radial and axial diffusivity are reported

Table 7.2

Comparison of ventricular and whole-brain tissue volumes between patients with anorexia nervosa (AN) and controls (HC)

	Group					
	AN $n = 25$		HC $n = 25$			
	M	*SD*	*M*	*SD*	*F*	*p*
Third ventricle	1.21	0.31	0.8	0.14	33.29	<.001
Lateral ventricles	19.54	9.54	10.73	3.94	21.96	<.001
Grey matter	582.05	50.64	640.82	38.70	6.74	.016
White matter	435.35	55.53	453.31	55.71	0.03	.861
CSF total	24.48	10.05	14.76	4.26	24.72	<.001

Note. Means represent absolute volumes (cm^3); statistics were calculated correcting for intracranial volume, controlling for age. *F* is the F-statistic and *p* the associated probability, false discovery rate corrected.

Table 7.3

Comparison of forniceal FA between patients with anorexia nervosa (AN) and controls (HC)

		Group						
		AN $n = 25$		HC $n = 25$				
Mask	Measure	*M*	*SD*	*M*	*SD*	*F*	η_p^2	*p*
$fornix_{broad}$	FA uncorrected	.24	.024	.28	.020	43.25	.53	<.0001
	FA corrected	.35	.018	.36	.018	0.82	.02	.37
$fornix_{centre}$	FA uncorrected	.31	.033	.37	.031	31.35	.45	<.0001
	FA corrected	.44	.041	.43	.026	1.64	.04	.21

Note. Group comparisons were calculated correcting for age, mean heart rate, and the four head motion parameters. $Fornix_{broad}$: values were derived using a traditional approach comprising the fornix in its natural shape; $fornix_{centre}$: values were derived from the tract centre.

in the Appendix B (Table B.2).

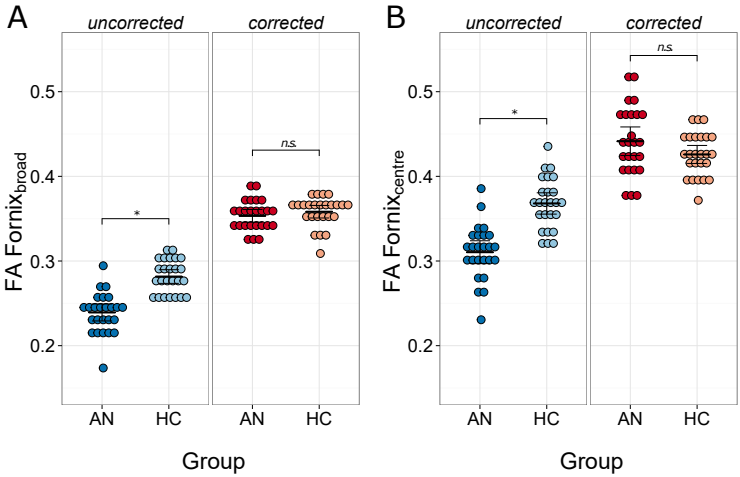

Figure 7.3. Scatter plots of fractional anisotropy (FA) with sample means and 95 % confidence intervals for each group, per-subject. Significant group differences of uncorrected values of (*A*) fornix$_{\text{broad}}$ and (*B*) fornix$_{\text{centre}}$ (blue dots) both disappeared after correcting for free-water (red dots). $^{*}p < .001$.

7.5 Discussion

This study investigated the influence of ventricular enlargement on diffusion properties of the fornix in acute AN. We found that increased volumes of the third and lateral ventricles present in AN, i.e., significantly augmented PVE in the nearby fornix, interfere with a valid assessment of forniceal diffusivity measures. Specifically, after appropriately correcting FA maps for free-water (Pasternak et al., 2009), the reduction of FA in AN patients as compared to HC was no longer observable.

PVE in the fornix, due to its anatomical position surrounded by the third and lateral ventricles, rely on a large body of empirical evidence (Concha, Gross, & Beaulieu, 2005; Hoy, Kecskemeti, & Alexander, 2015;

Jones & Cercignani, 2010). In the pre-study, we found that ventricular volumes correlated with reductions of forniceal FA in an independent sample of 32 healthy subjects, irrespective of the participants' age or sex. This has, to the best of our knowledge, not been demonstrated before and gave a basis to our analyses of data from AN patients and their HC.

In the main study, we first replicated the reduction of GM and correspondingly increased CSF in acute AN. Further, we replicated reduced FA of the fornix (Frank, Shott, Hagman, & Yang, 2013; Hayes et al., 2015; Kazlouski et al., 2011; Nagahara et al., 2014; Via et al., 2014), which has been suggested as anatomical representation of pathological emotional and motivational processes in recent AN research (Frank, 2015). Next, as the central goal of the present study, we sought to establish evidence for PVE in AN. The strong reduction of the group effect after including ventricular volumes as covariates supported this hypothesis. To prevent residual confounding, we further corrected FA maps for free-water with an established bi-tensor model (Pasternak et al., 2009), improving diffusion tensor estimates of conventional DTI images post-hoc by accounting for the fraction of CSF within a voxel. Remarkably, now groups no longer differed in their forniceal FA values and substantial increases in radial and axial diffusivity diminished to slight reductions compared to HC. This normalisation of diffusion indices in the AN group after correcting for free-water suggests that, contrary to previous assumptions, it is unlikely that considerable microstructural changes occur in the fornix of AN patients. The finding of reduced radial diffusivity found here in the centre of the fornix aligns with previously reported reduced radial diffusivity in wide-spread WM regions in AN (albeit adolescent) (Vogel et al., 2016).

Of note, CSF influenced even the TBSS-based FA values, i.e. values extracted only from the tract centre. TBSS is considered to achieve higher sensitivity for real effects compared to simple approaches (Smith et al., 2006) because of its robustness to ambiguous sites in the tract's periphery, where PVE-related influences should be strongest. However, for such a slim structure like the fornix, it seems that even TBSS cannot shield from PVE. Further, the analyses with free-water corrected FA pointed out the constraints of using ventricular volumes to account for PVE. While

strong correlations between CSF space and FA measures may serve as a good indicator of PVE, using ventricular volumes as covariate does not countervail sufficiently against the complex and potentially non-linear distortion effects of free-water.

From a methodological perspective, AN can serve as a model for increased probability of PVE caused by ventricular enlargement. Broadening this framework, our results point out two additional aspects: First, not only the fornix may be affected, but any site in WM located near CSF. For example, one recent study on AN patients (Frieling et al., 2012) identified reduced FA in the mediodorsal thalamus, positioned adjacent to the third ventricle, and in the posterior thalamic radiation, located near the lateral ventricles. Second, building on previous research that established the fornix as a PVE-prone structure (Concha et al., 2005; Hoy et al., 2015; Jones & Cercignani, 2010), the present results underline the importance to disentangle spurious from actual alterations of the fornix; a finding that is relevant for studies beyond AN and could apply to any condition characterized by increased CSF space. For example, findings in bulimic and obese patients' (Mettler, Shott, Pryor, Yang, & Frank, 2013; Stanek et al., 2011) may be similarly affected by PVE as these conditions have also been associated with increased CSF (Janowitz et al., 2015; Kaye, 2008). Moreover, the fornix has been implicated in the pathophysiology of various other disorders (Thomas, Koumellis, & Dineen, 2011) including schizophrenia (Fitzsimmons et al., 2009), a psychiatric condition also characterized by enlarged ventricles (Chua et al., 2007).

Alterations of forniceal fibre integrity with consideration of free-water have been reported in samples of healthy elderly participants (Metzler-Baddeley et al., 2012) as well as in a prodromal form of Alzheimer's disease (Berlot, Metzler-Baddeley, Jones, & O'Sullivan, 2014), where age or cognitive impairment were associated with reductions of forniceal FA. Suspected processes for this microstructural degeneration are age-related neuronal loss and subsequent degradation of axons (Wallerian degeneration) as well as myelin breakdown due to vascular changes (Lee et al., 2012). These processes induce irreversible changes in WM, this is likely not the case in AN, where no fornix alterations were observed

in weight restored patients and even the initially increased CSF seems to return to normal levels after a recovery period (Unsworth, Wells, Browning, Thomas, & Kendig, 2007). This being said, the fornix should still be in focus of research to further clarify its putative role in the pathophysiology of eating disorders as its microstructural properties have been validly associated with BMI (Metzler-Baddeley et al., 2013).

7.5.1 Limitations

This study should be seen in light of the following limitations. First, as DTI is sensitive to motion, cardiac pulsation can influence diffusion estimates (Skare & Andersson, 2001). Cardiac gating can counteract these influences by restricting acquisition to the diastole, i.e. the quiet portion of the cardiac cycle. Considering the prolonged acquisition time, cardiac gating was not employed in our study and a general overestimation of FA in both groups cannot be precluded. However, since the this study focuses on group comparisons and the same non-gated acquisition was used for both groups, the impact of the cardiac cycle should be negligible (Habib, Auer, & Morgan, 2010). Furthermore, all group comparisons were corrected for individual mean heart rates thus the reported group differences are not attributable to cardiac changes.

Second, the sample size is only moderate. Although the successful replication of group differences in the uncorrected FA values suggests a sufficiently large number of participants, it is still possible that minor differences between groups in free-water corrected values were not detected due to a lack of power and replication of our findings with a larger study sample is desirable.

Third, we used single-shell rather than multi-shell acquisition to keep acquisition time to a minimum. Single-shell acquired data are comparable to multi-shell acquisitions, however, multi-shell might have provided results that are even more accurate (Pasternak, Shenton, & Westin, 2012) and would have allowed for a closer examination of neurite morphology (Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012). Likewise, constrained spherical deconvolution, which seems to be more

robust against CSF-induced PVE (Roine et al., 2014), was not applied in the present study.

Fourth, despite TBSS being state of the art, there are some shortcomings of this analysis method that might affect fornix alignment (Bach et al., 2014). However, to meticulously check individual skeleton positioning visual inspection was performed and did not reveal any misalignments.

Finally, diffusion weighted images provide an indirect measure of potential pathological alterations of underlying structures. More direct examinations of the fornix, such as post mortem histological studies, are needed to confirm the present findings on a histological level.

7.5.2 Conclusion

The measurement of forniceal fibre integrity in AN by FA seems to be considerably biased by PVE. After controlling for free-water, identified alterations are no longer significant, suggesting a reconsideration of the proposed central role of the fornix in the pathophysiology of eating disorders. Future research applying DTI in disorders prone to PVE, such as AN, should incorporate new approaches and employ strategies for CSF correction either during acquisition (i.e., using fluid-attenuated inversion recovery prepulses) or during analysis (i.e., free-water correction) to gain deeper insight into structural changes independent of CSF effects.

7.6 Acknowledgements

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7.7 Financial disclosure

All authors report no biomedical financial interests or potential conflicts of interest.

CHAPTER 8

Additional data exploration

8.1 Association of functional brain alterations and behavioural measures

8.1.1 Weight gain estimation

8.1.1.1 Background

Fear of gaining weight is one of the core symptoms of AN (APA, 2013). To establish an empirical link between pathological cognitions associated with food and body-related beliefs (weight gain), AN patients of the present thesis participated in an additional computer-based nutrition estimation task which previously developed and is described in detail elsewhere (Milos et al., 2017). A previous cross-sectional study of our group with an independent sample of 24 AN patients and 27 HC showed marked differences in the mean weight gain estimation of AN patients during the stage of acute underweight. Specifically, when asked to estimate their personal expected weight gain, AN patients overestimated their expected weight gain by almost 10%, compared to HC (Milos et al., 2017).

Results of Study II demonstrated that recovery processes of rsFC within the fronto-basal ganglia/limbic network were negatively associated with changes in eating disorder symptoms, namely weight concerns, within the first half of treatment (between TP1 and TP2; see Chapter 6). To further explore additional relationships between changes in rsFC and weight gain expectations in that treatment period, the association of

rsFC recovery and alterations in weight gain estimations as described above were investigated.

8.1.1.2 Methods

The computer task was conducted three times over the course of treatment, corresponding to the three time points of the thesis project, described in section 4.2. In brief, patients were asked to rate different food items (snacks) on a scale from 0 to 100, indicating how much weight they expected to gain if they personally (intent-to-eat condition) were to eat this item additionally to their regular meals. In a second condition, they were asked to estimate how much weight anyone (general condition) would gain if they ate the item additionally to regular meals (Milos et al., 2017). The four different food items were chosen based on typical regional snacks, to ensure participants familiarity with the food selection and avoid cultural bias (Rozin, Fischler, Imada, Sarubin, and Wrzesniewski, 1999; Wardle et al., 2004). Pictures of food items are displayed in Fig. 8.1. Pictures were prepared and taken at the Division of Endocrinology, Diabetes and Clinical Nutrition of the University Hospital Zurich, Switzerland. Each snack item was displayed in four different sizes, with distinct nutritional values (melon: 19 kcal, 38 kcal, 76 kcal, 152 kcal; banana: 35 kcal, 65 kcal, 143 kcal, 286 kcal; bread roll: 44 kcal, 89 kcal, 178 kcal, 355 kcal; chocolate: 89 kcal, 178 kcal, 267 kcal, 623 kcal), unknown to the participants. Each picture was presented and rated once per condition, leading to a total of 32 trials. For the purpose of this exploratory analysis, only the ratings of the intent-to-eat condition were considered. To analyse the association of the individuals rsFC at TP1, as wells as rsFC recovery between TP1-TP2 and TP2-TP3 and alterations in weight gain estimations, correlation analyses between changes in rsFC and changes in weight gain estimations were computed for all AN patients of the sample described in Study II (Chapter 6).

8.1.1.3 Results

Mean values for weight gain estimation and rsFC per time point are reported in Table 8.1. In contrast to rsFC (see results Study II, Chapter

6), average values for weight gain estimates did not change significantly between TP1 and TP2 ($t(15)$ = -.085, p = .93, two-tailed), or TP2 and TP3 ($t(15)$ = -.338, p = .74, two-tailed). Pearson correlations between the individual change scores of rsFC and weight gain estimation for TP1-TP2 and TP2-TP3 yielded small to medium effects (TP1-TP2: r = -.23, TP2-TP3: r = -.43) which were however not significant (TP1-TP2: p = .39, TP2-TP3: p = .10; two-tailed). Furthermore, correlations between rsFC at TP1 and weight gain estimation scores yielded a medium effect at the trend level (r = -.47, p = .08; two-tailed).

Figure 8.1. Food stimuli presented in the weight gain estimation task (Milos et al., 2017). Four different sizes (ascending from left to right) of four snack types were used (top to bottom): melon (very low nutritional value), banana (low nutrition value), bread roll (modest nutrition value), and chocolate (high nutrition value).

Table 8.1

Descriptive statistics of the weight gain estimation task

	AN (n=16)				
Descriptives	WGE TP1	WGE TP2	WGE TP3	WGE TP2-1	WGE TP3-2
M	40.67	40.87	39.96	0.21	−0.91
SD	13.93	12.86	11.96	9.94	11.12

Note. WGE = Weight gain estimation score (intent-to-eat condition).

8.1.2 Body image assessment

8.1.2.1 Background

Another core symptom of AN is related to body image distortions (APA, 2013). Body image is generally conceptualised with two components: (1) body perception (size), and (2) attitudes towards the body (Skrzypek, Wehmeier, & Remschmidt, 2001). Here, the first component was explored. Some, but not all patients with AN significantly overestimate their body size (Probst, Vandereycken, Van Coppenolle, & Pieters, 1998). It has been suggested, that these patients form a subgroup within the patient group and that overestimation of body images could be a relevant factor for treatment outcome (Skrzypek et al., 2001).

8.1.2.2 Methods

Using a computer-adapted version of the widely used Figure Rating Scale (Stunkard, Sørensen, & Schulsinger, 1983), ideal and actual body image perception of AN patients were assessed at all three time points of the present thesis' project, described in section 4.2. The original task exists in a male and female version, consisting of nine figures with increasing size (Stunkard et al., 1983). It has demonstrated good test-restest reliability and is appropriate for the assessment of body image disturbances (Thompson & Altabe, 1991). To allow for a more precise assessment, the here used computer-adapted version provided more fine grained stages of body weight, indexed 1 to 50. A selection of the body

image avatars is displayed in Fig. 8.2. Patients were asked to indicate one of the 50 different body images that best resembled their ideal and actual body image. To evaluate associations with the fronto-basal ganglia/limbic network of impaired rsFC, correlation analyses between scores of the figure rating task and rsFC at TP1, as well as between changes over the course of treatment between TP1 and TP2 were calculated for all AN patients of the sample described in Study II.

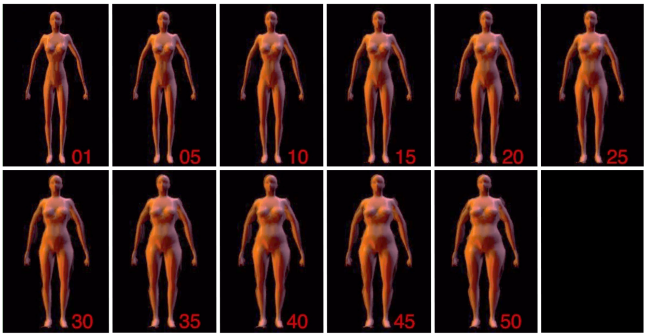

Figure 8.2. Selection of body avatars presented in the figure rating task (adapted after Stunkard et al., 1983). Fifty different body shapes were presented in ascending order.

8.1.2.3 Results

Mean values for body image evaluations of ideal and actual body per time point are reported in Table 8.2. Both ideal ($t(15)$ = -3.44, $p < .001$, two-tailed) and actual body image perception ($t(15)$ = -4.71, $p < .01$) increased significantly during the first therapy phase between TP1 and TP2. During the second therapy phase (TP2-TP3), only patients' actual body image increased significantly ($t(15)$ = -2.42, $p = .03$, two-tailed), while the ideal body image stayed the same ($t(15) = 0.68$, $p = .51$, two-tailed). Mean rsFC values per time point and group are displayed in Fig 6.2. Pearson correlations between the individual ideal body image and rsFC, as well as the actual body image and rsFC for TP1 and change

scores between TP1 and TP2 yielded no significant associations ($ps >$ .29, two-tailed).

Table 8.2

Resting-state functional connectivity of the network identified in Study II

	AN (n=16)				
Descriptives	rsFC TP1	rsFC TP2	rsFC TP3	rsFC TP2-1	rsFC TP3-2
M	0.082	0.160	0.165	0.078	0.004
SD	0.062	0.099	0.097	0.111	0.109

Note. rsFC = resting state functional connectivity.

Table 8.3

Descriptive statistics of the body image task

	AN (n=16)					
	TP1		TP2		TP3	
Descriptives	Ideal body	Actual body	Ideal body	Actual body	Ideal body	Acutal body
M	11.69	7.69	15.50	19.25	14.94	23.19
SD	5.77	9.56	8.39	9.55	7.43	10.30

8.1.3 Conclusion

The additional tasks presented above both captured body-related beliefs. While weight gain estimates on average stayed unchanged, body image assessment of both ideal and actual body image increased with treatment. These alterations might be attributable both to successful psychotherapeutic treatment, as well as to increasing girth due to weight gain. The improvements of rsFC observed in Study II (Chapter 6) were not related to changes in weight gain estimation and body image perception. These results might appear contradictory, considering the significant correlation between rsFC and the weight concern subscale

(EDE-Q) reported in Study II (Chapter 6). However, a closer examination of the items constituting the EDE-Q subscale reveals a clear focus on weight-, not shape-related cognitions (Hilbert & Tuschen-Caffier, 2006). The two tasks examined in the exploratory analyses above both were less targeted at weight concerns (i.e. desire to lose weight, being dissatisfied with one's weight) but rather captured shape-related estimates, more closely resembled in the EDE-Q shape concern subscale (i.e. feeling fat, fear of gaining weight, being dissatisfied with one's body shape). Although related, the two subscales are conceptually different which might explain the lack of significant associations with rsFC measures. An integrated discussion of these results can be found in the general dicussion (see Section 9.3.1.3).

8.2 Connection of structural and functional brain alterations

8.2.1 Background

Resting-state is a context independent quantification of brain activity and the fMRI measure most similar to structural measures and is closely related to the underlying anatomical connectivity, but their topography is also gated by the history of prior task activation (Fox & Greicius, 2010; van den Heuvel & Hulshoff Pol, 2010). In both longitudinal studies (see Chapter 5 and 6), changes in subcortical region were observed, namely decreased network connectivity and decreased structural volume at TP1. The rsFC network identified at TP1 comprised the subcortical regions displayed in Table 8.4, with a notable overlap with structural alterations in the bilateral nucleus accumbens, caudate nucleus, hippocampus, and putamen. Both measures demonstrated processes of recovery during weight gain treatment.

8.2.2 Methods

To investigate potential associations between the two measures, Pearson correlations between rsFC and subcortical volumes were calculated cross-sectionally for TP1, as well as longitudinally for changes between TP1 and TP3 within the group of AN patients described in Study II (Chapter 6). The subcortical regions were well comparable, as the parcellation schemes of Study I and II were both registered to the Montreal Neurological Institute (MNI) coordinate system (http://www.bic.mni.mcgill.ca/). Study I used the Aseg Atlas Fischl2002, based on the parcellation of the MNI305 template (Fischl et al., 2002). Study II used the Automated Anatomical Labelling atlas, based on the parcellation of the single subject MNI-space template brain (Tzourio-Mazoyer et al., 2002)). MNI coordinates of the subcortical regions identified in both studies are reported in Table 8.4.

Table 8.4

Subcortical regions of reduced tissue volume and functional connectivity in AN patients with severe underweight (TP1)

Structural volume				Functional connectivity			
	MNI coordinates [a]				MNI coordinates [a]		
Region	x	y	z	Region	x	y	z
Accumbens L	−10	10	−9	Accumbens L	−10	12	−7
Accumbens R	10	10	−9	Accumbens R	10	12	−7
Amygdala L							
Amygdala R							
Caudate L	−15	9	7	Caudate L	−13	11	9
Caudate R	16	10	8	Caudate R	14	12	9
Hippocampus L	−26	−24	−15	Hippocampus L	−26	−21	−10
Hippocampus R	28	−23	−15	Hippocampus R	28	−20	−10
Pallidum L							
Pallidum R							
Putamen L	−26	0	−2	Putamen L	−25	4	2
Putamen R	27	−1	−2	Putamen R	27	5	3
Thalamus L							
Thalamus R							

Note. [a]MNI coordinates of the centre of gravity (mm).

8.2.3 Results

At TP1, cross-sectional analyses of mean connectivity of the rsFC network and corresponding volumes of the subcortical structures of both hemispheres were not significantly correlated ($ps > .14$, two-tailed). Similarly, analyses of the longitudinal data did not reveal any significant correlations between changes of the two measures between TP1 and TP3 ($ps > .12$, two-tailed), suggesting that structural and functional brain alterations in AN patients are relatively independent of each other. These results will be discussed in more detail in the general discussion (see Section 9.2)).

CHAPTER 9

General discussion

The aim of the present thesis was to investigate brain alterations of AN patients during acute underweight, as well as temporal processes of neural and behavioural alterations induced by weight restoration treatment. The specific results of each study have been discussed in detail in the discussion sections of the respective studies. In the following, the hypotheses and key findings of these studies will be summarised briefly and integrated with respect to relationships between results. Furthermore, clinical and therapeutic implications of these findings, methodological considerations, and suggestions for future research will be outlined.

9.1 Summary of findings

The project of the present thesis is, to the be best of my knowledge, the first longitudinal project investigating neural changes and processes of reorganisation at three distinct time points during weight recovery of adult AN patients. To identify brain alterations in the acute phase of AN, as well as to help elucidate restorative or reorganizational mechanisms and potentially persisting brain alterations during and after weight restoration, structural and functional MRI measures were investigated cross-sectionally and longitudinally using advanced brain imaging analysis techniques. Additionally, associations with demographic and psychometric measures were explored.

9.1.1 Structural alterations

In accordance with previous studies (Bernardoni et al., 2016; Bomba et al., 2015), the AN group was hypothesised to demonstrate reduced cortical thickness and reduced subcortical brain volumes at the beginning of treatment, compared to HC. With weight restoration, at least a partial recovery of these expected alterations had been predicted.

Analyses of T1-weighted structural images of Study I (Chapter 5) revealed globally reduced cortical thickness and reduced subcortical volumes in AN patients at the beginning of treatment. These decreases seemed to be reversible over the course of treatment, associated with increasing BMI of patients. However, significant residual impairments remained in parietal and frontal brain regions even after weight restoration. Interestingly, restoration of cortical thickness and residual impairments in AN patients showed a strong negative association with age, outlining the high plasticity of the brain at young age (Pascual-Leone et al., 2011). The hypothesis of structural brain regeneration in adult AN patients is therefore clearly supported by our data. These findings suggest patients' age as a strong moderator of brain restitution, potentially indicating decreases of brain plasticity with older age (Pascual-Leone et al., 2011).

9.1.2 Functional connectivity

Resting-state activity of the brain constitutes patterns of functional activation associated with brain organisation (Damoiseaux et al., 2006; Deco & Corbetta, 2011; Weissman-Fogel, Moayedi, Taylor, Pope, & Davis, 2010) and has been shown to change with continuous task-training (Fauvel et al., 2014; Langer, von Bastian, Wirz, Oberauer, & Jäncke, 2013; Mackey, Miller Singley, & Bunge, 2013; Taubert, Lohmann, Margulies, Villringer, & Ragert, 2011). Based on the existing literature (for a review see Gaudio et al., 2016), it was hypothesized that rsFC in AN patients would be diminished at the beginning of treatment compared to HC. Over the course of weight restoration treatment, a reorganisation and recovery of rsFC was expected in the AN group.

Network analyses of rsFC showed reduced functional connectivity

in a distinct fronto-basal ganglia/limbic network of AN patients during severe underweight, compared to HC. Connectivity within this network significantly increased with weight restoration of patients. The observed changes in AN patients were associated with changes in eating disorder pathology, specifically with decreased weight concerns. No significant network differences between AN patients and HC were observed at the end of treatment. These findings support the hypothesis of disrupted, but reversible rsFC in AN patients. Moreover, they indicate that recovery processes may be related to changes in clinically relevant cognitions.

9.1.3 Methodological pitfalls of diffusion tensor imaging in anorexia nervosa

In the third study, insights from structural MRI and DTI were combined to investigate previously identified alterations of diffusion indices in the fornix, which had been implicated as a key structure in the pathomechanisms of AN (Frank, 2015; Frank, Shott, Hagman, & Mittal, 2013; Hayes et al., 2015; Kazlouski et al., 2011; Nagahara et al., 2014; Via et al., 2014). The fornix is anatomically adjacent to the ventricles of the brain and is thus susceptible to partial volume effects (PVE) (Concha et al., 2010; Jones & Cercignani, 2010; Pasternak et al., 2009). As Study I had demonstrated reduced brain mass and correspondingly increased sulcal and ventricular CSF in acute AN, it was hypothesised that previously reported disruptions of forniceal fibre integrity in AN are affected by ventricular volumes and thus biased by PVE. Specifically, the previously found differences in the fornix of AN patients were expected to diminish when appropriately controlling for the PVE.

Considering CSF as potential confounder of diffusion imaging, the hypothesis of Study I was investigated in two independent samples. First, the inverse associations between forniceal diffusion indices and volumes of the third and lateral ventricles were established in a pre-study with healthy subjects. Second, comparisons of AN patients and HC revealed that differences in forniceal fibre integrity disappear when using advanced analysis techniques. Hence, our data supported the postulated hypothesis: It is unlikely that microstructural alterations occurred in the fornix of AN patients. A valid assessment of diffusion indices of the fornix requires

adequate control of CSF-induced PVE that otherwise interfere with diffusion measurements and bias results.

9.2 Integrated discussion

9.2.1 Similarities and differences of structural and functional longitudinal findings

Comparing the two longitudinal studies, several commonalities stand out. The cross-sectional analyses at TP1 of both longitudinal studies revealed impaired subcortical regions by either reduced volume or rsFC. Overlapping regions included the bilateral nucleus accumbens, caudate nucleus, hippocampus, and putamen (Table 8.3). Networks of rsFC are known to be shaped by task-related activation as well as the underlying structural anatomy (for a review see Damoiseaux & Greicius, 2009) and combined plastic changes of both structural and functional modalities have been reported in learning processes (Fauvel et al., 2014).

Additional exploratory correlation analyses between individuals' volumetric and connectivity values yielded no significant association at TP1, as well as between TP1 and TP3. The observed cross-sectional and longitudinal alterations in Study I and II thus seem to reflect distinct changes and recovery processes in AN, corresponding to different clinical and demographic measures, as demonstrated by correlations with age (Chapter 5) and eating disorder symptoms (Chapter 6). The observed rsFC changes may represent inter-regional differences rather than local (intra-regional) dysconnectivity. The analyses of regional homogeneity (see Appendix A.1.1) support this hypothesis, as no differences in local intra-nodal homogeneity were found, compared to HC.

The long-term trajectories of recovery in structural and functional measures (see Fig. 5.1 and Fig. 6.2) demonstrated the steepest slope throughout the first phase of treatment, indicating a faster recovery between TP1 and TP2. This is in line with research demonstrating that learning-induced changes of grey matter and functional connectivity were most pronounced after an initial phase of 3 weeks of training (Taubert

et al., 2011). However, while increases of cortical thickness continued between TP2 and TP3, rsFC no longer advanced in the second phase of treatment. This trajectory of rsFC was paralleled by changes in weight concern, or lack thereof (see Table 6.1). Structural restitution progressed independent of eating disorder severity measures, such as weight concerns. Overall, the increase in cortical thickness was less pronounced in the second phase of treatment but still demonstrated a significant increase. Furthermore, changes of cortical thickness were strongly related to patients' age. Based on these findings, it seems plausible that grey matter changes chiefly reflect effects of starvation and re-alimentation, mediated by age-dependent plasticity (Pascual-Leone et al., 2011). The changes of neural activity during resting-state on the other hand may echo experience-dependent alterations and learning processes due to psychotherapeutic treatment (Linden, 2006).

9.2.2 Advantage of considering multiple modalities

Recently, multimodal MRI approaches have gained growing attention in neuroimaging research (Liu et al., 2015). Multimodal MRI offers the advantage to investigate complex and multifarious phenomena such as neuropathological alterations in AN from different viewpoints, thus allowing a more complete examination of research questions and a cross-validation of results (Cha et al., 2016; Liu et al., 2015).

The third study (Chapter 7) of the present thesis integrated measures of structural connectivity using DTI and volumetric information gained from structural T1-weighted data, to examine findings from previous studies implicating the fornix as a key structure in AN and eating disorder pathology in general. Combining these modalities drew previous findings into question and revealed the impaired structural connectivity of the fornix reported by unimodal diffusion-weighted studies was in fact biased by PVE. Due to the enlarged ventricles of AN patients during the phase of severe underweight, indices of water diffusion can be severely biased (see section 7.4). This has important implications for neuroimaging research in AN as it underscores the importance of combining different sources of information to better capture and understand the complexity of the

studied phenomena, e.g. neural alterations, which otherwise may easily lead to erratic or premature conclusions. These results may inform future DTI studies in the field of eating disorders and serve as a model for other disorders with enlarged ventricles, such as schizophrenia (Chua et al., 2007).

9.3 Clinical implications: contributions of a longitudinal multimodal MRI project to the understanding of anorexia nervosa

This project offered a unique opportunity to study mechanisms of brain plasticity and the gradual reorganisation of the brain during weight gain in severe AN. With regard to clinical symptoms, the temporal mapping of neural and behavioural changes induced by weight gain highlighted restorative mechanisms accompanying a successful therapy.

9.3.1 Updated aetiological model of Anorexia nervosa

As outlined in the theoretical background of the present thesis (see Chapter 2), a multitude of factors are currently being discussed as contributing to the aetiology of AN. A combination of factors arising prenatal or during childhood, including genetic predispositions, developmental features, and personality traits, together with cultural influences likely lead to initial eating restrictions and elicit weight loss. Subsequent neural alterations possibly reinforce disordered eating behaviour to counter negative emotionality, thus leading to additional weight loss (Herpertz-Dahlmann et al., 2011; Kaye, 2009). The findings of this thesis have important implications for the development and continued amendment of aetiological models of AN, which build a foundation not only for further research but also new treatment approaches. In the following, contributions of the present work to the understanding of the individual factors constituting the aetiological model of AN (see Fig. 2.2) will be discussed.

9.3.1.1 Sociocultural and developmental factors

The sample investigated in this work was recruited from a homogeneous sociocultural background. Thus, no empirically-based conclusions

can be drawn regarding influences of different cultural factors. However, developmental factors commonly reported to promote vulnerability, such as the development of certain personality traits, were assessed within the extensive questionnaire survey completed by the participants of the studies. While the study design of this thesis inherently does not permit any inferences regarding the causative relationship of these factors, the assessed questionnaires did confirm heightened levels of obsessionality, anxiety, and depression in the AN group compared to HC (see Chapter 5 and 6). Furthermore, diagnostic interviews conducted upon study participation demonstrated depression and anxiety as the main comorbid disorders in AN (see Table 3.1), thus supporting the concept of a close relationship of these aspects with AN.

9.3.1.2 Genetic factors

Knowledge from genetic research on AN has provided a basis for participant selection of this thesis project. As sex has been an important predictor of the disease (Mohler-Kuo et al., 2016), only female AN patients and sex-matched HC were included to achieve a homogenous sample and reduce confounding factors. With regard to HC, findings from twin-studies indicating a strong heritable component of AN (Yilmaz et al., 2015) informed the selection process as potential participants with first or second degree relatives with a history of eating disorders were excluded from the project. Results of group comparisons in the present work thus are likely to be reflective of genetic differences between groups. Further studies are needed to examine the relationship of genes and neurocircuitry in AN.

9.3.1.3 Neurobiological factors

The focus of the present thesis was on neurobiological factors associated with the pathophysiology of AN, specifically brain alterations captured by MRI. In the following, the contributions of each study to the understanding of AN will be discussed separately.

Structural volumetric brain alterations The findings of Study I provide support for the reduced grey matter and reduced subcortical volumes observed during acute underweight of AN patients. Furthermore, no global white matter changes were found in comparison to HC. This may indicate that potential changes of white matter are subtler and not detectable on a volumetric level. In fact, preliminary findings of DTI studies in adolescent AN patients point toward alterations in a number of white matter tracts (Travis et al., 2015; Vogel et al., 2016). The longitudinal examination of the grey matter reductions extends prior studies on adult AN patients by demonstrating a relatively fast but age-dependent recovery of these impairments. On a structural level, this brain restoration was independent of changes in eating disorder cognitions, as measured by the EDE-Q, but was rather associated with re-alimentation during weight restoration treatment. As discussed in Chapter 5, the histological foundation of the observed alterations is likely a reduction of glia cells, specifically astrocytes, which were found to decrease tremendously in a rat model of ABA, adapted to mimic chronic starvation in AN (Frintrop et al., 2017).

Importantly, regarding the aetiology of AN, these findings support the notion that drastic dieting behaviour and subsequent weight loss primarily leads to neural alterations in patients with AN. Structural brain impairments seem to appear secondary to the initial weight loss of patients and do not contribute to initial illness onset. However, once these brain alterations take place, they may affect behaviour and potentially enhance the pathology of patients. Additionally, residual alterations may have an impact on long-term recovery. The age dependence of the recovery process highlights the enhanced ability of younger AN patients to achieve structural brain recovery in a faster or more complete way. Looking at prognostic factors, these findings provide ground for a potential mechanism behind the observation that early onset AN has a better treatment outcome (Steinhausen, 2002). Moreover, they suggest age as a risk factor for persisting brain impairments and a chronic illness trajectory.

Functional connectivity Cortico-limbic circuits have previously been implicated in resting-state research of AN, employing mainly region-specific approaches (Gaudio et al., 2016). Findings of Study II support and extend these results by employing a novel approach to investigate networks of altered connectivity. At the beginning of treatment, AN patients showed disrupted connectivity in a fronto-basal ganglia/limbic network (Chapter 6). The basal ganglia are known to be highly interconnected and take an essential role in reward processing of the brain (Sesack & Grace, 2010). Furthermore, they project to frontal regions where decision making takes place (Sesack & Grace, 2010). Additional regions of the network comprised the anterior insular cortex and the fusiform gyrus, which are critical for interoception (Adolfi et al., 2017) and body recognition (Peelen & Downing, 2007). With regard to the aetiology of AN, these results may suggest a neural basis of distorted body perception in AN. However, within the additional exploratory analyses (Chapter 8), individual figure ratings of current body shape (ideal and actual) were not associated with reduced functional connectivity of the identified network, potentially suggesting a more complex relation of body perception and functional brain connectivity. Reduced functional connectivity of reward-related regions could indicate an impaired response in subcortical regions to rewarding stimuli such as food, potentially facilitating food avoidance despite low body weight. Negative correlations of patients' functional connectivity at TP1 with overestimation of expected weight gain upon food consumption (weight gain estimation task, Chapter 8), albeit at trend level, may further indicate a complex interplay of alterations in reward-related brain regions and behaviour.

The hypoconnected network in AN patients partially recovered with weight normalisation during a multi-modal inpatient treatment. Of note, the recovery processes within the network were strongest during the first half of treatment and significantly correlated with weight-related eating disorder cognitions (Table 6.1), emphasising the importance of the initial phase of therapy for a successful recovery process. Changes in this first half may be more pronounced, as the majority of new experiences likely takes place in that phase. While the treatment programme continues to

evolve with weight restoration, the essential elements of regular meals, group and individual therapies remain stable throughout the inpatient stay (Department of Psychiatry and Psychotherapy, 2016).

Exploratory analyses at the end of treatment provided evidence for residual subthreshold hypoconnectivity of the caudate nucleus and the putamen, regions part of the basal ganglia and key structures of reward processing (Sesack & Grace, 2010). In this context, a recently proposed top-down model of the persistence of AN is important (Steinglass & Walsh, 2016). The model integrates findings of abnormal connectivity in fronto-striatal regions and postulates chronic disadvantageous decision-making in AN may be fostered in a "top-down" manner, similar to habitual behaviour (Steinglass & Walsh, 2016). As the authors emphasise, their model is preliminary and much research needs to be done to confirm the hypothesis. Nonetheless, findings from Study II support and extend this line of theory as the regions with residual alterations are known to be central to habit learning (Knowlton, Mangels, & Squire, 1996; Yin & Knowlton, 2006).

Structural connectivity Study 3 investigated the role of the fornix in the pathophysiology of AN, which had been found to be severely impaired in adult (Hayes et al., 2015; Kazlouski et al., 2011; Nagahara et al., 2014; Via et al., 2014) and adolescent patients with AN (Frank, Shott, Hagman, & Mittal, 2013). Based on fornix alterations reported also in bulimia nervosa and obese patients, the fornix had been proposed as a main structure in eating disorder pathology in general (Frank, 2015). Findings from Study III demonstrated that previous DTI studies on AN were likely biased by PVE due to the enlarged ventricles of patients in the acute phase. Regarding the aetiological model of AN, these findings not only put the role of the fornix into perspective but also underscore the importance of considering the complexity of the disorder and the different facets accompanying it. The results may inform future DTI studies in the field of eating disorders to carefully deal with PVE when investigating structural connectivity in AN, which then will likely provide an important contribution in the pursuit of reconciling the above

discussed structural volumetric alterations (grey matter) with the changes in functional connectivity.

9.3.2 Current treatment approaches

The here presented findings provide evidence for successful brain restorative processes during weight restoration treatment in a multimodal interdisciplinary inpatient setting. The treatment concept consisted of several phases of structured re-nutrition with the main goal of normalisation and stabilisation of eating behaviour and weight. In addition, it comprised somatic checks and treatments, individual and group psychotherapy, as well as body and art therapy. The results of the present thesis underscore the importance of refeeding as first step in modern multimodal treatment of AN.

Particularly the results of the two longitudinal studies in Chapter 5 and 6 can be seen as encouragement for both therapists and patients: Unlike some of the other somatic issues accompanying AN (see Section 2.1.3), the severe impairments of brain structure and function seem to be largely reversible through refeeding therapy. Therapists should integrate these findings in psychoeducational elements of treatment to make patients aware of (1) the severe damage the underweight is causing and (2) of the possible reversibility with weight normalisation in the context of a multimodal treatment programme. This may not only support therapy motivation, but also facilitate the perceived control over treatment processes in their patients (Haggard & Chambon, 2012), which seems to be decreased specifically in AN patients (Dalgleish et al., 2001; Sassaroli, Gallucci, & Ruggiero, 2008).

It is conceivable that the observed alterations in brain function and structure are linked to cognitive impairments often observed during initial treatment, such as fatigue, diminished concentration and learning (Katzman, Christensen, Young, & Zipursky, 2001). This is important to consider for treatment planning and should find consideration in form of shorter treatment sessions and generous recreational time slots within an inpatient setting.

The remaining residual alterations in both structural and functional brain measures make the persistence of the disorder evident (Papadopoulos et al., 2009; Steinhausen, 2002; Zipfel et al., 2015). With regard to therapy programmes, these residual alterations underline the importance of outpatient aftercare upon discharge to further normalise and stabilise weight and eating behaviour of patients with AN.

9.4 Methodological considerations

9.4.1 Sample composition

All patients of the present thesis had a primary diagnosis of AN, as diagnosed with the SCID-I (First et al., 2002). Approximately 15% of participants met the criteria for the binge-purge subtype of AN at TP1, while 85% were diagnosed with restrictive AN at the beginning of treatment. This distribution remained stable over all three time points (see Table 3.1). Comorbid diagnoses were given to almost 50% of the patients at TP1, diagnoses included depressive disorders, dysthymia, anxiety disorders, and post-traumatic stress disorder. There were no proportional differences in comorbid diagnoses between time points (see Table 3.1), indicating that therapy completion was not predominantly driven by comorbidity, i.e. absence of comorbid diagnoses did not predict an overall more positive outcome. In the following, relevant factors regarding sample composition will be summarised and discussed.

9.4.1.1 Subtypes of Anorexia nervosa

Due to the limited number of the binge-purge subtype, no separate analyses of the two subtypes were possible for the present thesis. In general, analysis of the influence of AN subtypes is complicated due to the relative instability of diagnoses, as about half of the patients cross subtypes or even change diagnoses from AN to bulimia nervosa (Eckert, Halmi, Marchi, Grove, & Crosby, 1995; Eddy et al., 2002; Milos et al., 2005). To date, few studies have investigated the potential neural differences of the subtypes (van Kuyck et al., 2009). Results from single-photon emission computed tomography studies with acutely ill patients suggest

decreased blood perfusion in the restrictive subtype at rest (Naruo et al., 2001) and increased perfusion in the binge-purge subtype during a food task (Naruo et al., 2000), in comparison to the opposite AN subtype and HC. However, the two studies had small sample sizes (n=7 per subtype) and need replication. As the binge-purge subtype has been associated with a less positive outcome (Steinhausen, 2002; Treasure et al., 2015; Zipfel et al., 2015), a closer investigation of potential differences between subtypes with a larger sample could help elucidating corresponding neural representations of the behavioural differences.

9.4.1.2 Comorbid diagnoses

Influences of comorbid diagnoses on results of the present thesis cannot be excluded, as subgroup analyses were not feasible due to the small number of patients within the subgroups. However, the percentage of comorbid diagnoses of the investigated patient group is within the range commonly observed in adult AN patients (Hudson et al., 2007). Furthermore, the predominant comorbid diagnoses of the current sample are in agreement with previous studies, reporting depressive and anxiety disorders as the largest proportion of secondary diagnoses (Hudson et al., 2007; Kaye, Bulik, Thornton, Barbarich, & Masters, 2004; Milos et al., 2003). Thus, the observed brain alterations and restorative processes seem to be valid for a typical sample of AN patients with the commonly observed comorbid diagnoses (Hudson et al., 2007; Kaye et al., 2004; Milos et al., 2003). However, the datasets of the present work do not allow for more detailed conclusions regarding individual comorbid disorders.

9.4.1.3 Medication of patients

To avoid disruption of current inpatient treatment, patients were instructed to continue with their medication as normal. Due to the variety of different medications, specific influences of different medications could not be explored more specifically. However, measurements in the respective studies were compared for patients taking medication and patients without medication. Although it is possible that medications influenced the findings, results suggested that brain measurements were within the range of patients without medication (see Chapter 5 and 6). Thus, group differences in comparison to HC are unlikely to be driven solely by medication effects.

9.4.1.4 Sex

Female sex has commonly been associated with a greater prevalence of AN, with only approximately 10% of AN patients being men (Nagl et al., 2016; Treasure, Claudino, & Zucker, 2010). To exclude sex as a confounding factor, the present thesis has investigated exclusively female

patients with AN. Eating disorder pathology in male populations has been reported to be expressed in a more diverse way, with features of muscle dysmorphia, a specifier of the body dysmorphic disorder (APA, 2013; Grieve, Truba, & Bowersox, 2009). Little research is being conducted on male samples and to date there are no neuroimaging studies focussing specifically on male populations. The results of the present work are based on a female sample; thus, the conclusions drawn from this work may not extend to male AN patients.

The available evidence on male AN patients points out differences in comorbidity compared to female patients, with higher rates of substance abuse and sexual identity concerns (Carlat, Camargo, & Herzog, 1997; Sharp, Clark, Dunan, Blackwood, & Shapiro, 1994; Touyz, Kopec-Schrader, & Beumont, 1993). In terms of illness history, a delayed illness onset, as well as premorbid obesity seem to be more prevalent in male AN patients (Carlat et al., 1997; Sharp et al., 1994; Touyz et al., 1993). Whether these differences of presentation reflect differences in the pathomechanism of the disorder remains to be investigated.

9.4.2 Study design

The present thesis project consisted of three time points over the course of a specialised inpatient treatment, allowing for closer monitoring of recovery dynamics over time. The first time point of the project was defined by severe underweight of AN patients (BMI $\leq$ 15.5). After initial weight gain (15.5 $<$ BMI $<$ 17.5) of patients, as well as at the end of treatment (BMI $\geq$ 17.5), MRI scans were repeated. An aspect to keep in mind when interpreting the residual alterations at the end of treatment is the weight range of patients at TP3. A significant weight gain took place during treatment between TP1 and TP3. However, eligibility criteria for TP3 was a BMI $\geq$ 17.5, meaning that not all patients had yet reached a healthy BMI of 18.5. Furthermore, the phase of weight stabilisation at the end of treatment was comparatively short (2-4 weeks), thus residual alterations found at TP3 might be influenced by low BMI and recover after a longer follow-up period with further BMI increase. Future studies should include an additional time point after a longer interval

of weight stabilisation, to investigate post-treatment recovery processes and long-term outcomes after inpatient treatment. More specifically, this would allow for a closer investigation of the different types of treatment trajectories and potentially help elucidate factors predictive for a beneficial therapy outcome, as well as factors associated with a less positive therapy trajectory.

Measures of neuropsychological functioning were assessed at TP1 to ensure any differences found between groups would not be attributable to severely impaired cognitive functioning. This strengthened the reliability of the results of the present thesis. Future studies should examine these measures at all time points, to allow investigation of potential relationships between cognitive performance and recovery processes in the brain.

9.4.3 Potential nuisance factor for resting-state fMRI

The somatic complexity of AN has a strong influence on measures of the brain as demonstrated for instance by the findings of the present thesis. Two recent studies on respiratory functions in adolescents with AN have drawn attention to impairments, with consequences known as respiratory acidosis (Kerem, Averin, et al., 2012, 2012). Respiratory acidosis describes the accumulation of carbon dioxide (CO2) in the blood, followed by a dropping pH level of the blood and is commonly caused by insufficient expiration (WHO, 2009). An influential study by Xu et al. (Xu et al., 2011) has investigated the effects of increased blood CO2 (hypercapnia) on resting-state brain activity in a sample of healthy adults. The results demonstrated a strong reduction of resting-state activity upon inhalation of CO2, suggesting a suppressive effect on spontaneous neural activity of the brain (Xu et al., 2011).

Regarding AN, respiratory acidosis and correspondingly increased CO2 measures in AN patients present a potential nuisance factor which has been neglected in resting-state research on the disorder thus far. Studies on adult patients did not find altered blood gases (González-Moro et al., 2003; Murciano et al., 1994; Pieters et al., 2000), thus it can be argued that results of the present thesis are unlikely to be

caused by elevated blood-CO2 levels. However, respiratory acidosis is a potential nuisance factor for BOLD signal-dependent fMRI and should be considered in future studies, especially when investigating adolescent samples, where respiratory acidosis is more likely to occur (Kerem, Averin, et al., 2012; Kerem, Riskin, Averin, Srugo, & Kugelman, 2012).

9.5 Challenges and future work

The current thesis investigated processes of neural reorganisation during weight recovery. To this extend, only patients with a successful treatment trajectory (i.e. continuous weight gain) were considered for the longitudinal studies. Approximately half of the initially included patients fulfilled this requirement at the end of treatment. The other half of patients either gained some weight, but discontinued therapy before reaching a BMI $\geq$ 17.5, or were not able to gain weight at all even with therapeutic support.

The question of chronicity in AN poses one of the major challenges in AN research (Compan et al., 2015). Future studies should explicitly address the neural basis of the persistence of AN and investigate predictors of negative treatment trajectories by including patients with a chronic course of AN, who fail to gain weight during treatment, in longitudinal studies. Additionally, of those patients with a successful course of treatment and a discharge BMI in the desired range ($>$ 18.5), up to 50% relapse and return to the disastrous process of weight-loss and emaciation within 1 year after discharge from hospital (Carter, Blackmore, Sutandar-Pinnock, & Woodside, 2004; Eckert et al., 1995; Strober, Freeman, & Morrell, 1997). In order to obtain a better understanding, studies with an even longer time frame are required to clarify the role of the here identified residual brain alterations and to shed light on potential indicators of relapses or long-term recovery, which may help inform and improve treatment approaches.

As outlined above, small sample sizes limit possible analyses and in turn restrict the research questions that can be answered. To overcome the limitations of small sample sizes, multicentre studies or study consor-

tia with harmonised processing streamlines are indispensable. First steps in this direction were made in 2009, when the Enhancing Neuroimaging and Genetics through Meta-Analysis (ENIGMA) Network was founded (`http://enigma.usc.edu/`) (Mohammadi, 2015). ENIGMA is a network of researchers organised in different working groups investigating brain changes and genetics in disease and health, as well as specific methodological questions (Mohammadi, 2015). With regard to AN, a newly formed working group has set out to examine structural brain alterations associated with the disease on large samples (`http://enigma.usc.edu/ongoing/enigma-anorexia/`). Combined efforts of research groups may validate current findings on structural alterations and help identify consistent factors associated with a positive treatment outcome. Together with targeted investigation of candidate genes as done by Genome Wide Association Studies (Boraska et al., 2014; Duncan et al., 2016; Nakabayashi et al., 2009; Wang et al., 2011), this may even allow examination of the relationship between brain alterations and patients' genetics.

9.6 Conclusion

The present PhD thesis provided insight into brain alterations during acute underweight, as well as associated longitudinal regenerative processes throughout weight restoration treatment of adult patients with severe AN. Taken together, the longitudinal findings demonstrate a tremendous plasticity of young patients' brains and suggest that dramatic alterations in the structural and functional realm are largely reversible with specific treatment and careful weight restoration. However, residual alterations in both modalities (structural / functional) remained at the end of the weight normalisation during inpatient treatment, likely reflecting the persistence of the disorder with high relapse rates and often persisting psychopathology. The findings of the present work highlight the importance of sufficiently long and well-structured treatment programmes, including outpatient after-care to further normalise and stabilise weight and eating behaviour, as well as to improve psychopathology.

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A Study II - Supplemental material

A.1 Supplemental results

A.1.1 Functional connectivity in the phase of severe underweight

Table A.1

Network of reduced inter-regional connectivity

Network edges	
Nucleus accumbens R	- Anterior insula L
Nucleus accumbens R	- Anterior insula R
Caudate nucleus L	- Anterior insula L
Caudate nucleus L	- Putamen L
Caudate nucleus L	- Putamen R
Caudate nucleus R	- Putamen L
Caudate nucleus R	- Putamen R
Inferior frontal gyrus, triangular R	- Nucleus accumbens R
Middle fontal gyrus L	- Hippocampus L
Superior frontal gyrus, medial orbital L	- Hippocampus R
Hippocampus L	- Nucleus accumbens R
Hippocampus L	- Caudate nucleus L
Hippocampus L	- Caudate nucleus R
Hippocampus L	- Fusiform gyrus R
Hippocampus R	- Nucleus accumbens L
Hippocampus R	- Nucleus accumbens R
Hippocampus R	- Caudate nucleus L
Hippocampus R	- Caudate nucleus R
Putamen L	- Nucleus accumbens L
Putamen R	- Nucleus accumbens R

Note. Edges represent reduced functional connectivity in anorexia nervosa patients, compared to healthy controls at TP1 (t=3.5). L = left hemisphere; R = right hemisphere.

Table A.2

Intra-nodal homogeneity and correlations with inter-regional connectivity at TP1

	Intra-nodal homogeneity				Mean inter-regional connectivity				Correlation[a]		
	AN (n = 16)		HC (n = 20)		AN (n = 16)		HC (n = 20)		AN (n = 16)	HC (n = 20)	AN vs. HC[b]
Node	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*r*	*r*	CI
Nucleus accumbens L	−0.29	0.45	−0.25	0.47	0.16	0.10	0.33	0.10	−0.23	0.10	n.s.
Nucleus accumbens R	−0.41	0.63	−0.32	0.58	0.07	0.08	0.25	0.08	0.21	0.11	n.s.
Caudate nucleus L	−0.60	0.2	−0.51	0.23	0.11	0.09	0.32	0.14	−0.05	0.38	n.s.
Caudate nucleus R	−0.50	0.21	−0.38	0.22	0.10	0.12	0.35	0.12	−0.04	0.17	n.s.
Inferior frontal gyrus, tri. R	0.10	0.27	0.15	0.29	0.003	0.16	0.18	0.14	0.05	−0.07	n.s.
Superior frontal gyrus, mo. L	0.10	0.29	0.08	0.35	0.04	0.13	0.22	0.17	−0.35	0.20	n.s.
Middle fontal gyrus L	0.14	0.25	0.23	0.20	−0.02	0.15	0.20	0.21	−0.14	0.15	n.s.
Fusiform gyrus R	−0.14	0.2	−0.11	0.25	0.23	0.20	0.44	0.16	−0.03	0.23	n.s.
Hippocampus L	−0.33	0.34	−0.40	0.35	0.04	0.10	0.28	0.15	−0.02	−0.40	n.s.
Hippocampus R	−0.60	0.27	−0.56	0.22	0.01	0.12	0.22	0.13	−0.08	−0.12	n.s.
Anterior insula L	0.06	0.34	−0.08	0.25	0.01	0.12	0.22	0.15	−0.11	0.32	n.s.
Anterior insula R	−0.09	0.20	−0.05	0.20	0.06	0.15	0.27	0.15	0.03	−0.24	n.s.
Putamen L	−0.22	0.24	−0.08	0.30	0.24	0.10	0.44	0.15	−0.49	0.49*	[-1.39, -0.32]
Putamen R	−0.26	0.23	−0.14	0.30	0.21	0.08	0.38	0.12	−0.23	0.43	n.s.

Notes. Intra-nodal homogeneity measured as Kendalls's coefficient of concordance at the first time point. Mean values of intra-nodal homogeneity and inter-regional connectivity did not differ significantly between groups ($p >$ .05, two-tailed). [a]Correlation between intra-nodal homogeneity and inter-regional connectivity: Pearson correlations, $*p < .05$, two-tailed. [b]Comparison of Pearson's correlations using Fisher's r-to-z-transformation, acknowledging the asymmetry of sample distributions for single correlations (Zou, 2007). CI = confidence interval 0.95; L = left hemisphere; mo. = medial orbital; R = right hemisphere; tri. = triangular.

A.1.2 Functional connectivity after weight recovery

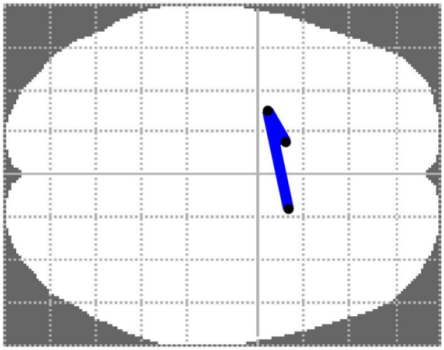


Figure A.1. Network of hypoconnectivity in AN compared to HC at the last time point, comprising nodes in the left and right caudate nucleus, and the left putamen. Displayed is the top-view onto the brain, from posterior (left) to anterior (right). Network-based statistics were applied to compare functional connectivity within the network identified at TP1 between the groups (t=2.0). The network displayed survived a statistical threshold (p=.10), corrected for multiple comparisons using family-wise error correction.

A.1.3 Individual-level motion correction

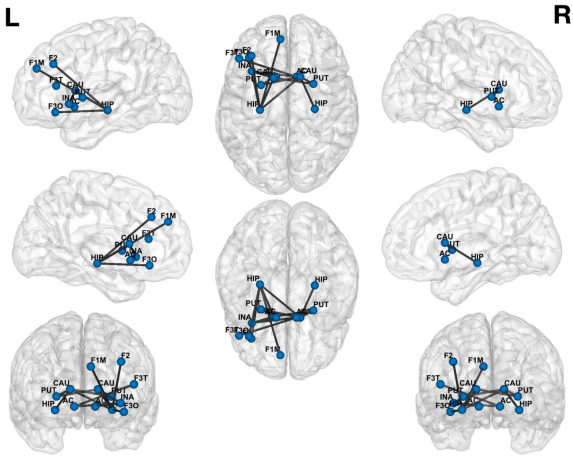


Figure A.2. Network of hypoconnectivity in AN compared to HC at TP1, after motion correction at individual-level using spike regression (Vinet & Zhedanov, 2010; Power et al., 2014). Network-based statistics were applied to compare whole-brain functional connectivity between the groups (t=3.5). The network consists of 13 nodes (blue spheres) and 14 edges (grey lines) that survived a statistical threshold (p=.05), corrected for multiple comparisons using family-wise error correction. The network comprised largely the same nodes compared to motion correction on group-level (differences: F1M instead of F1MO; F3O instead of F3T; no fusiform gyrus). The core nodes of the network (nucleus accumbens, nucleus caudatus, hippocampus, putamen) remained unchanged, supporting the robustness of the original network. *Left column* (top to bottom): Lateral and medial view of left hemisphere, anterior view. *Middle*: Top and bottom view. *Right column*: Lateral and medial view of right hemisphere, posterior view. AC=Accumbens; CAU=Caudate nucleus; F1M=Superior frontal gyrus, medial; F1MO=Superior frontal gyrus, medial orbital; F2=Middle frontal gyrus; F3O=Inferior frontal gyrus, orbital; F3T=Inferior frontal gyrus, triangular; HIP=Hippocampus; INA=Insula anterior; PUT=Putamen. Network visualised using BrainNet Viewer (Xia et al., 2013).

A.1.4 Test statistic threshold

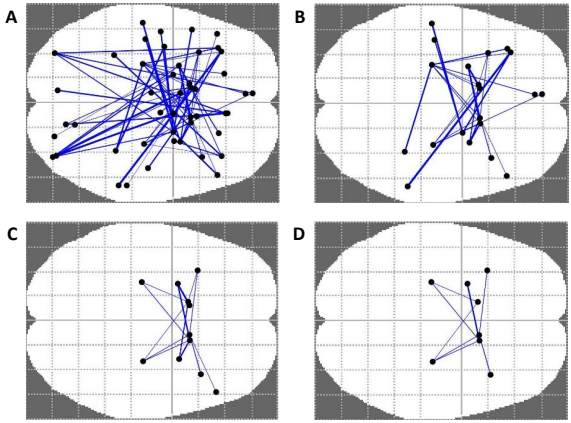


Figure A.3. Networks of hypoconnectivity in AN compared to HC at the first time point, for varying thresholds of the primary test statistic: (A) t=3.0; (B) t=3.3; (C) t=3.7; (D) t=4.0. Displayed is the top-view onto the brain, from posterior (left) to anterior (right). Network-based statistics were applied to compare whole-brain functional connectivity between the groups. The networks displayed were the only networks per threshold and survived a statistical threshold (p=.05), corrected for multiple comparisons using family-wise error correction.

A.1.5 Medication effects

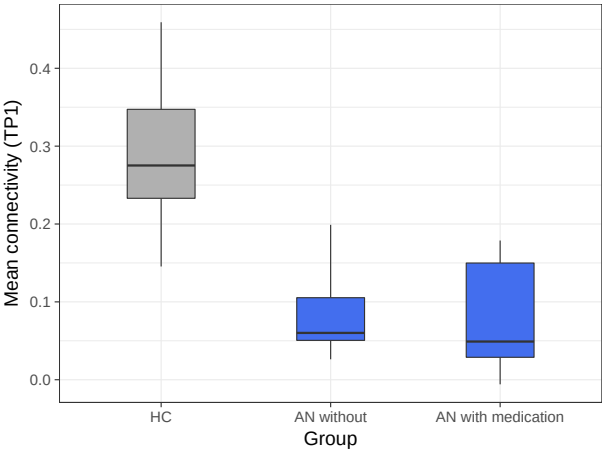


Figure A.4. Boxplots of mean network connectivity at the first time-point (TP1). Separate plots for HC and AN patients with and without medication. The horizontal mark signifies the median per group, edges of the box represent the 25th and 75th percentiles, and the whiskers correspond to the minimal / maximal data points. AN=Anorexia nervosa group; HC=Healthy control group.

B Study III - Supplemental material

B.1 Supplemental Methods

B.1.1 B0 field correction

The B0 magnitude and phase maps were reconstructed to a spatial resolution of $2.0 \times 2.0 \times 2.0$ mm^3 from a multiecho multislice gradient echo acquisition with a spatial resolution of $2.0 \times 4.0 \times 2.0$ mm^3. Further imaging parameters were: acquisition matrix 128×64 pixels, 77 slices, FOV=$256 \times 256 \times 154$ mm^3, dual echo-time (TE)=4.4 / 6.7 ms, repetition-time (TR)=400.0 ms, flip-angle =45°, acquisition time 1 min 46 s.

B.2 Supplemental Results (pre-study)

Table B.1

Ventricular volumes of the third and lateral ventricles [cm^3] and fornix FA within each of the two fornix masks for the pre-study sample of n = 32 healthy subjects

	M	*SD*
Third ventricle volume	0.85	0.22
Lateral ventricle volume	11.24	5.62
FA $\text{Fornix}_{\text{broad}}$	0.30	0.02
FA $\text{Fornix}_{\text{centre}}$	0.41	0.02

Note. The means reported represent the absolute volumes (cm^3) or FA; volumetric statistics (see Chapter 6) were calculated correcting for intracranial volume.

B.3 Supplemental Results (main-study)

B.3.1 Group comparisons of axial and radial diffusivity

Table B.2

Comparison of axial diffusivity (AD) and radial diffusivity (RD) [$\mu m^2/s$] of the fornix between patients with anorexia nervosa (AN) and controls (HC)

		Group						
		AN $n = 25$		HC $n = 25$				
Mask	Measure	*M*	*SD*	*M*	*SD*	*F*	${\eta_p}^2$	*p*
$\text{fornix}_{\text{broad}}$	AD uncorrected	2.17	0.15	1.87	0.12	70.94	.65	<.0001
	AD corrected	0.81	0.02	0.82	0.01	7.23	.16	.01
	RD uncorrected	1.58	0.17	1.27	0.12	70.78	.65	<.0001
	RD corrected	0.44	0.03	0.47	0.01	14.32	.27	.001
$\text{fornix}_{\text{centre}}$	AD uncorrected	2.04	0.18	1.70	0.16	53.25	.58	<.0001
	AD corrected	0.94	0.05	0.92	0.02	1.5	.04	.23
	RD uncorrected	1.31	0.18	0.97	0.13	55.25	.59	<.0001
	RD corrected	0.40	0.02	0.42	0.01	4.77	.11	.04

Note. Group comparisons were calculated correcting for age, mean heart rate, and the four head motion parameters. $\text{Fornix}_{\text{broad}}$: values were derived using a traditional approach comprising the fornix in its natural shape; $\text{fornix}_{\text{centre}}$: values were derived from the tract centre.

Focusing only on the uncorrected data, the pattern of increased axial diffusivity (AD), increased radial diffusivity (RD) (Table S2), and decreased FA values in AN patients (see main paper) points to a substantially increased free-water fraction within the fornix masks, where both AD and RD significantly increase with decreased tissue density (Beaulieu, 2002). However, after correcting for free-water, AD and RD increases in AN patients no longer exist. Within the broad mask, AN patients even demonstrate a slight reduction of AD and RD compared to HCs. Similarly, within the mask of the tract center AD values are no longer significantly elevated after correcting for free-water and RD values even show a minor reduction in the patient group.

C Project documents

C.1 Patient information

Patientinnen-Information
24.03.2015

"Reshaping" the Brain – Longitudinal Assessment of Changes in Structural and Functional Connectivity During Weight Gain in Anorexia Nervosa

Die "Neuformierung" des Gehirns – Evaluierung von Veränderungen der strukturellen und funktionellen Konnektivität während der Gewichtszunahme bei Anorexia Nervosa

Finanziert durch die Gottfried und Julia Bangerter-Rhyner-Stiftung, Hermann-Klaus-Stiftung und Parrotia-Stiftung

Sehr geehrte Teilnehmerin

1 Auswahl der Studienteilnehmerinnen

Wir fragen Sie an, ob Sie an einer Studie teilnehmen möchten, weil Sie entweder unter akuter Anorexia nervosa („Magersucht") leiden oder früher unter Anorexia nervosa gelitten haben.

2 Ziel der Studie

In dieser wissenschaftlichen Studie geht es um Veränderungen im Gehirn während der langsamen Gewichtszunahme im Rahmen der Therapie bei Patientinnen mit Anorexia Nervosa. Die Stärke der Verbindung und/oder der Kommunikation zwischen einzelnen Hirngebieten wird sowohl auf der Ebene der Hirn-Aktivität („funktionelle Konnektivität") als auch der Hirn-Anatomie („strukturelle Konnektivität") untersucht.

3 Allgemeine Informationen zur klinischen Studie

- Durch diese Studie soll eine Verbesserung des Verständnisses derjenigen biologischen Mechanismen erlangt werden, die zur Anorexia nervosa führen und die durch eine therapeutische Intervention angestossen werden.
- Jede Patientin mit akuter Anorexia nervosa wird im Längsschnitt über drei Messzeitpunkte innerhalb von sechs Monaten untersucht. Personen, die früher an Anorexia nervosa litten, werden nur einmal untersucht. Die Studie dauert insgesamt ca. zwei Jahre exkl. Daten-Auswertung und -Publikation. Es werden insgesamt 100 Teilnehmerinnen rekrutiert (50 Patientinnen mit akuter Anorexia nervosa, 25 geheilte Patientinnen, die früher Magersucht hatten und nun in einem stabilen Zustand sind, und 25 gesunde Vergleichspersonen).

- Diese Studie wird in Übereinstimmung mit der schweizerischen Gesetzgebung und nach international anerkannten Richtlinien durchgeführt. Sie wurde von der zuständigen, unabhängigen Ethikkommission des Kantons genehmigt.
- *Magnetresonanztomographie (magnetic resonance imaging, MRI):* Das MRI ist ein bildgebendes Verfahren zur Darstellung der Struktur und Funktion des Gehirns. Dabei können sowohl hochauflösende Bilder des Gehirns als auch die neuronale Aktivität des Gehirns aufgenommen werden. Das MRI beruht auf einem starken Magnetfeld, d.h. die Untersuchung ist frei von Röntgenstrahlen und gilt daher als ungefährlich. Sie ist ausserdem schmerzlos und nebenwirkungsfrei. Dennoch werden Schwangere von der Studie ausgeschlossen.
- *Zufallsbefunde:* Da es sich um bildgebende Untersuchungen des Gehirns handelt, könnten sich so genannte neurologische „Zufallsbefunde" aufdrängen. Im Zusammenhang mit MRI-Aufnahmen könnten sich Missbildungen oder andere Auffälligkeiten in den Aufnahmen zeigen. Im Rahmen Ihrer Einverständniserklärung werden Sie die Möglichkeit haben zu entscheiden ob Sie über einen neurologischen Zufallsbefund 1) direkt informiert werden möchten, 2) nicht informiert werden möchten oder 3) die Entscheidung einem Arzt überlassen.

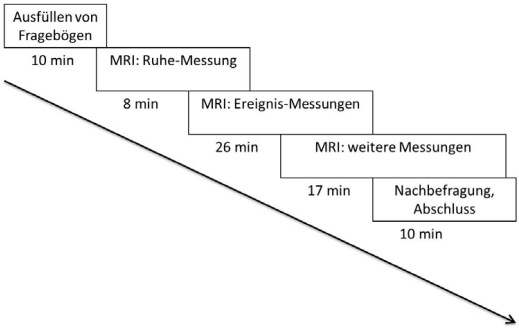
4 Freiwilligkeit der Teilnahme

Ihre Teilnahme an dieser Studie ist freiwillig. Wenn Sie nicht an dieser Studie teilnehmen wollen, haben Sie keine Nachteile für Ihre medizinische Betreuung zu erwarten. Das gleiche gilt, wenn Sie Ihre einmal gegebene Einwilligung zu einem späteren Zeitpunkt widerrufen. Diese Möglichkeit haben Sie jederzeit. Einen allfälligen Widerruf Ihrer Einwilligung bzw. den Rücktritt von der Studie müssen Sie nicht begründen. Im Fall eines Widerrufs werden die bis zu diesem Zeitpunkt erhobenen Daten weiter verwendet und die gelagerten Blut- und Stuhlproben werden für Forschungszwecke nicht mehr weiter verwendet.

5 Studienablauf

- Nachdem Sie die Einverständniserklärung unterschrieben haben, vereinbaren wir einen Termin mit Ihnen für die Voruntersuchung. Diese beinhaltet eine kurze Abklärung Ihres Gesundheitszustands und das Ausfüllen einiger Fragebögen zu Ihrem Gemütszustand. Sie dauert ca. 45 min.
- Ihre weitere Teilnahme an der Studie besteht aus drei MRI-Untersuchungen und drei Computer-Aufgaben innerhalb von ca. sechs Monaten. MRI-Untersuchung und Computer-Aufgaben müssen jeweils zeitnah (d.h. nicht länger als ca. 7 Tage) aufeinander folgen; die Termine sollen daher im Voraus (gemeinsam mit der Versuchsleitung) entsprechend abgestimmt werden. Der jeweilige Zeitpunkt dieser Untersuchungen ist abhängig von der Zunahme Ihres Gewichtes (BMI, body-mass index) im Laufe der Therapie. Jede MRI-Untersuchung dauert ca. 1,5 h, die Computer-Aufgaben dauern jeweils ca. 75 min. Ort der Untersuchungen ist das UniversitätsSpital Zürich. Bei jedem MRI-Termin werden Sie ausserdem gebeten einige Fragebögen auszufüllen (unten schematisch dargestellt). Zudem findet eine Blutentnahme statt, die es uns ermöglicht, hormonelle Parameter zu erfassen und genetische Analysen durchzuführen. Es werden dabei spezifische Gene analysiert, die mit der Entwicklung einer Essstörung in Verbindung gebracht wurden. Hormonelle und genetische Analysen wiederum werden mit der aus dem MRI gewonnenen Datenmenge in Verbindung gebracht. Da sich die Bakterienzusammensetzung im Darm durch eine Umstellung der Ernährung im Rahmen Ihrer Therapie verändern kann, werden sie gebeten, um den jeweiligen Messzeitpunkt herum (höchstens zwei Tage früher oder später als der MRI-Termin) eine Stuhlprobe abzugeben. Sie erhalten dazu ein Röhrchen; die Gewinnung ist einfach und erfolgt diskret auf der Toilette.
- Vor Beginn der Studie wird ein Schwangerschaftstest durchgeführt.

Im Folgenden ist der Ablauf einer MRI-Untersuchung schematisch dargestellt:



Während des MRI werden Ihre Herz- und Atemfrequenz aufgezeichnet. Dazu werden Ihnen vor der MRI-Untersuchung am Rippenbereich Elektroden angeklebt und es wird ein Atemgurt um den Bauch herum angebracht.

Instruktionen für die Teilnehmerinnen während des MRI:

- In der Ruhe-Messung bitten wir Sie, ihre Augen geschlossen zu halten und sich nicht zu bewegen. Sie können sich entspannen und Ihren Gedanken freien Lauf lassen. Sie sollten während der Ruhe-Messung nicht einschlafen.
- Im ersten Teil der Ereignis-Messung bekommen Sie verschiedene Bilder zu sehen, auf denen entweder Speisen/Nahrungsmittel oder Nicht-Nahrungsmittel (Gegenstände/Tiere/Pflanzen) abgebildet sind. Bei den Speisen sollen Sie sich vorstellen, davon zu essen. Bei den Nicht-Nahrungsmitteln sollen Sie sich vorstellen, sie zu verwenden bzw. zu berühren. Die Präsentation erfolgt in Blöcken (20 s) mit wechselnden Bildern (2 s pro Bild). Zwischen den Blöcken sehen Sie ein Fixationskreuz (ebenfalls 20 s), das Sie bitte mit Ihren Augen fixieren.
- Im zweiten Teil der Ereignis-Messung werden Ihnen in zufälliger Reihenfolge Bilder mit entweder nahrungsbezogenem oder nicht-nahrungsbezogenem Inhalt gezeigt. Ihre Aufgabe wird es sein, bei den nicht-nahrungsbezogenen Bildern so schnell wie möglich eine Taste zu drücken, während Sie diese Reaktion bei den nahrungsbezogenen Bildern unterdrücken sollten. Der Teil wird dann mit der umgekehrten Instruktion wiederholt.
- Im dritten Teil der Ereignis-Messung sehen Sie Bilder mit Szenarien bestimmter Kategorien: Die Szenarios können entweder neutralen, positiven oder negativen emotionalen Gehalt repräsentieren. Der Ablauf ist wie beim ersten Teil der Ereignis-Messung. Es gibt keine spezielle Aufgabe für Sie; nehmen Sie die Bilder einfach wahr und lassen Sie sie auf sich wirken.
- Bei den weiteren Messungen des MRI können Sie sich entspannen und – sofern Sie möchten und können – schlafen.
- **Die Qualität der Daten und damit der wissenschaftliche Wert hängt massgeblich davon ab, wie ruhig Sie während des MRI (ca. 50 min) liegen. Wir bitten Sie daher, sich währenddessen nicht zu bewegen (insbesondere Kopf und Schultern).**
- Nach dem MRI werden Sie gebeten, zu einigen der im Ereignis-Teil gesehenen Bildern eine persönliche Bewertung abzugeben.

Beschreibung der Computer-Aufgaben

Die Computer-Aufgaben werden unabhängig von den MRI-Untersuchungen im psychophysiologischen Labor des UniversitätsSpitals Zürich stattfinden. Beide Aufgaben zusammen inkl. Voraufgaben dauern ca. 75 min.

Voraufgaben: Hier lösen Sie visuell-räumliche sowie verbale Aufgaben.

Aufgabe 1: Hier geht es um das räumliche Erinnerungsvermögen. Für richtige Antworten können Sie dabei zusätzlich Geld verdienen (max. 26,40 CHF).
Aufgabe 2: Hier werden Ihnen verschiedene Portionen von Mahlzeiten gezeigt, deren Grösse Sie bewerten sollen.

Ausserdem bitten wir Sie,
- am Tag der Untersuchung *vor der Untersuchung keinen Kaffee und keinen Alkohol* zu trinken sowie *keine anderen auf die Psyche wirkende Substanzen* (z. B. Cannabis) zu sich zu nehmen und
- am Tag vor der Untersuchung *keinen Alkohol und keine anderen auf die Psyche wirkende Substanzen* einzunehmen. Vielen Dank.

6 Pflichten der Studienteilnehmerin

Als Studienteilnehmerin sind Sie verpflichtet,
- den medizinischen Anweisungen Ihres Studienarztes zu folgen und sich an den Studienplan zu halten,
- Ihren Studienarzt über den Verlauf der Erkrankung zu informieren und neue Symptome, neue Beschwerden und Änderungen im Befinden melden,
- Ihren Studienarzt über die gleichzeitige Behandlung bei einem anderen Arzt und über die Einnahme von Medikamenten zu informieren. Zu den Medikamenten gehören auch alle selbstgekauften, ohne ärztliches Rezept erhältlichen und/oder alternativmedizinischen Präparate.

7 Andere Behandlungsmethoden

Diese Studie beinhaltet kein Testen etwaiger Behandlungsmethoden (keine Medikamenten-Studie).

8 Nutzen für die Teilnehmer

Ihre Teilnahme an dieser klinischen Studie kann zur Verbesserung des Verständnisses und der Behandlung der Magersucht beitragen, ist für Sie jedoch nicht mit einem direkten Nutzen verbunden

9 Risiken und Unannehmlichkeiten

- Unannehmlichkeiten könnten beim MRI durch die längere Liegezeit (ca. 50 min) und durch etwaige Beklemmungsgefühle auftreten. Stark unruhige Personen und Personen mit ausgeprägter Platzangst sollten daher nicht teilnehmen.
- Da das MRI mit einem hohen Lautstärkepegel einhergeht, bekommen Sie Ohrstöpsel und einen Kopfhörer zum Schutz Ihres Gehörs. Wir bitten Sie, sich die Ohrstöpsel gewissenhaft einzusetzen.
- Bei evtl. plötzlich auftretenden Unannehmlichkeiten während des MRI können Sie jederzeit durch Drücken eines Knopfes Kontakt mit dem Versuchsleiter herstellen und die Untersuchung auf eigenen Wunsch abbrechen.
- Kurze Unannehmlichkeiten oder leichte Hautirritationen könnten beim Entfernen der auf die Haut geklebten Elektroden auftreten.
- Die Blutentnahme kann einen kurzen Schmerz und/oder einen leichten Bluterguss verursachen.
- Neu auftretende Symptome und Beschwerden sind dem Studienarzt zu melden.
- Der Stuhl kann am einfachsten auf der Toilette gesammelt werden, Sie werden hierzu von uns einen Plastikbecher zum Auffangen des Stuhles sowie ein Röhrchen zur eigentlichen

Aufbewahrung erhalten. Die Entnahme der Stuhlproben ist mit keinerlei Aufwand, Schmerzen oder Gefahr für Sie verbunden. Die Stuhlröhrchen mit einer Flüssigkeit zum Konservieren der Bakterien enthalten am Deckel einen Plastiklöffel, mit dem problemlos eine kleine Stuhlmenge in die Flüssigkeit gegeben werden kann.

Schwangerschaft
Teilnehmerinnen, die während der Studie schwanger werden, müssen ihren Studienarzt umgehend informieren und dürfen nicht weiter an der Studie teilnehmen). Der Studienarzt wird mit Ihnen das weitere Vorgehen besprechen. In diesem Fall werden Sie gebeten, Angaben über den Verlauf und den Ausgang der Schwangerschaft zu machen.

10 Neue Erkenntnisse

Der Studienarzt wird Sie während der Studie über alle neuen Erkenntnisse informieren, die den Nutzen der Studie oder ihre Sicherheit und somit Ihre Einwilligung zur Teilnahme an der Studie beeinflussen können. Sie werden die Information mündlich und schriftlich erhalten.
Bei Zufallsbefunden (z.B. vom MRI, genetische Analysen), die bei Ihnen zur Verhinderung, Feststellung und Behandlung bestehender oder künftig zu erwartender Krankheiten beitragen können, haben Sie die Wahl: a) Sie möchten über diese Befunde direkt informiert werden, b) Sie möchten nicht informiert werden, oder c) Sie überlassen die Entscheidung Ihrem behandelnden Arzt (s. Einverständniserklärung).
Die Ergebnisse genetischer Analysen haben für den einzelnen Teilnehmer keine Aussagekraft. Sie gelten lediglich für das untersuchte Kollektiv. Sie werden deshalb grundsätzlich nicht aktiv über diese Ergebnisse informiert, dürfen aber Einsicht in Ihre Daten haben.

11 Vertraulichkeit der Daten

In dieser Studie werden persönliche und medizinische Daten von Ihnen erfasst. Diese Daten werden verschlüsselt, d.h. mit einem Code versehen. Nur Mitglieder des Forschungsteams haben Zugang zu den Daten. Spezielle Fachleute des Sponsors (oder deren Beauftragte) können im Rahmen von Qualitätskontrollen die Durchführung der Studie überprüfen. Diese, sowie im Rahmen von Inspektionen auch die Mitglieder der zuständigen Behörden und Ethikkommissionen können über Ihren Studienarzt Einsicht in Ihre nicht codierte Krankengeschichten nehmen. Im Schadenfall erhalten Vertreter der Versicherung ebenfalls über Ihren Studienarzt Einsicht in Ihre medizinischen Daten, jedoch nur soweit dies zur Erledigung des Schadenfalles notwendig ist. Während der ganzen Studie und bei den erwähnten Kontrollen wird die Vertraulichkeit strikt gewahrt. Ihr Name wird in keiner Weise in Rapporten oder Publikationen, die aus der Studie hervorgehen, veröffentlicht.
Im Rahmen dieser Studie werden auch Blut- und Stuhlproben erhoben, welche am Institut für Medizinische Genetik, Universität Zürich bzw. an der Klinik für Gastroenterologie, UniversitätsSpital Zürich für den Zeitraum nach Daten-Erhebung bis kurz nach Daten-Analyse aufbewahrt werden. Die Proben werden mit einem Code, der Ihre vollste Anonymität gewährleistet (keine Rückschlüsse auf Ihre persönlichen Daten wie Namen und Geburtsdatum), versehen und aufbewahrt. Die Proben werden für die Erforschung der Anorexia Nervosa verwendet. Sie haben das Recht auf Einsicht in die Daten wie auch auf die Vernichtung der Proben. Die Proben werden nach der Analyse vernichtet.

12 Kosten

Die in dieser Teilnehmerinformation erwähnten studienspezifischen Untersuchungen bzw. Studienmedikamente sind kostenlos. Weder Ihnen noch Ihrer Krankenkasse entstehen im Zusammenhang mit Ihrer Teilnahme zusätzliche Kosten. Medikamente und Therapien, die Sie

unabhängig von der Studie einnehmen oder verwenden, werden nicht vom Sponsor dieser Studie übernommen.

13 Entschädigung für die Studienteilnehmenden

Für die Teilnahme an dieser klinischen Studie erhalten Sie folgende Entschädigung: CHF 100.— pro MRI-Termin. Auf Wunsch erhalten Sie auch ein Abbild Ihres eigenen Gehirns einige Tage nach der MRI-Messung auf CD ausgehändigt.
Zusätzlich kann bei Computer-Aufgabe 1 durch richtige Antworten Geld verdient werden.

14 Unfreiwilliger Studienabbruch

Ihre Teilnahme kann durch den Studienarzt oder den Studiensponsor abgebrochen werden. Folgende Gründe können dazu führen:

- Auftreten eines in den Ausschlusskriterien benannten Zustandes
- neue Erkenntnisse über potenziell schädliche Vorgänge in den angewandten Methoden (MRI, Blutentnahme)

15 Deckung von Schäden

Treten während oder nach dem klinischen Versuch gesundheitliche Störungen oder irgendwelche Schäden auf, so wenden Sie sich bitte an die verantwortliche Studienärztin Dr. Gabriella Milos. Sie wird für Sie die notwendigen Schritte einleiten. Das UniversitätsSpital Zürich ersetzt Ihnen Schäden, die Sie gegebenenfalls im Rahmen des klinischen Versuchs erleiden. Zu diesem Zweck hat das UniversitätsSpital Zürich zu Ihren Gunsten eine Versicherung bei der Zürich Versicherungsgesellschaft AG (Global Corporate Switzerland, Postfach, 8085 Zürich) abgeschlossen.

16 Kontaktperson(en)

Bei Unklarheiten, Notfällen, unerwarteten oder unerwünschten Ereignissen, die während der Studie oder nach deren Abschluss auftreten, können Sie sich jederzeit an die untenstehende Kontaktperson wenden:

Verantwortliche Studienärztin:
Prof. Dr. med. Gabriella Milos
Zentrum für Ess-Störungen, Klinik für Psychiatrie und Psychotherapie, UniversitätsSpital Zürich
Culmannstr. 8, 8091 Zürich
Tel.: 044 255 5160
gabriella.milos@usz.ch

Wir bedanken uns für Ihr Interesse und würden uns über Ihre Teilnahme an der Studie sehr freuen!

C.2 Participant information

Probandinnen-Information
02.04.2014

"Reshaping" the Brain – Longitudinal Assessment of Changes in Structural and Functional Connectivity During Weight Gain in Anorexia Nervosa

Die "Neuformierung" des Gehirns – Evaluierung von Veränderungen der strukturellen und funktionellen Konnektivität während der Gewichtszunahme bei Anorexia Nervosa

Finanziert durch die Gottfried und Julia Bangerter-Rhyner-Stiftung, Hermann-Klaus-Stiftung und Parrotia-Stiftung

Sehr geehrte Teilnehmerin

1 Auswahl der Studienteilnehmerinnen

Wir fragen Sie an, ob Sie an einer Studie teilnehmen möchten, weil Sie in guter Gesundheit sind und nicht unter einer Ess-Störung leiden oder gelitten haben.

2 Ziel der Studie

In dieser wissenschaftlichen Studie geht es um Veränderungen im Gehirn während der langsamen Gewichtszunahme im Rahmen der Therapie bei Patientinnen mit Anorexia nervosa („Magersucht"). Die Stärke der Verbindung und/oder der Kommunikation zwischen einzelnen Hirngebieten wird sowohl auf der Ebene der Hirn-Aktivität („funktionelle Konnektivität") als auch der Hirn-Anatomie („strukturelle Konnektivität") untersucht.

3 Allgemeine Informationen zur klinischen Studie

- Durch diese Studie soll eine Verbesserung des Verständnisses derjenigen biologischen Mechanismen erlangt werden, die zur Anorexia nervosa führen und die durch eine therapeutische Intervention angestossen werden.
- Jede Probandin dient als Vergleichsperson zu einer Patientin mit Anorexia nervosa und wird im Längsschnitt über zwei Messzeitpunkte innerhalb von sechs Monaten untersucht. Die Studie dauert insgesamt ca. zwei Jahre exkl. Daten-Auswertung und -Publikation. Es werden insgesamt 100 Teilnehmerinnen rekrutiert (50 Patientinnen mit akuter Anorexia nervosa, 25 geheilte Patientinnen, die früher Magersucht hatten und nun in einem stabilen Zustand sind, und 25 gesunde Vergleichspersonen).

- Diese Studie wird in Übereinstimmung mit der schweizerischen Gesetzgebung und nach international anerkannten Richtlinien durchgeführt. Sie wurde von der zuständigen, unabhängigen Ethikkommission des Kantons genehmigt.
- *Magnetresonanztomographie (magnetic resonance imaging, MRI):* Das MRI ist ein bildgebendes Verfahren zur Darstellung der Struktur und Funktion des Gehirns. Dabei können sowohl hochauflösende Bilder des Gehirns als auch die neuronale Aktivität des Gehirns aufgenommen werden. Das MRI beruht auf einem starken Magnetfeld, d.h. die Untersuchung ist frei von Röntgenstrahlen und gilt daher als ungefährlich. Sie ist ausserdem schmerzlos und nebenwirkungsfrei. Dennoch werden Schwangere von der Studie ausgeschlossen.
- *Zufallsbefunde:* Da es sich um bildgebende Untersuchungen des Gehirns handelt, könnten sich so genannte neurologische „Zufallsbefunde“ aufdrängen. Im Zusammenhang mit MRI-Aufnahmen könnten sich Missbildungen oder andere Auffälligkeiten in den Aufnahmen zeigen. Im Rahmen Ihrer Einverständniserklärung werden Sie die Möglichkeit haben zu entscheiden ob Sie über einen neurologischen Zufallsbefund 1) direkt informiert werden möchten, 2) nicht informiert werden möchten oder 3) die Entscheidung einem Arzt überlassen.

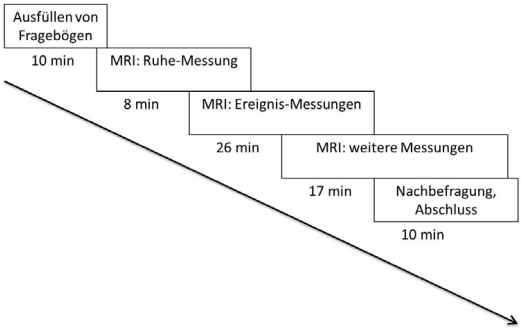
4 Freiwilligkeit der Teilnahme

Ihre Teilnahme an dieser Studie ist freiwillig und Sie können Ihre einmal gegebene Einwilligung zu einem späteren Zeitpunkt widerrufen. Diese Möglichkeit haben Sie jederzeit. Einen allfälligen Widerruf Ihrer Einwilligung bzw. den Rücktritt von der Studie müssen Sie nicht begründen. Im Fall eines Widerrufs werden die bis zu diesem Zeitpunkt erhobenen Daten weiter verwendet und die gelagerten Blutproben werden für Forschungszwecke nicht mehr weiter verwendet.

5 Studienablauf

- Nachdem Sie die Einverständniserklärung unterschrieben haben, vereinbaren wir einen Termin mit Ihnen für die Voruntersuchung. Diese beinhaltet eine kurze Abklärung Ihres Gesundheitszustands und das Ausfüllen einiger Fragebögen zu Ihrem Gemütszustand. Sie dauert ca. 45 min.
- Ihre weitere Teilnahme an der Studie besteht aus zwei MRI-Untersuchungen und zwei Computer-Aufgaben innerhalb von ca. sechs Monaten. Jede MRI-Untersuchung dauert ca. 1,5 h; die Computer-Aufgaben dauern jeweils ca. 75 min. Ort der Untersuchungen ist das UniversitätsSpital Zürich. Bei jedem MRI-Termin werden Sie ausserdem gebeten einige Fragebögen auszufüllen (unten schematisch dargestellt). Zudem findet eine Blutentnahme statt, die es uns ermöglicht, hormonelle Parameter zu erfassen und genetische Analysen durchzuführen. Es werden dabei spezifische Gene analysiert, die mit der Entwicklung einer Essstörung in Verbindung gebracht wurden. Hormonelle und genetische Analysen wiederum werden mit der aus dem MRI gewonnenen Datenmenge in Verbindung gebracht.
- Vor jedem der beiden MRI-Untersuchungen wird ein Schwangerschaftstest durchgeführt.

Im Folgenden ist der Ablauf einer MRI-Untersuchung schematisch dargestellt:



Während des MRI werden Ihre Herz- und Atemfrequenz aufgezeichnet. Dazu werden Ihnen vor der MRI-Untersuchung am Rippenbereich Elektroden angeklebt und es wird ein Atemgurt um den Bauch herum angebracht.

Instruktionen für die Teilnehmerinnen während des MRI:

- In der Ruhe-Messung bitten wir Sie, ihre Augen geschlossen zu halten und sich nicht zu bewegen. Sie können sich entspannen und Ihren Gedanken freien Lauf lassen. Sie sollten während der Ruhe-Messung nicht einschlafen.
- Im ersten Teil der Ereignis-Messung bekommen Sie verschiedene Bilder zu sehen, auf denen entweder Speisen/Nahrungsmittel oder Nicht-Nahrungsmittel (Gegenstände/Tiere/Pflanzen) abgebildet sind. Bei den Speisen sollen Sie sich vorstellen, davon zu essen. Bei den Nicht-Nahrungsmitteln sollen Sie sich vorstellen, sie zu verwenden bzw. zu berühren. Die Präsentation erfolgt in Blöcken (20 s) mit wechselnden Bildern (2 s pro Bild). Zwischen den Blöcken sehen Sie ein Fixationskreuz (ebenfalls 20 s), das Sie bitte mit Ihren Augen fixieren.
- Im zweiten Teil der Ereignis-Messung werden Ihnen in zufälliger Reihenfolge Bilder mit entweder nahrungsbezogenem oder nicht-nahrungsbezogenem Inhalt gezeigt. Ihre Aufgabe wird es sein, bei den nicht-nahrungsbezogenen Bildern so schnell wie möglich eine Taste zu drücken, während Sie diese Reaktion bei den nahrungsbezogenen Bildern unterdrücken sollten. Der Teil wird dann mit der umgekehrten Instruktion wiederholt.
- Im dritten Teil der Ereignis-Messung sehen Sie Bilder mit Szenarien bestimmter Kategorien: Die Szenarios können entweder neutralen, positiven oder negativen emotionalen Gehalt repräsentieren. Der Ablauf ist wie beim ersten Teil der Ereignis-Messung. Es gibt keine spezielle Aufgabe für Sie; nehmen Sie die Bilder einfach wahr und lassen Sie sie auf sich wirken.
- Bei den weiteren Messungen des MRI können Sie sich entspannen und – sofern Sie möchten und können – schlafen.
- **Die Qualität der Daten und damit der wissenschaftliche Wert hängt massgeblich davon ab, wie ruhig Sie während des MRI (ca. 50 min) liegen. Wir bitten Sie daher, sich währenddessen nicht zu bewegen (insbesondere Kopf und Schultern).**
- Nach dem MRI werden Sie gebeten, zu einigen der im Ereignis-Teil gesehenen Bildern eine persönliche Bewertung abzugeben.

Beschreibung der Computer-Aufgaben

Die Computer-Aufgaben werden unabhängig von den MRI-Untersuchungen im psychophysiologischen Labor des UniversitätsSpitals Zürich stattfinden. Beide Aufgaben zusammen inkl. Voraufgaben dauern ca. 75 min.

Voraufgaben: Hier lösen Sie visuell-räumliche sowie verbale Aufgaben.

Aufgabe 1: Hier geht es um das räumliche Erinnerungsvermögen. Für richtige Antworten können Sie dabei zusätzlich Geld verdienen (max. 26,40 CHF).
Aufgabe 2: Hier werden Ihnen verschiedene Portionen von Mahlzeiten gezeigt, deren Grösse Sie bewerten sollen.

Ausserdem bitten wir Sie,
- am Tag der Untersuchung *vor der Untersuchung keinen Kaffee und keinen Alkohol* zu trinken sowie *keine anderen auf die Psyche wirkende Substanzen* (z. B. Cannabis) zu sich zu nehmen und
- am Tag vor der Untersuchung *keinen Alkohol und keine anderen auf die Psyche wirkende Substanzen* einzunehmen. Vielen Dank.

6 Pflichten der Studienteilnehmerin

Als Studienteilnehmerin sind Sie verpflichtet, den Anweisungen Ihres Studienarztes zu folgen.

7 Andere Behandlungsmethoden

Diese Studie beinhaltet kein Testen etwaiger Behandlungsmethoden (keine Medikamenten-Studie).

8 Nutzen für die Teilnehmer

Ihre Teilnahme an dieser klinischen Studie kann zur Verbesserung des Verständnisses und der Behandlung der Magersucht beitragen, ist für Sie jedoch nicht mit einem direkten Nutzen verbunden.

9 Risiken und Unannehmlichkeiten

- Unannehmlichkeiten könnten beim MRI durch die längere Liegezeit (ca. 50 min) und durch etwaige Beklemmungsgefühle auftreten. Stark unruhige Personen und Personen mit ausgeprägter Platzangst sollten daher nicht teilnehmen.
- Da das MRI mit einem hohen Lautstärkepegel einhergeht, bekommen Sie Ohrstöpsel und einen Kopfhörer zum Schutz Ihres Gehörs. Wir bitten Sie, sich die Ohrstöpsel gewissenhaft einzusetzen.
- Bei evtl. plötzlich auftretenden Unannehmlichkeiten während des MRI können Sie jederzeit durch Drücken eines Knopfes Kontakt mit dem Versuchsleiter herstellen und die Untersuchung auf eigenen Wunsch abbrechen.
- Kurze Unannehmlichkeiten oder leichte Hautirritationen könnten beim Entfernen der auf die Haut geklebten Elektroden auftreten.
- Die Blutentnahme kann einen kurzen Schmerz und/oder einen leichten Bluterguss verursachen.
- Neu auftretende Symptome und Beschwerden sind dem Studienarzt zu melden.

Schwangerschaft
Teilnehmerinnen, die während der Studie schwanger werden, müssen ihren Studienarzt umgehend informieren und dürfen nicht weiter an der Studie teilnehmen). Der Studienarzt wird mit Ihnen das weitere Vorgehen besprechen. In diesem Fall werden Sie gebeten, Angaben über den Verlauf und den Ausgang der Schwangerschaft zu machen.

10 Neue Erkenntnisse

Der Studienarzt wird Sie während der Studie über alle neuen Erkenntnisse informieren, die den Nutzen der Studie oder ihre Sicherheit und somit Ihre Einwilligung zur Teilnahme an der Studie beeinflussen können. Sie werden die Information mündlich und schriftlich erhalten.
Bei Zufallsbefunden (z.B. vom MRI, genetische Analysen), die bei Ihnen zur Verhinderung, Feststellung und Behandlung bestehender oder künftig zu erwartender Krankheiten beitragen können, haben Sie die Wahl: a) Sie möchten über diese Befunde direkt informiert werden, b) Sie möchten nicht informiert werden, oder c) Sie überlassen die Entscheidung Ihrem behandelnden Arzt (s. Einverständniserklärung).
Die Ergebnisse genetischer Analysen haben für den einzelnen Teilnehmer keine Aussagekraft. Sie gelten lediglich für das untersuchte Kollektiv. Sie werden deshalb grundsätzlich nicht aktiv über diese Ergebnisse informiert, dürfen aber Einsicht in Ihre Daten haben.

11 Vertraulichkeit der Daten

In dieser Studie werden persönliche und medizinische Daten von Ihnen erfasst. Diese Daten werden verschlüsselt, d.h. mit einem Code versehen. Nur Mitglieder des Forschungsteams haben Zugang zu den Daten. Spezielle Fachleute des Sponsors (oder deren Beauftragte) können im Rahmen von Qualitätskontrollen die Durchführung der Studie überprüfen. Diese, sowie im Rahmen von Inspektionen auch die Mitglieder der zuständigen Behörden und Ethikkommissionen können über Ihren Studienarzt Einsicht in Ihre nicht codierte Krankengeschichten nehmen. Im Schadenfall erhalten Vertreter der Versicherung ebenfalls über Ihren Studienarzt Einsicht in Ihre medizinischen Daten, jedoch nur soweit dies zur Erledigung des Schadenfalles notwendig ist. Während der ganzen Studie und bei den erwähnten Kontrollen wird die Vertraulichkeit strikt gewahrt. Ihr Name wird in keiner Weise in Rapporten oder Publikationen, die aus der Studie hervorgehen, veröffentlicht.
Im Rahmen dieser Studie werden auch Blutproben erhoben, welche am Institut für Medizinische Genetik, Universität Zürich für den Zeitraum nach Daten-Erhebung bis kurz nach Daten-Analyse aufbewahrt werden. Die Proben werden mit einem Code, der Ihre vollste Anonymität gewährleistet (keine Rückschlüsse auf Ihre persönlichen Daten wie Namen und Geburtsdatum), versehen und aufbewahrt. Die Proben werden für die Erforschung der Anorexia nervosa verwendet. Sie haben das Recht auf Einsicht in die Daten wie auch auf die Vernichtung der Proben. Die Proben werden nach der Analyse vernichtet.

12 Kosten

Die in dieser Teilnehmerinformation erwähnten studienspezifischen Untersuchungen bzw. Studienmedikamente sind kostenlos. Weder Ihnen noch Ihrer Krankenkasse entstehen im Zusammenhang mit Ihrer Teilnahme zusätzliche Kosten. Medikamente und Therapien, die Sie unabhängig von der Studie einnehmen oder verwenden, werden nicht vom Sponsor dieser Studie übernommen.

13 Entschädigung für die Studienteilnehmenden

Für die Teilnahme an dieser klinischen Studie erhalten Sie folgende Entschädigung: CHF 100.— pro MRI-Termin. Auf Wunsch erhalten Sie auch ein Abbild Ihres eigenen Gehirns einige Tage nach der MRI-Messung auf CD ausgehändigt.
Zusätzlich kann bei Computer-Aufgabe 1 durch richtige Antworten Geld verdient werden.

14 Unfreiwilliger Studienabbruch

Ihre Teilnahme kann durch den Studienarzt oder den Studiensponsor abgebrochen werden. Folgende Gründe können dazu führen:

- Auftreten eines in den Ausschlusskriterien benannten Zustandes
- neue Erkenntnisse über potenziell schädliche Vorgänge in den angewandten Methoden (MRI, Blutentnahme)

15 Deckung von Schäden

Treten während oder nach dem klinischen Versuch gesundheitliche Störungen oder irgendwelche Schäden auf, so wenden Sie sich bitte an die verantwortliche Studienärztin Dr. Gabriella Milos. Sie wird für Sie die notwendigen Schritte einleiten. Das UniversitätsSpital Zürich ersetzt Ihnen Schäden, die Sie gegebenenfalls im Rahmen des klinischen Versuchs erleiden. Zu diesem Zweck hat das UniversitätsSpital Zürich zu Ihren Gunsten eine Versicherung bei der Zürich Versicherungsgesellschaft AG (Global Corporate Switzerland, Postfach, 8085 Zürich) abgeschlossen.

16 Kontaktperson(en)

Bei Unklarheiten, Notfällen, unerwarteten oder unerwünschten Ereignissen, die während der Studie oder nach deren Abschluss auftreten, können Sie sich jederzeit an die untenstehende Kontaktperson wenden:

Verantwortliche Studienärztin:
Prof. Dr. med. Gabriella Milos
Zentrum für Ess-Störungen, Klinik für Psychiatrie und Psychotherapie, UniversitätsSpital Zürich
Culmannstr. 8, 8091 Zürich
Tel.: 044 255 5160
gabriella.milos@usz.ch

Wir bedanken uns für Ihr Interesse und würden uns über Ihre Teilnahme an der Studie sehr freuen!

C.3 MRI security questionnaire

UniversitätsSpital Zürich

Klinik für Psychiatrie und Psychotherapie

MRI-Sicherheitsfragebogen für ProbandInnen und PatientInnen

Zentrum für Essstörungen

Dieser Fragebogen dient Ihrer Sicherheit im MR-Gerät. Wir bitten Sie daher, die Fragen gewissenhaft zu beantworten. Wenn Sie sich nicht sicher sind oder eine Frage nicht verstehen, wenden Sie sich bitte an den Untersucher/die Untersucherin.

Projektnummer FCA010413	Ethiknummer 2013-0273	Probandencode
Name	Vorname	Geburtsdatum (TT.MM.JJJJ)
Strasse, Hausnummer	PLZ, Wohnort	Gewicht (kg)

Wurden Sie jemals am Kopf, Herz oder Gefässsystem operiert?	☐ Ja	☐ Nein
Haben Sie einen Herzschrittmacher?	☐ Ja	☐ Nein
Haben Sie einen Nervenstimulator?	☐ Ja	☐ Nein
Haben Sie eine Insulinpumpe oder eine Schmerzpumpe?	☐ Ja	☐ Nein
Haben Sie irgendwelche Implantate (z.B. Cochleaimplantat, Marknägel)?	☐ Ja	☐ Nein
Haben Sie irgendwelche metallische Prothesen (z.B. Herzklappenprothese, Hüftprothese, Knieprothese)?	☐ Ja	☐ Nein
Tragen Sie ein Medikamentenpflaster (z.B. Nitro-Pflaster, Schmerzpflaster, Nikotinpflaster, Hormonpflaster, Reisepflaster)?	☐ Ja	☐ Nein
Haben Sie sonstige Metallteile oder -splitter im Körper? (z.B. Metall-splitterverletzungen, Schusswunden, Clips nach Operationen)	☐ Ja	☐ Nein
Hatten Sie jemals beruflich oder privat mit der Verarbeitung von Metallen zu tun (z.B. Schleifen, Fräsen)?	☐ Ja	☐ Nein
Tragen Sie ein Hörgerät?	☐ Ja	☐ Nein
Tragen Sie Kontaktlinsen?	☐ Ja	☐ Nein

UniversitätsSpital Zürich **Klinik für Psychiatrie und Psychotherapie**

Tragen Sie eine Zahnspange oder eine Zahnprothese?	☐ Ja	☐ Nein
Haben Sie eine Tätowierung (egal wie gross)? Wenn ja, wo?	☐ Ja	☐ Nein
Tragen Sie Permanent-Make-Up?	☐ Ja	☐ Nein
Tragen Sie Körperschmuck (ein Piercing)?	☐ Ja	☐ Nein
Haben Sie Angst vor geschlossenen oder engen Räumen (Klaustrophobie)?	☐ Ja	☐ Nein
Sind Sie lärmempfindlich oder schwerhörig?	☐ Ja	☐ Nein
Nehmen Sie zurzeit irgendwelche Medikamente ein?	☐ Ja	☐ Nein
Nehmen Sie zurzeit Aspirin oder andere Schmerzmittel ein?	☐ Ja	☐ Nein

Besteht die Möglichkeit, dass Sie schwanger sind? Falls ja: Bitte Schwangerschaftstest durchführen.	☐ Ja	☐ Nein
Schwangerschaftstest durchgeführt am _____.____.20_____	☐ Pos.	☐ Neg.
Tragen Sie eine Kupferspirale?	☐ Ja	☐ Nein

Ich bin über die Risiken der bevorstehenden MR-Untersuchung aufgeklärt worden und stimme der Durchführung zu.

_____ _____

Ort und Datum Unterschrift (ProbandIn)

_____ _____

Ort und Datum Unterschrift (UntersucherIn)

C.4 Ethics approval

Kantonale Ethik-Kommission Zürich (KEK)

Kantonale Ethikkommission (KEK)
Präsident
Prof. Dr. med. Peter Meier-Abt
Stampfenbachstrasse 121
8090 Zürich
Tel. +41 (0)43 259 79 67
Fax +41 (0)43 259 79 72
Peter.Meier-Abt@kaz.zh.ch

Juristischer Sekretär
lic. iur. et theol. Niklaus Herzog
Tel. +41 (0)43 259 79 60
Fax +41 (0)43 259 79 72
niklaus.herzog@kaz.zh.ch

UniversitätsSpital Zürich
Frau PD Dr. med. Gabriella Milos
Zentrum für Essstörungen
Klinik für Psychiatrie und Psychotherapie
Culmannstrasse 8
8091 Zürich

Zürich, 28. Januar 2014

Formular für die
Beschlussmitteilung der Ethikkommission Zürich

Die Kantonale Ethikkommission des Kantons Zürich hat das folgende Forschungsprojekt per Präsidialentscheid begutachtet.

Titel des Forschungsprojektes Studiencode: Ref. Nr. KEK-ZH-Nr. 2013-0273

Amendment (gemäss Schreiben vom 11.12.2013 und 27.01.2014) zur Studie: "Reshaping" the Brain – Longitudinal Assessment of Changes in Functional and Structural Connectivity During Weight Gain in Anorexia Nervosa

Zusammensetzung der Ethikkommission

Die Ethikkommission tagte in der nachfolgend erwähnten Zusammensetzung und war damit beschlussfähig (Art. 7 Abs. 1 lit. f der Organisationsverordnung zum Humanforschungsgesetz vom 20.09.2013).

					am Beschluss beteiligt		
					ja	nein	
	Name, Vorname	Berufliche Stellung / Titel	m	f		abwesend	In Ausstand
Vorsitz	Meier-Abt Peter	Prof. Dr. med.	☒	☐	☒	☐	☐

Hauptprüfer/in (verantwortliche/r Studienleiter/in am Versuchsstandort)

Name, Vorname, Titel: Milos Gabriella, PD Dr.

Funktion: Leitende Ärztin

Adresse: Klinik für Psychiatrie und Psychotherapie, Zentrum für Essstörungen, USZ, Culmannstrasse 8, 8091 Zürich,

2013-0273 2 / 4

Die Ethikkommission stützt ihre Beurteilung auf die Unterlagen, wie sie aufgeführt sind:

☐ im beiliegenden „Basisformular zur Einreichung eines biomedizinischen Forschungsprojektes“ vom

☒ im Begleitbrief des Gesuchstellers an die KEK vom 11. Dezember 2013 und 27. Januar 2014

☒ in der Rubrik „begutachtete Unterlagen“ (siehe weiter unten)

☐

Art des Verfahrens:

☐ normales Verfahren

☐ vereinfachtes Verfahren

☒ Präsidialentscheid

Art des Forschungsprojekts:

Forschungsprojekt der Kategorie A mit Personen zur Erhebung von Personendaten und zur Entnahme von biologischem Material gemäss Art. 7 Abs. 1 der Humanforschungsverordnung vom 20.09.2013

Die Ethikkommission kommt zu folgendem **Beschluss**:

☒ **Positiv** [1]

☐ **Auflagen** [2] (sind vor der Genehmigung zu erfüllen)

- □ Die revidierten Dokumente werden im ordentlichen Verfahren geprüft (Anzahl Kopien: ...)
- □ Die revidierten Dokumente werden im vereinfachten Verfahren geprüft (Anzahl Kopien: 2)
- □ Die revidierten Dokumente werden im Präsidialverfahren geprüft (Anzahl Kopien: 2)

☐ **Negativ** [3] (mit Begründung)

☐ **Nicht zuständig** [4] (mit Begründung)

[1] Bedeutet:
- Die Studie kann gestartet werden

[2] Bedeutet:
- Die betroffenen Dokumente müssen revidiert der Ethikkommission eingereicht werden,
- Der Versuch kann bis zum Erhalt eines positiven Votums weder notifiziert noch begonnen werden

[3] Bedeutet:
- Die Studie kann in der vorliegenden Form nicht durchgeführt werden. Eine Neueinreichung ist möglich.

[4] Bedeutet:
- Die Ethikkommission ist für die Beurteilung rechtlich nicht zuständig. Entweder ist eine andere Stelle für die Bewilligung zuständig, oder sie kann ohne Bewilligung durchgeführt werden.

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Begutachtete Unterlagen
- Studienprotokoll Version Amendment 11.12.2013
- Zusammenfassung Version Amendment 11.12.2013
- Patientinnen-Information Version Amendment 11.12.2013
- Patientinnen-Inforamtion Track-Version 11.12.2013
- Probandinnen-Inforamtion Version Amendment 11.12.2013
- Probandinnen-Inforamtion Track-Version 11.12.2013
- Einverständniserklärung Patientin Version Amendment 11.12.2013
- Einverständniserklärung Probanden Version Amenment 11.12.2013
- Modifikation des MRI-Protokolls
- Modifikation der Verhaltensexperimente
- Fragebogen: Temperament and Character Inventory, Kurzversion
- Fragebogen: Altruismus-Skala

(erweiterbar)

Empfehlungen

(erweiterbar)

Auflagen

(erweiterbar)

Begründung für negativen Beschluss und Erläuterung für Neubeurteilung

(erweiterbar)

Begründung für Nicht-Eintreten

(erweiterbar)

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Pro Memoria: **Pflichten des/der Hauptprüfers/in**

Meldepflichten gemäss Art. 20, 21 und 22 der Humanforschungsverordnung vom 20.09.2013

Die Kantonale Ethikkommission Zürich bestätigt, dass sie nach ICH-GCP-Richtlinien arbeitet.

Rechtsmittelbelehrung:

Gegen diesen Beschluss kann innert dreißig Tagen, von der Mitteilung an gerechnet, beim Regierungsrat des Kantons Zürich schriftlich Rekurs eingereicht werden. Die Rekursschrift muss einen Antrag und dessen Begründung enthalten. Der angefochtene Entscheid ist beizulegen oder genau zu bezeichnen. Die angerufenen Beweismittel sind genau zu bezeichnen und soweit möglich beizulegen.

Für die Ethikkommission:

Ort, Datum: Zürich, 28. Januar 2014

Unterschrift(en):

Prof. Dr. med. Peter Meier-Abt, Präsident KEK

Niklaus Herzog

lic. iur et theol. Niklaus Herzog, Juristischer Sekretär der KEK

Kanton Zürich
Kantonale Ethikkommission

Prof. Dr. med. Peter Meier-Abt
Präsident

Niklaus Herzog, lic. iur. et theol.
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Fax +41 43 259 79 72
jana.amberg@kaz.zh.ch
www.kek.zh.ch

UniversitätsSpital Zürich
Zentrum für Essstörungen
Klinik für Psychiatrie und Psychotherapie
Frau PD Dr. med. Gabriella Milos
Culmannstrasse 8
8091 Zürich

02. Juni 2015
Beschlussmitteilung der Kantonalen Ethikkommission Zürich

Amendment 3, datiert 07.05.2015

Gesuch KEK-ZH-Nr. 2013-0273
"Reshaping" the Brain – Longitudinal Assessment of Changes in Functional and Structural Connectivity During Weight Gain in Anorexia Nervosa

☒ **Monozentrisches Forschungsprojekt**

☐ **Multizentrisches Forschungsprojekt**

☐ BE ☐ NZ ☐ GE ☐ SG ☐ TI ☐ VD ☐ ZH ☐ VS ☐ TG

Zentren
Professor Dr. Gabriella Milos, Zentrum für Essstörungen, UniversitätsSpital Zürich

Entscheid

☐ Das Amendment wird bewilligt.

☐ Das Amendment wird nicht bewilligt.

☐ Gegenwärtig kann das Amendment noch nicht bewilligt werden
Bedeutet: Das Forschungsprojekt kann noch nicht gemäss Amendment durchgeführt werden. Die nachfolgenden Bedingungen sind zu erfüllen. Die revidierten Dokumente werden nach Einreichung von der Ethikkommission geprüft.

Folgende Bedingungen müssen erfüllt werden:

Kantonale Ethikkommission
2/2

☐ Wir bitten Sie, die geänderten Dokumente den beteiligten Ethikkommissionen zur erneuten Stellungnahme einzureichen.

☒ Das Amendment wird mit Auflagen bewilligt.
Bedeutet: Das Forschungsprojekt kann gemäss Amendment durchgeführt werden
Folgende Auflagen müssen innert angemessener Frist erfüllt werden:

- Bitte unterzeichnen Sie das Studienprotokoll

☐ Wir bitten Sie, die bewilligten Dokumente den beteiligten Ethikkommissionen zur Kenntnisnahme einzureichen.

Begründung
Die Ethikkommission stützt ihre Begründung auf die Unterlagen, wie sie aufgeführt sind:

☐ in der/den beiliegenden Checkliste/n unterschrieben am

☐ in der /den Stellungnahme/n der Kantonalen Ethikkommission/en:

☐ Stellungnahmen der beteiligten Ethikkommissionen nicht notwendig

☒ im Schreiben vom 07.05.2015

☐ sowie auf folgende Unterlagen:

Kosten
Die Gebühren betragen CHF 400.- (Tarifcode 6.0.)[1].

Mitteilung an den Gesuchsteller
und in Kopie an:

☐ Sponsor
☐ beteiligte, lokale EKs (multizentrische Studien)
☐ andere:

Peter Meier-Abt

Niklaus Herzog

[1] Art. 3 Gebührenreglement swissethics 2014

UniversitätsSpital Zürich

Klinik für Psychiatrie und Psychotherapie

21. Mai 2015

Zentrum für Essstörunge

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7. Mai 2015

KEK-ZH-Nr. 2013-0273

Amendment

"Reshaping" the Brain – Longitudinal Assessment of Changes in Functional and Structural Connectivity During Weight Gain in Anorexia Nervosa

Prof. Dr. G. Milos, Dr. V. Baur, Prof. Dr. L. Jäncke, Prof. Dr. S. Kollias, Prof. Dr. U. Schnyder, Prof. Dr. C. Martin-Soelch

Sehr geehrte Damen und Herren

Für unsere MRI-Studie hat sich eine für uns interessante Kooperation mit der Gastroenterologie des UniversitätsSpitals Zürich ergeben. Nach produktiver Auseinandersetzungen mit aktuellsten Erkenntnissen und Forschungstrends bei psychiatrischen Erkrankungen, insbesondere bei der Anorexia nervosa, möchten wir unsere MRI-Studie um einen Teil erweitern, den wir Ihnen hiermit als Gesuch in Form eines Amendments vorlegen.

Es handelt sich hierbei um die Untersuchung der mikrobiellen Zusammensetzung im Darm (Darmflora, Mikrobiom). Neueste Studien haben gezeigt, dass die Art und Häufigkeit der vorhandenen Bakterienpopulationen im Darm auch beim Menschen eine signifikante Rolle für das Entstehen oder Aufrechterhalten psychischer Erkrankungen (z.B. Depression und Angststörungen) spielen können.

Untersuchungen der Darmflora haben bis jetzt kaum stattgefunden, jedoch könnte diese Art von Forschung bedeutende Resultate für ein neues Verständnis der Erkrankung liefern. *(Gut feelings: A role for the intestinal microbiota in anorexia nervosa? Kleiman et al., Int J Eat Disord 2015).*

Zu den laufenden Untersuchungen möchten wir auch Stuhlproben am Beginn der Behandlung und während der Gewichtszunahme in unserem Studiensample gewinnen. Damit können schliesslich die Resultate der Darmflora-Analyse mit neuronalen Parametern in Bezug auf funktionelle und strukturelle Konnektivität in Verbindung gebracht werden.

Bei allen ab jetzt in die Studie eingeschlossenen **Patientinnen mit Anorexie** möchten wir, zeitnah zu jedem der **drei** MRI-Messzeitpunkte, eine Stuhlprobe sammeln. Dies kann unkompliziert auf der Station am Zentrum für Essstörungen geschehen.

Da wir mitten in der Rekrutierung sind und ein bedeutender Teil der Daten insbesondere bei den **gesunden Probandinnen** schon erhoben wurde, soll eine Stuhlprobe pro Probandin im Nachhinein gesammelt werden. Dazu werden die Probandinnen per Briefpost angeschrieben und über die Studien-Erweiterung aufgeklärt. Zunächst werden sie gefragt, ob sie daran teilnehmen möchten und es wird eine schriftliche Einverständniserklärung beigelegt sowie das Material zur Stuhlproben-Gewinnung (Röhrchen). Sie werden anschliessend gebeten, eine Stuhlprobe zu sammeln und diese mitsamt der unterschriebenen Einverständniserklärung an uns zu retournieren. Da die Darmflora bei Gesunden als weithin konstant angenommen wird, genügt für unsere Zwecke **eine einzige Stuhlprobe pro Probandin**. Unser Ziel ist die Sammlung von **zehn Datensätzen** bei den Gesunden.

Die Gewinnung von Stuhlproben ist einfach und mit keinerlei Risiken verbunden. Näheres wird im Studienprotokoll und in den Probandinnen- und Patientinneninformationen beschrieben.

Im Rahmen unserer Kooperation mit Dr. med. Luc Biedermann, Oberarzt an der Klinik für Gastroenterologie und Hepatologie (USZ), sowie mit Dr. M. Schuppler und Dr. J. Klump vom Institut für Lebensmittelchemie (ETH), wird das nötige Material bereitgestellt und die gesammelten Proben werden innerhalb einer bestehenden Infrastruktur analysiert.

Bei Fragen stehen wir Ihnen gerne und jederzeit zur Verfügung.

Mit herzlichem Gruss

Gabriella Milos

<u>Anlagen</u>

- Basisformular 24.03.2015

verändert:

- Studienprotokoll Version Amendment 24.03.2015
- Zusammenfassung Version Amendment 24.03.2015
- Patientinneninformation Version Amendment 24.03.2015
- Einverständniserklärung Patientin Version Amendment 24.03.2015

neu:

- Anschreiben und Einverständniserklärung Probandin 24.03.2015

Kanton Zürich
Kantonale Ethikkommission

Prof. Dr. med. Peter Meier-Abt
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9. Juni 2015

Erfüllung der Auflage
KEK-ZH-Nr: 2013-0273
"Reshaping" the Brain – Longitudinal Assessment of Changes in Functional and Structural Connectivity During Weight Gain in Anorexia Nervosa

Sehr geehrte Frau Professor Milos

Wir beziehen uns auf unsere Beschlussmitteilung mit Auflage vom 2. Juni 2015 und Ihr Schreiben vom 5. Juni 2015 und die darin aufgelisteten Dokumente zur obgenannten Studie.

Wir teilen Ihnen mit, dass die in der Beschlussmitteilung vom 2. Juni 2015 formulierte Auflage mit Ihrem Schreiben vom 5. Juni 2015 und dem beigefügten Dokument erfüllt sind.

Freundliche Grüsse

Peter Meier-Abt

Niklaus Herzog

Beschluss_Abt. A_Version_20140811

Curriculum Vitae

Lisa-Katrin Kaufmann

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Academic education

10.2013–present	**PhD student** University of Fribourg (Switzerland) Prof. Dr. phil. Chantal Martin Soelch (University of Fribourg) Prof. Dr. med. Gabriella Milos (University of Zurich) Prof. Dr. rer. nat. Lutz Jäncke (University of Zurich) Funded by the Swiss Anorexia Nervosa Foundation (SANS)
09.2010–01.2013	**Master of Science in Psychology** University of Zurich (Switzerland)
10.2007–09.2010	**Bachelor of Science in Psychology** University of Konstanz (Germany)

06.2010 University of Jyväskylä (Finland)

Work and Research Experience

05.2016–10.2016 **Clinical Psychologist**
Centre for Eating Disorders
University Hospital Zurich (Switzerland)

01.2011–03.2013 **Research Assistant**
University of Zurich (Switzerland)

06.2011–09.2011 **Clinical Intern**
Treatment Centre for Torture Victims, Ulm (Germany)

12.2009–09.2010 **Administrative Assistant**
Reichenau Psychiatry Centre, Konstanz (Germany)

05.2008–09.2009 **Research Assistant**
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Publications

in preparation **Kaufmann, L.-K.**, Hänggi, J., Jäncke, L., Baur, V., Piccirelli, M., Kollias, S., Schnyder, U., Martin-Soelch, C., Milos, G. (in prep.). Longitudinal investigation of brain plasticity and the influence of age on structural brain recovery in anorexia nervosa.

Kaufmann, L.-K., Hänggi, J., Jäncke, L., Baur, V., Piccirelli, M., Kollias, S., Schnyder, U., Martin-Soelch, C., Milos, G. (in prep.). Longitudinal investigation of resting-state functional connectivity in women with anorexia nervosa before, during, and after weight restoration.

2017 **Kaufmann, L.-K.**, Baur, V., Hänggi, J., Jäncke, L., Piccirelli, M., Kollias, S., Schnyder, U., Pasternak, O., Martin-Soelch, C., Milos, G. (2017). Fornix under water? Ventricular enlargement biases forniceal diffusion MRI indices in anorexia nervosa. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. doi:10.1016/j.bpsc.2017.03.014

2015 Cosco, T. D., Brehme, D., Grigoruta, N., **Kaufmann, L.-K.**, Lemsalu, L., Meex, R., Schuurmans, A. A. T., Sener, N., Stephan, B. C. M., Brayne, C. (2015). Cross-cultural Perspectives of Successful Aging: Young Turks and Europeans. *Educational Gerontology*, *41*(11), 800–813. doi:10.1080/03601277.2015.1050899

Cosco, T. D., Lemsalu, L., Brehme, D. F., Grigoruta, N., **Kaufmann, L.-K.**, Meex, R., Schuurmans, A. A. T., Sener, N., Stephan, B. C. M., Brayne, C. (2015). Younger Europeans' Conceptualizations of Successful Aging. *Journal of the American Geriatrics Society*, 63(3), 609–611. doi:10.1111/jgs.13307

2014 Cosco, T. D., Brehme, D., Grigoruta, N., **Kaufmann, L.-K.**, Lemsalu, L., Meex, R., Schuurmans, A. A. T., Sener, N. (2014). Ageing Perspectives. *Journal of European Psychology Students*, *5*(2), 29–33. doi:10.5334/jeps.cb

Erklärung der Selbstständigkeit

Ich erkläre ehrenwörtlich, dass ich meine Dissertation selbständig und ohne unzulässige fremde Hilfe verfasst habe und sie noch keiner anderen Fakultät vorgelegt habe.

Zürich, 18.04.2017, _____

Lisa-Katrin Kaufmann