Eating disorders, eating pathology and ESSENCE

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Abstract

BACKGROUND: Eating and mealtime problems are among the most common problems in individuals with autism spectrum disorder (ASD). Despite this, no systematic way of exploring these problems has been available for persons with ASD and normal intelligence. Furthermore, little is known about the prevalence of traditional eating disorders (EDs) such as anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED), and eating pathology in individuals with Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE, which describes the overlap between neurodevelopmental conditions, e.g. ASD and attention-deficit/hyperactivity disorder (ADHD)). A link between EDs and ESSENCE is highly topical but the knowledge about the similarities between the two conditions in terms of eating behaviours and potential neurobiological commonalities is scarce. **AIMS**: The overall aim of this thesis was to incorporate knowledge from different angles in order to better understand the coexistence of ESSENCE and EDs. The specific aim of each study was as follows: (**I**) to validate a newly developed instrument, the SWedish Eating Assessment for Autism spectrum disorders (SWEAA); (**II**) to examine the prevalence of EDs and eating pathology in adults with ASD and/or ADHD; (**III**) to examine cortical grey matter volume in brain areas connected to social cognition in AN, and compare these data with matched healthy comparison cases and ASD patients; (**IV**) and to examine the presence of "autistic eating behaviours" among female patients with AN. **METHODS**: The following individuals have been examined; adolescents and adults with ASD and/or ADHD, current AN patients (at admission and at 1-year follow-up), partially recovered (weight restored) AN patients, and healthy matched comparison groups in all but one study. The SWEAA has been validated and information on autistic eating behaviours in patients with ASD, patients with AN and matched healthy comparison cases has been investigated. Differences in grey matter volumes have been examined with magnetic resonance imaging (MRI) in patients with AN and compared with the volumes of matched healthy individuals and patients with ASD. All studies used validated psychiatric questionnaires and interviews. **RESULTS**: The validation of the SWEAA showed good psychometric properties. Patients with current AN scored higher on the SWEAA than patients

with ASD. At 1-year follow-up AN patients still had high scores on the autism specific items and partially recovered AN patients had the same total score as patients with ASD. In a large sample of adults with ASD and/or ADHD a total of 8% had a current or previous eating disorder and the male to female ratio was 1:2.5. The most common EDs were AN and BED. The MRI study showed specific grey matter reductions in brain areas connected to social cognition both in females with AN and in females with ASD. **CONCLUSIONS**: The compilation of the studies in the present thesis gives further support to the notion of common denominators between EDs and ASD, both in terms of behaviour and neurobiological deviations. This knowledge is important not only to researchers but also to clinicians to enable individually tailored treatment, using strategies from both the eating disorder and the ASD realm.

Keywords

Autism spectrum disorder, anorexia nervosa, eating disorders, cortical grey matter, ADHD

Sammanfattning på svenska

Stört ätbeteende anses vara bland de vanligaste problemen hos personer med autism. Trots detta har det saknats ett instrument för att systematiskt kunna undersöka dessa svårigheter hos normalbegåvade personer med autism. Denna avhandling avser att undersöka; hur bra är validiteten och reliabiliteten och vad är en lämplig cut-off poäng för det nyutvecklade frågeformuläret The SWedish Eating Assessment for Autism spectrum disorders (SWEAA)? Hur utbrett är det med traditionella ätstörningar och ätstörningssymptom hos vuxna patienter med autism och/eller ADHD? Förekommer typiska autistiska ätbeteenden vid anorexia nervosa (AN)? Finns det neurobiologiska likheter mellan autism och AN gällande den grå hjärnsubstansen i områden som är associerade till social kognition (de kognitiva processer som ligger till grund för social interaktion)?

För att besvara ovannämnda frågor har följande grupper undersökts; ungdomar och vuxna patienter med autism och/eller ADHD, patienter med AN (nyinsjuknade och vid 1-årsuppföljning), AN patienter som befinner sig i partiell remission och matchade jämförelsegrupper (i alla utom en studie). I alla studier har validerade psykiatriska frågeformulär och intervjuer använts och i en studie genomgick individerna magnetkameraundersökning (MRI).

Valideringen av SWEAA, det första instrumentet i sitt slag, visade höga nivåer av reliabilitet, konvergerande och diskriminerande validitet och skal-egenskaper. Med hjälp av logistisk regressionsanalys kunde man urskilja de bästa prediktorerna för autism (delskalorna Simultankapacitet och Social situation vid måltid). SWEAA har dessutom använts för att undersöka autistiska ätbeteenden hos patienter med AN samt patienter i partiell remission och jämfört resultaten med friska jämförelsepersoner och personer med autism. Patienterna med pågående AN hade högre SWEAA-poäng jämfört med patienterna med autism. De AN-patienter som hade återgått till normal vikt visade sig ha lika mycket autistiska ätbeteenden som patienterna med autism. I en grupp med vuxna med autism och/eller ADHD hade totalt 8% en pågående eller tidigare ätstörning (vanligast förekommande var AN och hetsätningsstörning). Förekomsten av ätstörning hos män respektive kvinnor förhöll sig 1:2.5, vilket motsvarar

en jämnare könsfördelning än i den allmänna befolkningen. MRI visade att hos kvinnor med pågående AN och kvinnor med autism fanns likadana specifika förtunningar av den grå hjärnsubstansen i områden som är kopplade till social kognition. Dessa förtunningar sågs däremot inte hos de friska jämförelsegrupperna eller hos män med autism.

Sammantaget ger studierna i denna avhandling ytterligare stöd för att det finns gemensamma nämnare mellan ätstörningar och autism, både vad gäller beteende och neurobiologiska avvikelser. Denna kunskap är viktig inte bara för forskare utan även för kliniker för att möjliggöra individuellt anpassad behandling, där man måste använda sig av strategier från både ätstörnings- och autismområdet.

List of papers

This thesis is based on the following studies, referred to in the text by their roman numerals.

I. Karlsson, L., Råstam, M., & Wentz, E. The SWedish Eating Assessment for Autism spectrum disorders (SWEAA) –Validation of a self-report questionnaire targeting eating disturbances within the autism spectrum. *Research in Developmental Disabilities 2013; 34*: 2224-2233.

II. Karjalainen, L., Gillberg, C., Råstam, M., & Wentz, E. Eating disorders and eating pathology in young adult and adult patients with ESSENCE. *Comprehensive Psychiatry 2016; 66*: 79-86.

III. Björnsdotter, M*., Davidovic, M*., Karjalainen, L., Starck, G., Olausson, H., & Wentz, E. Shared superior temporal gray matter reductions in women with anorexia nervosa and autism spectrum disorder. *Shared contribution. *Submitted*.

IV. Karjalainen, L., Råstam, M., Paulson-Karlsson, G., & Wentz, E. Autistic eating behaviours in anorexia nervosa. *Submitted*.

Table of Contents

Abbreviations

AB-unit	Anorexia-Bulimia Unit
ABIDE	Autism Brain Imaging Data Exchange
ADHD	Attention-Deficit/Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview -Revised
ADOS	Autism Diagnostic Observation Schedule
AN	Anorexia Nervosa
AN-C	Anorexia Nervosa, current
AN-C-1YR	Anorexia Nervosa, current at 1-year follow-up
AN-PR	Anorexia Nervosa, partial remission
ARFID	Avoidant/Restrictive Food Intake Disorder
ASD	Autism Spectrum Disorder
ASDI	Asperger Syndrome (and high-functioning autism) Diagnostic Interview
AQ	Autism Spectrum Quotient
BAMBI	Brief Autism Mealtime Behaviour Inventory
BDI	Beck Depression Inventory
BED	Binge Eating Disorder
BMI	Body Mass Index
BN	Bulimia Nervosa
CBT	Cognitive Behavioural Therapy
CLG	Clinical Group (Study I)
CNC	Child Neuropsychiatry Clinic
COG	Comparison Group (Study I)
COMP	Comparison Group (Study IV)
CRT	Cognitive Remediation Therapy
CT	Computed Tomography
DASH-II	Diagnostic Assessment of the Severely Handicapped-II
DCD	Developmental Coordination Disorder
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EAT	Eating Attitudes Test
ED	Eating Disorder
EDs	Eating Disorders
EDI	Eating Disorder Inventory
EHI	Edinburgh Handedness Inventory
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
fMRI	Functional Magnetic Resonance Imaging
ICC	Intraclass Correlation Coefficient
ID	Intellectual Disability
MRI	Magnetic Resonance Imaging
NPG	Neuropsychiatric Genetic Study
ROC-curve	Receiver Operating Characteristic-curve
ROIs	Regions of Interest
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-II	Structured Clinical Interview for DSM-IV Axis II Disorders
SD	Standard Deviation
SPECT	Single-Photon Emission Computed Tomography
STEP	Screeing Tool for Feeding Problems
STS	Superior Temporal Sulcus
SWEAA	SWedish Eating Assessment for Autism spectrum Disorders
TPJ	Temporoparietal Junction
VBM	Voxel-Based Morphometry
WAIS-R	Wechsler Adult Intelligence Scale -Revised

INTRODUCTION

Traditional eating disorders (EDs) (e.g. anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED)) and neurodevelopmental disorders (i.e. impairments in development of the brain and/or nervous system), such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD) and tic disorders are prevalent in children, adolescents and adults. The idea that there is a link between EDs and neurodevelopmental disorders was first suggested by Gillberg (1), and has become a hot topic in the last few years (2-5).

Recently the notion that AN is a disorder of neurodevelopmental origin or that there is a neurobiological overlap or connection between AN and conditions such as ASD has gained increasing research interest. Clinically AN patients are often described in terms recognised from ASD; e.g. socially withdrawn, with small social networks, few friends and obsessive and ritualistic behaviours (6, 7). Neurocognitive similarities are presented in terms of rigidity (5), weak central coherence (8-10) and impaired theory of mind (11) –all of which are traditionally considered as ASD traits. Research pertaining to cognitive as well as behavioural overlaps between AN and ASD is increasing. However few studies have focused on whether there are neuroanatomical and neurophysiological similarities.

The prevalence of traditional EDs within the autism spectrum population is sparsely investigated, although eating and mealtime problems are well known by parents as well as clinicians. The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) (12) acknowledges restrictive behaviour with and in relation to food, as well as extreme reactions to the taste, smell and appearance of food as features of ASD. However, the research on the overlap of these eating disturbances and the prevalence of the clinically significant EDs is limited and has focused on eating disturbances in individuals with ASD and a concurrent intellectual disability (ID), (13, 14). Eating disturbances often recognised in ASD with co-existing ID are selective eating, food neophobia, pica, rumination, overeating, and polydipsia (14).

Autism Spectrum Disorder

ASD encompasses a number of core features: persistent impairment in reciprocal social interaction and communication (criterion A), together with restricted and repetitive behaviours, interests or activities (criterion B). The traits should be present from early childhood, and cause a limitation or impairment in function (criteria C and D) (12). In the DSM-IV, diagnoses of Asperger's syndrome (15) and Autistic disorder (15) were diagnoses of their own, while they today are incorporated under the umbrella term ASD. Furthermore, in the DSM-5 the previous DSM-IV criteria A1 and A2, impairments in social interaction and in communication, are now compiled into the A-criterion. According to the DSM-5, criterion B encompasses symptoms such as motor stereotypies, special interests and excessive adherence to routines along with rigidity of thinking and hyper- or hyporeactivity to sensory stimuli. The hyper- or hyposensitivity may manifest itself in a number of ways, for example, through the perception of taste, smell, temperature and texture, as well as excessive food restrictions. The disorders encompassed by ASD differ in terms of the levels of social impairment but most importantly, they often vary strongly with regard to intellectual skills, and speech and language abilities. In the general population, the prevalence of ASD is 0.5-1.2% (16-20). The majority of individuals with ASD have normal intelligence (21, 22) and predominantly males are affected with a median ratio of 6 males to every 1 female. The corresponding figure in those with a moderate to severe ID is 1.7 male to 1 female (23).

The view on ASD has shifted from autism as a separate disorder towards the modern theories of a spectrum of functional disabilities (24). All disorders within the spectrum have traits of classical autism, but with a considerable variation in clinical manifestations. To this date, there is no known neuroanatomical abnormality or other biological way of diagnosing ASD; hence, the diagnosis is based on a clinical assessment. Over the years, it has also become clear that "pure" diagnoses are rare and that comorbidity is the rule (25). Due to the versatility of autism and its many underpinning factors, Mary Coleman and Christopher Gillberg have suggested it is rather a notion of autisms than purely autism (26). Furthermore, the cause of the autisms can be understood through neurogenomics suggesting that there is an interruption or misdirection during neurodevelopment in the foetus caused by genetic errors (26). In relation to this, it is also important to note that the heritability is high for ASD and estimated to be up to over 90% (27).

Diagnostic criteria for Autism Spectrum Disorder, DSM-5

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive):

1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a lack of facial expressions and nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):

1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Attention-Deficit/Hyperactivity Disorder

ADHD is the most common neurodevelopmental disorder and affects approximately 5-8% of the young population (28, 29), mainly males. More than one-half of these have symptoms that persist into adulthood (30). Core symptoms include difficulty with attention, impulsivity and activity regulation i.e. either hyper- or hypoactivity. ADHD is often seen in combination with other psychiatric disorders, and it is rare that clinically referred individuals have ADHD only (31).

Anorexia Nervosa

AN is a condition characterised by restricted eating leading to underweight, intense fear of weight gain and a disturbed perception of body weight and shape. In the most recent version of the DSM, the previous AN criterion of amenorrhea (i.e. the absence of menstruation in a fertile woman) was omitted. Furthermore, in the DSM-5, for AN as well as for other conditions, the possibility to grade the severity of the illness has been added. For AN this severity grading is based on body mass index (BMI, kg/m^2). AN is a detrimental psychiatric illness which has, according to a meta-analysis, a standardised mortality ratio (i.e. the ratio of the observed deaths in the patient group to that of a comparable group in the general population) of 5.86 (32).

The incidence of AN has been reported to be 205.9 cases/100 000 persons in the peak age categories (14-15 years) (33) and has a prevalence of 0.3-0.9% in the general population (34). However, some researchers have found, using a slightly higher BMI level, lifetime prevalence rates towards 3.6% (35). AN affects mainly young adolescent girls and has a male to female ratio of 1:10 (34). Lately though, it has been reported that AN in men is underdiagnosed and many cases go undetected (36, 37).

The aetiology suggests a complex interaction of biological, psychological and socio-cultural factors that interplay over time together with individual and familial predisposing factors (38, 39) generally referred to as a multifactorial model. The genetic factor explains at least 40-60% in terms of heritability (40) and even more when strict AN criteria are used (i.e. the individual fulfils all criteria for the disorder as opposed to including subclinical cases) (41, 42). Furthermore, the concordance in monozygotic twins is up to 50% (compared to 0-5% in dizygotic twins) (43, 44). In addition, biological pubertal development results in major changes in the appearance of the body which predomi-

nantly in girls can create feelings of discontentment with the body weight and shape, and can trigger dieting as a tool to achieve thinness, control, autonomy and self-worth in teenagers (45, 46).

Family-based therapy is the only evidence-based treatment for adolescents with AN while there is no evidence-based alternative for adult patients. Despite this around 80% of adult patients fully recover or improve while about 20% develop a chronic condition (47) and for younger patients only 11% can be categorised as having poor outcome after treatment (48). Research suggests that the earlier the treatment starts and the younger the patients are the better the prognosis (47), unless the illness debut is at a prepubertal age which worsens the prognosis (49). For many individuals with AN, thoughts and feelings around food and body shape are present, to different extents, for the rest of their lives (49).

Psychiatric comorbidities, including anxiety and affective disorders and self-injurious behaviour are common in individuals with AN (50-53). A systematic investigation of ASD in individuals with AN was first introduced in the partly population-based Gothenburg study (54-57). The prevalence of ASD was estimated to at least 12% (56). The prognosis for AN with co-existent ASD is worse concerning psychosocial status (e.g. social relationships, employment) and psychosexual status (e.g. attitude towards sexual matters) (49, 58). At the same time there are also reports that adherence to treatment is better for individuals with AN and comorbid ASD compared to those with AN only (59).

Diagnostic criteria for Anorexia Nervosa, DSM-5	
A.	Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.
B.	Intense fear of gaining weight or becoming fat or persistent behaviour that interferes with weight gain, even though at a significantly low weight.
C.	Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

Bulimia Nervosa & Binge Eating Disorder

Bulimia nervosa (BN) evolved from early beliefs of demons causing a great hunger and the ability to eat an entire ox (bulimia in Latin translates to “ox hunger”) to its own ED diagnosis in the late 1970’s by Russell (60). Criteria

for BN originated from the 1979 paper by Gerald Russell, and include episodes of binge eating and compensatory behaviours such as induced vomiting or use of purgatives. As in AN, the core psychopathology of BN is characterised by self-evaluation on the basis of weight and body shape, and the extreme fear of getting fat, as part of the criteria in the DSM-5. BN has a prevalence of 1-2% in the population (34), mainly in girls/women with one male to every ten females.

In the DSM-5, binge eating disorder (BED) was launched as a separate ED diagnosis. BED is characterised by periods of binge eating, like in BN, but without the compensatory behaviour to follow. There is a marked distress in these individuals concerning their binge eating and the episodes are characterised by for example fast eating and/or eating despite absence of hunger feelings. BED affects 1-2% of the population with a male to female ratio of approximately 1:7 (61). A recent report from the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) shows that interpersonal psychotherapy and cognitive behavioural therapy (CBT) are the most effective treatments for BED, and that antidepressants and psychostimulants also seem to have an effect in decreasing or ceasing the binge eating episodes (62). Although comorbidity rates of other psychiatric disorders are high for all EDs, a recent clinical register study found that the highest levels were found among men with BN and women with BED (63).

Other eating and feeding disorders

The DSM-5 introduced a new feeding and eating disorder, avoidant/restrictive food intake disorder (ARFID), to encompass severe eating disturbances which also lead to underweight and detrimental effects on health as well as everyday living. This is not an eating disorder in the traditional sense, but rather manifests with symptoms like selective eating, fear of eating, perceptional deviances in terms of smell or taste or lack of interest in food. Unlike traditional EDs, ARFID is neither characterised by weight phobia or disturbed bodily perception nor is it attributable to a medical condition. A recent study evaluated the prevalence of ARFID in all patients at a treatment-seeking paediatric gastroenterology setting and found 1.5% meeting full criteria, of whom 67% were males (64). A retrospective study of medical records of children and adolescents in a day program for EDs found that one in three of the patients with ARFID were boys and the total ARFID prevalence was 22.5% (65).

One of the most common types of aberrant eating recognised in ASD is selective eating. This is characterised by a highly limited food intake, where the individual has never had a normal food repertoire and presents with food neophobia: i.e. refusal to try new foods (66). One study reported that more than 50% of children with ASD displayed selective eating (67) while another suggested that having an extremely limited diet is a problem in a majority of children with ASD (83%) (68). Selective eating may result in severe problems for the individual and his/her family, as the behaviour may cause malnutrition and a poor general condition (66, 69). With DSM-5, ARFID will, in many cases henceforth, include selective eating.

Pica is a type of aberrant eating behaviour where the individual eats what is generally considered inedible substances. This has been reported in up to 70% of individuals with ASD and comorbid ID (70). In some cases pica may lead to poisoning, e.g. when the individual eats cigarettes or wall paint (71).

Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE)

Over the years, it has become clear that "pure" diagnoses are rare and that comorbidity is the rule. The acronym ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) describes the overlap between neurodevelopmental conditions, suggesting that a child presenting with one or more major neurodevelopmental concerns in a clinical setting before the age of 5 often signals problems in the same or overlapping areas later in life (72). ESSENCE encompasses symptoms that may develop into diagnoses such as ADHD, ASD, Tourette's disorder, ID, language disorder, developmental coordination disorder (DCD), seizures and other neurological problems in childhood. Symptoms include for example hyperactivity, regulatory problems during infancy (e.g. feeding, sleeping), or mood swings, language delay and social impairments. It is often hard and not so obvious to pinpoint the "right" diagnosis at an early age assessment, but the symptoms seen are according to the ESSENCE-concept a signal that there will also be difficulties later in life. ESSENCE is not a diagnosis in itself but an umbrella term for this compilation of early life symptoms. ESSENCE, has a male preponderance with a gender ratio of about 2-3:1 and an overall prevalence for children of 5-7% (72).

Anorexia nervosa and neuroimaging

The first neuroimaging studies in AN were published in the early 1990's. Using computed tomography (CT) and magnetic resonance imaging (MRI) Kornreich and colleagues showed that patients with AN had smaller brain volumes due to increased number of sulci and enlarged ventricles (73). Single-photon emission computed tomography (SPECT) studies, measuring cerebral blood flow, showed hypoperfusion in parts of the temporal and orbital lobes in brains of those with ongoing AN as well as in individuals who had recovered from AN (74, 75).

Since the early 2000's functional MRI (fMRI) has been implemented to study brain functions in AN. One study used images of food and aversive emotions, and ED patients reported feelings of disgust and threat when exposed to food images (76). fMRI studies using taste stimuli have found heightened brain reward sensitivity in AN (77). These results suggest that individuals with AN may be more responsive to food stimuli than individuals with for example obesity and furthermore that these responses could be dopamine related. The same study also points out that increased activation of certain brain regions in AN but not in obesity indicates the high level of control of food intake in AN. Recent research furthermore turns to fMRI as a means of understanding the pathophysiology of AN, which is largely unknown, and suggests that brain circuit alterations connected to cognitive control and emotion are central in this comprehension (78) and affect both ill as well as recovered patients. Moreover, there is evidence suggesting that individuals with AN have alterations in areas involved in inhibition (prefrontal and anterior cingulate cortices) which result in less inhibitory resources needed to withstand whatever tasks they are doing even when inhibitory demand is increasing (79, 80). This may explain part of the extraordinary ability in individuals with AN to maintain obsessive behaviour in many situations instead of stopping or changing the behaviour. Furthermore, fMRI has shown that there seems to be persistent alterations in brain areas connected to theory of mind in AN (81). These alterations, in terms of hypoactivation in networks supporting functions like theory of mind, (middle, anterior temporal cortex and medial prefrontal cortex), have been suggested to indicate impairments in social functioning in AN. More importantly, these impairments seem to predict a poorer outcome at follow-up for these individuals. Alongside these findings MRI has been used in a study to illustrate the potential of brain gyrification as another predictive factor for outcome in AN (82).

Aims

1. To determine the internal and external validity and test-retest reliability of a newly developed questionnaire, The SWedish Eating Assessment for Autism spectrum disorders (SWEAA), pertaining to disturbed eating behaviours and aberrant behaviours at mealtimes in adolescents and young adults with ASD and normal intelligence, and to determine a cut-off for clinical and research purposes.

2. To examine the prevalence of EDs and ED symptoms in adults with ASD and/or ADHD.

3. To examine whether female AN and ASD patients exhibit common brain areas of reduced cortical grey matter relative to their respective matched control participants, in areas connected to social cognition.

4. To examine the presence of "autistic eating behaviours" among female adolescents and young adults with AN, using the SWEAA.

METHODS

Firstly, participants and procedures are described study by study, followed by shared subchapters describing instruments and statistical methods. An overview of compiled methods can be seen in Table 1 below.

Table 1. *Study groups and methods used in Study I-IV*

Study	I	II	III		IV
Object of study	Validation of an instrument assessing autistic eating behaviours	EDs and eating pathology in ESSENCE	Grey matter volume in AN and ASD		Autistic eating behaviours in AN
Target group (n)	202 CLG 56 COG	273 adults referred for neuropsychiatric work-up	38 AN* 25 COMP*	12 ASD* 22 COMP*	36 AN-C* 32 AN-C-1YR* 23 AN-PR* 19 ASD* 30 COMP*
Group examined (n)	57 CLG(ASD) 31 COG	228 ASD: 74 ADHD: 109 ASD+ADHD: 45	25 AN* 25 COMP*	12 ASD* 22 COMP*	See Target group
Attrition (n)	145 CLG 25 COG	45**	13 AN	n/a	4 AN-C-1YR
Male to female ratio	38:19 CLG 15:16 COG	127:101	0:25 0:25	0:12 0:22	0:36, 0:32, 0:23, 0:19, 0:30
Instruments	SWEAA	SCID-I, SCID-II, WAIS-R, EAT	MRI, BDI, EHI, SCID-I (ED module only), AQ	MRI	SWEAA, AQ

* females only
** were not included due to ID or no ASD or ADHD

Study I –The SWedish Eating Assessment for Autism spectrum disorders (SWEAA) -Validation of a self-report questionnaire targeting eating disturbances within the autism spectrum

Participants

The participants consisted of firstly a clinical group (CLG) with individuals between 15 to 25 years of age with an ASD diagnosis. This group was recruited from the clinical patient base at the specialist unit the Child Neuropsychiatry Clinic (CNC) at the Queen Silvia Children's University Hospital in Gothenburg, Sweden, in 2010. The participants were randomly selected from a list of all previous and current patients at the CNC. One male and one female patient born each month, each year (years 1986 - 1995), were picked from the patient base list. Each selected individual was checked for diagnosis and intelligence level (individuals with ID were excluded). Participants had previously been thoroughly neuropsychiatrically and neuropsychologically evaluated and assigned their ASD diagnosis based on current DSM-criteria (DSM-III, DSM-III-R or DSM-IV depending on when they were diagnosed).

Out of 202 contacted patients, 57 (28%) responded and completed the SWedish Eating Assessment for Autism spectrum disorders, SWEAA (83) (males: 66.7%, n=38; females: 33.3%, n=19). A dropout analysis was conducted to investigate possible significant differences between participants and abstainers in the study. The gender distribution in the CLG was the same as among the non-respondents (n=123; 67% male and 33% female), and no significant age difference was found, which helps supporting the external validity of the study.

A gender-, age- and educational level matched healthy comparison group (COG) was recruited among offspring of colleagues and friends of the researchers. In the COG, 31 (males: n=15; females: n=16) out of 56 individuals (55%) accepted the invitation. The mean age of the CLG was 18.7 years (SD 2.94) and of the COG 19.5 years (SD 2.5). No significant difference was found regarding age (p=0.19). However, with regard to educational level the COG attained higher educational levels than the CLG (p<0.001). Mean BMI yielded no significant differences on group level (CLG: mean 23.0 kg/m^2, SD 4.5; COG: mean 21.7 kg/m^2, SD 2.2; p=0.52) or between genders (CLG: male 22.9 kg/m^2; female 23.2 kg/m^2; p=0.90; COG: male 21.0 kg/m^2; female 22.4 kg/m^2; p=0.12),

no significant differences in BMI were found when comparing females and males of the two groups separately ($p_{females} = 0.39$ and $p_{males} = 0.18$).

Procedure

Based on a thorough literature review by Råstam (14), and the combined clinical experience of eating disturbances in ASD over several decades, our research group developed the items in the SWEAA. The instrument was intended as a web-based multidimensional self-report questionnaire assessing eating behaviours and eating disturbances in ASD (see Appendix for final version of the questionnaire).

The instructions for submitting the SWEAA was sent by post, to the above mentioned participants, with information on how to submit the questionnaire anonymously via a web-link. A number of the respondents completed the SWEAA a second time in order to assess the test-retest reliability (on two occasions with a mean interval of 34 days). Several statistical analyses were then carried out to establish various forms of validity and reliability for the instrument (in further detail under Statistical methods).

Study II –Eating disorders and eating pathology in young adult and adult patients with ESSENCE

Participants

Between 2001 and 2003 the "Neuropsychiatric Genetic Study" (NPG) was carried out at the specialist clinic, CNC, in Gothenburg. The participants were individuals referred on suspicion of ESSENCE conditions, to the project either by self-referral, general practitioners, or through secondary or tertiary referrals by specialists in psychiatry. All consecutively referred patients were asked about participation in the project, and 273 individuals provided informed consent (84). During the project, participants were assessed and diagnosed by experienced clinicians in multi-professional teams. Thirty-two of the 273 individuals, had no ESSENCE diagnosis (neither ADHD nor ASD) and they were excluded from the present study. Thirteen individuals were not assessed regarding EDs. Therefore the final study group consisted of 228 individuals.

The ESSENCE diagnoses among the remaining 228 subjects were distributed as follows: ADHD only: n=109 (47.8%); ASD only: n=74 (32.5%); ADHD+ASD: n=45 (19.7%).

Procedure

As part of a larger study, participants were assessed in depth regarding psychiatric (including EDs) and personality disorders with the Structured Clinical Interview for Diagnosis according to the DSM-IV Axis I Disorders (SCID-I) (85) and the Structured Clinical Interview for Diagnosis according to the DSM-IV Axis II Personality Disorders (SCID-II) (86). ESSENCE diagnoses were assigned based on clinical status together with information from the Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI) (87), criteria checklists for current and lifetime DSM-IV ASD, ADHD, tic disorders and other disorders not included in any of the cited instruments, currently and retrospectively. Intelligence was assessed by the Wechsler Adult Intelligence Scale -Revised (WAIS-R) (88). Eating pathology was measured by using the Eating Attitudes Test (EAT) (89) and was completed by 138 of the 228 participants (those with ID or no ESSENCE excluded). Hospital records were scrutinised and anthropometric data were gathered.

Study III – Shared superior temporal grey matter reductions in women with anorexia nervosa and autism spectrum disorder

Participants

Females with AN (n=25) were recruited consecutively from the in- and outpatient specialist Anorexia-Bulimia unit (AB-unit) at the Queen Silvia Children's University Hospital in Gothenburg, Sweden. All patients were diagnosed with AN according to the DSM-IV (15), by a psychiatrist at the first assessment (all patients also fulfilled the DSM-5 criteria for AN). Patients ranged in age from 16 to 25 (mean: 20.32; SD 2.23). Their BMI ranged from 14.1 to 17.5 kg/m^2 (mean: 16.3; SD 0.93). Patients with dental braces, pacemaker or any other metal implant were excluded due to technical reasons with the camera (the strong magnetic field may destroy metal parts in im-

plants such as pacemakers. Furthermore, metal items are drawn to the camera with an enormous force and can cause serious injury and harm).

For the age- and gender matched comparison group (n=25), female participants were recruited through the university and high schools in Gothenburg, Sweden. The advert for participation in the project requested healthy individuals. Additionally, they were interviewed using semi-structured instruments to exclude neurological disorders and ongoing ED and they were asked about medication before the experiment was conducted (none of the participants in the comparison group was excluded due to medication). For this group the age range was 17 to 25 (mean: 21.3; SD 2.1) with a BMI range from 16.9 to 25.5 kg/m^2 (mean: 21.1; SD 2.27). The same exclusion criteria were applied to the comparison group. BMI was reported by the comparison individuals themselves. All participants were asked the same control questions, ensuring their suitability for the MRI examination.

A group of ASD females (n=12) and an age- and gender matched comparison group (n=22) were included in the study. Data for these two groups were obtained from the Autism Brain Imaging Data Exchange (ABIDE) (90). ABIDE is a multicentre collaboration that shares neuroimaging data from 1,112 participants with ASD and age-matched typical comparison cases. Most sites, where data are acquired from in ABIDE, use the Autism Diagnostic Interview-Revised (ADI-R) (91) together with the Autism Diagnostic Observation Schedule (ADOS) (92) for ASD diagnoses, however with some variation. Age range for these two groups was 16 to 25 and mean age for ASD 19.9 (SD 3.04) and comparison group 18.11 (SD 4.65). Data were also compared to a group of males with ASD (n=137) and their corresponding comparison group (n=149) also with age range 16 to 25, all from the ABIDE. There are no data on BMI for these two groups.

Procedure

The AN participants and their corresponding comparison group completed a scanning session in a magnetic resonance camera, in which various images (anatomical, functional, resting state and diffusion weighted) were collected.
All the participants were given the same instructions before the start of the scanning. Their heads were stabilised to ensure that they were kept still for the duration of the examination. The scanning session took around 40 minutes to acquire all images.

In the present study anatomical imaging data were used for investigation of the cortical grey matter volumes. The brain scans were collected using a Philips Gyroscan 3T Achieva, software release 3.2 (Philips, Eindhoven, The Netherlands). The scanner's 2 channel parallel transmit was used for improved signal homogeneity over the field of view (32 channel SENSE, same manufacturer as the scanner). Anatomical scans were performed with scan resolution of 1.0x1.0x1.0 mm^3.

Regional alterations in cortical grey matter volume in brain regions linked to social cognition were examined by conducting voxel-based morphometry (VBM) analyses of anatomical brain scans. Two recent technological advances in neuroimaging were used; the meta-analysis software Neurosynth, to define unbiased regions of interest (ROIs), and the multicentre ABIDE-program, to obtain structural brain scans of the female age-matched ASD patients and their control participants for comparison with our locally acquired AN data and their corresponding comparison cases, alongside the data from ABIDE's group of males with ASD.

Study IV –Autistic eating behaviours in anorexia nervosa

Participants

Thirty-six females with current AN (AN-C), and twenty-three females in partial remission (BMI ≥18.5) (AN-PR) one year after admission at the AB-unit, all within the age range 15 to 25, were included in the study. Additionally, the AN-C group was followed-up approximately one year after admission (AN-C-1YR, n=32). The group of patients in partial remission was included at the start in order to compare the results from the AN-C-1YR group with the results from individuals who had a restored body weight. Mean BMI for the different groups were: AN-C: 16.1 kg/m^2 (SD 0.9), AN-C-1YR: 18.2 kg/m^2 (SD 1.7), AN-PR: 19.8 kg/m^2 (SD 0.9), ASD: 23.2 kg/m^2 (SD 5.5) and COMP: 21.3 kg/m^2 (SD 2.2).

The SWEAA data from these groups were compared with data from Study I; i.e. a group with ASD and a healthy comparison group matched for age, gender and education. The majority of patients in Study I were males but in Study IV only data from females were used; the female ASD group (n=19) and the healthy comparison group (n=16) plus another 14 healthy matched females from parallel studies (to increase the healthy comparison group)

(COMP: n=30). For the development of cut-off scores all available data (including males, ASD: n=38, COMP: n=20 (the initial 15 males were supplemented with n=5 COMP from parallel studies using the same instruments to increase the group)) were used (ASD_{total} n=57, $COMP_{total}$ n=50).

Procedure

Consecutive patients at the AB-unit at the Queen Silvia Children's University Hospital were asked to participate during a visit to the unit. AN-C were followed up one year after admission to the AB-unit (AN-C-1YR), either being given the same questionnaires in person or sent via the post. The individuals in the AN-C, AN-C-1YR, AN-PR and the COMP groups completed the SWEAA and the AQ (individuals of the COMP group originating from Study I did not complete the AQ) (93).

Instruments

The SWedish Eating Assessment for Autism spectrum disorders (SWEAA) (I, IV)

The SWEAA is a self-report questionnaire pertaining to eating and mealtime problems in individuals with ASD and normal intelligence developed by Karlsson, Råstam and Wentz in 2013. The SWEAA is based on 60 items divided into a number of subscales; A. Perception, B. Motor control, C. Purchase of food, D. Eating behaviour, E. Mealtime surroundings, F. Social situation at mealtime, G. Other behaviours associated with disturbed eating (items aimed at traditional ED symptoms), H. Hunger/satiety, I. Simultaneous capacity, and J. Pica (83). The cut-off score on the total score is 12. The subscale based cut-off (based on the mean of subscales F and I), developed to differentiate between ASD and no ASD, has a value of 10 (Karjalainen et al., unpublished data).

The Autism spectrum Quotient (AQ) (III, IV)

The AQ is a self-report questionnaire based on autism spectrum symptomatology and was introduced by Baron-Cohen and colleagues (93). The instrument comprises fifty items based on five different areas (Communication, Social, Imagination, Local details, Attention switching) to find clinically significant levels of autistic traits, and the instrument has a total score cut-off of 32. AQ has good test-retest and interrater reliability and reasonable construct and face validity (93).

The Eating Attitudes Test (EAT) (II)

The EAT is a self-report questionnaire, with 26 items (originally 40) aimed at eating symptomatology. A score of 20 or more indicates referral to an ED specialist (89) and for sub-threshold cases a cut-off of 10 has been suggested as a sufficiently distinct measure to indicate disturbed eating behaviours and attitudes (94, 95). The EAT-26 was originally validated for AN and has shown high levels of internal consistency (89).

The Structured Clinical Interview for Diagnosis according to the DSM-IV Axis I Disorders (SCID-I) (II, III) and the Structured Clinical Interview for Diagnosis according to the DSM-IV Axis II Personality Disorders (SCID-II) (II)

The SCID-I (85) is a structured clinical interview for evaluation of psychiatric disorders based on the DSM-IV criteria. The SCID-II (86) is also an interview but it is aimed at personality disorders based on the DSM-IV criteria. SCID-I and II were used in the NPG project where data for Study II were collected. In Study III only the ED module was used from SCID-I to exclude ongoing ED cases in the comparison group.

The Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI) (II)

The ASDI pertains to symptoms of Asperger syndrome, according to the criteria suggested by Gillberg & Gillberg, and is a semi-structured interview (87). The ASDI was used as part of the NPG project where data were collected for Study II. The instrument was validated in a clinical sample showing excellent inter-rater and test-retest reliability and good validity (87).

Checklists for current and lifetime DSM-IV ASD, ADHD, tic disorders and other disorders (II).

Criteria checklists based on DSM-IV criteria of above mentioned disorders and for example Tourette's syndrome.

Wechsler Adult Intelligence Scale –Revised (WAIS-R) (II)

The WAIS-R (88) was the current version of the Wechsler adult scales, thus used to assess intelligence in the NPG project.

Beck Depression Inventory (BDI) (III)

The self-report measure for symptoms of depression, the BDI (96), was used for AN patients and their matched comparison group in Study III to exclude that any difference in MRI results was due to depression levels. A score of 0-9 points refers to: minimal depression, 10-18 points: mild depres-

sion, 19-29 points: moderate depression and 30-63 points: severe depression.

Edinburgh Handedness Inventory (EHI) (III)

The EHI was used on AN patients and comparison individuals to investigate possible differences in handedness in Study III (97).

Structural Magnetic Resonance Imaging (MRI) (III)

An MRI camera was used as primary method in Study III and is described in detail under Procedure –Study III.

Statistical analyses

An overview of statistical methods is presented in Table 2, followed by a detailed description for each study.

Table 2. *Overview of statistical methods used in Study I-IV*

	Study			
Analyses	**I**	**II**	**III**	**IV**
For comparison between two groups:				
-Mann-Whitney U-test for continuous variables	x	x		x
-Mantel-Haenszel chi^2 test for ordered categorical variables	x			
-Fisher's exact test for dichotomous variables	x	x		
-T-test for continuous normal distributed variables			x	
Analysis for change over time: Wilcoxon signed rank test	x			x
Univariable logistic regression analysis	x	x		x
Stepwise forward logistic regression analysis	x	x		x
Spearman's correlation coefficient, r_s				x
Pearson's correlation coefficient, r	x		x	
Exploratory factor analysis with Scree plot and Varimax rotation	x			
Internal validity: Cronbach's alpha, correlation item to scale corrected for overlap, item convergent and item discriminant analysis	x			
Effect sizes	x			
Reliability: Test-retest, distribution of changes, intra-individual SD, intra-class correlation coefficient for subscales and Weighted kappa and percent agreement for single items	x			

Study I

Study I was a validation study including several statistical methods in order to firstly create a comprehensively structured instrument through different types of validity and reliability tests and secondly, with regards to clinical practice, to find out what items and subscales differentiate individuals with ASD from healthy comparison cases.

To begin with, three different methods were used to achieve content validity (items and scales should cover the construct(s) they intend to cover). Firstly, a literature search was conducted by Råstam (14), secondly, items were con-

structed on the basis of the clinical experience of the research team; and thirdly, items were tested in a pilot study (involving both patients and care givers) for opinions and ideas of the items' relevance for the instrument as well as wordings. Clinical relevance served as a tool throughout the process and was the final judgement when for instance deciding which items to keep in the instrument.

The following analyses formed the basis of the internal validation where the construction of subscales and distribution of items was established:

-Exploratory factor analysis with Principle Components Analysis with Varimax Rotation, was used to determine the number of subscales and to select items into the subscales.

-To measure the internal consistency (reliability) of the subscales, Cronbach's alpha was used. Item-internal consistency (item-convergent validity within each subscale) was analysed using Pearson's correlations between each item and the own subscale (corrected for overlap, scale – actual item). To ensure that each item had the highest correlation with the own subscale and not to any of the others, items were correlated with each of the other subscales (item-discriminant validity). Moreover, the number and percentage of scaling success (items significantly more correlated with the own subscale than to any other subscale) and scaling error (items significantly more correlated with another subscale than to the own subscale) were calculated for each item in each subscale.

The second part of the validation was to ensure external validity of the instrument. Known-groups validity (differences between groups that should differ) was explored using the Mann-Whitney U-test for continuous variables, the Mantel-Haenszel Chi^2 test for ordered categorical variables and the Fisher's exact test for dichotomous variables. For each subscale, effect sizes were calculated (the difference of the mean in the CLG and the mean in the COG divided by the SD of the COG, except for the single item Pica where SD from the CLG was used because of the 0-value in the COG). Ideally, concurrent validity should have been measured by comparison to a similar or equivalent instrument but at the time of the study no such instrument was available.

To assess repeatability and reproducibility of the SWEAA a test-retest reliability analysis was performed as a last step in the initial validation. For each subscale the following statistics were calculated, the distribution of differences between two occasions (mean duration 34 days between the two occasions),

within-individual SD and Intraclass Correlation Coefficient (ICC). For test of systematic differences between the two occasions Wilcoxon signed rank test was used (second occasion minus first occasion). Calculations of the ICC were done according to Shrout and Fleiss (98) and with single rating with visit as a random effect.

Apart from the internal and external validation, further analyses were made with regards to clinical implications. Univariable and Stepwise Forward Logistic Regression analyses were used to find which items and subscales best discriminate the CLG from the COG. All significance tests were two-sided and conducted at the 5% significance level.

Study II

In Study II, comparisons between different diagnostic groups were made with Mann-Whitney U-test for continuous variables and Fisher's exact test for dichotomous variables. Univariable logistic regression analyses were performed, with all 26 items of the EAT as independent variables, to discern independent discriminatory items between ASD-only vs. ADHD-only and between ASD plus ADHD vs. ADHD-only. Each item was first included in the univariable logistic regression, with the group variables as dichotomous outcome variable and each item as explaining variable. Items with $p<0.10$ were then entered into a stepwise forward multiple logistic regression analysis to find independent explanatory variables. All significance tests were two-sided and conducted at the 5% significance level. Furthermore, analyses were adjusted for age and education according to differences between groups.

Study III

In order to find relevant brain regions at which to focus the MRI-analyses in Study III, a reverse inference meta-analysis of studies targeting theory of mind was performed. Previous studies focusing on theory of mind were included and analysed by the software Neurosynth (neurosynth.org) to identify regions of interest (ROIs). Furthermore, the MarsBaR toolbox (http://marsbar.sourceforge.net/) was used in order to assess if the same areas were affected in AN as well as ASD, and in females as well as in males. Comparisons between groups for continuous normal distributed variables were made with t-tests and correlations were calculated with Pearson's correlation coefficient.

Study IV

Two different cut-offs, one based on the total score of the SWEAA and one based on the mean of the two subscales discriminating best between individuals with ASD and the matched healthy comparison group (i.e. the mean of the subscales Social situation at mealtime and Simultaneous capacity), were developed with data from Study I. The first cut-off was calculated through logistic regression analysis of the total score, with data from individuals with ASD and a healthy age-matched comparison group. The second was based on a stepwise logistic regression analysis with ROC-curves over sensitivity and 1-specificity.

Comparisons were made between the different groups; AN-C, AN-C-1YR, AN-PR, ASD, and COMP with Mann-Whitney U-test for continuous variables and Fisher's exact test for dichotomous variables. In order to analyse change between the AN-C group and the AN-C-1YR group, the Wilcoxon Signed rank test was used. For all correlation analyses, Spearman's correlation coefficient was used. All significance tests were two-sided and conducted at the 5% significance level.

To find items discriminating between two groups (between the AN-C and the ASD groups and between the AN-C and the COMP groups), univariable logistic regression analyses were performed. Moreover, the independent variables discriminating between the groups were discerned by entering the items with $p<0.10$ into a stepwise forward logistic regression analysis and a goodness of fit for the model, and the area under the ROC-curve was calculated.

Ethical considerations

All four studies were approved by the Regional Ethical Review Board at the University of Gothenburg, Sweden (I: GU668-10; II: Ö586-99; III: GU007-14 IV: GU264-12). All studies included human participants and were in accordance with the 1964 Helsinki declaration. All participants received oral and/or written information about the study and consented to participate voluntarily. When applicable, participants were informed that participating or abstaining did not affect their course of treatment in any way.

Although careful considerations were made throughout this thesis, different ethical questions nonetheless arose. When informing patients and parents, care was taken to write information adjusted for each age group (in Study I).

It was decided to contact participants through mail rather than telephone at first instance in order not to appear too confrontational for this particular patient group (i.e. adolescents and young adults with ASD).

In Study III a comparison person presented with an anatomical deviation of the brain in the MRI examination. In this particular case the person was immediately referred to a specialist and taken care of and this routine had been established when planning the study as it was a potential scenario that could be anticipated beforehand. In Study IV some of the AN and the COMP participants reacted to some of the questions in the SWEAA as awkward and these issues were then explained by the researcher. Furthermore, the researchers were prepared to handle possible ASD cases among the AN patients.

RESULTS

Study I

The resultant instrument, the SWEAA, consisted of 60 items divided into eight subscales (determined through explorative factor analysis) and 2 single items (see Table 3 for complete subscales). As a complement for specific matters within the ASD symptomatology, additional sections were added (five items from the AQ, special dietary requirements/food allergies, medication, somatic and psychiatric comorbidity; these sections were not included in the validation process). The final subscales were as follows; A. *Perception*: reflects sensoric input around food e.g. smell, taste, textures or noises, B. *Motor control*: assesses different aspects of movement e.g. chewing, spilling or table manners, C. *Purchase of food*: concerns the individual's control of purchases e.g. brands or type of groceries, D. *Eating behaviour*: indicates selectivity in eating e.g. certain colours, limited repertoire or trying new foods, E. *Mealtime surroundings*: reflects routines around mealtime e.g. where to eat or how cutlery is placed, F. *Social situation at mealtime*: assesses the situation around others at a mealtime e.g. adapting own behaviour to others or liking company around a meal, G. *Other behaviour associated with disturbed eating*: comprises questions of traditional ED symptomatology e.g. fasting, purging or dieting, H. *Hunger/satiety*: measures whether the individual can feel when hungry or full, and the two single items: I. *Simultaneous capacity* which indicates if the individual finds it hard to do two things at the same time when eating, and J. *Pica* measuring if the respondent eats inedible things e.g. soil or mortar.

Item convergent and item discriminant validity were investigated with correlations between item and own scale and correlations between item and the other scales, and results showed good validity (see Table 4). Mean Cronbach's alpha was 0.83 for the subscales combined (8 subscales). The test-retest reliability analysis showed good agreement between the two occasions (mean ICC was 0.860). Alongside this, logistic regression analysis was used to discern the best subscale/single item predictors for discriminating between the ASD group and the healthy comparison group, resulting in *Social situation at mealtime* and *Simultaneous capacity*. Additionally, there was a negative correlation between BMI and the subscales *Social situation at*

mealtime and *Eating behaviour* in the ASD group indicating the more eating problems, the lower the BMI.

Table 3. *Subscales and example items of the SWEAA, complete instrument in Appendix*

Subscales	Example items
A. Perception (11 items)	A2. I am over sensitive to certain flavours.
B. Motor control (7 items)	B1. I find it difficult to chew.
C. Purchase of food (3 items)	C2. My food must be of a certain brand.
D. Eating behaviour (6 items)	D4. I only eat a limited menu, maximum of 10 dishes.
E. Mealtime surroundings (11 items)	E3. I have certain rituals around meal.
F. Social situation at mealtime (10 items)	F6. I look down at my food most of the time during the meal.
G. Other behaviour associated with disturbed eating (8 items)	G1. I induce vomiting after meals.
H. Hunger/satiety (2 items)	H1. I feel when I am hungry.
Single items	
I. Simultaneous capacity	I1. I find it difficult to do two things simultaneously during a meal, e.g. chewing and cutting the food.
J. Pica	J1. I eat things that others consider inedible (e.g. mortar or soil).

Table 4. *Item scaling tests of the SWEAA: item-internal consistency, item-discriminant and convergent validity and reliability*

Scale	Item convergent validity[a]	Item discriminant validity[b]	Scaling success[c]	Scaling correct[d]	Reliability Cronbach's α
A	0.37-0.69	0.01-0.60	68/77(88%)	77/77(100%)	0.87
B	0.44-0.61	0.01-0.56	46/49(94%)	49/49(100%)	0.81
C	0.62-0.80	0.02-0.65	21/21(100%)	21/21(100%)	0.81
D	0.34-0.65	0.05-0.64	36/42(86%)	41/42(98%)	0.76
E	0.47-0.87	0.05-0.67	71/77(92%)	77/77(100%)	0.92
F	0.44-0.79	0.01-0.50	69/70(99%)	70/70(100%)	0.87
G	0.41-0.86	0.01-0.53	56/56(100%)	56/56(100%)	0.88
H	0.57-0.57	0.01-0.31	14/14(100%)	14/14(100%)	0.73

[a] Item Convergent validity = Item Internal Consistency = Correlation between each item and its scale corrected for overlap
[b] Correlations between the items within the subscale, and with other subscales. Range of correlations.
[c] Number of convergent correlations (with own subscale) significantly higher than discriminant correlations (other subscales) / The total number of correlations (in parenthesis, scaling success rate as a percentage).
[d] Number of correlations higher with own subscale than with other, but not significantly higher (in parenthesis, scaling success rate as a percentage).

In order to discriminate between ASD and a healthy comparison group with the SWEAA, two different cut-off scores were produced based on data collected in Study I (83) (complete instructions for scoring can be found in Appendix A of Study IV). The first one, a mean total score, based on the mean of all 60 items (scored 0-4, including a number of reversed items (i.e. B6-B7, F1, F3-F5, F7-F9, H1-H2)) was set to 12 (which gave sensitivity: 0.70, specificity:

0.50) in relation to a 0-100 scale. This score had too low sensitivity to accurately distinguish between ASD and a healthy comparison group, but gives an indication of the overall behaviour incorporating all items.
The other cut-off was based on the mean of the subscales that best distinguished between ASD and a healthy comparison group, i.e. *Social situation at mealtime* and *Simultaneous capacity*. The cut-off score of 10, was chosen based on sensitivity and specificity (0.80 and 0.60, respectively), with the emphasis on sensitivity.

The SWEAA is currently available in English and Swedish and by the end of 2017 translations into the following languages will be completed: German, Portuguese, Norwegian, French and Japanese. The SWEAA is also indexed in the American Psychological Association's online database for psychological measures, the PsycTESTS.

Study II

Using the SCID-I, out of the entire sample (n=228), 18 individuals (7.9%) reported a current or previous ED and the distribution of ED diagnoses can be seen in Table 5 below. EDs were most common in the ASD group where almost 11% had, or had had an ED. BN was the least common ED diagnosis and occurred only among individuals with ASD. The ED gender ratio for the total group was one male to every 2.5 females (males: n=127, EDs: 6 (4.7%); females: n=101, EDs: 12 (11.9%); (p=0.052).

Just over 10% (n=14) of the individuals reported current severely disturbed eating behaviour and another 13% (n=18) current moderately disturbed eating behaviour measured with the EAT. Twelve of the individuals who completed the EAT had a current or previous ED, according to the SCID-I (3 males, 9 females; AN: n=7 (5.1%); female: 5, male: 2; BED: n= 5 (3.6%); female: 4, male: 1). Those with an ED had a mean EAT score of 22.3 (SD 17.13) which was significantly higher compared to those without an ED, 6.39 (SD 7.53) (p=0.001). For the whole group the mean EAT score was 7.77 (SD 9.77) (females: 11.29 (SD 12.64); males: 5.01 (SD 5.14), p=0.273) and for the ESSENCE groups the means were 8.19 (SD 9.94) for ADHD, 6.94 (SD 9.43) for ASD and 7.71 (SD 9.98) for ASD+ADHD. According to the EAT, ADHD eating behaviour was distinguished from ASD by the items "I think about burning calories when I exercise", "I am preoccupied with the thought of having fat on my

body" and "I enjoy trying new rich foods"–all three items were unlikely for the ASD group to engage in.

Table 5. *Eating disorders in individuals with ASD and ADHD*

	ASD GROUP n=74	ADHD GROUP n=109	ASD+ADHD GROUP n=45	TOTAL n=228
AN	5 (6.7%)	2 (1.8%)	1 (2.2%)	8 (3.5%)
BN	2 (2.7%)	0 (0%)	0 (0%)	2 (0.9%)
BED	1 (1.4%)	7 (6.4%)	0 (0%)	8 (3.5%)
TOTAL	8 (10.8%)	9 (8.3%)	1 (2.2%)	18 (7.9%)

Study III

The determined regions of interest (ROIs) pertaining to brain areas associated with theory of mind abilities were bilateral superior temporal cortex (specifically the superior temporal sulcus (STS)), extending into the temporoparietal junction (TPJ) and medial frontal areas. Areas can be seen below in Figure 1.

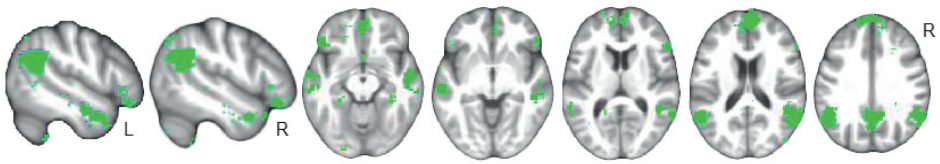

Figure 1. *Regions of interest as defined by a reverse inference meta-analysis based on a Neurosynth search of 140 studies.*

Structural MRI in AN and the age- and gender- matched comparison group showed reduced cortical grey matter volume, bilaterally, in the STS extending into the TPJ (left coordinates: xyz=[-60.00 -55.50 12.00]; right coordinates: xyz=[46.50 -43.50 19.50]) (Figure 2A). For the ASD group, compared to its comparison group, the same reduction was seen in left but not right STS (xyz=[-48.00 -60.00 30.00]) (Figure 2B). None of the patient groups had increased volumes compared to their comparison groups and both the AN and the ASD comparison groups had significantly more grey matter volume than the patient groups (in left TPJ regions (all $p<0.03$)).

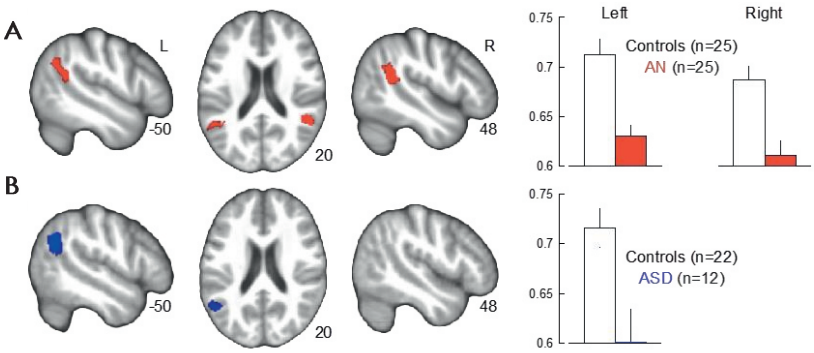

Figure. 2: Grey matter alterations in the AN and the ASD groups.
Grey matter reductions in females with AN and in the matched comparison group (A), and grey matter reductions in females with ASD and their matched comparison group (B).

Furthermore, the left, but not right, TPJ grey matter volume correlated negatively with AQ scores in AN patients (left: r=-0.41, p=0.045, right: r=-0.03, p=0.902). There were no significant correlations between BMI and grey matter volumes in the AN group. Additionally, there were no significant differences regarding grey matter volumes between males with or without ASD in the above-mentioned ROIs (Figure 3).

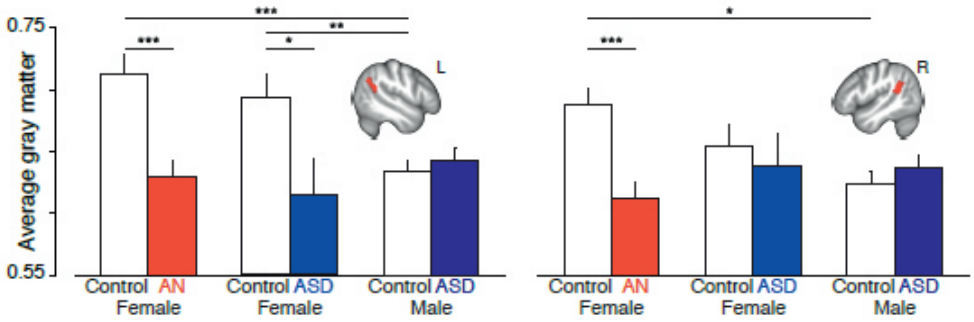

Figure 3. *Average grey matter volumes of left and right superior temporal regions in individuals with AN, ASD and their comparison groups, separated by gender.*

Lastly, the results of the analyses examining whether there was a significant difference between the female ASD group and the AN group compared to their respective comparison groups in the same brain areas (i.e. if the brain area affected in AN was also affected in ASD, and vice versa, hence, the AN and the ASD groups were never compared directly –but only to their respective comparison groups) showed that the same areas seem to be affected in females with AN as in females with ASD. In the AN group significantly reduced grey

matter volumes in the left STS-region (as identified in the ASD group comparison) (p=0.002) (Figure 3) were observed, and females with ASD showed significant reductions of left (p=0.027) but not right (p=0.630) regions (Figure 3) (as identified in the AN group comparison).

Study IV

All groups (AN-C, AN-C-1YR, AN-PR and ASD), except the COMP group, had a mean score above cut-off based on the *total score* as well as based on the *subscale score* on the SWEAA (See Table 6 for mean scores and comparisons for all groups). There were no correlations between BMI and either of the SWEAA scores (total or subscale) for any of the groups. A majority of participants with ASD scored above both types of cut-off on the SWEAA (65% (n=39) on the total score and 81% (n=46) on the subscale based score). No significant gender differences were found for scoring above either cut-off (66% of males with ASD scored above the total score cut-off and 84% scored above the subscale-based cut-off. In females with ASD 74% scored above both cut-offs). For the AN-C group the mean SWEAA total score decreased significantly after one year, while the ASD-specific subscale score did not. The AN-C group scored significantly higher than the ASD group on 5 out of 10 subscales (Purchase of food, Eating behaviour, Mealtime surroundings, Other behaviours associated with disturbed eating, Hunger/satiety) and the total score. At follow-up, the AN-C-1YR group only scored significantly higher on the Purchase of food-subscale compared to the ASD group. The AN-C group scored significantly higher than the COMP group regarding all subscales except Motor control and Pica and these differences remained when comparing the AN-C-1YR group with the COMP group. The same results were observed for the AN-PR group compared to the COMP group i.e. significant differences on the same subscales as for the AN-C and AN-C-1YR groups compared to the COMP group.

Multivariable predictions of AN against ASD found two independent significant items: “If I buy food with someone else, I want to check what goods are purchased” and “I diet even if other people think I am too thin”, this model had an area under the ROC-curve of 0.90 (0.81-0.98). In all three AN-groups (AN-C, AN-C-1YR, AN-PR) both types of mean SWEAA scores (i.e. the one based on the total score and the one based on the mean of two subscales) correlated significantly with AQ, i.e. the higher the results on the SWEAA, the higher the AQ score. For the AN-C group the mean AQ score had significantly decreased at the one-year follow-up (AN-C-1YR).

Table 6. The *SWEAA scores for each subscale, total score and subscale-based score and AQ scores for all groups*

	AN-C n = 36	AN-C-1yr N = 32	Change AN-C to AN-C-1yr	AN-PR n = 23	AN-PR vs. AN-C p-value	AN-C-1yr vs. AN-PR p-value	ASD n = 19	ASD vs. AN-C p-value	ASD vs. AN-C-1yr p-value	ASD vs. AN-PR p-value	COMP n = 30
Perception	34.4***(20.3) 0.0; 70.5	27.8**(19.1) 0.0; 65.9	-4.14 (19.60) (36.36; 50.00 p=0.089	32.6***(19.4) 6.8; 75.0	0.69	0.42	26.4*(19.7) 0.0; 61.4	0.22	0.88	0.31	14.6 (11.4) 0.0; 54.5
Motor control	15.4 (13.0) 0.0; 50.0	13.4(10.6) 0.0; 42.9	-2.31 (10.84) -25.00; 25.00 p=0.20	11.5(11.7) 0.0; 50.0	0.28	0.37	15.4(16.5) 0.0; 67.9	0.72	0.97	0.49	11.7 (8.2) 0.0; 32.1
Purchase of food	59.0***(23.5) 0.0; 100.0	43.8***(24.4) 0.0; 100.0	-14.1 (23.0) -58.3; 41.7 p=0.0015	45.5***(27.2) 0.0; 100.0 (n=22)	0.042	0.88	26.9(28.1) 0.0; 83.3 (n=18)	0.0003	0.027	0.033	20.3 (18.1) 0.0; 58.3
Eating behaviour	41.1***(20.7) 0.0; 87.5	31.9***(17.8) 0.0; 62.5	-7.42 (18.98) -58.33; 33.33 p=0.025	32.0***(19.4) 0.0; 70.8 (n=22)	0.10	0.87	22.9(24.0) 0.0; 80.0	0.0026	0.084	0.10	12.5 (8.6) 0.0; 33.3
Mealtime surroundings	38.2***(21.2) 0.0; 77.3	31.7 **(23.1) 0.0; 77.3	-4.50 (20.26) -34.09; 50.00 p=0.14	33.1***(24.0) 0.0; 84.1	0.34	0.82	26.8***(24.2) 0.0; 88.6	0.030	0.44	0.42	5.76 (5.81) 0.00; 18.18
Social situation at mealtime	31.2***(13.2) 12.5; 65.0	27.3**(14.5) 7.5; 60.0	-3.46 (10.64) -25.00; 17.50 p=0.083	31.0***(13.4) 7.5; 57.5	0.99	0.29	30.4*(23.7) 5.0; 92.5	0.34	0.88	0.45	16.9 (7.3) 2.5; 30.0
Other behaviour associated disturbed eating	18.8***(14.2) 0.0; 59.4	12.6***(14.1) 0.0; 46.9	-5.08 (12.92) -37.50; 31.25 p=0.018	13.2***(15.2) 0.0; 59.4	0.079	0.94	6.93**(15.54) 0.00; 68.75	0.0001	0.087	0.10	1.74 (3.95) 0.00; 17.86
Hunger/Satiety	39.6***(20.4) 0.0; 75.0	33.6***(20.7) 0.0; 87.5	-5.08 (23.52) -50.00; 62.50 p=0.20	45.7***(23.7) 0.0; 100.0	0.48	0.024	27.6*(19.8) 0.0; 75.0	0.029	0.30	0.0083	15.0 (13.7) 0.0; 62.5
Pica	0(0) 0; 0	0(0) 0; 0	0(0) 0; 0	0(0) 0; 0	1.00	1.00	1.32(5.74) 0.00; 25.00	0.18	0.21	0.29	0(0) 0; 0
Simultaneous capacity	23.6***(27.3) 0.0; 100.0	22.7***(27.2) 0.0; 100.0	3.13 (28.93) -75.00; 100.00 p=0.59	21.6***(33.0) 0.0; 100.0	0.45	0.57	13.9*(28.7) 0.0; 100.0 (n=18)	0.078	0.12	0.38	0.833 (4.56) 0; 25
SWEAA total score	32**(13.8) 8; 56	25.6***(13.4) 5; 53	-4.7(11.94) -27.9; 24.2 p=0.001	27.6***(15.3) 5.8; 66.3	0.23	0.73	22.4**(16.2) 2.5; 54.6	0.017	0.29	0.18	10.9(4.9) 1.7; 25
SWEAA subscale score	27***(18.4) 6.3; 72.5	25.0***(17.2) 3.8; 63.8	-0.17(15.1) -43.8; 45.0 p=0.86	26.8***(20.7) 6.3; 78.8 (n = 22)	0.83	0.91	20.4**(15.0) 2.5; 53.8 (n = 18)	0.20	0.38	0.45	8.85(4.7) 1.25; 25
AQ total score	17.6**(8.2) 5; 41 (n=34)	14.1(7.0) 4; 36	-2.93(5.6) -14.0;7 p=0.012	16.9**(8.1) 4; 37(n = 22)	0.79	0.19	n/a	n/a	n/a	n/a	10.71(4.71) 7; 21(n=14)

Values are given as mean(SD)min; max. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ statistically significant difference compared with COMP

DISCUSSION

General discussion of major findings

This thesis comprises four studies of which all are based on pioneering work exploring areas in particular fields that have not previously been investigated; a questionnaire for ASD eating behaviours, EDs in adults with ESSENCE, a possible neurobiological link between AN and ASD, and autistic eating behaviours in AN. Looking at EDs through ASD glasses and vice versa has opened up new pathways that were previously unknown. Some findings were unexpected, including the fact that individuals with current AN scored higher on the SWEAA than individuals with ASD, while some results stood out as significant such as the possible neurobiological link between females with AN and females with ASD (with reduction of the same brain areas involved in social cognition). The findings will be discussed in further detail below.

The fact that individuals with AN did score higher on the SWEAA than the ASD group leads us to believe that in the acute phase of the AN illness the eating and mealtime problems seem to be comprising a very wide array of behaviours while individuals with ASD are more specific and limited in nature of their problems. Furthermore, the AN patients did have a diagnosed ED while among the individuals in the ASD group there was only one (who reported having BN). This discrepancy in terms of current ED diagnoses has most certainly contributed to the higher scores in the AN group.

Another striking result was the fact that the total score on the SWEAA seemed to decrease in the AN-C-1YR group. However, the autism specific subscale-based score remained stable and was at the same level as in those with ASD. This indicates that specific autistic eating behaviours are still present in AN even after one year when, on a group level, the individuals exhibited a significant weight gain. Hence, at follow-up the overall levels of disturbed eating are less whilst the unique autistic eating behaviours remain.

In all, together with the findings of neurobiological similarities in females with ASD, it brings one more piece to the puzzle of AN as a neurodevelopmental disorder as suggested already in the 80's and 90's (1, 99). Furthermore, the findings of autistic eating behaviours in the acute stage of AN as well as at

partial remission, emphasise the notion of autistic traits as a part of AN. Alongside this the results from the AQ give support to the idea of autistic traits as an actual part of the symptomatology of acute AN.

The SWedish Eating Assessment for Autism spectrum disorders (SWEAA)

Eating and mealtime problems are frequent and well-known but overlooked in individuals with ASD. Thanks to the development of the SWEAA it is now possible to detect and explore the scope and the nature of the problem, both in a research context and in clinical settings. As previous instruments (100-104) have not pertained to these specific issues (e.g. not self-report, aimed at individuals with an ID), the SWEAA provides an important contribution to the field. Furthermore, the SWEAA adds knowledge and insight into the specific nature of eating disturbances in each unique patient. The internal consistency analyses showed high values, suggesting overall coherent stable subscales in the SWEAA, which indicate that the instrument measures what it is intended to. Additionally, the instrument also showed an ability to differentiate between the individuals with ASD and matched healthy comparison cases in areas linked to autism symptomatology; e.g. Social situation at mealtime, as identified by logistic regression analysis. Moreover, the data were used to produce two cut-off scores, one based on the whole instrument and intended to give an overall view of all behaviours incorporated in the SWEAA (intended primarily for clinical use), and the second one was based only on the subscales that were best intended to differentiate between those with and without ASD. These two kinds of cut-offs further contribute to the usability of the instrument. The SWEAA is the first instrument providing the possibility to systematically investigate eating and mealtime problems in individuals with ASD and normal intelligence.

Eating disorders and eating disorder symptoms in adults with ASD and/or ADHD

We found an overrepresentation of EDs in adult patients with ESSENCE (specifically with ASD and/or ADHD) compared to the population in general which could indicate susceptibility for EDs and other psychiatric conditions in this particular ESSENCE group (105-107). In addition, the male to female gender ratio in our study was 1:2.5 compared to 1:10 which is considered to be the gender ratio for EDs in the general population, although these estimates usu-

ally are based on the EDs AN, BN and ED not otherwise specified (15, 34, 108). Our group consisted of a number of individuals with BED, an ED with less skewed gender ratio compared with other EDs, which can partly explain why our results are more in line with the gender distribution of BED in the general population. This may suggest that EDs among male patients with ESSENCE occur more often than previously thought (as has been suggested also for males in the general population (36, 37)) and it highlights the importance of investigating these issues, as they can be detrimental if they go undetected. Studies have suggested that men with ASD are more often under- or overweight compared to the general population (109-111) and led to our hypothesis that our participants would belong to these extreme weight groups rather than the normal range BMI. Regarding underweight, this could not be confirmed in our findings, as the majority were normal- or overweight/obese. The individuals with ADHD in our study were prone to having thoughts about calories, exercise, and body fat distribution as opposed to those with ASD. Individuals with ASD displayed, in accordance with a previous study (83), problems in other areas rather than the traditional ED symptoms (rigidity and problems with social situations rather than ED specific issues).

Taken together, individuals with ESSENCE seem to be a group not easily captured by the traditional ED descriptions even though presenting with similar impairments and suffering. The EAT seems to be a relatively good measure when screening for traditional EDs or eating problems in ESSENCE populations. In the present study, the questionnaire identified two out of three of those with EDs as having moderate to severe eating disturbances as opposed to those without EDs. It is important to keep in mind that our data on ED diagnoses also included those with an ED in the past, which makes the instrument perhaps even more suitable to find ongoing active ED problems. However, the EAT was originally developed for AN (112), which could limit the type of problems being illuminated and captured by using the instrument in a group with mixed ED symptomatology.

Grey matter reductions in AN and ASD

The results from the MRI show that AN females share similar focal decrease of cortical grey matter with age-matched females with ASD. Those reductions are, on the other hand, not present in age-matched males with ASD. The literature shows rather puzzling gender differences with inconsistent findings, in men and women, on grey matter alterations in ASD (113-117). Our findings

contribute further to this divided view suggesting that more research is needed to further understand the gender aspect of the disorders. Alongside this the results also give support to the considerable amount of literature on structural brain alterations in AN, such as grey matter reductions in the temporal lobe (118-120). At least according to the findings in the acute state, and in girls, this gives an indication of AN as a possible neurodevelopmental disorder, but it is crucial to investigate if the alterations are purely due to starvation, before drawing further conclusions. Follow-up studies with weight restored AN cases are therefore warranted.

The fact that these deficits, i.e. reduced volumes, in areas linked to social cognition (for AN and ASD the left STS and TPJ), were found in females but not in males, leads us to contemplate what this could mean for the gender perspective of these conditions. It has yet to be investigated what specific structural and functional differences there are between genders in ASD and AN to give further insight into the mechanisms behind a possible neurobiological link between the two conditions. However, it has been suggested that for a girl to develop ASD, more severe brain anomalies are required compared to boys (121).

Autistic eating behaviours in AN

In this first systematic study of autistic eating behaviours in AN, the SWEAA showed unexpectedly high levels of specific autistic eating behaviours, even after partial recovery. The findings reinforce the notion of a link between AN and ASD, also after weight restoration, and inform us that these similarities have to be taken into account during the treatment process in AN (58). The fact that individuals with AN scored higher on the SWEAA than the ASD group leads us to believe that in the acute phase of their illness the eating and mealtime problems seem to be comprising a very wide array of behaviours while individuals with ASD exhibit a more specific and limited repertoire of eating and mealtime problems. Moreover, on a group level, the AN group had significantly gained weight at follow-up and despite this their eating behaviours looked very much like the ASD group. This adds evidence for a behavioural overlap between the two conditions (3, 5, 49, 56, 122, 123).

Although the AN groups showed higher scores than expected on the SWEAA compared to the ASD group, the items may have different meanings for the individuals with AN and ASD respectively. The most striking differences be-

tween the AN and the ASD group, in terms of SWEAA items, were involving control of purchases and dieting (where AN had higher scores than ASD). These are distinct features of AN but can, due to rigidity, also be seen in ASD. Furthermore, the patients with AN did have a diagnosed ED while in the ASD group there was only one with a reported ED. Moreover, eating habits, such as only eating food of certain colours (124), is well-known in individuals with ASD and other patients with selective eating only, but surprisingly it turned out to be even more common in the individuals with AN. Possibly this could be assigned to the obsessive-compulsive behaviours in AN and give a hint of AN traits that reinforce the illness and make it difficult to defeat.

Even at follow-up (AN-C-1YR) the patients with AN presented with disturbed eating behaviours compared to healthy individuals. This was also true for the partially recovered individuals (AN-PR). This is in accordance with the clinical impression of ED behaviours, such as strict control and adherence to routines, which require considerable effort and time to change. What is surprising though, is the finding that perception was still highly affected even at partial remission and after one year. Distorted visual perception has been thoroughly scrutinised in relation to AN (125). Our findings suggest that other aspects of perception usually linked to ASD (e.g. smell, taste, sound) also need to be investigated in AN to fully understand the meaning of these results.

Due to the difficulty of correctly assessing ASD in underweight individuals with AN, this is a unique study, prospectively following the same AN patients looking at autistic traits in terms of AQ scores (the scores had significantly decreased at follow-up). Hence, it is an important contribution to the field as the lack of these types of studies has been illuminated in a recent review (126). In fact this is a first attempt to shed more light on the presence of autistic traits in AN, during starvation as well as after weight restoration.

Methodological discussion

This thesis is based on a deductive reasoning with clear hypotheses formed at the start of each study. As it is pioneering work with new findings in all of the projects, they would all benefit from being replicated. Throughout the thesis all instruments were well established, valid and reliable both for clinical and research purposes. Study I was a validation study in itself. Careful consideration was taken into planning and executing the validation process to be as thorough as possible. In Study III, a sample of ASD and matched com-

parison individuals were used from a large database of MRI-data to compare with our own original data. This is a common way of sharing available data in MRI-studies. The diagnostic methods of the ASD sample in Study III was, for the participating centres, in most cases the golden standard instruments (such as the ADI-R and the ADOS), however we were not able to control further how diagnoses were assigned.

All samples were clinical (except the healthy comparison groups). The assessments were all cross-sectional except for one of the samples in Study IV, the AN-C group, which was followed up after one year. Because of the nature of the samples, the results have limited generalisability to the population as a whole but give important information on these specific diagnostic groups. At first sight it might seem questionable to have included both the AN-C-1YR group and the AN-PR group in Study IV. Discussions regarding this study design were based upon two factors; firstly, the uncertainty of how many out of the individuals of the AN-C group that would be willing to participate at a 1-year follow-up and secondly, the uncertainty of what level of recovery the individuals would have after one year. Based on this it was decided to include a group of partially recovered individuals (all with BMI $\geq$18.5) in order to ensure that we had the possibility to explore autistic eating behaviours in partially recovered patients as well. In hindsight, the results revealed that the AN-C-1YR and the AN-PR groups were very similar in terms of their autistic eating behaviours. No significant differences were found on the SWEEA subscales between the two groups, apart from the Hunger/satiety-subscale, and both groups differed significantly from the comparison individuals on the same subscales, as well. Both groups had similar results on score based on the autism specific subscales, this even though the AN-PR group had higher BMI than the AN-C-1YR group. The AN-PR group had significantly more autistic traits (AQ scores) compared to the COMP group which leads us to speculate that autistic traits seem to remain even though body weight has normalised. These results need to be taken into account and implemented in clinical work by for example following up AN patients during a longer period of time, since ASD related difficulties seem to remain even after weight gain.

In Study I, the response rate for the clinical group was low and due to the psychopathology of ASD, it might have been more suitable to use face-to-face interviews. On the other hand, there is a possibility that it might have been even more difficult to recruit had it been interview-based. To raise response rates reminders were used which has been suggested as the most effective way (127) and proved to yield more responses. Care was also taken to maxim-

ise response rates by creating an appealing instrument (e.g. by performing a pilot study to decrease misunderstandings and ambiguous phrasing) (128).

Strengths and limitations

An obvious limitation for most of the studies in this thesis is the relatively small sample sizes. However, power calculations were made at the start to find the minimum number of participants required for the data to be useful, and recruitment of participants was ongoing to reach these levels. Furthermore, non-parametric statistical methods were used in light of this, and due to the clinical nature of the samples (which cannot be considered normally distributed).

A consideration that occurred during the development of the SWEAA was the lack of possibility to validate the instrument against other similar ones i.e. to assess concurrent validity. As there were none at the time (and still is not), this was not possible. A search was performed and similar measures were either for younger children, based on parent report, such as the Brief Autism Mealtime Behaviour Inventory (BAMBI) (100) or not aimed specifically at eating disturbances or for ASD, like the Child Eating Behaviour Questionnaire (101), and the Parent Mealtime Action Scale (102). Some measurements were found to be aimed at patients with ID and intended for adults, for example the Screening Tool for Feeding Problems (STEP) (103) and the Diagnostic Assessment of the Severely Handicapped-II (DASH-II) (104) which is an overall measure including a subscale for "eating". It could have been an alternative to validate against any of these scales for individuals with ID –although one has to consider that our participants were of normal intelligence so that would not be an optimal solution either. However, to further strengthen the psychometric values of the SWEAA in the future, a validation against any other instrument that emerges would be preferable. In Study IV, no ED instrument was used (patients were already diagnosed with AN). In hindsight, based on the results, it would have been informative to validate the SWEAA against the Eating Disorder Inventory (EDI) (129) to see if eating pathology correlated with the SWEAA scores, i.e. did the individuals with high levels of ED symptoms also exhibit the highest scores on the SWEAA.

The fact that SWEAA was initially web-based can be seen both as an advantage and as a disadvantage. Since this was the format of choice, the pro's outweighed the con's initially. It was believed that with individuals with ASD

as the target group a web-based instrument would appeal to more participants and allow for answers that are more honest. A paper-version would possibly generate fewer answers as it requires more activity for the respondent for example by posting it in a mail box rather than just submitting electronically at home. A direct disadvantage is that there is no one for the respondent to ask if they have questions, which could lead to faulty answers instead. For this particular reason, an attempt to omit ambiguous or offending phrasing was made by first testing the questionnaire in a smaller group of participants. Moreover, it has been shown that response rates are similar through any means of distribution (i.e. post, fax, web-based etc.) (130) and that web-based self-report measures could be preferable when targeting certain issues (including medical) (131).

In Study I there were limitations concerning the participants. Firstly, there was a large number of non-responders. We did however investigate these individuals in terms of demographic characteristics and found no differences compared to the responders. Nonetheless there is never a certain way of knowing, if these were the individuals with less or more problems in the area of study. Secondly, there was a significant difference in educational level between patients and the comparison group in Study I. This was not seen as a major limitation as we knew that both groups had normal intelligence and the difference in educational level was most certainly due to the fact that, healthy individuals would to a larger extent attend higher education than any group of patients with a psychiatric disability. In Study II no comparison group was available to compare the results. In light of this it is necessary to view the results as preliminary and representing this clinical group only. There is a limitation regarding sampling in Study III. Data generated from the AN and ASD groups came from different studies and we were not able to compare these two groups directly. The highly similar results in both groups compared to their respective comparison groups do however suggest that the results can be used for comparison. Furthermore, we had no possibility to control for BMI in the ASD group. This might pose as a problem as ED symptomatology is overrepresented in adults with ESSENCE (132), nevertheless there were no such comorbidities reported in the ABIDE records.

There are some strengths and limitations concerning choices of instruments. Firstly, a major advantage is that all measures used are well established in psychiatric research as well as in clinical settings. The SCID-I and II, the AQ, the Wechsler-scales and the BDI are used widely throughout the field today. A disadvantage of the results in Study II is that the EAT has been replaced

with other measures such as the more extensive EDI which may make our results a little less comprehensible in terms of comparisons to other studies.

Clinical implications

Based on the overall results of this thesis it seems like there are many features in common between AN and ASD, features that could be a strength as well as a hindering factor for both patient groups –nevertheless inevitable and highly important to address. It is no longer accurate to treat one of these conditions without knowledge of the other. At present, most ED units treat the majority of patients according to a similar manual and it is only when conventional treatment is failing one turns to examining obstructing factors, which could be a comorbid disorder like ASD or ADHD.

There is a potential to save time and energy for both patients and professionals with implementing screening tools for ADHD and ASD in ED units. It is always arguable that a person with low weight will have reduced cognitive capabilities so this kind of screening would of course have to be evaluated carefully and data collected should be based on premorbid traits and behaviours.

To deal with the autistic traits in individuals with AN it seems reasonable to learn from autism pedagogics. Using CBT or cognitive remediation therapy (CRT) (133) in AN is already a fairly concrete approach but refining these methods would be an advantage in all cases with acute AN and in those AN cases with comorbid ASD. However, it would be crucial to add social training as an element of treatment in AN. It is essential to take into account that the clinical work is *not* over with the AN patients as soon as normal body weight is maintained. Based on results in this thesis it is apparent that specific autistic eating behaviours and mindsets remain even after weight gain in AN. Treatment needs to carry on, not only focusing on bodyweight and working with AN thoughts, but also taking autistic traits into account.

Reversely, for individuals with ASD and a very low weight, including individuals with comorbid AN, treatment might be more about trying new foods, changing special interests, setting specific medically sound goals (e.g. a precise weight goal). This kind of treatment, a more pragmatic treatment approach, might be more comprehensible to patients with ASD rather than for example focusing on emotions, talking about anxiety, motivation etc.

The SWEAA has paved the way into deeper knowledge about previously unknown areas. We have learnt that there are other disturbed eating behaviours in AN that are clinically not typically measured -the SWEAA has been an eye-opener giving a wider perspective of AN symptomatology. There is a risk that we are missing important information on patients when mainly focusing on traditional ED specific questions in ED clinics.

Thanks to the SWEAA we now know what eating behaviours distinguish individuals with ASD and normal intelligence from healthy comparison cases as well as from individuals with traditional EDs. The SWEAA can be used clinically to get a qualitative picture of which eating and mealtime problems are most troublesome to the individual. The SWEAA covers a large number of areas from sensoric difficulties to social situations and it is the first systematic tool in order to ask the individuals themselves about these issues. This information has previously only been based on clinical examination or collateral information.

For parents of individuals with ASD, the eating and mealtime problems are in many cases the hardest issue to deal with in everyday life. The SWEAA offers the possibility to scan a wide array of problems to get an idea of the nature of the patient's eating and mealtime behaviours. Clinically the SWEAA provides an instrument that is based on both clinical knowledge and scientific literature. By switching perspectives we have had the possibility to examine how autistic the eating behaviours in AN are, and how the alleged connection between AN and ASD really relate to each other. The SWEAA is a tool that can be helpful for clinicians in order to establish whether the patient's behaviours resemble that of ASD or that of healthy comparison persons, and target treatment accordingly. Although the research on the overlap of these conditions has increased, knowledge is still scarce. This could potentially contribute to the fact that all patients initially are treated like traditional ED patients until conventional treatment fails and the multi-professional team is forced to rethink. In these cases, the SWEAA could add information on possible autistic eating behaviours.

EDs in adults with ESSENCE have not previously been fully acknowledged. Furthermore, there seems to be a larger proportion of men within this group than in the general population. This is important to acknowledge and keep in mind when meeting men with ESSENCE as eating disturbances can be a debilitating factor also for adults in everyday life. In the adult ESSENCE group AN and BED were the most common EDs. Thus, it can be useful to screen for

EDs since there seems to be more EDs than expected in adult individuals with ESSENCE.

With the new knowledge of a neurobiological link between AN and ASD, based on the reduction in grey matter volumes in the social cognition areas of the brain, we are given indications that it might be helpful to include social training in some form in AN treatment. For example we could possibly be one step closer to develop working treatment approaches for the severe and hard-to-treat subgroup of AN, with longstanding illness duration.

CONCLUSIONS and IMPLICATIONS for RESEARCH

To conclude, the SWEAA is a valid and reliable instrument for detecting disturbed eating behaviours in individuals with ASD and normal intelligence. EDs appear to be overrepresented in adults with ESSENCE with a more equal gender distribution compared to the general population. Females with AN and females with ASD share the same alterations -reduced cortical grey matter volumes- in brain areas involved in social cognition. Moreover, autistic traits are connected to these reductions in females with AN. Furthermore, autistic eating behaviours seem to be frequent in AN, even after weight restoration, and this indicates that autistic traits in AN also involve the eating behaviours.

Taken together, the results from all studies in this thesis pave the road towards unexplored areas of the different fields. Future research could, based on the findings of the current thesis, focus on making a short version of the SWEAA in order to provide a tool for quick screening of autistic eating behaviours in ASD and other diagnostic groups. Further validation studies could incorporate items pertaining to autistic eating behaviours as a subscale in existing ED instruments. Additionally, since we have highlighted autistic eating behaviours in individuals with ASD and AN, it would be interesting to implement the SWEAA in other groups of psychiatric disorders including ADHD, BN, and BED. It is also crucial that our findings are replicated, especially the high levels of autistic eating behaviours in individuals with current and partially recovered AN. These findings indicate new aspects of the eating behaviours in traditional EDs and call for further exploration, e.g. looking at individuals who are fully recovered from AN. Regarding our MRI findings a highly interesting perspective for future research would be to follow up the AN individuals after remission to further explore the neurobiological and neurodevelopmental facets.

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APPENDIX

The SWedish Eating Assessment for Autism spectrum disorders (SWEAA)

Code: ☐☐☐☐☐☐ **Today's date:** ☐☐☐☐☐☐

Age: ☐☐

Tick one option per line:

☐ Girl/woman ☐ Boy/man
☐ I live alone ☐ I live together with other people

I go to: ☐ junior high school ☐ high school ☐ folk high school ☐ college/university ☐ do not study

Tick one or multiple options:

I have completed: ☐ middle school ☐ junior high school ☐ high school ☐ folk high school ☐ college/university

Tick the option that is most appropriate:

A	never correct	seldom correct	sometimes correct	usually correct	always correct
1. I am plagued by food smells, e.g. I must leave the room or the meal due to the smell	☐	☐	☐	☐	☐
2. I am over sensitive to certain flavours	☐	☐	☐	☐	☐
3. I find it difficult to tell what the food tastes like	☐	☐	☐	☐	☐
4. I am sensitive to the food's special texture	☐	☐	☐	☐	☐
5. I prefer that the food has a smooth texture, as e.g. puree	☐	☐	☐	☐	☐
6. I find it difficult to eat dishes where several ingredients are mixed, e.g. stews	☐	☐	☐	☐	☐
7. I am disturbed by the sound of when I chew certain food, e.g. Swedish cracker	☐	☐	☐	☐	☐
8. I am disturbed by the sounds others make when eating	☐	☐	☐	☐	☐
9. I am disturbed by other people talking while I am eating	☐	☐	☐	☐	☐
10. It is important that the food is sorted on the plate	☐	☐	☐	☐	☐
11. I eat the food on the plate in a certain order (e.g. first meat, then potatoes)	☐	☐	☐	☐	☐

The SWedish Eating Assessment for Autism spectrum disorders (SWEAA)

B	never correct	seldom correct	sometimes correct	usually correct	always correct
1. I find it difficult to chew	☐	☐	☐	☐	☐
2. I am drooling during the meal	☐	☐	☐	☐	☐
3. I get food around the mouth while I am eating	☐	☐	☐	☐	☐
4. I find it difficult to swallow	☐	☐	☐	☐	☐
5. I spill when I eat	☐	☐	☐	☐	☐
6. I have good table manners	☐	☐	☐	☐	☐
7. I drink out of a glass without spilling	☐	☐	☐	☐	☐
C					
1. I buy groceries from a special supermarket/business chain	☐	☐	☐	☐	☐
2. My food must be of a certain brand	☐	☐	☐	☐	☐
3. If I buy food with someone else, I want to check what goods are purchased	☐	☐	☐	☐	☐
D					
1. I prefer certain food depending on the colour of the food	☐	☐	☐	☐	☐
2. I eat the same food every day	☐	☐	☐	☐	☐
3. I avoid trying new food/new dishes	☐	☐	☐	☐	☐
4. I only eat a limited menu, maximum of 10 dishes	☐	☐	☐	☐	☐
5. I eat smaller amounts of food than others	☐	☐	☐	☐	☐
6. I drink excessive fluids	☐	☐	☐	☐	☐
E					
1. I require the glass, plate and cutlery to be placed in a certain way, different from standard table setting	☐	☐	☐	☐	☐
2. I find it difficult to change seats at the dinner table	☐	☐	☐	☐	☐
3. I have certain rituals around meal	☐	☐	☐	☐	☐

The SWedish Eating Assessment for Autism spectrum disorders (SWEAA)

	never correct	seldom correct	sometimes correct	usually correct	always correct
4. I get outbursts at the dinner table	☐	☐	☐	☐	☐
5. I whine at the dinner table	☐	☐	☐	☐	☐
6. I find it difficult to eat at school/ workplace/activity centre or similar	☐	☐	☐	☐	☐
7. I find it difficult to eat with relatives	☐	☐	☐	☐	☐
8. I find it difficult to eat with friends	☐	☐	☐	☐	☐
9. I find it difficult to eat in the café	☐	☐	☐	☐	☐
10. I find it difficult to eat in a restaurant	☐	☐	☐	☐	☐
11. I find it difficult to eat when I am abroad	☐	☐	☐	☐	☐
F					
1. I eat together with the one/ones I live with	☐	☐	☐	☐	☐
2. I eat in my bedroom	☐	☐	☐	☐	☐
3. I adapt my behaviour to others who sit around the table (e.g. table manners, conversation)	☐	☐	☐	☐	☐
4. I like company around a meal	☐	☐	☐	☐	☐
5. I talk during the meal	☐	☐	☐	☐	☐
6. I look down at my food most of the time during the meal	☐	☐	☐	☐	☐
7. I say if I think the food is good (when I am invited for a meal)	☐	☐	☐	☐	☐
8. I thank people for the food (when I have been invited for a meal)	☐	☐	☐	☐	☐
9. I eat with a knife and fork	☐	☐	☐	☐	☐
10. I leave the table as soon as the food is eaten	☐	☐	☐	☐	☐

The SWedish Eating Assessment for Autism spectrum disorders (SWEAA)

G	never correct	seldom correct	sometimes correct	usually correct	always correct
1. I induce vomiting after meals	☐	☐	☐	☐	☐
2. I use diuretics	☐	☐	☐	☐	☐
3. I use diet pills	☐	☐	☐	☐	☐
4. I diet even if other people think I am too thin	☐	☐	☐	☐	☐
5. I fast	☐	☐	☐	☐	☐
6. I am replacing meals with nutritional drinks/powder	☐	☐	☐	☐	☐
7. It is important that one person (the same person) prepares my food	☐	☐	☐	☐	☐
8. I refuse to eat	☐	☐	☐	☐	☐
H					
1. I feel when I am hungry	☐	☐	☐	☐	☐
2. I feel when I am full	☐	☐	☐	☐	☐
I					
1. I find it difficult to do two things simultaneously during a meal, e.g. chewing and cutting the food	☐	☐	☐	☐	☐
J					
1. I eat things that others consider inedible (e.g. mortar or soil)	☐	☐	☐	☐	☐
K					
1. I prefer to do things with others rather than on my own	☐	☐	☐	☐	☐
2. I prefer to do things the same way over and over again	☐	☐	☐	☐	☐
3. I tend to notice details that others do not	☐	☐	☐	☐	☐
4. I frequently find that I don't know how to keep a conversation going	☐	☐	☐	☐	☐
5. I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.)	☐	☐	☐	☐	☐

L

L1. I am on a diet because of the following illness:	Yes	No
a) Diabetes type I	☐	☐
b) Diabetes type II	☐	☐
c) Gluten intolerance	☐	☐
d) Lactose intolerance	☐	☐
e) Other food intolerance	☐	☐
f) Other, what:		

L2. I am on a diet because I am:	Yes	No
a) Overweight	☐	☐
b) Underweight	☐	☐

L3. I avoid eating:	Yes	No
a) Dairy products	☐	☐
b) Beef and pork (e.g. steaks, hamburgers or pork chops)	☐	☐
c) Poultry (e.g. chicken)	☐	☐
d) Fish and seafood	☐	☐
e) Vegetables	☐	☐
f) Fruit	☐	☐
g) Other, what:		

M

M1. I have received any of the following diagnoses	Yes	No
a) ADHD	☐	☐
b) Asperger's syndrome	☐	☐
c) Autism/autistic syndrome	☐	☐

	Yes	No
d) Autistic like condition/ atypical autism	☐	☐
e) Tourette's syndrome	☐	☐
f) Obsessive compulsive disorder (OCD)	☐	☐
g) Anorexia nervosa	☐	☐
h) Bulimia nervosa	☐	☐
i) Other eating disorder e.g. binge eating disorder	☐	☐
j) Depression	☐	☐
k) Other psychiatric disorder, what:		
l) Hyperthyroidism	☐	☐
m) Diabetes type I	☐	☐
n) Diabetes type II	☐	☐
o) Gluten intolerance	☐	☐
p) Lactose intolerance	☐	☐
q) Other food intolerance, what:		
r) Bowel disease, what:		

M2. I am treated with any of the following medications	Yes	No
a) Growth hormone	☐	☐
b) "Precocious puberty prevention" (e.g. Decapeptyl, Suprefact, Procren)	☐	☐
c) "Antidepressants" (e.g. Fluoxetine, Prozac, Sertraline, Zoloft, Citalopram, Cipramil)	☐	☐
d) "ADHD-medication" (e.g. Concerta, Ritalin or Strattera)	☐	☐
e) Neuroleptics (e.g. Risperidone, Risperdal, Olanzapine, Zyprexa, Seroquel, Abilify)	☐	☐
f) Other, what:		