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2 Summary in Danish

Dette forskningsprojekt undersøgte social funktion hos unge mennesker, der har eller har haft anoreksi (AN). Social funktion spiller formentlig en rolle både for livskvalitet, for respons på behandling og for udkomme af AN. Studiets formål var at øge vores forståelse for den adfærdsmæssige manifestation af de evner, der er involveret i social funktion hos unge med AN. Yderligere var formålet at undersøge de kognitive elementer, som social funktion er baseret på. De kognitive elementer, som undersøgtes var social kognition, neurokognition og lugtesans. Desuden kombineredes kliniske, eksperimentelle og observatør-baserede metoder, og studiet sammenlignede test-præstation, naturalistisk eksperimentel observation og beskrivelse fra forældre om den unges funktionsniveau i hverdagslivet. Vi inkluderede unge, som for nyligt havde debuteret med deres første episode med AN, unge som var blevet raske af AN gennem i barndommen eller ungdommen, og kontrolpersoner. Hypotesen var, at nyligt debuterede deltagere med AN eller deltagere der var blevet raske af AN ville udvise nedsat evne til social funktion, og desuden nedsatte evner i social kognition og neurokognition. Den første del af hypotesen blev bekræftet, idet vi fandt vanskeligheder ved social funktion hos begge de grupper, der havde eller havde haft AN, på trods af at potentielle deltagere, som desuden havde en autisme spektrum lidelse, omhyggeligt var blevet ekskluderet. Yderligere fandt vi, at dem, der nu var blevet raske af AN præsterede lidt ringere i enkelte aspekter af social kognition. Derimod præsterede de på samme niveau som kontrolpersonerne i de fleste social-kognitive funktioner og i alle de undersøgte neurokognitive funktioner. Deltagere med nuværende AN udviste normal funktion på både alle social-kognitive og neurokognitive områder. Vi fandt, at de unge med nuværende eller tidligere AN havde en højere sensitivitet overfor dufte. Vi viste desuden, at de vanskeligheder ved social funktion, som vi fandt i begge de kliniske grupper, ikke var associeret med social kognition, med neurokognition, eller med lugtesans. Vanskelighederne ved social funktion kunne heller ikke forklares ved symptomer på ængstelighed eller depression. Da studiets design er et tværsnits-studium, er det ikke muligt at drage endelige konklusioner om, hvorvidt vanskelighederne ved social funktion er udtryk for en forbigående tilstand eller afspejler varige træk hos den enkelte. Dog er der god grund til at vurdere sådanne vanskeligheder i klinisk praksis, og behandlingseffekten vil måske forbedres, hvis den suppleres med strategier til at forbedre patienters sociale funktion.

3 Summary in English

The present study investigated social function in young individuals affected by anorexia nervosa (AN). Social function may play a role in quality of life, treatment response, and outcome of AN. The study's aim was to enhance our understanding of the behavioral manifestation of social function capacities in young persons with AN, and to supplement this with an investigation of cognitive components underpinning social function. The cognitive components that were investigated were social cognition, neurocognition, and olfaction. Moreover, the study combined clinical, experimental, and observer-based methods, and compared test performance, naturalistic experimental observation, and reports from parents concerning the young person´s functioning in everyday life. We included young persons with recent onset of their first-episode of AN, young persons recovered from AN during childhood or adolescence, and control participants. We hypothesized that participants with first-episode AN or recovered from AN would display deficits in social function as well as social cognition and neurocognition. Confirming the hypothesis, we found that both groups displayed impairments in social function, even when individuals with comorbid autism spectrum disorder were carefully excluded. We also documented that those recovered were less competent in a few aspects of social cognition. However, the recovered group displayed normal performance on most social cognitive and all neurocognitive tasks. The first-episode AN group showed normal performance across these tasks. Moreover, young individuals with AN or recovered from AN had superior olfactory sensitivity. We documented that the impairments of social function in the clinical groups neither were associated with social cognition, with neurocognition, nor with olfaction, and the impairments were not explained by symptoms of anxiety and depression. The study´s cross-sectional design prohibits firm conclusions regarding the state or trait nature of social function deficit. However, assessment for such impairment in clinical practice is warranted, and treatment may benefit from including strategies to enhance social function.

4 Introduction

4.1 Background and rationale of the present thesis

4.1.1 Anorexia nervosa in adolescents and young adults

"If social life is a jigsaw puzzle, I´m the piece not fitting the gaps," said a 16-year old girl with anorexia nervosa (AN) during a clinical interview for the present study. She was alluding to the struggle and sense of alienation in social interaction often described in the AN literature.[1,2]

Anorexia nervosa is a serious psychiatric disorder with dire consequences for the individual´s somatic and psychological health. Core symptoms are weight loss due to severely restricted eating, possibly in combination with other weight-reducing methods, a disturbed body image with feeling of fatness and fear of weight gain accompanied by exaggerated concerns over weight, shape or control over eating.[3,4] The symptom presentation for adults and younger individuals is basically the same,[5] with the exceptions that the psychological symptoms may be less verbally expressed, and lack of expected growth may precede or replace weight loss in children.[6]

Studies focusing on AN in adolescence and early adulthood are important for several reasons. First, age of onset have decreased during the last decades,[7] and more than half of all patients treated for AN in psychiatric services in Denmark during 2015 were 18 years old or younger.[8] Second, while family-based treatment is the first line of treatment for adolescent AN and shows promising results, [9,10] there is nonetheless a substantial subgroup of non-responders, and they are at risk for a chronic and debilitating course of illness.[11,12]

4.1.2 Reasons for studying social function in young individuals with AN

Studies focusing specifically on social function in young individuals with AN are important for several reasons. Social capabilities undergo a major development during adolescence,[13–15] and the impact of undernourishment on the developing brain may differ from its effect in adults.[16] Further, adolescents are vulnerable to the impact of social isolation, anxiety, and depression, which often accompany AN.[17] Gillberg and Råstam were the first researchers to point out the relevance of social function in understanding individuals with anorexia nervosa by documenting elevated autistic traits.[18,19] Furthermore, current models of vulnerability to and maintenance of AN integrate social function difficulties (see Chapter 4.2), and they are targeted in a growing body of research. The present study aims to add to these findings by investigating social function in AN-affected young

individuals. The term 'social function' is a broad and loosely defined construct, which I will use in the following to cover adaptive social interaction and socio-emotional reciprocity.[20] Social function thus encompasses social behavior, which relies on a broad range of capacities, both cognitive and emotional. The focus of the present study is to enhance our understanding of the behavioral manifestation of these social capacities. Thus, the present study investigates social function by assessing socio-emotional reciprocity as manifested behaviorally, as well as its cognitive underpinnings, by measuring social cognition and neurocognition. The study further combines clinical, experimental, and observer-based methods.

The focus of the introduction is first to introduce three theoretical models of AN which outline a role of social function in AN, and secondly to review the existing empirical literature on social function in young individuals with AN and in recovered individuals. Finally, the introduction presents a few specific cognitive domains, which we included as predictors in the present study to further characterize changes in social function in young individuals: social cognition, neurocognition, and olfaction.

4.2 Social function in current models of AN

In light of the modest success rates of available treatments,[21] models of the development and maintenance of AN are central starting points to identify avenues for more effective interventions. The following section briefly and in a cursury manner presents three models of AN with an emphasis on how they may provide a framework for understanding social function in AN. The models emphasize different perspectives on and assign different roles to impairment of social function in relation to AN.

4.2.1 The neurodevelopmental model of AN

Gillberg et al. [19] found that individuals with a history of AN in adolescence had elevated rates of autism spectrum disorder (ASD). These observations have led to the suggestion that AN may be a neurodevelopmental disorder, possibly a female version of ASD.[18,19,22] Following up on that hypothesis, Zucker et al.[23] reviewed the evidence supporting phenotypic similarities between ASD and AN, and proposed that individuals with AN are "*systemizers of social information*" by referring to the detail-oriented processing style typical of ASD in combination with a strong desire to be socially acceptable. Several studies have demonstrated elevated autistic features in adult AN populations.[22,24] Furthermore, elevated rates of ASD in adult eating disorder populations have been documented.[25] ASD is marked by changes in communication and social interaction along with

rigidity or stereotypies of behavior, manifested early in development.[3,4] Along the same lines, inflexibility, weak central coherence, and impaired social cognition have been documented in many studies of adults with AN.[26–28] Consequently, cognitive inflexibility, weak central coherence, and social cognitive impairment have been suggested as possible endophenotypes for AN,[29–31] thus focusing on the cognitive aspects of similarities with ASD. This possibility has gained support from a study showing similar profiles in sisters of individuals with AN,[31] and in offspring of mothers with a history of eating disorder.[32] Observations like these inspired the development of new interventions such as Cognitive Remediation Therapy (CRT), which targets cognitive flexibility and central coherence.[33]

Most studies supporting the neurodevelopmental hypothesis have focused on adults with AN, with the notable exception of the longitudinal study mentioned above.[34] However, other lines of evidence did not confirm that young persons with a short duration of AN display elevated rates of ASD,[35] or reduced flexibility,[36,37] weak central coherence,[38] or deficits of social cognition.[39] Based on the existing evidence, it is thus not clear whether the neuropsychological deficits documented in adults with AN are already present from the beginning of the disorder. Recent studies examining young individuals with AN suggest that this may not be the case, but the evidence is scarce and the paucity of longitudinal studies has hampered any firm conclusions to date.

Moreover, the overlap between AN and ASD appears to be non-specific on an epidemiological level, as the risk for comorbid ASD is similar to the risk for comorbid depression or any psychiatric disorder in individuals with AN.[40]

4.2.2 The social-emotional maintenance model of AN

This model posits an interaction between intrapersonal and interpersonal factors, reinforced by the effects of starvation, in maintaining AN.[41,42] The model accounts for the observation that recovery becomes less likely with illness duration, and it proposes a multi-faceted treatment approach, not focusing solely on nutritional rehabilitation. The intrapersonal factors comprise traits associated with obsessive-compulsive personality, e.g. perfectionism, cognitive rigidity, and emotional avoidance. The interpersonal factors cover maladaptive interaction between the patient and close others, which may be either overly hostile or overly accommodating, both of which reinforce AN behaviors.[43,44]

In the initial formulation of the model the role of pro-anorectic beliefs in forming a vicious circle

was emphasized together with the effect of a high level of expressed emotions.[41] In the updated formulation of the model, however, the authors emphasized the role of deficits of cognition in AN, such as inflexibility and exaggerated attention to detail, and deficits in social cognition, such as attention to threat, and finally reduced Theory of Mind (ToM) and alexithymia.[42] The updated formulation of the social-emotional maintenance model thus takes into account the recent advances in evidence of cognitive style in individuals AN, and the model presents an integrative perspective. In an empirical exploration of the model, an inflexible cognitive style and social-emotional difficulties emerged as two uncorrelated factors, suggesting that they may represent independent pathways to maintenance of AN.[45] This opens the possibility that observed cognitive deficits in AN per se do account for interpersonal difficulties, and that emotional and personality factors are other important aspects.

4.2.3 The pathological fear model of AN

This model views AN as primarily a disorder of emotional processing driven by mechanisms similar to anxiety disorders; a greater tendency for fear-based learning, rapid fear conditioning and encapsulation, and prolonged resistance to fear extinction, in which weight loss and rigid and compulsive behaviors reinforce and maintain the anxious mood.[46] The model is corroborated by reports of hyper-sensitivity to emotional stimuli,[47] and alteration of serotonin function in adults with AN.[48]

Furthermore, social anxiety is highly prevalent in AN,[49] core symptoms such as overestimation of body size in adults with AN are associated with anxiety,[50] and higher self-reported anxiety predicted lower socio-emotional processing in a sample of adults with AN.[51] The over-responsive fear learning and avoidance of emotional stimuli may be generalized to difficulties of social function. Social function difficulties in individuals with AN may thus develop from social anxiety, pathological fear learning and avoidance.[52] In the framework of the pathological fear model, social function difficulties in individuals with AN thus may be a learned response developed as one of several consequences of pathological fear, another consequence being the fear of fatness.

4.2.4 Conclusion

The theoretical models of AN outlined above take social difficulties into account in their models, though with different lenses and approaches. The neurodevelopmental hypothesis places impairment of social function as possibly inherited traits akin to developmental disorders that precede and may predispose for AN.[19,53] The social-emotional maintenance model emphasizes the

interaction of predisposing temperamental traits with pathological, social, and emotional processes that evolve with AN.[41] Lastly, the pathological fear model views deficits of social function as a result of anxious avoidance and fear learning, and thus secondary to anxiety.[46] The integration of new evidence into these existing models and the attempt to test whether emerging data, e.g. in a younger population, confirm one model or the other will contribute to updating and testing these theories.

4.3 Social function in empirical studies of individuals with AN

A meta-analysis reviewing the NIMH Research Domain Criteria (RdoC) construct "Systems for Social Processes" across eating disorders[54] documented evidence for a number of difficulties affecting social function; on a group level, eating disordered individuals had impaired facial emotion recognition, they subjectively perceived insecurity in relationships, and they evaluated themselves more negatively than others.

A number of limitations in the literature on social function in AN require mention. First, the majority of studies have investigated adult patient samples, but adults and adolescents may differ concerning social function variables, although the presentation of AN symptoms may be similar, and the literature on social function specifically in young individuals with AN is still limited. Furthermore, the majority of studies have investigated samples that were quite heterogeneous concerning age, comorbidity, and duration of illness, although theoretically these factors may influence social function and may confound findings if they are not controlled for.

In addition, it is essential to examine individuals after recovery to disentangle stable traits from state-factors related to the ill state, e.g. effects of starvation, but the literature on recovered individuals is still limited.

In the following, the existing literature on social function in young individuals with current AN and in those recovered from AN will be presented. Only seven longitudinal studies have investigated social function in young individuals recovered from AN, and therefore we also include (as a supplement) studies concerning social function in adults recovered from AN.

4.3.1 Review of the literature on social function in young individuals with AN

The electronic databases Medline®, Embase®, and PsycInfo® were searched by May 2016 for studies investigating social function in young persons with AN, supplemented with inspection of reviews and reference lists of included publications. Search terms concerning social function were

social function, interactive behavior, social skill, social communication, social interaction, social reciprocal, interpersonal functioning, social adjustment, social aptitude, autism spectrum trait, social ineffectiveness, interpersonal deficit, social anxiety, social emotional. The search was filtered with a number of words for young persons and also included publications not indexed specifically with adults (flow chart in Appendix 1). Studies with clinical samples of children, adolescents, or young adults presenting with AN, atypical AN (according to DSM or ICD criteria),[3,4] or early-onset AN[55] were included, if they investigated a behavior, propensity, or ability involved in interpersonal functioning, displayed or reported by the individual with AN. Thus, studies investigating the social environment of patients, e.g. family climate or childhood experiences, and studies investigating non-clinical samples were considered outside the scope of the present work. Individual case studies were also excluded. The search resulted in 16 publications on cross-sectional studies (Table 1), and 12 publications describing longitudinal studies (Table 2). Only the longitudinal studies involved young patients after recovery, and they used rather crude measures of social function. Therefore, findings from recovered adults (Table 3) are reported after the summaries of literature on young patients, as these may give pointers as to social function in recovered young individuals as well. Details concerning included studies (Tables 1-3), such as instruments used, participants´ age, and duration of AN, along with methodological issues can be found in the appendices (Appendices 2-4).

4.3.2 Cross-sectional studies of social function in young individuals with AN

Six of 16 studies reported self-report questionnaires as their outcome measure, five studies combined self-report with other measures, one solely used parent report, and three studies reported observer-based ratings. Lastly, five studies reported experimental studies, alone or in combination with self-report. The subdomains according to the RdoC [56] definition of 'systems for social processes' that are covered in the 16 studies were: affiliation and attachment (4 studies), social communication (7 studies), self-knowledge (5 studies, 4 of which concerned alexithymia), understanding of others (1 study), and social hierarchy (4 studies, all on social anxiety) (See Appendix 5 for description of the RdoC subdomains). Six of the 16 studies lacked a healthy control group. Four of the five experimental studies investigated emotion recognition, an aspect of the RdoC subdomain social communication, with inconclusive results; they found either normal [39,57] or reduced [58,59] performance compared with controls. Only two experimental studies adjusted for the possible confounding effect of depression.[39,58] Another possible explanation for difference between studies is different salience of the emotional display used as stimuli, as this affects the difficulty of the task and its sensitivity, especially in populations with near-normal performance.[28]

Regarding self-knowledge, the ability to make judgments about one's current internal states, the patients consistently reported higher levels of alexithymia across studies.[39,57,59,60] Social anxiety (an aspect of the subdomain of social hierarchy) has been reported in uncontrolled studies only, but seems associated with higher levels of other clinical features, such as body dissatisfaction,[61] low self-esteem,[62] and distress.[63,64] Two of the four studies concerning the subdomain affiliation and attachment used parent-report instruments to measure ASD traits,[35,65] pointing to higher levels of peer problems, although the prevalence of individuals with manifest ASD was not higher than in the control groups. However, different instruments and small samples render conclusions difficult.

Further, although self-report measures are useful for characterizing the subjective experience of social functioning, they may, as pointed out by some authors, be vulnerable to respondent bias due to lack of insight or a desire for social achievement.[28]

Table 1. Empirical studies of social function in young individuals with AN.

Authors (yr)	N adolescents (% female)	Study design	Type of measurement	Subdomain of Systems for Social Processes (RdoC)	Main findings related to social function in young persons with AN
Cipolli et al. 1989[66]	7 AN (100%)	cross-sectional, controlled	observer-based	social communication	Looked less frequently towards the interviewer's eyes, less frequent reciprocal gaze.
Lattimore, Wagner & Gowers 2000[67]	20 (100%)	cross-sectional, controlled (healthy and clinical controls)	observer-based	social communication	AN daughter-mother dyad more destructive communication, reciprocated more destructive than constructive communication.
Broberg, Hjalmers & Nevonen 2001[68]	84 mixed ED (17 AN)(100%)	cross-sectional, controlled	self-report	affiliation and attachment	ED more often insecure attachment (in the AN subgroup: 53%, controls with no history of ED: 26%, controls with history of ED: 45%)
Zonnevijlle-Bendek et al. 2002[59]	30 mixed ED (16 AN) (100%)	cross-sectional, controlled	self-report, experimental	self-knowledge, social communication	Higher level of alexithymia and performed worse on emotion recognition, but equal to controls on non-social tasks.
Zonnevylle-Bender et al. 2004[57]	28 (100%)	cross-sectional, uncontrolled (compared adolescent to adult AN)	self-report, experimental	self-knowledge, social communication	Adult and adolescent AN similar on alexithymia and emotion recognition. Adolescents had lower prevalence of specific and social phobia.
Ruuska et al. 2007[69]	34 (100%)	cross-sectional, clinical control group (BN)	semi-structured interview	affiliation and attachment	Similar proportions of AN and BN severe impairment of global function. More BN than AN reported work/school impairment. 59% of AN participants reported minimal social contacts outside family.
Buchholz et al. 2007[61]	149 mixed ED (49 AN) (100%)	cross-sectional, uncontrolled	self-report	self-knowledge, social hierarchy (social anxiety)	Self-silencing behaviors and social anxiety were associated with body dissatisfaction and drive for thinness.
Pooni et al. 2012[35]	22 (86%)	cross-sectional, healthy and clinical controls (ASD)	parent interview, parent questionnaire	affiliation and attachment	Similar to controls on communication and social interaction scales (trend towards higher scores), more frequent repetitive and restricted behaviors.
Obeid et al. 2013[62]	344 mixed ED (182 AN)(100%)	cross-sectional, uncontrolled	self-report	social hierarchy (social anxiety)	Inverse relationship between self-esteem and social anxiety, regardless of age group or diagnostic group.

Authors (yr)	N adolescents (% female)	Study design	Type of measurement	Subdomain of Systems for Social Processes (RdoC)	Main findings related to social function in young persons with AN
Schulze et al. 2013[64]	23 (100%)	cross-sectional, uncontrolled (published norms)	self-report	social hierarchy (social anxiety)	35% AN fulfilled criteria for social phobia. Higher on SPAI-C, SPAI-C correlated with EDI-subscales Ineffectiveness and Interpersonal distrust.
Lule et al. 2014[39]	15 (100%)	cross-sectional, controlled	self-report, experimental	self-knowledge, social communication	Higher alexithymia, social distrust, social insecurity, depression, and anxiety. Identified emotions faster. When controlling for depression: non-different emotion recognition skills.
Bomba et al. 2014[60]	60 (100%)	cross-sectional, controlled	self-report, experimental	self-knowledge	Overgeneralized memories for positive and negative experiences. Overgeneralization associated with duration of illness.
Rhind et al. 2014[70]	17 (100%)	cross-sectional, controlled	observer based	social communication	Less positive expression in reaction to positive films and less negative expression in reaction to negative films.
Rhind et al. 2014[65]	150 (91%)	cross-sectional, uncontrolled	self- and parent-report	affiliation and attachment, understanding of others	Lower social aptitude and greater peer problems. 4% possibly met criteria for an autism spectrum diagnosis. Not correlated with clinical characteristics.
Lang et al. 2015[58]	97 (36 adolescents) (100%)	cross-sectional, controlled	experimental	social communication	Poorer recognition of sadness (but not fear, anger or happiness). Performance not associated with autistic features.
Dakanalis et al.2015[63]	703 mixed ED (212 AN)(90%)	cross-sectional, uncontrolled	self-report	social hierarchy (social anxiety)	Social appearance anxiety was associated with social avoidance and social distress in combined ED.

ED=Participants with eating disorders; AN=Participants with anorexia nervosa; ASD=Participants with autism spectrum disorder; BN=Participants with bulimia nervosa.

Table 2. Longitudinal studies of social function in young individuals with AN.

Authors (yr)	N adol-escents (% female)	Study design, FU time	Type of instrument	Subdomain of Systems for Social Processes (RdoC)	Main findings related to social function in young persons with AN
Leon et al. 1985[71]	31(100%)	controls at pre-treatment, and patients at pre- and post-treatment	self-report	affiliation and attachment, knowledge of self	AN displayed lower scores than controls on self-rated social skills at pre-treatment, and significant improvement between pre- and post-treatment.
Anckarsäter et al. 2012; I.C. Gillberg et al. 1995; I.C. Gillberg et al. 1994; Nilsson et al 1999; Råstam, GIlberg & Gilberg 1995; Wentz et al.2001;[34,72–76]	51 (94%)	prospective (6, 10 and 18 yr FU after initial assessment)	interview, clinician's ratings	affiliation and attachment	5 yr FU: 53 % not recovered. Difference between recovered and non-recovered participants was most pronounced regarding social contacts and activities. More AN had empathy disorder, including Asperger or other ASD conditions (30% vs 4 % in controls). 10 yr FU: 27 % had poor outcome, mostly explained by either persisting ED, obsessive-compulsive symptoms or persisting social-communicative problems. 18 yr FU: ASD at onset and/or 6 yr FU predicted global functioning. AN without ASD had higher ASDI scores than controls.
Herpertz-Dahlman et al. 2001; Herpertz-Dahlman et al. 2011 [77,78]	39 (82%)	prospective (3, 7 and 10 yr FU after discharge), controlled	interview	affiliation and attachment	3 yr FU: AN were similar to controls concerning occupational adjustment, social contacts and dependency on family, but lower on psychosexual adjustment (MROAS). Strong link between continued ED and depression. 10 yr FU: long-term recovered AN participants similar to controls on MROAS subscales, but unrecovered and short-term recovered had lower social contacts and psychosexual adjustment.
Halvorsen, Andersen & Heyerdahl 2005[79]	48 mixed ED, 25 siblings (100%)	FU mean 8,8 yr from treatment, siblings as controls	self-report and parent report	affiliation and attachment	AN group had lower mean adaptive functioning than the sibling group. Nine (19%) had ED at FU.
Lázaro et al. 2011[80]	95 (94%)	pre- and post-treatment	self-report	affiliation and attachment	AN showed improvement between pre- and post-treatment on the self-report subscales Social withdrawal and Leadership
Schulte-Rüther et al. 2012[81]	19 (100%)	tested at intake and discharge, prospective FU 1 yr, controlled	experimental	perception and understanding of others	No group difference in the accuracy of verbal classification of films. AN had reduced activation of brain networks supporting Theory of Mind. Reduced activation predicted worse outcome 1 yr later.

Courty et al. 2015[82]	60 (100%)	prospective (6, 12, 18 months)	self-report, semi structured interview	knowledge of self, social anxiety	Alexithymia was associated with self-reported interpersonal mistrust and interviewer-assessed social anxiety and social avoidance, independent of nutritional state.

FU=Follow-up time; ED=Participants with eating disorders; AN=Participants with anorexia nervosa; ASD=Participants with autism spectrum disorder; BN=Participants with bulimia nervosa.

Table 3. Empirical studies of social function in adults recovered from AN.

Authors (yr)	N (% females)	Type of instrument	Subdomain of Systems for Social Processes (RdoC)	Main findings related to social function in adults recovered from AN
Study design: cross-sectional, controlled				
Bachner-Melman et al. 2007[83]	42 AN, 78 recAN (100%)	self-report	affiliation and attachment	AN but not recAN higher level of selflessness, associated with ED severity.
Connan et al.2007[84]	18 AN, 13 recAN (100%)	self-report	affiliation and attachment	RecAN higher social comparison. Combined submissive behavior and social comparison mediated between childhood interpersonal adversity and AN group membership.
Bachner-Melman et al. 2009[85]	17 AN, 106 partially recovered, 71 recAN (100%)	self-report	self-knowledge	Not different on other-directedness and extraversion.
Oldershaw et al. 2010[86]	40 AN, 24 recAN (96%)	experimental, self-report	social communication, self-knowledge	RecAN performed similarly to controls in emotion ToM tasks, but lower on emotion recognition.
Tchanturia et al. 2012[87]	72 AN, 14 recAN (no info)	self-report	self-knowledge	AN but not recAN expressed elevated social anhedonia. Social anhedonia associated with alexithymia, depression and anxiety.
Oldershaw et al. 2012[88]	40 AN, 24 recAN (96%)	self-report	affiliation and attachment	AN higher on all three subscales, recAN participants higher on Externalising self-perception only.
Cowdrey et al. 2012[89]	16 recAN (100%)	experimental	social communication	No difference between recAN and controls in neural response to emotional faces.
Harrison et al. 2012; Harrison et al. 2010[45,90]	50 AN, 35 recAN (100%)	experimental, self-report	social communication	AN and recAN higher social and angry-threat bias and lower emotion recognition. No difference in self-report.
Davies, Schmidt & Tchanturia 2013[91]	49 AN, 31 recAN (100%)	experimental, self-report	social communication	RecAN more negative expressions to amusing film, AN also less positive expressions. Same subjective experience as controls.
Cardi et al. 2013[92]	29 AN, 13 recAN (100%)	experimental, self-report	affiliation and attachment	AN and recAN attentional bias towards rejecting faces and disengagement from accepting faces. RecAN retrospectively lower levels of care from mother and overprotection from father.

Authors (yr)	N (% females)	Type of instrument	Subdomain of Systems for Social Processes (RdoC)	Main findings related to social function in adults recovered from AN
Brockmeyer et al. 2013[93]	33 AN, 26 recAN (100%)	self-report	affiliation and attachment	RecAN stronger motivation for intimacy, AN and recAN more avoidance concerning dependency/autonomy loss.
Morris et al. 2014[94]	28 AN, 23 recAN (100%)	self-report	perception and understanding of others	AN but not recAN less empathy and less antisocial behaviors.
Harrison, Mountford & Tchanturia 2014[95]	105 AN, 30 recAN (100%)	self-report	self-knowledge	AN more social anhedonia and poorer work and social adjustment, recAN intermediate levels. Social anhedonia associated with AN duration.
Study design: prospective, controlled				
Striegel-More, Seeley & Lewinsohn 2003[96]	36 (100%)	self-report	affiliation and attachment	Low social support from family and low social network size loaded on discriminating factor. Comorbidity may account for the result.
Beadle et al. 2013[97]	20 (100%)	self-report	self-knowledge	AN higher level of alexithymia and more emotional empathy at both time points.
Study design: pre- and post-treatment, uncontrolled				
Hartmann, Seeck & Barrett 2010[98]	208 mixed ED (113 AN)(94%)	self-report	self-knowledge	AN more distress in all domains but dominance, and improvement after treatment in the domains social inhibited/avoidant and non-assertive.

ED=Participants with eating disorders; AN=Participants with anorexia nervosa; WR-AN=Weight-restored participants with AN, recAN=Participants recovered from AN.

4.3.3 Longitudinal studies of social function in young individuals with AN

On the basis of a literature search for social function in young persons with AN, we identified six longitudinal or follow-up studies (described in 12 articles) that provide insight into the trait or state nature of the observed social function difficulties (Table 2). Two samples of adolescent participants with AN were followed up long-term (up to 10 and 18 years) and were compared with matching controls [34,72–76][77,78]. However, social function in the latter was measured by the Morgan-Russell Outcome Assessment Schedule (MROAS),[99] which is a suitable instrument for evaluation of outcome, but a rather crude measure of social function. This study found overall normalized social function at six and 10 years after discharge from inpatient treatment for AN. However, there was a significant association between continued eating disorder (ED) symptoms and poorer social function, and between continued ED symptoms and psychiatric comorbidity. The population-based study from Gothenburg documented that more AN participants than controls had ASD-like conditions, and that this subgroup had a worse outcome of AN. However, the instruments and criteria used for assessing the ASD-like conditions are not entirely aligned with current diagnostic criteria in DSM-IV, rendering comparisons across studies difficult.[4,25]

4.3.4 Social function in persons recovered from anorexia nervosa

A number of studies have investigated cross-sectional samples of adults recovered from AN. In light of the meager literature specifically concerning recovered young persons, studies of recovered adults may provide cues as to whether impairment of social function normalizes fully with recovery. In the search outlined above, six publications assessed recovered adults. A supplementary search for publications with the terms *recovered* and AN was screened for the social function search terms mentioned above and resulted in 10 additional studies (described in 11 articles) to those identified in the main search. We required in the adult cross-sectional studies that the criteria for recovery also included measures of psychological and/or behavioral recovery besides weight restoration. Additionally, we identified a few longitudinal studies. Cross-sectional and longitudinal studies are presented in Table 3. Eleven of 16 studies used exclusively self-report measures of social function. Importantly, criteria for recovery vary between studies, and with respect to the time span in which recovery must have been maintained (see Appendix 4 for criteria for recovery in the individual studies). The five experimental studies suggest that adults recovered from AN had a reduced capacity to recognize emotions,[86,90] showed attentional bias toward negative emotional

stimuli,[90,92] and produced fewer reciprocal behaviors[100] along with more negative facial expressions in reaction to amusing films.[91] The recovered adults reported more social anhedonia,[87,95] and more social comparison/externalizing self-perception than controls,[84,88] but similar levels of empathy and social behaviors.[85,94]

To sum up, recovered adults seem to experience some impairment of social functioning. Moreover, according to the self-report measures, they experience more distress in the social function domain. It is plausible that these stressors might represent a factor of vulnerability for psychiatric symptoms.

4.4 Social function and selected aspects of cognition

We included a few specific cognitive functions (social and non-social domains of cognition) as predictors in the present study due to their relevance for social function. Differences in these aspects of cognition may help understanding in more detail the processes underlying a reduced social function among young individuals with AN, if present.

4.4.1 Social function and social cognition

Social cognition describes the mental operations underlying social interaction[101] and has been defined as "*the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behavior*".[102] Social cognition thus refers to an array of cognitive operations devoted to the processing of social stimuli. Impairment in any social cognitive ability may in consequence influence social function unless the individual manages to compensate for the impairment. Social cognition has received attention as a potential mediator for outcome in psychiatry in general, but is difficult to define as a unitary concept. One attempt stems from the "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS)[103] consensus battery, which proposes four subdomains of social cognition, though with a certain degree of overlap in function: (i) emotion processing, (ii) social perception, (iii) attributional bias, and (iv) theory of mind (ToM).[104–106] On the subject of the present study, a meta-analysis of nine studies concluded that individuals with AN show poorer affect recognition,[28] and a review found altered attentional response to faces.[107] The findings were less robust when social cognitive performance after recovery in individuals with AN were measured. On the background of the existing literature, the influence of age per se, the developmental stage, as well as the duration of illness for the domain of social cognition in persons with AN are not mapped in details. Further, the possible confounding role of comorbidities, such as anxiety and depression has not been taken

into account sufficiently.

4.4.2 Social function and neurocognition

Social function is a complex, higher order capacity of humans, which depends on the functioning of several basic, non-social neurocognitive domains. It is thus crucial to discern whether deficits of any aspect of social function may represent the down-stream effects of lower order neurocognitive deficits.[108]

Aspects of neurocognition such as executive functions, memory, and processing speed, play together in social, as well as non-social contexts.[109,110] Several impairments of neurocognition, specifically in set-shifting,[26,107] and central coherence,[27,30] have consistently been reported among adults with AN. The former, set-shifting, is the ability to move flexibly between tasks, rules, or strategies,[111] possibly associated with the behavioral rigidity often observed among individuals with AN. Interestingly, cognitive inflexibility is associated with eating problems and social insecurity in non-clinical populations as well.[112] The latter, weak central coherence, is a construct originating from the field of ASD research, and involves both a bias towards local processing, with a strong focus on the details, and a reduced global processing.[113] Weak central coherence may underlie distorted body perception in eating disorders that typically presents with a preoccupation with certain parts of the body.[114]

A number of findings suggest that impaired neurocognitive functions may play a role in the maintenance of AN. Thus, a higher level of set-shifting difficulties was associated with longer duration of AN and a higher psychiatric comorbidity.[115] Poor working memory was associated with worse outcome in adolescents with AN and with elevated autism traits in a long-term follow-up study.[116] Rather than assuming one single characteristic neurocognitive profile for individuals with AN, several distinct profiles have been suggested recently,[117,118] in parallel with the growing knowledge of the heterogeneity of profiles within many psychiatric domains in general.[119]

In contrast to the literature about adults with AN, it is not clear whether children and adolescents with AN differ from non-affected peers in terms of their neurocognitive profile. A review of set-shifting in young individuals with AN concluded that set-shifting difficulties appear not to be as pronounced in young patients as they are in adult patients, and the review points to a number of methodological limitations making conclusions exploratory.[38] Later studies found normal set-shifting performance.[37,120,121] In contrast, one study reported significantly more perseveration in

children and adolescents with AN, representing difficulties with shifting strategy.[111] To the best of our knowledge, only reduced global processing, but not bias towards local processing has been assessed in young individuals with AN so far.

4.4.3 Social function and olfaction

Reduced olfaction may represent a biomarker for a range of psychiatric disorders because different aspects of this ability seem altered in several disorders. Olfaction is involved in regulation of food intake,[122] and processing of illness-related stimuli, such as odors, is altered in individuals with AN.[48,123,124]

Specifically relevant for the study of social function in AN, olfactory impairment is common in individuals with ASD,[125] and poorer olfactory identification in individuals with schizophrenia is associated with social function.[126] The process of smelling, or olfaction, shares brain networks, including the orbitofrontal cortex (OFC), with processes of executive functions, such as flexibility.[127] The ability of flexibility is in turn affected in adults with AN and associated with the outcome of the disorder,[115] which in consequence raises the question whether olfaction is also associated with outcome of AN. Although findings concerning olfactory function in AN have been inconsistent.[128], it may be valuable to test whether olfaction may be a marker in young individuals with AN or recovered from AN for their specific patterns of cognitive deficits or impairment of social function, if present.

4.5 Summary: the current knowledge gap

Some important gaps in current knowledge need further exploration in order to better understand impairment of social function in individuals with AN. First, adolescents and young persons with AN have by far not been studied as detailed as adults with AN, even though the neurocognitive profile of individuals falling ill in adolescence may differ from those who develop AN later in life. Second, individuals with a short duration of AN have received little attention. Many adult patients have already had symptoms since adolescence and the inclusion of adults thus emphasizes evidence from participants who have been ill for a longer period of time. This makes it difficult to distinguish traits or illness effects from long-term or scarring effects, and existing studies rarely control for length of illness. The study of individuals with recent AN onset thus allows for a more developmental and longitudinal perspective. Third, individuals recovered from AN, especially at a young age, have been neglected, even though the comparison of those with acutely ill individuals

would highlight important clues for understanding the disorder. Given that impairment of social function may exist as a trait or vulnerability factor before the onset of AN, young individuals with first-episode AN and young recovered individuals may well show some of the impairment found in adult AN patients. On the other hand, these impairment may develop over time and persist afterwards, and one may therefore expect that recently diagnosed young AN patients may show normal performance, whereas the performance of recovered individuals may vary depending on duration or other factors of their AN. Fourth, comorbid depression and anxiety are frequent in AN,[17,129,130] and both disorders affect social function,[131,132] but existing studies in AN have not consistently controlled for the effect of these disorders on the individual's social function. Finally, the association between social function and other domains, such as social cognition, neurocognition and olfaction has not yet been adequately described in young populations of individuals with AN.

These gaps in our knowledge have clinical implications. If impairment of social function are in fact present in young individuals with AN, it may prove beneficial for the planning of their treatment to assess such impairment routinely in clinical practice. Even though the available clinical measures and experimental tests have mainly been developed in the fields of ASD or schizophrenia, where individuals may have more pronounced deficits, we measured social function and social cognition with these instruments in a group of individuals with recent-onset AN and those recovered from the disorder.

5 Objectives

The aim of the present study was to investigate social function in adolescent and young adult females with first-episode AN, and in adolescents and young adult females with full recovery from AN compared with control participants in a cross-sectional design. We combined clinical and experimental measures with information from participants and parents in order to assess social function from different perspectives. We further aimed to investigate possible associations between social function and the domains of social cognition, neurocognition, and olfaction, respectively, in order to characterize in detail the nature of impairment of social function, if found in any of the clinical groups.

5.1 Paper 1

The primary aim of Paper 1 was to assess social function as observable communicative and reciprocal social behavior in a naturalistic laboratory observation in the two clinical groups. We supplemented this assessment with parent reports of social function in everyday life, and with experimental tests of social cognition. Lastly, we explored associations between social function and social cognition across diagnostic groups.

The hypotheses were that young females with first-episode AN would show more impairment than control participants in social function, and that those recovered from AN would perform intermediary between those with first-episode AN and controls.

5.2 Paper 2

In Paper 2 we aimed to test whether groups differed on a range of neurocognitive functions. We further aimed to test whether these neurocognitive functions contributed to the variation in social function in the two clinical groups. Our hypothesis was that the young individuals with first-episode AN and those recovered would display deficits in neurocognitive functions, and that impaired neurocognitive functions in both of the clinical groups would be associated with reduced social function.

5.3 Paper 3

The aim of Paper 3 was to measure olfactory sensitivity and olfactory identification in the two clinical groups compared with the control participants. In addition, we aimed to assess the subjective importance of olfaction in these groups, and to examine whether olfactory sensitivity and identification were associated with social function and with a range of clinical symptoms. Our hypothesis was that participants with first-episode AN and recovered from AN would display increased olfactory sensitivity and more precise identification in line with the largest study on adults with AN, and in line with some studies on adolescent AN participants.

6 Methods

6.1 Participants

6.1.1 Recruitment

First-episode AN patients

All eligible AN patients who began treatment at Child and Adolescent Mental Health Centre, Mental Health Services in the Capital Region of Denmark, (CAMHS) between July 2012 and March 2015 were invited to participate, unless their treatment team deemed participation contraindicated due to their somatic condition (Figure 1). Patients under the age of 18 are referred to CAMHS, where they are offered inpatient, day treatment and outpatient treatment. The therapist gave the initial information, and research staff followed up with further information and obtained informed consent from parents and patients. In total, 51% of the invited patients at CAMHS accepted the invitation. The wish to focus on the ongoing treatment was the main reason for declining participation.

We further invited selected adults with first-episode AN, 18–22 years old, from Psychotherapy Centre Stolpegaard, Mental Health Services in the Capital Region of Denmark into the study, to match the age of those recovered from adolescent-onset AN. However, due to the fact that the invitation was restricted to few patients, only three adult patients agreed to participate (not shown in Figure 1).

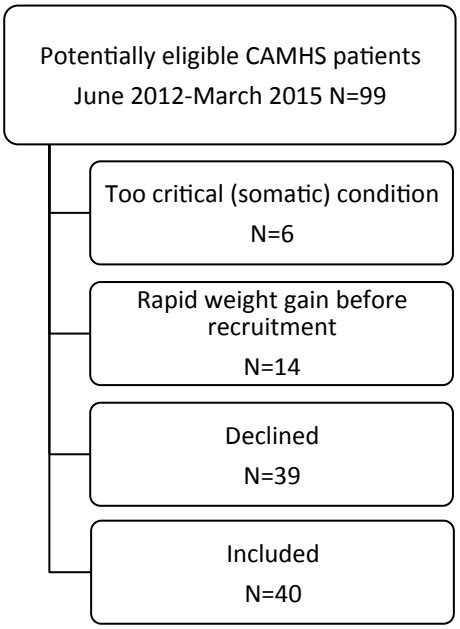

Figure 1. Flowchart: recruitment of first-episode AN participants from CAMHS.

Recovered patients

We invited recovered patients who received treatment between mid-2008 and January 2012 at BUC Bispebjerg, or at a similar clinic for child and adolescent eating disorders in the north of the Capital Region of Denmark (Hillerød). They were identified through a survey mapping the quality of the clinical care after completed treatment, where they had indicated their interest of participating in research projects. Of the persons invited, 34% (N=45) accepted the invitation and of those 13% (N=17) were excluded for not meeting criteria for full recovery (Figure 2).

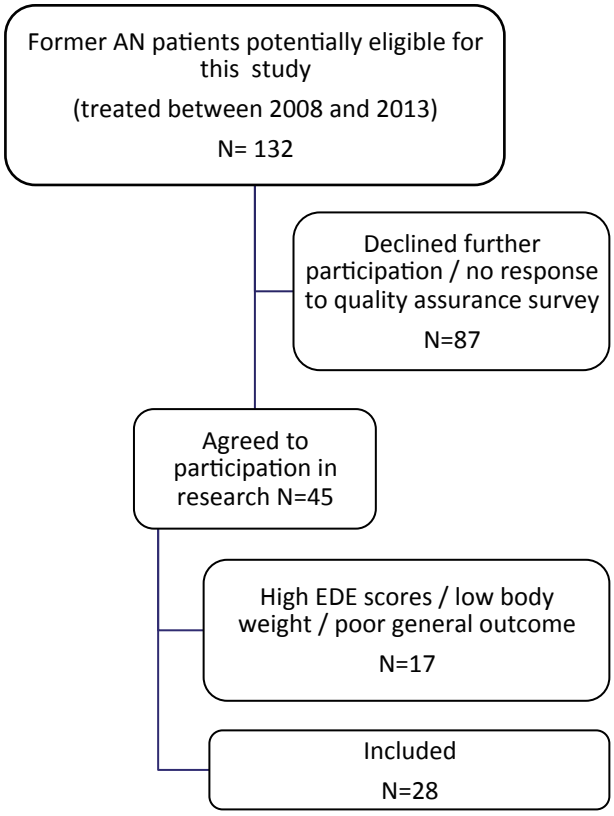

Figure 2. Flowchart: recruitment of recovered participants.

Healthy controls

We invited healthy controls from state schools, halls of residence, and colleges in the catchment area via advertisements and oral information about the project in classes in collaboration with teachers or study counsellors.

6.1.2 Inclusion and exclusion criteria

Inclusion criteria for each participant group are listed in Table 4.

Table 4 – Inclusion and exclusion criteria

Inclusion criteria	First-episode AN participants	Recovered participants	Control participants
Age (years)	*14-22*	*14-22*	*14-22*
Eating disorder	*F50.0 or F50.1 (ICD-10), first-episode with duration <*	*History of F50.0 or F50.1 (ICD-*	*Never*

diagnosis	*12 months*	*10)*	
Body weight	*Underweight*	*Normal weight for the last 12 months*	*Normal weight and no lifetime underweight*
Eating disorder status	*Meet criteria for F50.0 or F50.1*	*Global EDE max 1.74, do not fulfill criteria for any eating disorder. MROAS score ≥ 9*	*Normal EDI-3, or normal global EDE and do not fulfill criteria for any eating disorder*
Psychotropic medication	*Not allowed ever*	*Allowed, past or present*	*Not allowed ever*
Psychiatric comorbidity	*Allowed*	*Allowed*	*No lifetime Axis 1 diagnosis assessed by K-SADS-PL, except for minor and transient episodes*

Legend: BMI=Body Mass Index, MROAS=Morgan-Russell Outcome Assessment Schedule, K-SADS-PL= Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version.

Weight Criteria for participants with first-episode AN

We defined normal weight as a body mass index (BMI) >18.5 for participants 16 years of age or older, and by BMI percentile corrected for age >25th percentile [133] for 14–15-year-old participants. First-episode AN participants had to have a body weight below normal as defined by these criteria. Weight criteria for F 50.0 according to International Classification of Diseases (ICD-10)[3] is <10th BMI percentile for children and BMI <17.5 for adults. We used weight criteria to secure homogeneity in nutritional status for first-episode AN participants, but allowed a somewhat higher weight than F50.0 diagnostic criterion to include underweight individuals with F50.1, because severity and symptomatology are similar in the two disorders.[134] Ideally, it would have been preferable to use individual growth trajectories to establish the individual´s ideal body weight,[135,136] but this information was not consistently available at the point of inclusion in the study.

Criteria for recovery in the group recovered from AN

We defined recovery as maintenance of normal weight for the last 12 months, not meeting diagnostic criteria for any current eating disorder, and with a level of eating disordered thoughts and concerns within one SD from published non-clinical norms (global EDE≤1.74),[137] as well as a

generally favourable outcome, defined as a score of 9 or more on the Morgan-Russell Outcome Assessment Schedule (MROAS), assessed via interview.[99] The presence of regular menstruation was omitted from the MROAS calculation, if the participant took contraceptives. The combination of a normal body weight and absence of psychological eating disorder symptoms is deemed to be the most consistent and prognostically meaningful definition of recovery in young individuals.[135,138] However, we added MROAS score criteria as a supplement to assure an overall normal psychosocial functioning.

Due to the elevated incidence of psychiatric problems in individuals with a history of AN [139] we did not exclude persons with either past or present psychopharmacological treatment or past or present Axis 1 diagnosis other than eating disorders, as long as this did not impact their level of functioning expressed by their MROAS score. This was chosen to assure a representable sample of recovered participants.

Controls

If a control individual scored in the typical clinical range on the Eating Disorder Inventory (EDI-3) Eating Disorder Risk Composite, we conducted an Eating Disorder Examination (EDE) interview to ascertain that this person did not meet the diagnostic criteria for any eating disorder and had a global EDE score within 1 SD of published non-clinical norms (global EDE≤1.74).[137]

Exclusion criteria

Exclusion criteria for all groups were a diagnosis of infantile autism (F84.0) or Asperger´s syndrome (F84.5) (ICD-10)[3], IQ below 70, not fluent in Danish, birth before 36th week of gestation, history of head trauma with loss of consciousness, and history of neurological illness involving the central nervous system.

6.1.3 Ethical considerations

We obtained written, informed consent in accordance with the guidelines of the Danish Health Authority, and the study was approved by The Regional Scientific Ethical Committee in the Capital Region of Denmark (project number H-2-2012-027) and The Danish Data Protection Agency. For all participants under the age of 18, the invitation and information were presented to the parents, as well as the participants themselves. Finally, patients and their parents were informed that their

decision regarding participation would not influence treatment.

6.2 Instruments

6.2.1 Psychiatric assessment

Psychiatric morbidity was assessed through the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version (K-SADS-PL) interview [140]. K-SADS is part of the standard clinical assessment at intake for patients at CAMHS, and therefore clinicians conducted the interview with first-episode AN-participants recruited there. For all other participants, two PhD fellows and a trained research assistant conducted the K-SADS-PL interview. All interviewers from the clinical department and the research unit are offered continual joint rating of K-SADS-PL to secure reliability. Participants completed the questionnaire Beck Youth Inventory (BYI),[141] which includes dimensional measures of anxiety (BAI-Y) and depression symptoms (BDI-Y).

Parents completed the Social Communication Questionnaire (SCQ),[142] and the Asperger´s Syndrome Screening Questionnaire-Revised Extended Version (ASSQ-REV)[143] to ensure that no participants fulfilled diagnostic criteria for ASD. If ratings were above the established cutoffs, we interviewed parents with the Autism Diagnostic Interview-Revised.[144]

6.2.2 Paper 1

We measured social function using the Autism Diagnostic Observation Schedule – second edition, Danish version (ADOS-2).[145] ADOS is a standardized instrument that assesses social interaction, communication, and imagination during a semi-structured interaction with an examiner during approx. 45-60 minutes. The ADOS includes four modules suited for individuals with different developmental and language levels, ranging from children without expressive language to older and verbally more capable individuals. In this study we used the Module 4 developed for adolescents and adults with fluent speech.

The ADOS is designed to provide a sample of naturalistic social communicative situations without explicit instructions. It has a total of 32 items scored according to a standardized set of instructions. A subset of items is combined in an algorithm based on specificity and sensitivity to ASD, and the algorithms yield subscale scores for Communication (4 items), Reciprocal Social Interaction (7 items), Imagination/Creativity (1 item) and Stereotyped Behaviors and Restricted Interests (4

items). Module 4 provides a limited opportunity to demonstrate creativity, as well as stereotyped behaviors and restricted interests, and we did not include these two subscales in our analyses, because they are not in the scope of this study. Importantly, a diagnosis of ASD cannot be decided from an ADOS observation alone, and ADOS is a quantification of social behaviors without assumptions of possible underlying mechanisms or causes.[145]

All ADOS-2 observations were conducted and scored by the same researcher (MB), who met the standard requirements for research reliability (min 80% single item agreement). Interrater reliability of cases in the study was monitored through re-scoring of 15 cases (16.7%) by an experienced, certified ADOS supervisor who was blind to group. The 15 cases comprised 5 randomly chosen cases from each participant group. Scores were identical in 79%, one point apart in 12%, and two points apart in 1% of all single-item scores. Accordingly, weighted Kappa for all items (.77) was substantial.

Additionally, we used the Socialization Domain of Vineland-II[146] as probe of parent-reported social function measuring adaptive behaviors in everyday life. Participants older than 20 years of age were given scale scores for the oldest age group of the norm material, 20-year-olds.

The social cognitive tests were chosen to measure the above-mentioned four subdomains of social cognition according to MATRICS.[104] We chose tests suitable for 14-year-olds with demonstrated sensitivity in adolescent, as well as adult populations in the literature to avoid ceiling effects. We used the following tests in the study:

Emotion perception: "Reading the Mind in the Eyes-Revised" (RME-R).[147]

Social perception: The "MiniPONS", a short version of the Profile of Nonverbal Sensitivity test.[148]

Theory of Mind (ToM): Animated Triangles (AT) using the multiple choice response format,[149] and The Awareness of Social Inference Test (TASIT), Part 2: Social Inference-Minimal, Danish version.[150]

Affective bias: CANTAB Affective Go/No-go (AGN).[151]

6.2.3 Paper 2

The independent measures in Paper 2 were a range of established neurocognitive tests, chosen to tap into domains with potential relevance for social function. Set-shifting and local processing bias were included, because deficits have been documented in adults with AN,[26,27] and because mental flexibility and central coherence (involving no local processing bias) are involved in social processes, such as perspective-taking, conversation, and empathy. Processing speed, working memory, and sustained attention were included on the basis of their association with social function in populations with ASD and schizophrenia.[152–154] Lastly, verbal memory and verbal abstraction were included, because verbal behavior is an integral part of social interaction in adolescence and adulthood. Moreover, memory for complex materials is often reduced in individuals with ASD.[155,156] Further, the main outcome measure of social function, Module 4 of ADOS-2, relies heavily (although not exclusively) on social skills that are demonstrated verbally.[145]

We used the following tests of neurocognition:

Set-shifting: The Delis-Kaplan Executive Function System (D-KEFS)[157] the shift-conditions of Verbal Fluency, Design Fluency, and Trail Making.

Local processing: Group embedded Figures Test (GEFT)[158] were administered individually, timing each search.[159]

Processing speed: D-KEFS Trail Making, conditions 1, 2 and 3.[157]

Working memory Paced Auditory Serial Addition Test (PASAT), Danish version, part 2,[160], Digit Span and Letter-Number Sequencing from The Wechsler Adult Intelligence Scale (WAIS-IV), Danish version[161], and CANTAB Spatial Working Memory (SWM) and Spatial Span (SSP).[151]

Sustained attention: Test of Variables of Attention (TOVA) visual.[162]

Verbal memory: Immediate and the delayed version of the subtest Memory for Stories from Tests of Memory and Learning (TOMAL-2), Danish version.[163]

Verbal abstraction: D-KEFS Proverbs, condition 1.[157]

6.2.4 Paper 3

We used the Sniffin' Sticks Odor Threshold Test and Odor Identification Test to assess olfactory performance,[164] and adopted a few modifications in administration to make participants comfortable and to avoid the potential effect of fatigue.

Figure 3. Sniffin´Sticks ® used for testing olfaction.

We further used the questionnaire 'Importance of Olfaction' to assess subjectively experienced significance of smell.[165] The questionnaire assesses associations to odors, application of the sense of smell, and behavioral consequences of olfaction, and these aspects of olfaction have to the best of our knowledge not previously been investigated in individuals with AN. Five of its 20 items have food-related content, which may have induced a bias for participants with AN.

6.2.5 Other instruments

We assessed intelligence with the Reynolds Intellectual Assessment Scales (RIAS).[166]

6.2.6 General considerations concerning test sessions

All social cognitive and cognitive tests were administered in a fixed order during 2–3 meetings along with clinical interviews and questionnaires. Participants were tested and interviewed for approx. 8 hours, preferably in the afternoons after school hours. They were offered breaks when needed.

6.3 Statistics

6.3.1 Paper 1

We analysed the main outcome, ADOS, with a nonparametric test of group differences, because of a non-normal distribution with a score of 0 representing the most normal behavior, and because of high-scoring outliers. Next, to assess whether ADOS scores were influenced by other clinical features accompanying AN, we used a Spearman´s rank correlation coefficient to assess the association between ADOS and depression or anxiety within each group, as these variables showed a distribution in all groups. Similarly, we assessed the association between ADOS and BMI-percentile and between ADOS and severity of the eating disorder in the first-episode AN participants only. We used analyses of Variances (ANOVAs) to examine differences between groups in exploratory analyses of Vineland-II, and of the tests of social cognition. Finally, we used an ordinal logistic regression analysis to explore whether social cognitive test performance predicted social cognition.

Prior to analysis, we adjusted social cognitive test scores by age by weighting cases with a standardized frequency weight [167] based on four age groups. We chose this procedure to adjust for the between-group difference in age without adding age as a covariate and losing a degree of freedom. Before performing the weighting procedure, we inspected scatterplots of each variable with age and observed no outliers.

6.3.2 Paper 2

We assessed group difference in the profile of neurocognitive functions by applying a mixed effects model, within-participant repeated measure design. We further analysed the effect of neurocognition on social function with ADOS-Total as outcome in an ordinal logistic regression due to a non-normal distribution of residuals from parametric analysis. The neurocognitive tests were standardized (z-score transformed) and combined into 7 domain scores prior to the main analyses.

6.3.3 Paper 3

Odor Threshold Test scores and Odor Identification Test scores were analyzed separately with ANOVAs. In sensitivity analyses, we repeated these ANOVAs, each time excluding participants

with one of several characteristics known to impact olfaction (smoking, depressive disorder, anxiety disorder and serotonergic medication).

For the exploratory analyses of Paper 3, we analyzed the subscales of the Importance of Smell questionnaire with a one-way multivariate analysis of variance (MANOVA). In a sensitivity analysis, we repeated the MANOVA excluding questionnaire items with food-related content.

We used Pearson´s correlation analyses of potential associations between the two objective olfaction tests and ANCOVAs to assess their association with social function impairment (ADOS) and relevant clinical parameters (severity of depression symptoms). Lastly, multiple regression analyses in the group of participants with first-episode AN served to analyze associations between the olfaction tests and parameters related to AN (BMI adjusted for age and EDI-3 Body Dissatisfaction Scale score).

7 Summary of the findings

7.1 Paper 1

Both clinical groups had higher ADOS scores than controls, and a similar proportion in both clinical groups had ADOS scores above cutoff. We thus demonstrated impairment at the group level, assessed by standardized observations, in young females with first-episode AN, as well as young recovered females, after excluding participants with ASD. Reports by parents confirmed reduced social function only for the first-episode AN participants. ADOS Communication and Social Interaction Total scores were not associated with clinical features in any group.

First-episode participants performed similarly to controls on tests of social cognition. In contrast, recovered participants showed reduced social perception in a few tasks, more specifically perception of body gesture and perception of vocal prosody.

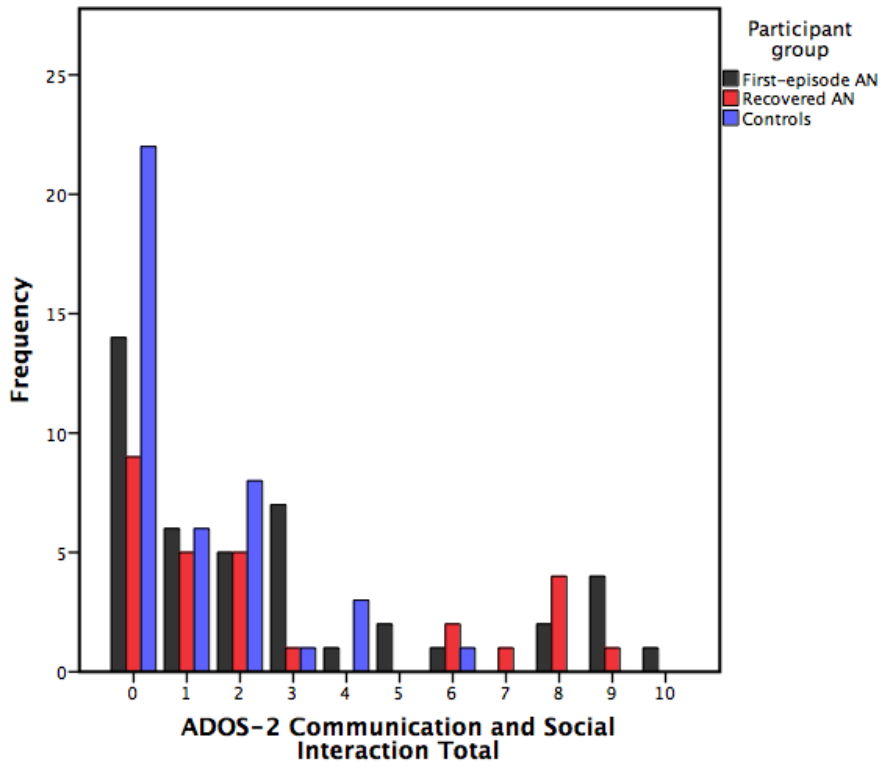

Figure 4. Frequencies of ADOS-Total scores for each participant group.

7.2 Paper 2

Groups displayed no significant difference in profile or level of neurocognitive functioning. Further, one neurocognitive domain significantly contributed to the prediction of ADOS-Total category beyond group and age: verbal memory. Lower verbal memory was associated with higher ADOS-Total category.

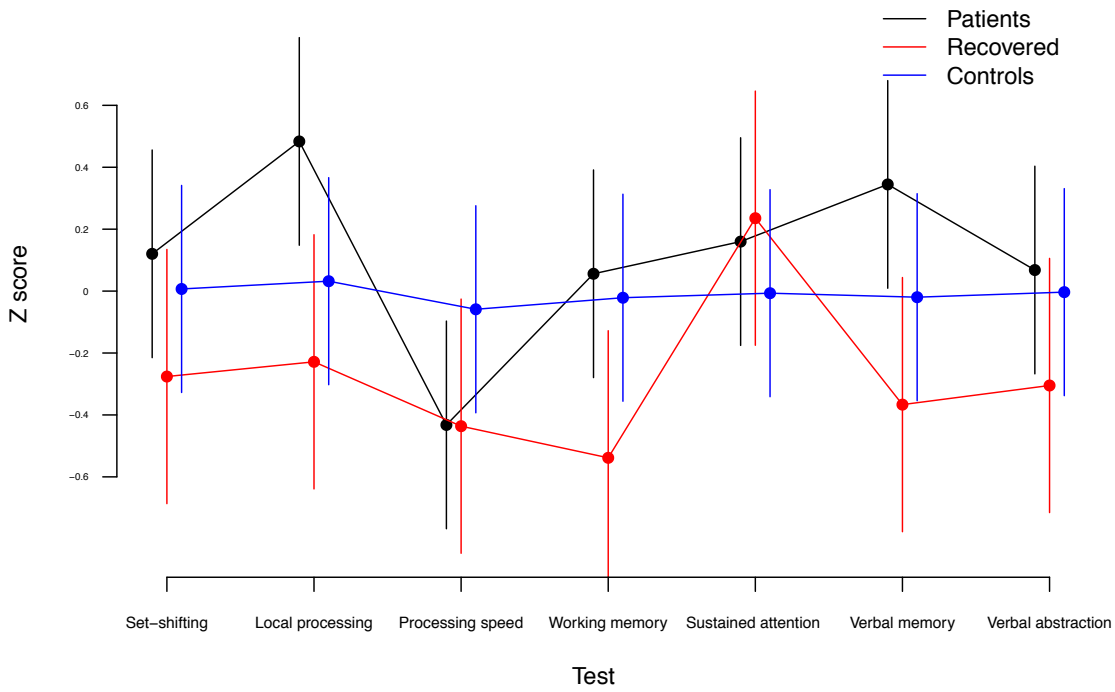

Figure 5. Z-scores of seven neurocognitive functions per group.

7.3 Paper 3

We observed higher olfactory sensitivity in both clinical groups compared with controls. Olfactory identification did not differ between groups in the full sample, but when we excluded participants with a depressive disorder, the participants with first-episode AN identified significantly more odors than participants recovered from AN. These results were not associated with the observed social function, reported in Paper 1. Further, they remained unchanged when controlling for the effect of self-reported depressive symptoms and anxiety, and the association between these symptoms and olfactory sensitivity was small and non-significant. Within the group of first-episode AN participants, olfactory sensitivity was unchanged when adjusting for BMI-percentile adjusted for age and for level of body dissatisfaction. In contrast, more precise olfactory identification was associated with less severe body dissatisfaction in participants with first-episode AN.

The subjectively perceived importance of olfaction did not differ between groups, when food-related items from the questionnaire were discounted. When food-related items were included,

participants with first-episode AN ascribed significantly less importance to olfaction than did the other two groups.

8 Discussion

The overall purpose of the work described in the present thesis was to study the ability of social function in the first phases of AN and after recovery in young individuals. We measured social function at the behavioral level using the best-validated instrument from the field of autism, ADOS. This was supplemented by assessing social cognition, neurocognition, and olfaction in the same participants to measure the association of social function with those domains to elucidate their possible role in the impairment of social function. As far as we know, this is the first study to screen out individuals with ASD to ensure that findings are not attributable to a subgroup with this comorbidity. Moreover, it is the first study that used the ADOS instrument systematically in a young sample of individuals with AN, and the first to study social function at the behavioral level in young individuals recovered from AN. The only prior study using ADOS to assess individuals with AN investigated a sample of adults who had difficulties with interaction or flexibility, and the two studies thus are not directly comparable.[168]

We documented that the young persons with first-episode AN, as well as those recovered from AN displayed impairments in communicative and reciprocal behavior that are typical in ASD, although they were not meeting diagnostic criteria for ASD. We also documented that those recovered were less effective in certain aspects of social cognition, and that young individuals with AN or recovered from AN had enhanced olfactory sensitivity. However, the impairments of social function in individuals with first-episode AN and in those recovered from AN on a group level were neither associated with social cognition nor with neurocognition or with olfaction. The following section discusses conclusions of the three papers taken together, as well as their contribution to the existing knowledge base, along with their limitations and implications.

8.1 Impairment of social function in non-ASD sample

Our findings confirm that impairment of social function of the kind typically observed in individuals with autism is present in young people with AN and in young people recovered from

AN, even after individuals with a diagnosis of ASD have been carefully excluded. This suggests firstly that impairment of social function occur at a higher level in non-ASD individuals with or recovered from AN compared with non-affected peers, and secondly, that the higher prevalence of individuals with ASD in prior studies of individuals with AN does not completely account for differences in social function between populations with AN and comparison populations. The presence of impairment of social function in both clinical groups may align with the developmental hypothesis that some traits of aberrant social functioning are stable and may precede AN and even remain present after recovery.

It is important to note, however, that the degree of impairment of social function in the young participants with AN for the majority (83%) lies below the range of impairment indicative of potential ASD.[145] Further, the phenotypical and descriptive nature of the present study was not designed to distinguish between mechanisms underlying the observed impairment of social function. Hence, we cannot conclude that the underlying mechanisms are similar between individuals with AN and individuals with ASD, because different underlying factors and mechanisms may well lead to a similar behavioral presentation.

8.2 Independence of social function and social cognition

Rather surprisingly, the individual's competence in social interactions as measured with the ADOS was not associated with the performance on a range of social cognitive tests. The absence of an association in any of the examined groups suggests that the observed impairment of social function may not be a straightforward down-stream effect of impaired social cognition in young people.[108] We expected to find this association, because social cognitive deficits have been documented in adults with AN.[28] It further suggests that the cognitive "building blocks" of social function may be intact in the early phases of AN. However, we cannot entirely discern whether the absence of an association between social function and social cognition is related to developmental timing, as social cognition continue to develop during adolescence, and a potential difference between individuals with AN and healthy individuals may not be detectable until later (see also Sections 8.4 and 8.10).

8.3 The role of neurocognition

The clinical groups in our study did not differ significantly from controls in any of the measured neurocognitive domains. This finding conflicts with the neurodevelopmental hypothesis of AN, which suggests that reduced set shifting and weak central coherence may represent viable neurocognitive markers for AN, however, based on impairments of that domain in adult AN samples,[169,170]. Further, our finding also seems to contrast with a clinical perspective, because young individuals with AN often demonstrate a behavioural rigidity, a strong attention to detail, and a resistance to change similar to observed behaviour in adult AN patients.[26] However, we cannot exclude that the behavioral signs of reduced flexibility or weak central coherence may be limited to illness-related areas of functioning or situations involving strong emotions, such as eating. Moreover, mental flexibility as assessed by set shifting task performance does not equal behavioral flexibility.[107]

In spite of the generally normal performance across neurocognitive domains, reduced verbal memory emerged as a predictor for social function across groups. The variance of verbal memory scores and ADOS-Total scores was smaller in the control group, and therefore the two clinical groups were chiefly responsible for the association between verbal memory and social function. Verbal memory may reflect episodic and associative memory for social interactions, which may normally provide a "road map" or a set of heuristics that are useful during social interaction.[171,172] Consequently, reduced verbal memory may result in less flexible and less spontaneous behaviors in real-life social interaction, which leads to reduced reciprocity. Deficits of episodic and associative memory may be reflected in reduced autobiographical memory, which has been documented in young persons and adults with AN.[60,173,174] Autobiographical memory is an important source of self-knowledge, and it may suffer in individuals with alexithymia, which is also well documented in young people and adults with AN (Tables 1 and 3).

8.4 Social cognition in recent-onset of AN

Our sample was homogeneous with regard to a recent onset of their first episode for the participants with AN. This is an important step towards distinguishing effects of chronicity from the effect of primary AN and possible antecedents of AN. Our sample of individuals with AN demonstrated a performance similar to that of controls in terms of social cognition and neurocognition. This suggests that either a) deficits in these domains observed in previous studies may be the effect of

AN duration, or b) individuals with such deficits may have a less favorable prognosis and therefore be overrepresented in samples with a longer history of AN, or c) social cognition is still developing during adolescence, and difference between normal and subnormal development is not measurable until later, or d) the state of AN may interfere with normal development and hamper the development of a range of until then normally developing capacities.

In support of the hypothesis of the effect of prolonged illness, mean duration of illness in prior studies of adults [25,28,54] is considerably longer (typically 3 - 9 years) than in our first-episode AN participants (less than 1 year). However, the association between reduced social function and poorer outcome of AN in the Gothenburg cohort [116] supports the hypothesis of poorer prognosis resulting in an overrepresentation of individuals with social difficulties in samples of adults. Our finding that the recovered group performed less competent than first-episode AN and control groups on two social cognitive tasks is in line with the possibilities that either subnormal development is not detectable until a later age, or that the presence of AN in a young person may hamper the natural development of social cognition.

Unfortunately, the present study is not able to conclude between these potential explanations. The answer would be highly relevant for young patients, because if duration of illness was the main reason for reduced social cognition, it would make a compelling case for early intervention, as well as underscore even more the importance of rapid weight restoration. If, on the other hand, a subgroup too small to detect in small samples such as ours had more trait-like deficits in those domains, it may prove essential for their outcome to detect and ameliorate these deficits early in the course of treatment to avoid poor long-term outcomes.[11]

8.5 Social function after recovery

Recovered participants met strict criteria for physiological and psychological recovery and had a history of not more than a few years of exposure to AN. Our young recovered group thus fills an important gap in the existing literature. The fact that both clinical groups similarly had impairment of social function underlines the stability of these findings. Notably, the recovered participants had normal adaptive social functions as assessed by Vineland-II Socialization domain and MROAS. Vineland-II measures the social functioning observed by parents.[146] The greater part of social life in adolescence and young adulthood takes place in other contexts than those observed by parents, which may explain the difference between parent reports and observational scores. MROAS is

based on self-report and adopts a much broader perspective on social function than ADOS,[99] asking, e.g., about the frequency of social contacts and social activities outside the home. In contrast, ADOS quantifies more fine-grained nuances of real-time social interaction, which may explain the differences between the two measures.

Moreover, the recovered participants performed worse than controls and first-episode AN participants in two aspects of social cognition (perception of bodily gesture and vocal prosody), but not in the remaining aspects tested. On the basis of the study design, we can only speculate that the effect of illness duration may have induced subtle impairments that survive the recovery from the manifest signs of illness.

8.6 The role of comorbid symptoms for social function

Our findings suggest that impairment in social function cannot be explained as epiphenomena to symptoms of anxiety or depression, although these are common in individuals affected by AN.[17,77,130] The recovered individuals had similar levels of self-reported depressive and anxiety symptoms (BYI-scores) as the controls, but they had elevated ADOS scores in line with the first-episode AN participants. The BYI-scores did not correlate significantly with ADOS scores within any of the groups.

8.7 Olfaction in AN

The heightened sensitivity to olfaction in our clinical groups and higher odor identification in first-episode AN participants without depression align with the pathological fear model of AN.[46] Our finding of a low and non-significant association between self-reported symptoms of anxiety and olfactory sensitivity or identification, however, does not seem to corroborate this. Possibly, the BAI-Y does not tap specifically into illness-related anxiety, but more into a general subjective distress. A high collinearity between BAI-Y and BDI-Y supports the latter hypothesis.

It has been suggested that individuals with AN have altered processing of reward,[48] but recent evidence suggests that this may be specific for illness-related stimuli, i.e. food tastes and smells, body sensations of satiety or fullness, and stimuli related to body image.[175] This has relevance for olfaction in AN, because smells stimulate appetite and attention to food,[122] experiences inherently anxiety-provoking for individuals with AN. An altered processing of illness-related stimuli such as odors may thus be driven by anxiety. Anxiety enhances olfaction, aligning with our finding of

higher olfactory sensitivity in both clinical groups. However, the lack of an association between social function and olfaction in our study confutes a role for olfaction in understanding the nature of impairment of social function in young persons with AN, and, given the contrasting results across studies, olfaction does not appear to be a valid marker for AN nor for the different phases of illness.

8.8 Findings of the present study in the context of AN models

8.8.1 The neurodevelopmental AN model

The absence of neurocognitive and social cognitive deficits early in the course of the disorder does not support the assumption of the neurodevelopmental model positing that young people with AN already have subtle cognitive deficits before the manifestation of the disorder. Further, the hypothesis of shared developmental mechanisms between AN and ASD is not supported by our findings of near to normal social cognition, normal set-shifting ability, and normal local processing in the clinical groups, functions that are typically affected in individuals with ASD. In spite of normal performance in these areas, both clinical groups displayed impairment in social function. This raises the question whether the behavioral manifestation of difficulties of social function may have different underpinnings in the two groups.

8.8.2 The social-emotional maintenance AN model

The interpersonal maintenance model of AN proposes a reinforcing interaction between trait and state factors and between intrapersonal and interpersonal factors in AN. This process may explain why first-episode AN participants in our study performed similarly to controls and not similarly to adult AN populations in other studies; because participants with first-episode have not yet been influenced by the effects of prolonged illness. It may further explain why our recovered sample displayed a few subtle deficits in social cognition not seen in first-episode AN participants: the recovered group had been ill for some time before recovery, although a shorter time than populations in most adult studies. Finally, our finding that the performance in the domains of neurocognition, social cognition, and social function were not associated (apart from the association between social function and verbal memory) is in line with the model´s suggestion of cognitive and socio-emotional factors as two distinguishable aspects in AN.[45]

8.8.3 The pathological fear AN model

The pathological fear model places learning and continuation of anxiety as central processes for

understanding social function AN. Turning to models of ASD, reduced empathy, reduced theory-of-mind, and reduced flexibility are thought to hamper social function.[154] However, the present study cannot discern the mechanisms responsible for the reduced social reciprocity observed during the ADOS in young individuals affected by AN. We controlled for the effect of self-reported symptoms of anxiety, but we cannot entirely discard the possibility that anxiety towards social interaction may account for some or all of the observed impairment of social function. A process of pathological fear learning as suggested by the pathological fear model in a subgroup of individuals with AN may explain a learned avoidance of social cues and situations, resulting in the observed impairment in social function in the absence of social cognitive deficits.

Impairment of social function was associated with verbal memory. One may speculate that anxiety and avoidance of social cues may be intensified in the case of impaired verbal memory, which puts the individual at risk for arriving at inaccurate interpretations in social situations. Alterations in anxiety networks may further explain the enhanced sensitivity to odors in our clinical groups. However, self-reported anxiety was not associated with olfaction or with social function in our study. In sum, our study cannot confirm or disconfirm the pathological fear model. However, the model offers a possible explanation for the contrasting findings of reduced social function in the context of normal social cognition and normal neurocognition. This possibility may be tested in future studies with a design that specifically addresses these questions.

8.8.4 Findings of the present study in the context of other empirical studies

Our findings confirm that social function is affected in young individuals with AN, and thus they supplement the inconclusive results regarding social communication in young persons with AN.[58,59,65,70] Further, our results demonstrated that impairment of social function cannot be reduced to a secondary effect of depression. We also confirmed that participants with first-episode AN display normal performance regarding an array of social cognitive tasks, thus we contributed to broaden the existing, limited results in this domain.[39,57] Finally, we confirmed that impairment of social function is present, even in the state of full recovery in young individuals. Direct comparisons with other studies including young recovered individuals are difficult due to less fine-grained measures of social function[77,116] or the inclusion of individuals with autistic traits.[34]

8.9 Methodological considerations

Several methodological choices have led to strengths as well as limitations in this clinical study. First, the study object of social function is not a clearly defined construct. Nevertheless, it captures the behavioral manifestations of social skills rather than their cognitive and emotional components, which is relevant because behavioral manifestations of impairment of social function often seem to interfere with treatment in clinical practice. Second, the main outcome measure of social function, ADOS, is arguably more ecologically valid than tests and self-report measures of social function due to its naturalistic observational nature. However, ADOS was developed in the field of autism and may not be sensitive to features specific to other patient groups. Third, if our groups had displayed a clear pattern of differences in the array of supplementary experimental social cognitive tests chosen, then we might have been able to further characterize the nature of impairment of social function in this particular population, but this was not the case; our clinical groups resembled controls in almost all tests of social cognition. This leaves us to consider either the possible dissociation between social function and social cognition, or the influence of the fourth methodological consideration: the validity of the social cognitive test battery employed. The ceiling effect compelled us to analyse subsets of items from each test, thus compromising the validity of the tests. If subtle differences in social cognition do exist in young persons with AN, it will require more challenging and thus more sensitive tests to measure them. The ceiling effect that we observed in all social cognitive tests is remarkable, because these tests have demonstrated sensitivity in other populations. For instance, the TASIT test has shown sensitivity in adolescents with brain injuries[176] and schizophrenia,[177] and in adults with brain injuries,[178] depression,[179] ASD,[180] and schizophrenia.[150,181] These patient groups, however, may display more pervasive difficulties in social cognition than individuals with AN. This is corroborated by the only other study using TASIT in AN, which did not find differences between adult patients and controls.[182]. Fifth, with regard to comorbid symptoms, we used a well-validated self-report measure, the BDI. However, it may measure transient experience of distress, which does not adequately account for the more pervasive effect that comorbid conditions may have on social function. The subgroups with different comorbid disorders were too small for subgroup analyses, and a larger sample size would be preferable to ascertain the true effect of comorbidity. Finally, initial power calculations based on social cognitive test results in adult samples had led us to believe that a sample size of 30 in each group would be sufficient. Based on the above observations, however, a larger sample would be preferable in order to discern no real effect as opposed to subtle effects and insensitive instruments,

and to analyse subgroups within the sample. In fact, we extended the recruitment period longer than initially planned to approach the desired number. Given the challenges of recruiting this patient group, a multi-site study might be the more realistic approach to generating a sufficient sample size.

8.10 Clinical implications

We identified a subgroup with impairment of social function that was not explained by symptoms of anxiety and depression after a carefully screening to exclude individuals with ASD. This finding in the absence of manifest ASD points to a need for individualized clinical assessment and personalized treatment options.

Based on our findings, ADOS is sensitive for and useful in assessing this impairment. Unfortunately, ADOS is time-consuming and requires specialized training and is therefore less attractive for screening purposes. Shorter interview or questionnaire measures exist and could be useful, but their sensitivity has yet to be demonstrated against ADOS in this particular patient group. Until then, ADOS represents the most reliable measure.

Moreover, we do not yet know the implications of the observed level of impairment of social function, or what degree of impairment (e.g. as ADOS-Total score) is associated with poorer treatment response, prognosis, or life quality in this population. A longitudinal follow-up of samples such as ours may provide this information in the future. Until such knowledge is available, the conventional ADOS threshold may be useful, because scores above threshold signal a high chance of pervasive impairments.

With regard to treatment options, several approaches appear relevant based on our findings. Cognitive Remediation Therapy for AN has shown promising results in focusing on the "how rather than the what" of cognition,[33,183] and modules facilitating verbal or episodic memory may further improve this approach and make it more specific. In general, however, our findings imply that neurocognitive deficits should not serve as a primary focus when treating young persons with AN, because neurocognition seems basically intact in these patients. It may, however, be beneficial to focus on recruiting these functions more effectively in social situations.

Most psychotherapy approaches entail considerable demands on implicit social reciprocity as a vehicle for reflection and corrective experiences. For young persons with AN, therapists should use verbal and visual techniques to provide explicit information on agenda, intention, and expectations,

and share their intentions as explicitly as possible. Techniques from mentalization-based therapy,[184] or the use of social scripts and stories[185] may be adapted for targeting core AN symptoms in treatment while taking impairment of social function into account. Social anxiety may be important to target in treatment, as it may hamper treatment response via impact on social functioning, even in the absence of a diagnosis of social phobia.[49]

9 Conclusions and perspectives for further research

We have confirmed, that both individuals with first-episode AN and those recovered display social function impairments on a group level, even in the explicit absence of a diagnosis of infantile autism or Asperger syndrome. These impairments of social function were not explained by symptoms of anxiety or depression, and in participants with a first-episode AN, they were not related to AN symptom severity. In clinical practice, consequently, it is important to assess impairment of social function in youth with AN, and include such impairment in treatment planning for those who need it.

Importantly, the observed impairment of social function was not associated with specific social cognitive deficits. Additionally, it was not associated with local processing bias or with cognitive inflexibility, traits that are frequently reported in adults with AN. In contrast, reduced verbal memory was associated with reduced social function. Lastly, both individuals with first-episode AN and those recovered displayed higher olfactory sensitivity. Those with first-episode AN who did not have a comorbid depressive disorder additionally showed better olfactory identification ability. This finding suggests that the processing of such sensory stimuli is altered already in the early phases in AN.

This study highlights an urgent need for longitudinal studies of social function, social cognition, neurocognition, and olfaction in AN. These longitudinal studies should aim to trace the development of impairment of social function, as well as their interaction with treatment response and risk of relapse. Furthermore, ecologically valid social-cognitive tests should supply current methodologies to avoid ceiling effects in adolescents and young adults with normal intelligence.

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11 Papers and declarations of co-authorship

11.1 Paper 1: Impairment of Social Function in Young Females With Recent-Onset Anorexia Nervosa and Recovered Individuals

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Original article

Impairment of Social Function in Young Females With Recent-Onset Anorexia Nervosa and Recovered Individuals

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A B S T R A C T

Purpose: A subgroup of individuals with anorexia nervosa (AN) displays social difficulties; however, it is not clear if individuals with comorbid autism spectrum disorders account for these difficulties.
Methods: We compared social function using the Autism Diagnostic Observation Schedule in 43 young females with first-episode AN who did not have comorbid autism spectrum disorder, 28 individuals recovered from adolescent-onset AN, and 41 healthy comparison individuals (age range 14–22 years). We measured adaptive behavior with the Vineland-II parent questionnaire, and aspects of social cognition with psychological tests, such as the Reading-the-Mind-in-the-Eyes test, Profile of Nonverbal Sensitivity short version, The Awareness of Social Inference Test, Animated Triangles, and the CANTAB Affective Go/No-go task.
Results: Participants with first-episode AN and those recovered from AN displayed difficulties in social function, which were not associated with body mass index or other state factors of the disorder in those with first-episode AN. Mood problems and anxiety were not associated with these difficulties. Parents rated participants with first-episode AN lower than recovered and control participants on the Socialization Domain of Vineland-II. Finally, only participants recovered from AN demonstrated deficits in specific domains of social cognition: perceiving nonverbal bodily gesture and vocal prosody.
Conclusions: Young females with first-episode AN and those recovered from AN displayed impairments in social function, which may represent more stable traits of the disorder. Only participants recovered from AN demonstrated deficits in social cognition.

IMPLICATIONS AND CONTRIBUTION

On the group level, young females with anorexia nervosa without autism spectrum disorders displayed impaired social function but no inferior social cognition capacity. Recovered individuals were impaired in their social function and showed few social cognitive deficits. State factors of the illness did not explain impairment of social function.

Conflicts of Interest: The authors report no conflicts of interest.

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Social difficulties are inherent in current models of vulnerability and maintenance of anorexia nervosa (AN) [1], and a better understanding of these may refine interventions and improve outcome for this serious disorder. However, evidence of social difficulties in young individuals with a recent onset AN and in those recovered from AN is limited. We studied these difficulties at two descriptive levels: social function and social cognition.

Social function encompasses interactive behavior and capacity for socioemotional reciprocity [2]. Social cognition is broadly defined as the mental operations underlying social interaction [3]. Deficits in social cognition are documented in individuals with AN [4,5]. However, the relationship between behavioral and cognitive aspects of social difficulties is not clear, and instruments to reliably quantify difficulties in social function are scarce. The Autism Diagnostic Observation Schedule (ADOS) measures observable interactive behavior in a standardized form [6]. It is intended to qualify a diagnosis of autism spectrum disorder (ASD), a spectrum of developmental disorders characterized by sociocommunicative deficits, and mental and behavioral inflexibility. However, the ADOS quantifies behaviors without assumptions of possible underlying mechanisms, and we therefore used the ADOS to assess social function in AN.

We investigated social function in young females with first-episode AN and those recovered from adolescent-onset AN, both groups without comorbid ASD. In exploratory analyses, we assessed social function via parent reports and social cognition via experimental tests. Finally, we explored associations between social function and social cognition across diagnostic groups.

We hypothesized that young females with first-episode AN would show impairments in social function and that those recovered from AN would perform intermediate between those with first-episode AN and controls.

Methods

Subjects

We invited young females with a recent onset of their first episode of AN (International Classification of Diseases [ICD-10]: F50.0 or F50.1) from the Centre for Child and Adolescent Mental Health Services (CAMHS; 14- to 17-year-old patients), the Capital Region of Denmark. Recent onset was defined as onset within a maximum of 12 months. Prior psychological treatment was allowed but infrequent, as CAMHS is usually the first line of treatment in Denmark. Inclusion criteria for this group included a body mass index (BMI) percentile corrected for age $<$25th for 14–15 year olds and a BMI $<$18.5 kg/m^2 for participants 16 years or older. All eligible CAMHS patients between July 2012 and March 2015 were invited if possible. In addition, we recruited a few young adults with first-episode AN from the Stolpegaard Psychotherapy Centre (18- to 21-year-old patients), the Capital Region of Denmark. Our first-episode AN participants thus were representative of a young population with a recent onset, without substantial epiphenomena of chronicity.

Second, we invited young females recovered from AN (ICD-10: F50.0 or F50.1) with onset in late childhood or adolescence. They were identified through a quality assurance survey. Recovery was defined as Eating Disorders Examination (EDE) global score within one standard deviation (SD) of non-AN norms [7], $\geq$9 points on the Morgan Russell Outcome Assessment Schedule [8], and no current eating disorder pathology or current treatment for an eating disorder. We established the absence of eating disorder pathology for the last 3 months with EDE diagnostic questions and normal body weight for the last 12 months via self-report.

Finally, we invited control participants via advertisements in state schools, halls of residence, and colleges in the catchment area of the hospital. Inclusion criteria were a normal body weight and absence of psychiatric disorders throughout their lifetime (minor exceptions included transient childhood tics and adjustment disorders).

Comorbidity is well documented during and after the course of AN [9], and accordingly, we did not exclude recovered individuals with past or present psychopharmacological treatment. To address our primary question of whether social deficits were confined to individuals with comorbid ASD, exclusion criteria further included ASD for all three groups. As a screening for undetected ASD, parents completed the Social Communication Questionnaire [10] and the Asperger Syndrome Screening Questionnaire-Revised Extended Version [11]. If ratings were above the established cutoffs, we interviewed parents with the Autism Diagnostic Interview-Revised [12]. Combined, these procedures ensured that no participants fulfilled diagnostic criteria for childhood autism (F84.0) or Asperger syndrome (F84.5).

We assessed psychiatric symptoms with the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version [13] and the Beck Youth Inventory [14], and intelligence with the Reynolds Intellectual Assessment Scales [15]. Clinical data at the time of treatment for AN were available for the recovered participants, enabling comparison of AN severity at onset between the clinical groups. Finally, the regional Scientific Ethical Committees (project number H-2-2012-027) and the Danish Data Protection Agency approved the study, and participants and legal caretakers gave informed consent according to the guidelines of the Danish Health and Medicines Authority.

Outcome measures

We measured social function with the ADOS-2, Danish version, module 4 [6]. During the ADOS observation, the observer orchestrates a series of situations with a social press for communication and interaction. The ADOS algorithm yields two subscales: Communication and Reciprocal Social Interaction, and a "Communication and Social Interaction Total" (ADOS-Total). Our main outcomes were the ADOS-Total and the two subscales. In module 4, the clinical cutoff for ADOS-Total is $\geq$7, for the Communication Subscale is $\geq$2, and for the Reciprocal Social Interaction Subscale is $\geq$4. These cutoffs represents a 90% sensitivity and a 93% specificity for distinguishing ASD from non-spectrum cases [16].

Interrater reliability of the main rater and an experienced ADOS-certified psychologist blind to group was monitored in 15 randomly chosen cases, and weighted Kappa for all items was satisfactory (.77).

We used the Socialization Domain of Vineland-II [17] as an additional probe of parent-reported social function measuring adaptive behaviors in everyday life.

We documented social cognitive performance with tests tapping into the following four subdomains identified by the Measurement and Treatment Research to Improve Cognition in Schizophrenia [18].

Emotion perception. "Reading the Mind in the Eyes—Revised" (RME-R) [19] displays photos of the eye region and words describing complex feelings.

Social perception. The "MiniPONS" [20], a short version of the Profile of Nonverbal Sensitivity test, consists of 64 short film clips of body gestures, facial expressions, and/or vocal prosody.

Theory of Mind (ToM). Twelve cartoons of Animated Triangles (AT) [21] were presented in a fixed, random order using the multiple-choice response format [21]. The Awareness of Social Inference Test (TASIT), Part 2: Social interference—Minimal, Danish version [22], presents short movies with either sincere, simple sarcastic, or paradoxical sarcastic interactions.

Affective bias. CANTAB Affective Go/No-go (AGN) [23] consists of briefly displayed positive and negative words where target category alternates.

We translated phrases and questions for the RME-R, Mini-PONS, and AT into Danish in agreement with the authors of the tests. Tests were presented in a fixed order along with interviews and questionnaires during 2–3 appointments, scheduled as soon as possible.

Statistical procedures

Statistical analyses were carried out in IBM SPSS Statistics version 22 (IBM Corp., Armonk, New York). We tested our main hypothesis with ADOS-Total, Communication Subscale, and Reciprocal Social Interaction Subscale as dependent variables and group as independent variable using analyses of variance (ANOVAs). If assumptions for parametric analyses were not met, the test was replaced by nonparametric alternatives, that is, independent samples Kruskal–Wallis tests. We used Bonferroni correction of the alpha level according to three main analyses ($p < .017$) to control the type I error, and we used independent samples Mann–Whitney *U* Tests for post hoc analyses. ADOS scores were not adjusted for age because of age independence of the algorithms of ADOS, module 4 [24].

All remaining analyses were regarded as exploratory. We used Spearman's ρ to analyze the association between ADOS-Total and Beck Depression Inventory Youth and Beck Anxiety Inventory Youth within each group. We explored the association of social function with body weight and symptom severity among individuals with first-episode AN by calculating bivariate correlations of the ADOS-Total with BMI adjusted for age, EDE global score, and each of the four EDE subscales.

We used independent samples Kruskal–Wallis tests and a forest-type plot to detail profiles of single-item differences in ADOS. Vineland-II Socialization domain Index scores was analyzed with one-way ANOVA. We weighted cases with a standardized frequency weight based on four age groups, to adjust the social cognitive test scores for group difference in age. Preliminary inspections revealed substantial ceiling effects, and consequently we excluded items, which 95% of controls answered correctly (2 of 36 RME-R photos; 17 of 64 MiniPONS clips; 5 of 15 TASIT films; 8 of 12 AT film–type questions). We used ANOVAs to investigate between-group differences of these reduced test sets and followed up with Tukey or Games-Howell post hoc test. We assessed normality of residuals by inspection of Q-Q plots and inspected box plots to secure there were no extreme outliers.

Affective bias was calculated as difference between mean response time of positive and negative blocks of the AGN. Finally, to explore associations between social function and social cognition, we entered those social cognition test variables showing group difference and age as independent variables in an ordinal logistic regression (proportional odds) with ADOS-Total cut into categories as the dependent variable, as model assumptions for ADOS-Total as continuous outcome was questionable. The categories were zero (no observed deviation), low (scores of 1 through 3), medium (scores of 4 through 6), and high (scores above clinical cutoff, i.e., ≥7). Interaction terms with groups were inspected, and if significant, groups were to be analyzed separately.

Results

Subjects

In total, 43 first-episode AN participants, 28 recovered participants, and 41 healthy participants agreed to participate (Table 1). Mean weight gain among individuals with acute AN from clinical assessment to first testing session was 2.1 kg (median = 1.7 kg, SD = 2.3), and mean duration from first to last visit was 8.0 days (median = 7.0 days, range = 1–23 days, SD = 6.3). Duration from first to last visit was similar between groups (recovered participants mean = 5.6 days [median = 3 days, range = 1–28, SD = 6.7], controls mean = 8.2 days [median = 6.5, range = 1–35, = SD 8.2], independent samples Kruskal-Wallis Test: χ^2 [2] = 3.866, $p = .15$). Current comorbidity was comparable across first-episode AN participants and those recovered from AN (Table 1). The three groups did not differ with respect to intelligence, parental education, or family structure; however, the group of recovered participants was older (Table 1).

Severity of illness at onset was comparable between the diagnostic groups; they had similar mean BMI percentiles corrected for age at onset (first-episode AN = 3.84 [SD = 5.4]; recovered = 4.83 [SD = 6.0]), rate of AN subtypes (binge/purge: first-episode AN = 9%; recovered = 14%), rate of comorbid depression (first-episode AN = 18.6%; recovered = 14.3%), and mean EDE scores (Table 1) when first presenting to the clinic. However, the recovered participants had a lower mean age at time of treatment onset (Table 1).

Primary analyses of social function

Participants with first-episode AN and those recovered from AN demonstrated higher mean rank of ADOS-Total scores than controls (independent samples Kruskal–Wallis Test: χ^2 [2] = 8.277, $p = .002$; Table 2 and Figure 1). Moreover, groups differed in mean rank of their Reciprocal Social Interaction Subscale score (independent samples Kruskal–Wallis Test: χ^2 [2] = 11.954, $p = .003$; Table 2). The two clinical groups did not differ on any ADOS scale. A subgroup of participants with first-episode AN (N = 7; 16%) and of those recovered (N = 6; 21%) exceeded an ADOS-Total score above the clinical cutoff for an autism spectrum classification according to the ADOS system (≥7), and most of these (first-episode AN: N = 6, recovered: N = 4) also exceeded the clinical cutoff on each subscale separately (Communication [≥2], Social Interaction [≥4]), suggesting two distinguishable subgroups: "normal" scorers and "high" scorers on the ADOS-Total. None of the control participants exceeded clinical cutoff on the ADOS classification (Table 2).

Table 1
Sample description

	First-episode AN (N = 43)	Recovered AN (N = 28)	Controls (N = 41)	Test statistics	Pairwise comparison (p)
Age in years, mean (SD)	16.1 (1.5)	18.4 (1.6)	17.7 (2.2)	ANOVA F (2,109): 16.119 $p < .001$	First-episode<recovered $p < .001$ First-episode<controls $p < .001$ Recovered-controls ns
Age at time of treatment, mean (SD)	16.1 (1.5)	14.8 (1.6)	n/a	Independent Samples t(69):3.357 $p = .001$	First-episode>recovered $p = .001$ First-episode-controls ns Recovered-controls ns
Parents' highest education, years, mean (SD)	16.1 (2.3)	14.8 (2.8)	15.3 (2.4)	ANOVA F (2,109): 2.591 $p = .08$	First-episode-recovered ns First-episode-controls ns Recovered-controls ns
Living with both parents together, N (%)	24 (56%)	17 (61%)	21 (51%)	Kruskal-Wallis: χ^2 (2) = .613 $p = .74$	First-episode-recovered ns First-episode-controls ns Recovered-controls ns
BMI (kg/m^2), mean (SD)	16.6 (1.2)	21.3 (1.8)	22.0 (2.6)	ANOVA F (2,109): 92.608 $p< .001$	First-episode<recovered $p < .001$ First-episode<controls $p < .001$ Recovered-controls ns
BMI percentile corrected for age, mean (SD)[a]	7.5 (7.6)	47.3 (19.0)	56.9 (21.2)	ANOVA F (2,109): 101.948 $p < .001$	First-episode<recovered $p < .001$ First-episode<controls $p < .001$ Recovered-controls ns
EDI eating disorder risk composite, mean (SD)[b]	47.7 (10.1)	36.5 (6.4)	36.1 (7.0)	ANOVA F (2,105): 24.861 $p < .001$	First-episode>recovered $p < .001$ First-episode>controls $p < .001$ Recovered-controls ns
EDE global score at time of treatment, mean (SD)[c]	2.8 (1.5)	2.8 (1.3)	n/a	Independent Samples t-test t(54): − .051 $p = 1.0$	First-episode-recovered ns
EDE global score at time of testing, recovered participants, mean (SD)	n/a	.6 (.5)	n/a		
Duration of treatment for recovered participants (months) mean (SD)	n/a	23.9 (11.8)	n/a		
General intelligence quotient, RIAS, mean (SD)	107.7 (10.5)	102.8 (11.5)	107.3 (9.5)	ANOVA F (2,109): 2.137 $p = .12$	First-episode-recovered ns First-episode-controls ns Recovered-controls ns
Comorbid depressive disorder, N (%)[d,e]	8 (19)	3 (11)		Fishers exact (2-sided)	.51
Comorbid OCD, N (%)[e]	3 (7)	0 (0)		Fishers exact (2-sided)	.27
Comorbid anxiety other than OCD, N (%)[e]	4 (9)	5 (18)		Fishers exact (2-sided)	.30

BMI = body mass index; EDE = Eating Disorder Examination; EDI = Eating Disorder Inventory-3; n/a = not applicable; ns = non-significant; RIAS = Reynolds Intellectual Assessment Scales.

[a] BMI percentiles corrected for age <.02, calculated as = .02. Participants >20 yr old given percentile of 20 yr.

[b] EDI-3 answers are missing from four FeAN.

[c] EDE data available from time of treatment for recovered participants, N = 13 (46%). T-scores are derived from American norms in the absence of Danish norms for adolescents.

[e] Depressive disorder includes mild depression, moderate depression and severe depression according to ICD-10.

[f] We used the term "comorbid" although anxiety and depression are only comorbid to AN in the case of the participants with first-episode AN.

Exploratory analyses

In bivariate within-group analyses, ADOS-Total showed nonsignificant correlations with self-reported symptoms of depression and of anxiety. However, there was a trend toward a significant correlation between ADOS-Total scores and symptoms of depression in the first-episode AN group (Table 3). In bivariate analyses within first-episode AN participants, ADOS-Total scores were not associated with BMI percentile, EDE global score, nor EDE subscales (Table 3).

Participants with first-episode AN differed from controls concerning the algorithm items "Offers Information," "Emphatic or Emotional Gestures," "Facial Expressions Directed to Others," "Communication of Own Affect," "Amount of Social Overtures," "Amount of Reciprocal Social Communication" and "Overall Quality of Rapport." Recovered participants differed from controls concerning the items "Offers Information," "Reporting of Events," "Facial Expressions Directed to Others," "Communication of Own Affect," "Amount of Social Overtures," "Amount of Reciprocal Social Communication," and "Overall Quality of Rapport" (Table 3; Figure 2).

Vineland-II

Participants with first-episode AN, but not those recovered, were reported to have reduced adaptive function with a small effect size (Table 3). The correlation between ADOS-Total and Vineland-II Socialization Domain was small ($r = -.2$, $p = .03$).

Social cognition

Groups differed in specific aspects of social perception: MiniPONS body gestures with a medium effect size ($R^2 = .14$), and MiniPONS vocal prosody with a small effect size ($R^2 = .07$; Table 3). Post hoc tests showed that recovered participants performed worse than first-episode AN participants in these two tests (Cohen's $d = -0{,}89$ and $-.64$, respectively) and had lower scores than controls in MiniPONS body gestures (Cohen's $d = -.77$). However, groups did not differ regarding the two other classes of stimuli in the MiniPONS (facial expression, and facial expression and vocal prosody), nor regarding RME-R, TASIT, AT, or AGN. Participants with first-episode AN performed similar to control participants on all tests of social cognition.

Association between social function and social cognition

In an ordinal regression model for prediction of ADOS-Total category, neither age, MiniPONS body gestures, nor MiniPONS

Table 2
Main analyses of group differences in ADOS

ADOS algorithm scores	First-episode AN (N = 43)	Recovered AN (N = 28)	Controls (N = 41)	Test statistics[a]		Post hoc comparisons[b] (unadjusted *p* value, effect size[c])
ADOS-Total (= ADOS Communication and Social Interaction); mean (SD), mean rank	2.77 (3.1), 63.5	2.79 (3.2), 62.1	1.05 (1.5), 45.3	χ^2 (2) = 8.277	.02	First episode–recovered: ns First episode > controls: .008, abs(*r*) = .29 Recovered > controls: .03, abs(*r*) = .27
ADOS Communication Subscale; mean (SD), mean rank	1.35 (1.6), 61.0	1.36 (1.6), 61.8	.66 (1.0), 48.1	χ^2 (2) = 4.928	.09	
ADOS Reciprocal Social Interaction Subscale; mean (SD), mean rank	1.42 (1.8), 64.7	1.43 (1.8), 62.3	.39 (.9), 44.0	χ^2 (2) = 11.954	.003	First episode–recovered: ns First episode > controls: .001, abs(*r*) = .37 Recovered > controls: .01, abs(*r*) = .31
Participants with ADOS-Total exceeding cutoff (≥7), N (%)	7 (16%)	6 (21%)	0 (0%)			

ADOS = Autism Diagnostic Observation Schedule; AN = anorexia nervosa; ns = nonsignificant; SD = standard deviation.
[a] Independent samples Kruskal–Wallis test unless otherwise specified.
[b] Mann–Whitney *U* test.
[c] Effect size calculated as *r* = standardized test statistic/√N, reported in absolute values.

vocal prosody was significant predictors, and only group was a significant factor.

Discussion

Participants with first-episode AN and recovered from AN displayed similar degrees of impairments of social function on the group level, confirming that social deficits in AN are not limited to the acute state of illness—a finding that was driven by a subgroup of participants in each clinical group. Moreover, participants recovered from AN demonstrated impairments of their perception of social stimuli, whereas participants with first-episode AN demonstrated normal performance on these measures.

The impairment in social function measured with ADOS highlights some similar traits between individuals with AN and those with ASD, although the social impairments we observed in most AN participants were smaller than those reported in ASD [6]. Elevated autistic traits have been confirmed in studies of adults with AN using other instruments, that is, questionnaires [25], or the ADOS [26]. Two studies assessed social function in young AN patients with other instruments and reported similar findings as ours [27,28]. However, our study extended and clarified these observations by using the ADOS instrument in a representative sample of young females with AN and by excluding individuals with known or detected comorbid ASD.

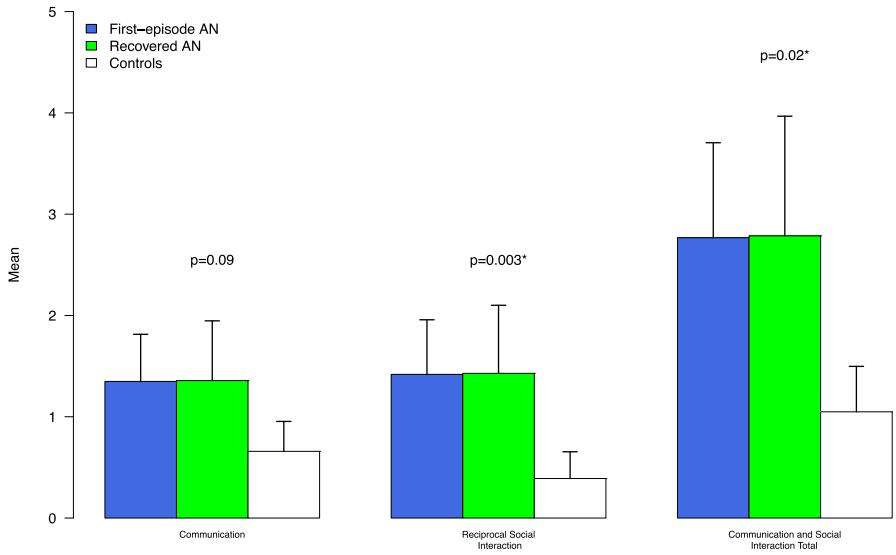

Figure 1. ADOS algorithm scores. *Significant group differences. Error bars represent 95% confidence interval.

Table 3
Exploratory analyses of ADOS, Vineland-II and tests of social cognition

Exploratory measures	First-episode AN (N = 43)	Recovered AN (N = 28)	Controls (N = 41)	Test statistics[a]	*p*	Post hoc comparisons[b] (unadjusted *p*-value, effect size[c])
Supplementary ADOS subscales (beyond study hypotheses)						
ADOS Imagination/Creativity, mean (SD)	.51 (.6)	.68 (.5)	.32 (.6)	Kruskal-Wallis $\chi^2(2)$: 7.114	.03	First-episode<recovered ns First-episode>controls ns Recovered>controls $p = .02$
ADOS Stereotyped behaviors and restricted interests, N with score > 0	N = 1 (2%)	N = 0 (0%)	N = 0 (0%)	$\chi^2(2)$:1.619	.5	
Associations between social function and clinical variables (bivariate within-group correlations)						
ADOS and BDI-Y	$r_s = .29$, $p = .06$	$r_s = .10$, $p = .62$	$r_s = .11$, $p = .49$			
ADOS and BAI-Y	$r_s = .25$, $p = .10$	$r_s = -.19$, $p = .35$	$r_s = -.003$, $p = .99$			
ADOS and BMI percentile corrected for age (*)	$r_s = -.03$, $p = .86$	n/a	n/a			
ADOS and EDE global score	$r_s = .08$, $p = .61$	n/a	n/a			
ADOS and EDE subscale Restraint	$r_s = .10$, $p = .54$	n/a	n/a			
ADOS and EDE subscale Eating Concern	$r_s = .11$, $p = .51$	n/a	n/a			
ADOS and EDE subscale Weight Concern	$r_s = .12$, $p = .53$	n/a	n/a			
ADOS and EDE subscale Shape Concern	$r_s = .26$, $p = .14$	n/a	n/a			
ADOS single items: between-group differences[d]						
ADOS item: A5, Offers Information, mean rank	58.65	64.09	49.06	Kruskal-Wallis $\chi^2(2) = 8.715$	.01	First-episode AN>controls: $p = .03$, abs(r) = .2 Recovered>controls: $p = .002$, abs(r) = .4 First-episode AN<Recovered ns
ADOS item: A7, Reporting of Events, mean rank	54.88	71.11	48.22	Kruskal-Wallis $\chi^2(2) = 12.903$	.002	First-episode AN>controls ns Recovered>controls: $p < .001$, abs(r) = .4 First-episode AN<Recovered: $p = .02$, abs(r) = .3
ADOS item: A10, Emphatic or Emotional Gestures, mean rank	63.15	56.18	49.74	Kruskal-Wallis $\chi^2(2) = 6.090$	.05	First-episode AN>controls: $p = .01$, abs(r) = .3 Recovered>controls ns First-episode AN>Recovered ns
ADOS item: B2, Facial Expressions Directed to Others, mean rank	57.43	68.50	47.33	Kruskal-Wallis $\chi^2(2) = 11.641$	.003	First-episode AN>controls: $p = .05$, abs(r) = .2 Recovered>controls: $p = .001$, abs(r) = .4 First-episode AN<Recovered ns
ADOS item: B5, Communication of Own Affect, mean rank	61.31	65.14	45.55	Kruskal-Wallis $\chi^2(2) = 10.747$	.005	First-episode AN>controls: $p = .01$, abs(r) = .3 Recovered>controls: $p = .002$, abs(r) = .4 First-episode AN<Recovered ns
ADOS item: B10, Amount of Social Overtures, mean rank	58.59	69.75	45.26	Kruskal-Wallis $\chi^2(2) = 12.918$	.002	First-episode AN>controls: $p = .02$, abs(r) = .2 Recovered>controls: $p < .001$, abs(r) = .4 First-episode AN<Recovered ns
ADOS item: B12, Amount of Reciprocal Social Communication, mean rank	65.64	59.54	44.84	Kruskal-Wallis $\chi^2(2) = 14.606$	.001	First-episode AN>controls: $p > .001$, abs(r) = .4 Recovered>controls: $p = .006$, abs(r) = .3 First-episode AN>Recovered ns
ADOS item: B13, Overall Quality of Rapport, mean rank	60.98	63.36	47.12	Kruskal-Wallis $\chi^2(2) = 8.119$	.02	First-episode AN>controls: $p = .01$, abs(r) = .2 Recovered>controls: $p = .01$, abs(r) = .3 First-episode AN<Recovered ns
Vineland-II and social cognition tests[e]						
Vineland II Socialization Domain, Index score	106.1 (10.5)	108.8 (9.1)	111.8 (4.9)	F (2,90): 3.794 $R^2 = .08$	.03	First-episode AN<controls: $p = .009$, $d = -.7$ Recovered<controls ns First-episode AN<Recovered ns
MiniPONS Total, correct answers*	35.6 (3.2)	32.5 (4.6)	33.9 (3.3)	F (2,109): 6.666 $R^2 = .11$	.002	First-episode AN>controls: $p = .05$, $d = .5$ Recovered<controls ns First-episode AN>Recovered: $p = .008$, $d = .8$

(*continued on next page*)

Table 3
Continued

Exploratory measures	First-episode AN (N = 43)	Recovered AN (N = 28)	Controls (N = 41)	Test statistics[a]	*p*	Post hoc comparisons[b] (unadjusted *p*-value, effect size[c])
MiniPONS Body Gestures, correct answers*	9.2 (1.3)	7.7 (1.9)	9.0 (1.3)	F (2,109): 9.161 R^2 = .14	<.001	First-episode AN>controls ns Recovered<controls: p = .01, d = −.8 First-episode AN>Recovered: p = .003, d = .9
MiniPONS Facial Expression, correct answers*	5.0 (1.1)	4.6 (1.4)	5.0 (1.1)	F (2,109): 1.431 R^2 = .03	.24	
MiniPONS Vocal Prosody, correct answers*	11.1 (1.4)	10.1 (2.0)	10.3 (1.7)	F (2,109): 3.939 R^2 = .07	.02	First-episode AN>controls ns Recovered<controls ns First-episode AN>Recovered: p = .04, d = .6
MiniPONS Facial Expression, and Vocal Prosody correct answers*	10.3 (1.5)	10.1 (1.2)	9.6 (1.4)	F (2,109): 2.755 R^2 = .05	.07	
RME-R, correct answers*	25.6 (3.2)	23.8 (2.7)	24.1 (3.7)	F (2,109): 3.223 R^2 = .06	.04	First-episode AN>controls ns Recovered<controls ns First-episode AN>Recovered ns
AT Film type, correct answers*	2.6 (.7)	2.4 (.9)	2.7 (.7)	Kruskal-Wallis $\chi^2(2)$ = 7.997	.24	
AT feelings questions, correct answers	6.4 (1.3)	6.3 (1.2)	6.1 (1.2)	F (2,109): .513 R^2 = .01	.60	
TASIT Total, correct answers*	33.9 (3.2)	32.4 (2.8)	33.4 (3.7)	F (2,109): 1.935 R^2 = .03	.15	
TASIT Sincere, correct answers*	16.4 (2.3)	15.8 (2.9)	16.2 (3.2)	Kruskal-Wallis $\chi^2(2)$ = .726	.70	
TASIT Sarcastic, correct answers*	17.5 (1.9)	16.6 (2.1)	17.2 (2.1)	F (2,109): 1.795 R^2 = .03	.17	
AGN, difference in correct latency	9.2 (31.7)	5.7 (31.1)	10.2 (34.8)	F (2,103): .161 R^2 = .003	.85	

* = reduced test sets excluding items with ceiling effect. ADOS = Autism Diagnostic Observation Schedule; AGN = CANTAB Affective Go/No-go test; AT = Animated Triangles; BAI-Y = Beck Anxiety Inventory Youth; BDI-Y = Beck Depression Inventory Youth; BMI = body mass index; EDE = Eating Disorder Examination; MiniPONS = Profile of Nonverbal Sensitivity, short version; n/a = not applicable; ns = non-significant; RME-R = Reading-the-Mind-in-the-Eyes Revised; SD = standard deviation; TASIT = The Awareness of Social Inference Test.

[a] One-way ANOVA if not otherwise specified.

[b] Post hoc analyses for parametric tests: Tukey or Games-Howell, for nonparametric tests: Mann-Whitney U Test.

[c] Effect size: d = Cohen's d. r calculated as r = standardized test statistic/√N, reported in absolute values.

[d] Only displaying those ADOS items (communication and social interaction clusters), where one or both clinical groups displayed a distribution significantly different from controls (after post hoc Bonferroni correction).

[e] MiniPONS Total and TASIT total are not used in analyses, but are included here for information.

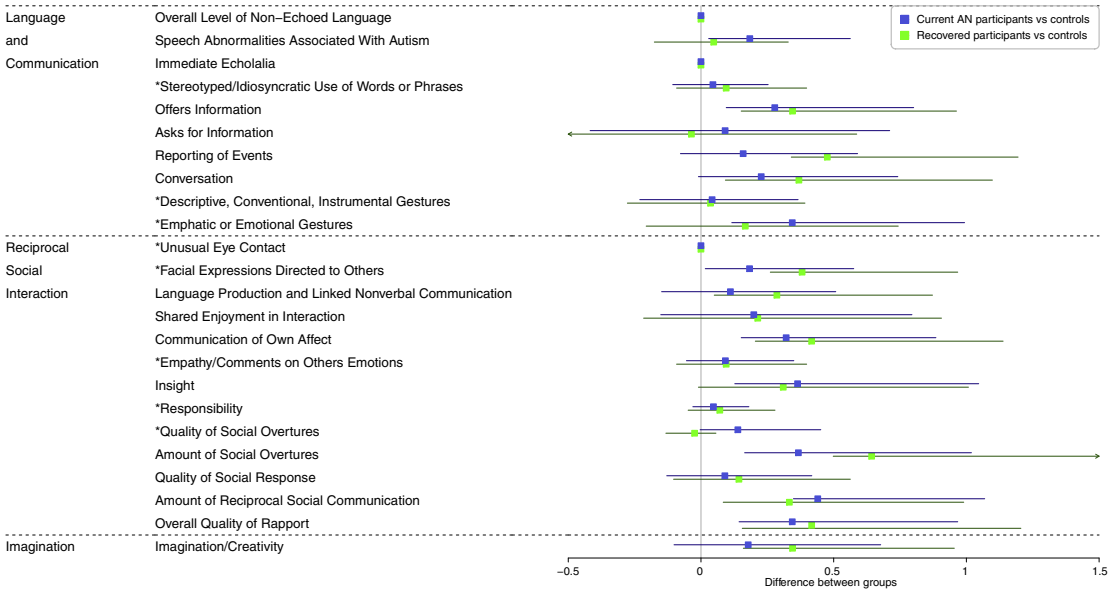

Figure 2. Comparing first-episode AN and recovered participants with controls; mean difference and confidence intervals for ADOS single items. Vertical axis (marked 0) represents no difference to controls, right-hand side of the vertical axis represents higher mean scores (more impairment) than controls, left-hand side of the vertical axis represents lower mean scores (less impairment) than controls. Family-wise Bonferroni corrected confidence intervals shown: for "Language and Communication" cluster 99.5%, for "Reciprocal Social Interaction" cluster 99.6%, for "Imagination" 95%. Items from clusters "Restricted Interests," "Stereotyped Behaviors," and "Other Abnormal Behaviors" are not shown due to lack of variation. *Items included in the ADOS-2 algorithms.

Reduced social function has not been previously documented in individuals fully recovered from AN. Other studies suggest that difficulties in social and adaptive function may persist after recovery from adolescent AN [29]. In this regard, our finding extends earlier reports and suggests that impairments in social function may persist, also after recovery.

Possibly, social difficulties in AN may in fact reflect other factors, such as social anxiety and emotional avoidance, possibly reinforced by starvation, but be mislabeled as autistic traits [30]. In the present study, however, social function was not associated with BMI percentile, eating disorder symptoms, depression, or anxiety symptoms. Alexithymia, which is well documented in individuals with AN, may also affect social function [31]. Indeed, groups differed on the ADOS item *Communication of Own Affect* (an item not included in the ADOS algorithm). However, the interactional style in both AN groups indicated impairment of several other social behaviors, such as *Amount of Social Overtures* and *Amount of Reciprocal Social* Communication, suggesting that alexithymia may not explain the entire impairment measured during social interaction.

Participants with first-episode AN performed equal to or better than controls in tests of social cognition. This somewhat perplexing observation is not in line with studies of social cognition in adults with current AN [4,5]. Indeed, a meta-analysis of the RME-R confirmed reduced performance in adults with AN [4]. Duration of illness might explain the difference in RME-R performance [32]. The average duration of illness in our first-episode AN participants was shorter (<1 year) than that reported in prior studies of adults (duration between 3.6 and 9.9 years) [4,5]. Interestingly, a functional magnetic resonance imaging (fMRI) study in adolescents with current AN reported normal verbal performance in a ToM task but reduced activation of brain networks supporting ToM [33]. Moreover, reduced fMRI activation during the acute phase in that study was associated with poorer outcome a year later. This finding may suggest that differences in social information processing, which are too subtle to measure with a behavioral task, may already be present in the early phases of AN and that individuals with such impairments are at risk for a longer duration of illness and therefore might be over-represented in samples of adults with AN.

The recovered participants displayed a few deficits in social cognition; they performed lower than both other groups on the MiniPONS body gesture, and lower than first-episode AN participants on vocal prosody. The MiniPONS test has not been used in individuals with AN before, but another study of social perception in AN used the Interpersonal Perception Task and described a trend toward reduced performance in adult participants with current AN [34]. The difference in social perception between our recovered and first-episode AN participants corroborates the hypothesis that social cognitive deficits might be associated with duration of illness. Alternatively, the younger mean age at AN onset in our recovered participants might have struck a critical "window" of development where the illness impeded their learning of social perception skills.

Strengths and limitations

A strength of our study is that the first-episode AN participants were recently diagnosed young females, consecutively

recruited, and the recovered participants met strict criteria for recovery. Unfortunately, consideration of participants' treatment sessions, education, and unplanned cancellations induced a considerable variation among participants with regard to the time span between first and last testing session. Although groups did not differ in this aspect, we cannot rule out that the medical condition of participants with first-episode AN might have changed between sessions. It would be preferable to have equal sample sizes, age matching, and a contrast group with ASD without AN, along with blinding of raters, but this was not possible. More sensitive tests of social cognition might detect more subtle differences between groups. Owing to the low number of participants with social anxiety disorder in the sample, it is not likely that our findings were influenced by social anxiety, and symptoms of anxiety did not explain the ADOS score. However, it would be most valuable for future studies to characterize the group of individuals with AN and co-occurring anxiety disorders further. Moreover, larger samples would allow comparison between individuals with different subtypes of AN or different profiles of symptoms to identify a particular subgroup in need of treatment for their social function impairment. Finally, with the cross-sectional design, we cannot be entirely sure that the two groups of affected participants did not differ with respect to severity of AN at onset, and this study cannot determine the state or trait nature of the observed deficits in social function.

We thus conclude that both individuals with first-episode AN and those recovered from AN on a group level displayed impairment of social function, even in the absence of a diagnosis of autism or Asperger syndrome. These impairments of social function were not explained by symptoms of anxiety or depression. In participants with first-episode AN, impairments of social function were not related to symptom severity of AN. However, we cannot discern whether our findings of normal performance of social cognition tasks may reflect a lack of sensitivity of the tests in this specific group of participants or whether the observed impairment of social function may be related to other factors than those tapped by tests of social cognitive function (e.g., factors of "nonsocial" cognition).

The presence of social function deficits in other patient populations has led to targeted interventions to enhance social skills [35]. In young individuals with AN, it is crucial for prognosis to address the core symptoms and secure weight restoration [36], for example, in the context of family-based treatment (FBT), which is the recommended first line of treatment for the young [37]. Impairments in social function, such as understanding and interpreting social cues, however, may hamper treatment response in FBT by evoking misunderstandings and feelings of disempowerment. FBT for youth with AN might be enhanced by integrating explicit psychoeducation and behavioral strategies to enhance intrafamilial interaction. In the later phases, interventions that specifically address social skills may further facilitate recovery. The significance of the communication with peers, both gestures of acceptance and rejection, becomes more central during the teenage years. Focusing on enhancing social function in this age group may thus facilitate the social reintegration of the patients, such that social relations may take over the fundamental importance that ruminations of thoughts about eating and body shape have provided during disorder.

Several treatment strategies aimed at adults target social skills and may well be adapted to the subgroup of young patients with deficits in social function, such as Interpersonal Therapy [38], the "Maudsley Model of Anorexia Nervosa Treatment for Adults" [39], or the "Radically Open-Dialectic Behavior Therapy" [40]. Future research should target the potential impact of social function as a moderator for treatment efficacy and as a predictor for relapse in young people with AN because this area still lacks evidence from rigorous empirical studies.

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11.2 Paper 2: Specific Neurocognitive Performance and Social Function in Young Females with Recent-Onset Anorexia Nervosa and Recovered Individuals

Specific Neurocognitive Performance and Social Function in Young Females with Recent-Onset Anorexia Nervosa and Recovered Individuals

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ABSTRACT

Introduction: Young individuals with AN or recovered from AN display impairments of social function. To date, however, it is not clear whether they differ from controls with respect to neurocognitive performance and whether those functions contribute to the compromised social function observed in individuals with AN.

Methods: We included 43 young females with first-episode AN, 28 individuals recovered from adolescent-onset AN, and 41 control individuals (14-22 yr), all without comorbid autism spectrum disorder. We compared the performance of participants across groups in seven neurocognitive functions relevant to social functioning: set-shifting, local processing, processing speed, working memory, sustained attention, verbal memory, and verbal abstraction. Further, we tested the association between neurocognitive function and social function, measured by Autism Diagnostic Observation Schedule (ADOS), with an ordinal logistic regression model.

Results: First, participants did not differ on any neurocognitive function across groups. Second, only the neurocognitive function "verbal memory" was significantly associated with social function. Higher performance in verbal memory was associated with lower odds of impaired social function. Diagnostic group remained a significant factor, but the absence of an interaction between group and neurocognitive performance indicated that the association between verbal memory and social function was independent of group membership.

Conclusion: Young individuals with AN and those recovered from AN did not differ from controls with respect to neurocognitive performance. Verbal memory was associated with social function in all groups.

PLAIN ENGLISH SUMMARY

Difficulties in interacting with others are more common among young persons with anorexia nervosa than among their peers, and the same holds for persons who are recovered from anorexia nervosa in young age. We thus investigated whether young individuals with anorexia nervosa and those recovered from anorexia nervosa showed difficulties in specific areas of mental abilities: the ability to switch between tasks and strategies, the tendency to focus overly on details, speed of problem solving, the ability to keep information in mind when needed, memory for spoken information, the ability to stay attentive, and finally the ability to interpret sayings in a non-literal

fashion. We further investigated whether performance in these domains was associated with the ability of social function in this patient group. We found normal level of functioning in all mental tasks. Moreover, those with less accurate memory for spoken information were more likely to show difficulties in social interaction. This information might be useful in planning treatments that are helpful for the individual patient in the future.

INTRODUCTION

Anorexia nervosa (AN) is a life-threatening psychiatric disorder characterized by distorted body image and a refusal to maintain a normal body weight, often by applying inflexible rules and rigid behaviors around eating.[1,2] Moreover, specific neurocognitive characteristics described in individuals with AN resemble those seen in individuals with autism spectrum disorders (ASD): cognitive inflexibility and superior local processing in the context of weak central coherence.[3] Several lines of evidence suggest that difficulties in social function, similar to those seen in individuals with ASD, are present to some extent in at least a subset of adolescents with AN.[4,5] However, in-depth knowledge of what characterizes such social function difficulties in this patient group is limited. To date, it is not clear whether specific neurocognitive deficits, similar to deficits seen in individuals with ASD, explain impaired social function in adolescents and young adults with AN, or whether other factors related to the disorder may exert a more prominent influence on social functioning. This gap of evidence is surprising, because knowledge of such associations could potentially lead to interventions that target enhancing social function, e.g. by remediating neurocognitive impairment in young individuals with AN.

Evidence from other neurodevelopmental disorders suggests that specific neurocognitive functions play a role in the capacity of social function. For instance, a broad range of neurocognitive functions predicts approximately a quarter of the variance in social functioning among individuals with schizophrenia.[6] Further, social and executive impairments co-occur and interact in individuals with ASD.[7,8] Finally, a study demonstrated that neurocognitive deficits co-occurred with social cognitive deficits in a subgroup of adults with AN.[9] Studies derived in adolescents with AN propose that the co-existence of neurocognitive deficits and ASD-traits predict a worse outcome in terms of recovery rate.[10–12] Even though neurocognitive functioning seems less impaired in adolescents than adults with AN,[13–17] they may still influence social function competency. In other words, a within-group association between neurocognition and social functioning may exist, although young individuals with AN display neurocognitive function comparable to controls on the group level. This association, however, has not been investigated to date.

In the present study, we sought to: (i) compare neurocognitive functioning in young individuals with first-episode and in those recovered from AN, and (ii) test whether specific neurocognitive functions contributed to the variation of social functioning previously reported in the same population.[18] We assessed a range of neurocognitive functions that have consistently been associated with social functioning among individuals with developmental disorders:[7,12,19–21] set-

shifting, local processing bias, processing speed, working memory, sustained attention, verbal memory and verbal abstraction.

We hypothesized first, that young individuals with first-episode AN and recovered individuals would display deficits in neurocognitive function, and second, that specific neurocognitive functions in the young individuals with first-episode AN and those recovered would be associated with social function.

Methods

Participants

Participants in the first-episode AN group were young females with a recent onset of their first episode of AN (International Classification of Diseases (ICD-10): F50.0 or F50.1),[1] consecutively invited to participate when presenting for treatment in the Mental Health Services, Capital Region of Denmark. Individuals in the recovered group had an onset of AN in late childhood or adolescence (ICD-10: F50.0 or F50.1)[1] and were invited during participation in a clinical follow-up. Control participants were recruited via billboard advertisements in schools, halls of residence, and colleges in the catchment area of the hospital. Inclusion criteria for participants with first-episode AN were underweight, defined as BMI $\leq$ 18.5 kg/m^2 for participants older than 16 yr and a BMI-percentile corrected for age $\leq 25^{th}$ percentile in those 14-15 yrs.[22] Inclusion criteria for participants recovered from AN were maintenance of normal body for a minimum of one year, no present eating disorder pathology, a global score of the Eating Disorders Examination (EDE) within one standard deviation (SD) of non-AN mean,[23] and a generally favorable outcome with a score of $\geq$ 9 on the Morgan Russell Outcome Assessment Schedule (MROAS).[24] Participants with infantile autism (F84.0) or Asperger´s syndrome (F84.5) were excluded, to ensure that our findings were representative of young individuals with AN and not explained by a few outliers with comorbid ASD. Participants with any past or present major psychiatric disorder were excluded in the control group (exceptions were mild episodes of transient tics earlier in childhood, or brief episodes of adjustment disorder after traumatic loss). Current treatment with psychotropic drugs was an exclusion criterion for individuals with first-episode AN and controls. We did not deem this criterion to compromise the representativeness of individuals with first-episode AN, because the use of psychotropic drugs is not typical in the early phases of treatment in young participants in our services. In contrast, we did not exclude recovered participants with current psychopharmacological

treatment, because those individuals often experience other comorbid psychiatric disorders, such as anxiety and depression for which they receive medication.[11,25] Comorbidity was assessed with the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version (K-SADS-PL),[26] and the Beck Youth Inventory (BYI),[27] yielding dimensional measures of anxiety (BAI-Y) and depression (BDI-Y). We assessed general intelligence with the Reynolds Intellectual Assessment Scale (RIAS), Danish version.[28]

Measures

Social functioning We assessed social functioning with the Autism Diagnostic Observation Schedule (ADOS-2), Danish version, module 4,[29] in which a higher score reflects a higher degree of deviation of social and communicative behaviors. We used the combined scale "Communication and Social Interaction Total" (ADOS-Total) as outcome measure of social functioning and observed significantly higher scores in both clinical groups compared with controls.[18]

Neurocognitive function We measured the following seven neurocognitive functions due to their potential relevance to social functioning:

Set-shifting *The Delis-Kaplan Executive Function System* (D-KEFS)[30] is a battery of nine co-normed tests of executive functions. We employed the shift-conditions of Verbal Fluency, Design Fluency, and Trail Making. We compared groups on the scores of these specific shift conditions rather than on the secondary contrast scores provided in D-KEFS, because the reliability of these has been questioned.[31] These three task scores were combined into a set-shifting composite measure of cognitive flexibility.

Local processing *Group embedded Figures Test* (GEFT)[32] measures local processing with simpler shapes hidden in 18 complex geometric designs, and it benefits from a detail-focused processing style. We administered GEFT individually, timing each search,[33] and provided a separate sheet with target shapes to eliminate the reliance on memory.[34] The outcome measure was the number of shapes identified correctly within 120 seconds for each design (Table 2).

Processing speed We used D-KEFS Trail Making score of condition 1, 2 and 3 as a composite measure of processing speed.[30]

Working memory We assessed working memory with a composite formed by three verbal and two nonverbal subtests: *Paced Auditory Serial Addition Test (*PASAT), Danish version, part 2,[35] Digit Span and Letter-Number Sequencing from *The Wechsler Adult Intelligence Scale* (WAIS-IV), Danish version[36], and *CANTAB® Spatial Working Memory* (SWM) and Spatial Span (SSP).[37] We

used total errors in the most difficult 8-box problems of SWM and span length of the SSP as outcomes.

Sustained attention We used the total response time variability of the *Test of Variables of Attention* (TOVA) visual[38] as outcome measure assessing sustained attention. TOVA is a 22-minute computerized continuous-performance test.

Verbal memory We assessed verbal memory with a composite of the immediate and the delayed version of the subtest Memory for Stories from *Tests of Memory and Learning* (TOMAL-2), Danish version.[39] We administered story 3 and 4 of Memory for Stories to all participants regardless of age and compared raw scores across groups.

Verbal abstraction The ability to form novel, verbal abstractions was measured with D-KEFS Proverbs condition 1, which requires the participant to explain in her own words the abstract meaning of a series of proverbs.[30]

Statistical procedures

We evaluated the effect of group on the seven neurocognitive functions in a within-participant repeated measure design, by applying a mixed effects model. We tested equal group effect on the seven different neurocognitive functions (parallelism) by evaluating the interaction between group and type of neurocognitive function, the latter as a categorical variable with seven levels. If the hypothesis of parallelism could not be rejected, we tested a hypothesis of similar mean scores across neurocognitive functions by evaluating the main effect by group. All tests were likelihood ratio tests comparing hierarchical models. A 5% significance level was applied.

Second, we tested the association between the seven neurocognitive functions and social functioning using an ordinal logistic regression model (proportional odds model). We categorized the ADOS-Total dependent variable, because the ADOS-Total did not meet the model assumption as continuous outcome, into the following categories: zero (no deviation), low (scores of 1 through 3), medium (scores of 4 through 6), and high (scores above clinical cut-off, i.e. ≥7). Age was entered as a covariate, group as a factor, and the seven neurocognitive functions were entered as independent variables or predictors. Interaction terms of each neurocognitive function with group were inspected. Only significant neurocognitive functions were retained in the final model. Finally, we repeated the first analysis while adjusting for the potential effects of depressive and anxiety symptoms by adding BDI-Y as covariates in one and BAI-Y in another reiteration of the repeated measures mixed effects model, and we repeated the second analysis, by entering BDI-Y and BAI-Y

separately as covariates in the ordinal logistic regression model. Prior to all analyses, four missing data points were replaced with the age-weighted group mean. Further, the raw scores of neurocognitive tests were transformed (by either square root, logarithmic or square root and reflect transformation) where appropriate. Extreme outliers were truncated to ±3SD from the sample mean, and all scores converted to z-scores (standardized), based on the age-weighted mean and SD of the control participants. We reversed z-scores for easier comparison across tests, in the tests where higher scores indicated poorer performance. For those neurocognitive functions measured with several single tests, we summed and re-standardized the included z-scores. Prior to combining test scores we inspected correlations between tests and confirmed that within each of the combined neurocognitive function z-scores, the included tests were significantly inter-correlated.

RESULTS

Participants

Our sample comprised 43 participants with first-episode AN, 28 recovered participants, and 41 controls (Table 1). Individuals with first-episode AN were tested as close to admission date as possible; mean duration from first to last visit was 8,0 days (median 7.0 days, range 1-23 days, SD 5.8) and participants gained a mean of 2.1 kg from clinical assessment to first testing session (median 1.7 kg, SD 2.3). The two clinical groups did not differ regarding current comorbidity at time of study participation (Table 1a), and the three groups were comparable regarding intelligence and family background; however, mean age of participants with first-episode AN was lower (Table 1a).

At time of treatment onset, the two clinical groups were comparable in terms of symptom characteristics (Table 1b), but the recovered participants were younger than first-episode AN participants at the time they entered treatment.

Insert table 1 approximately here.

Group differences in specific tests of neurocognition

The three groups displayed parallel profiles of neurocognitive functions ($\chi 2$=20.0, df=12, p= .07) (Figure 1).

Insert Figure 1 approximately here.

Figure title: Figure 1 Profile plot, neurocognitive functions

Further, groups showed similar mean scores across neurocognitive functions and thus performance did not differ across groups (equal levels) ($\chi 2$=4.7, df=2, p= .10). Scores on each neurocognitive function are presented for information in Table 2.

Table 2 Neurocognitive function z-scores

Neurocognitive function	FeAN (N=43)		RecAN (N=28)		Controls (N=41)		Effect size[a]
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	R^2
Set-shifting	0.31 (1.40)	(-2.55) -(3.48)	-0.37 (1.25)	(-2.48) -(1.62)	0 (1)	(-2.37) -(2.38)	0.05
Local processing	0.27 (1.06)	(-2.97) -(1.46)	-0.18 (0.88)	(-1.96) -(1.46)	0 (1)	(-2.18) -(1.46)	0.03
Working memory	0.02 (0.97)	(-2.28) -(2.24)	-0.52 (1.16)	(-2.67) -(1.20)	0 (1)	(-2.91) -(1.75)	0.05
Processing speed	-0.33 (1.10)	(-3.04) -(1.35)	-0.45 (0.96)	(-1.98) -(0.90)	0 (1)	(-3.65) -(1.66)	0.03
Sustained attention	0.02 (1.12)	(-2.71) -(2.10)	0.22 (0.98)	(-1.52) -(2.31)	0 (1)	(-2.48) -(2.34)	0.008
Verbal memory	0.21 (1.15)	(-2.05) -(3.10)	-0.47 (1.35)	(-2.05) -(3.02)	0 (1)	(-2.52) -(1.85)	0.05
Verbal abstraction	-0.06 (1.04)	(-2.58) -(2.16)	-0.16 (1.04)	(-2.58) -(1.65)	0 (1)	(-2.19) -(1.65)	0.004

Table legend: Neurocognitive function: age-weighted z-scores, based on mean and SD of controls; FeAN=first-episode AN participants; RecAN=recovered AN participants; Controls=control participants; SD=standard deviation

Table notes:

a. Age-weighted ANOVAs for each function separately, descriptive purposes only

Effect of neurocognition on social functioning

Both of the clinical groups displayed lower levels of social functioning than controls (Independent-Samples Kruskal-Wallis Test: $\chi 2(2)$=8.277, p= .02; first-episode AN: mean=2.77, SD=3.1, range=0-10; recovered: mean=2.79, SD=3.2, range=0-9; controls: mean=1.05, SD=1.5, range=0-6).[18] In an ordinal logistic regression predicting ADOS-Total categories, only the neurocognitive function of verbal memory was a significant predictor. Interactions between group and

neurocognitive functions were not significant. Accordingly, a final model with group, age, and verbal memory as predictors yielded a Nagelkerkes pseudo-R^2 of 21% ($\chi^2(5)=23.709$, $p< .0005$). The odds of a higher ADOS-Total category were reduced to approximately half (Exp(B)=0.584, 95% CI 0.423-0.808) with every increase in verbal memory (expressed as 1 point higher z-score)(Wald $\chi^2(1)=10.601$, $p= .001$), and the final model predicted ADOS-Total significantly better than the simple model using only group and age as predictor ($p< .001$).

The odds of first-episode AN participants having a higher ADOS-Total classification were more than two times higher than controls in the final model, i.e., adjusted for verbal memory and age (Exp(B)=2.490, 95% CI 1.013-6.117), Wald $\chi^2(1)=3.954$, $p= .05$. The odds of recovered participants having a higher ADOS-Total classification compared with controls were three times higher (Exp(B)=3.048, 95% CI 1.169-7.947), Wald $\chi^2(1)=5.195$, $p= .02$.

Effect of depression and anxiety

The pattern of results for the analyses, both regarding group difference in neurocognition and effect of neurocognition on social functioning remained similar when adjusting for the possible confounding effects of depression and anxiety symptoms.

DISCUSSION

Young individuals with AN and those recovered from AN did not differ from controls in terms of their neurocognitive performance on the group level. However, we confirmed a positive association between social functioning and verbal memory across groups. Verbal memory contributed to the variance in social functioning above that accounted for by diagnostic group. The fact that diagnostic group remained a significant factor indicated that aspects of AN, other than verbal memory, also influenced the level of social functioning among individuals with AN.

Reduced cognitive flexibility has been documented in adults with AN,[40] but not consistently in young persons with AN.[17,19,41] Reduced cognitive flexibility in individuals with AN has been associated with difficulties to adjust behavior in the context of a changing feedback.[42,43] These observations informed the hypothesis of Zucker et al.[3] concerning "*systemizing of social information*" as a compensatory strategy for individuals with AN in the face of difficulties in social interaction. However, clinical groups did not differ in flexibility from controls. Indeed, groups did not differ significantly on any measure of neurocognitive function, confirming recent reports of generally normal neurocognitive performance in children and adolescents with AN, [13,14,17,44] in

contrast to findings in adults with AN.[40,45,46] Small effect sizes of differences of neurocognitive function across groups in the current study further support a generally normal performance of the young clinical participants, rather than a type II error due to small sample size. Along the same lines, a meta-analysis of the Trail Making Test, one of several set-shifting tasks in our study, showed a negligible and non-significant effect size comparing young individuals with AN to controls.[19] However, it is not clear, whether the difference between adult and young samples might represent a "scar" related to longer duration of starvation in adults with AN, or whether the lower recovery rate in those with neurocognitive deficits, may lead to a selection bias in adult samples. Finally, maturational effects may explain differences across age groups suggesting that abnormalities may not be evident or detectable until full maturation in adult age. This relevant topic requires further investigation in longitudinal studies.
Reduced verbal memory was associated with higher impairment of social functioning. It is noteworthy that the association between social functioning and verbal memory applied to all three groups, suggesting that verbal memory remains an important index for understanding the level of social functioning in general. In the absence of an interaction between group and verbal memory, this finding does not offer a disorder–specific explanation for impairments in social functioning. However, due to the smaller variance of ADOS-Total scores in the control group, the present association was mostly driven by the two clinical groups whose participants demonstrated a larger variance in ADOS-Total scores and in their level of verbal memory.

We assessed verbal memory with the "Memory for Stories" subtest, in which the stimuli were presented as a coherent narrative and challenged capacity of episodic rather than semantic memory. Episodic memory is the ability to learn, store, and retrieve information about unique experiences, and thus stores pieces of information together with the relations between them.[47] Performance in episodic memory benefits from associative encoding and retrieval.[48] Individuals of normal intelligence with ASD show normal memory for specific items, but are less likely to spontaneously recall relations between items.[49] Individuals with ASD thus tend to rely more on effortful executive control than on automatic associative processes in tasks of episodic memory.[50] In parallel, an impairment of associative encoding and retrieval[48] may contribute to the association between verbal memory and social function in our study population. Episodic memory is important for social function, especially for the context-sensitive regulation of interactions, because individuals need to keep track of the past behaviors of others they interact with.[51]

Another line of evidence corroborates the fact that certain aspects of episodic memory may be affected in individuals with AN, namely the autobiographical memory recall, which is impaired in adults and adolescents with AN, along with a tendency to report overgeneralized memories.[52–54] Interestingly, both clinical groups in our study differed significantly from controls on the ADOS single items "*Offers Information*" and "*Communication of Own Affect*", and the recovered participants on "*Reporting of Events*"[18] all of which evaluate the amount and quality of the participant´s propensity to share autobiographical information.[29,55]

We controlled for depressive and anxiety symptoms in the present study given their potential influence on social functioning.[46,56–58] However, the association between social functioning and verbal memory was stable, even when adjusting for depressive and anxiety symptoms, discounting the hypothesis that these symptoms might underlie and confound the observed association.

Strengths and limitations

The main strength of the current study is the comprehensive assessment of social functioning and neurocognition. Also, few studies among adolescents with AN have included recovered individuals as a contrast group to disentangle more stable traits from state factors related to the acute illness. To the best of our knowledge, potential associations between social function and neurocognition have not been studied in young individuals with first-episode AN, or in those fully recovered from AN. Some limitations, however, must be noted. First, our limited sample size did not allow subgroup analyses. Second, it would be preferable to assess the global integration aspect of central coherence skills in the same participants besides the local processing aspect. Third, while TOMAL Memory for Stories present coherent stimuli, the scores simply reflect the number of elements recalled. A scoring system rewarding cohesion of the recalled material might be more sensitive to associative encoding and recall ability.

Conclusion and implication

The clinical groups displayed generally normal neurocognitive functions. The neurocognitive function of verbal memory was associated with social functioning in all three groups. This association was robust when controlling for the effect of anxiety and depression. Verbal memory may provide a clue for understanding those who need additional interventions to improve social function. Individuals with lower verbal memory may benefit from strategies aimed at enhancing episodic memory in line with the principles of cognitive remediation therapy,[59] which has also been adapted to the family treatment modality for the younger patients.[60] Psychoeducation for

parents may prove beneficial if their child has a reduced verbal memory. For instance, psychoeducation on the specific role of verbal memory in social function may encourage parents to make connections between past and present verbal interactions more explicit. Psychoeducation may also help parents to plan careful exposures to help their child strengthen verbal memory in social contexts. Longitudinal studies may enhance our understanding of the development of social and neurocognitive functions and the interaction between the two functions among individuals with AN.

List of abbreviations

ADOS: Autism Diagnostic Observation Schedule

AN: Anorexia nervosa

ASD: autism spectrum disorders

BAI-Y: Beck Anxiety Inventory-Youth (subscale of BYI)

BDI-Y: Beck Depression Inventory-Youth (subscale of BYI)

BYI: Beck Youth Inventory

D-KEFS: The Delis-Kaplan Executive Function System

EDE: Eating Disorders Examination

GEFT: Group embedded Figures Test

ICD-10: International Classification of Diseases, 10th edition

K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version

MROAS: Morgan Russell Outcome Assessment Schedule

PASAT: Paced Auditory Serial Addition Test

RIAS: Reynolds Intellectual Assessment Scale

SD: standard deviation

SSP: Spatial Span

SWM: Spatial Working Memory

TOMAL: Tests of Memory and Learning

TOVA: Test of Variables of Attention

WAIS: The Wechsler Adult Intelligence Scale

Declarations

Ethics approval and consent to participate

The study received approval from the regional Scientific Ethical Committees (project number H-2-

2012-027) and The Danish Data Protection. Participants and legal caretakers gave informed consent according to the guidelines of the Danish Health and Medicines Authority.

Consent for publication

Not applicable.

Availability of data and material

The dataset analyzed during the current study is available in anonymized form from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MB, KJP and JRMJ designed the study. MB took primary responsibility for data collection and writing the manuscript, supervised by KJP. UM contributed in recruitment, TP contributed in testing of participants, MB analyzed data, MB, KJP and JRMJ interpreted the analyses, GKT contributed in data management, KJP, JRMJ and CMB made substantial input to the manuscript. All authors have revised the manuscript critically and approved the final manuscript.

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11.3 Paper 3: Heightened Olfactory Sensitivity in Young Females with Recent-Onset Anorexia Nervosa and Recovered Individuals

Heightened Olfactory Sensitivity in Young Females with Recent-Onset Anorexia nervosa and Recovered Individuals

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Abstract: 154 words

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Keywords: anorexia nervosa, olfaction, recovered, adolescents

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Abstract

Introduction: Olfaction may be related to food restriction and weight loss. However, reports regarding olfactory function in individuals with anorexia nervosa (AN) have been inconclusive.

Objective: Characterize olfactory sensitivity and identification in female adolescents and young adults with first-episode AN and young females recovered from AN.

Methods: We used the Sniffin' Sticks Odor Threshold Test and Odor Identification Test to assess 43 participants with first-episode AN, 27 recovered participants, and 39 control participants. Participants completed the Importance of Olfaction questionnaire, the Beck Youth Inventory and the Eating Disorder Inventory. We also conducted a psychiatric diagnostic interview and the Autism Diagnostic Observation Schedule with participants.

Results: Both clinical groups showed heightened olfactory sensitivity. After excluding participants with depression, participants with first-episode AN identified more odors than recovered participants.

Conclusion: Heightened olfactory sensitivity in AN may be independent of clinical status, whereas only individuals with current AN and without depression show more accurate odor identification.

Introduction

Anorexia nervosa (AN) is characterized by egosyntonic food restriction, a disturbed body perception and a persistent pursuit of thinness, which may lead to a state of severe underweight.[1] AN most often emerges in adolescence and occurs more frequently in girls than in boys.[2]

Olfactory abilities increase with age until approximately 20 years.[3,4] Females tend to display olfaction ability that is superior to males.[5] States of hunger and satiety modulate olfaction in healthy individuals,[6] and pleasant odors activate the reward system of the brain.[7] Studies have suggested that individuals with AN have altered reward processing of illness-related stimuli including food, and these alterations may also involve odors.[7–9] The possible role of olfaction in food restriction has motivated studies of olfactory characteristics in individuals with AN. Moreover, evidence of altered olfaction in a number of psychiatric disorders, e.g. depression, anxiety, and schizophrenia, has identified olfaction as a possible avenue for gaining further insight into the pathophysiology of these disorders.[10,11]

Olfactory function involves peripheral, as well as central processes.[12] The peripheral processes include odor sensitivity and occur primarily in the olfactory receptors of the nasal epithelium and olfactory bulb. The central processes include odor identification and involve the primary olfactory cortex in the temporal lobes, higher order brain processes, such as reward processing in the orbitofrontal cortex, attention and memory.[8,12–14]

Few studies have assessed olfaction in AN, seven of which included adolescents. However, only three studies reported results separately for this age group.[15–17] One of these three studies in adolescents observed lower odor sensitivity (higher threshold) and normal odor identification,[15] whereas another study observed normal sensitivity and more precise identification in adolescents with AN.[16] The third and largest study with adolescents observed higher sensitivity in participants with AN.[17] The largest reported study included 64 adults with AN and observed higher odor sensitivity but normal odor identification compared with controls.[18] Interestingly, participants with AN showed an association between olfactory sensitivity and illness-related factors related to positive outcome, e.g. higher BMI and less body dissatisfaction were associated with superior sensitivity.

Neither odor sensitivity nor identification have been investigated in individuals who have fully

recovered from AN. However, two longitudinal studies observed improvement of a reduced sensitivity after short-term weight gain in adolescents only[15] and in a combined sample of adolescents and adults with AN,[19], whereas another study reported no change in adolescents with AN.[17] Additionally, a longitudinal study observed improvement in overall olfaction in adults with chronic AN after weight gain.[20]

Depression and anxiety are associated with reduced and increased olfaction, respectively.[21,22] Thus, depression and anxiety may influence findings in individuals affected by AN due to their common co-occurrence.[23] Indeed, a study of adolescents with AN observed increased identification ability only when participants with psychiatric comorbidity, mainly depression, were omitted from analysis.[16]

Olfaction plays an important, but often not consciously perceived, role in human social interaction.[24] Odors may enhance detection of fear in others, and odors from well-known others may reduce stress in disturbing situations.[24] Individuals with schizophrenia exhibit an association between impaired odor identification and social dysfunction.[25,26] A review also confirmed impaired odor identification in individuals with autism spectrum disorder, a disorder characterized by impairment of social function.[27] Although subgroups of individuals with AN repeatedly have shown impaired social function,[28–30] potential associations with aspects of olfaction in AN remain unexplored.

A recent review of olfaction in AN concluded that findings are contradictory regarding several aspects of olfaction.[11] Furthermore, the authors note that comparisons between studies have been hampered by differences in methodology, age and sex of participants, duration of illness, and control of confounders.[11] Specifically, few studies controlled for the effects of depression, duration of illness and age.

Olfactory impairments are associated with lower quality of life in individuals with olfactory dysfunction.[31,32] Healthy subjects vary greatly in the relevance they ascribe to olfaction,[33] but it has not yet been studied in individuals with AN. However, in two studies underweight and weight-recovered individuals with AN reported higher sensitivity to a broad array of sensory stimuli than control participants,[34,35] and the self-reported sensory sensitivity was associated with difficulties in emotional regulation.[34] Finally, underweight individuals, as well as those weight-recovered from AN indicated avoidance toward sensory experiences, and higher levels of perceived sensitivity, both of which were

associated with a higher body dissatisfaction.[35] Such findings link the subjective experiences of bodily senses, including smell, to a core feature of AN, namely body dissatisfaction.

The primary aim of the current study was thus to characterize olfactory sensitivity and identification of odors in adolescent and young adult females with first-episode AN and in adolescents and young adult females that were fully recovered from AN while taking duration of illness, comorbid disorders, and illness-related factors into account. Exploratively, we further aimed to assess the attributed importance of olfaction in these two groups. Additionally, we aimed to examine whether a potential difference between groups in olfactory sensitivity and identification was associated with relevant clinical features such as symptoms of depression or anxiety in any of the groups, or with AN-specific features in the first-episode AN group. Finally, we aimed to assess a possible association between olfaction and social function within each diagnostic group.

We hypothesized that participants with first-episode AN and recovered from AN would display increased olfactory sensitivity and more precise odor identification than control participants. In the face of inconsistent earlier findings, we based this hypothesis on the two largest prior studies in adolescents with AN on olfactory sensitivity[17] and identification.[16]

Methods

Participants

We consecutively invited 14-17 yr old female patients with AN at the Child and Adolescent Mental Health Centre (CAMHS) between July 2012 and March 2015, unless participation was contraindicated due to their physical condition. In addition, we recruited three 18-21 yr old patients with AN from the Stolpegaard Psychotherapy Center. Both centers are part of Mental Health Services in the Capital Region of Denmark, where treatment is covered by state insurance and initiated soon after referral. The inclusion criteria for participants with first-episode AN included a recent onset (within a maximum of 12 months), first-episode of AN (ICD-10: F50.0 or F50.1)[1] and a BMI $\leq$ 18.5 kg/m^2 for participants 16 years or older or a BMI-percentile corrected for age $\leq 25^{th}$ percentile for 14-15 yr old participants.[36] Prior psychological treatment of the current episode was allowed, but prior episodes of AN were not.

Eligible participants recovered from AN were identified through a quality assurance survey.[37] Inclusion criteria included recovery from AN (ICD-10: F50.0 or F50.1),[1] a normal body weight for a minimum of one year prior to inclusion, eating and weight concerns within normal range [defined as a global score of the Eating Disorders Examination (EDE) within one standard deviation (SD) of the published mean],[38] no eating disorder pathology as assessed by EDE diagnostic questions, no ongoing treatment for an eating disorder, and a generally favorable outcome [≥ nine points on the Morgan Russell Outcome Assessment Schedule (MROAS)].[39] We assessed severity of prior AN (at onset) in the participants recovered from AN using clinical data recorded when they were admitted to treatment. The cohort participating in the present study was assessed in a prior study investigating social functioning.[30]

We invited control participants via notice board advertisements for the main study concerning social functioning. Advertisements were distributed in colleges, state schools and halls of residency in the catchment area of the hospital. Inclusion criteria for controls included a normal body weight throughout lifetime and no history of mental illness (Axis I disorders), [40] (minor exceptions included transient childhood tics and adjustment disorders).

Exclusion criteria for all three groups included infantile autism (F84.0) or Asperger´s syndrome (F84.5). We also excluded participants with first-episode AN and controls that currently were treated with psychotropic drugs, due to their potential influence on olfaction, e.g. selective serotonin reuptake inhibitors (SSRI).[15] This did not compromise the representativeness of individuals with first-episode AN, because we recruited participants early in their treatment, when psychotherapeutic intervention usually is the first choice of treatment. Evidence suggests that individuals recovered from AN often have psychiatric disorders such as anxiety and depression.[23,41] Therefore, we did not exclude recovered individuals with past or present psychopharmacological treatment.

Participants or legal caretakers gave written and informed consent according to the guidelines of the Danish Health Authority. The Danish Data Protection Agency and The Regional Scientific Ethical Committee in the Capital Region of Denmark (project number H-2-2012-027) approved this study.

Our final sample included 43 females with first-episode AN, 28 females recovered from AN, and 41 control participants (Table 1).[42]

Table 1. Demographic and clinical characterization of participants with first-episode AN, participants recovered from AN, and controls.

				Test statistics		Effect size[a] (p)		
	FeAN (N=43)	**RecAN (N=28)**	**Con-trols (N=41)**		**p**	**FeAN vs. RecAN**	**FeAN vs. Con**	**RecAN vs. Con**
1.a AT THE TIME OF STUDY PARTICIPATION								
Age, mean (SD) range	16.1 (1.5) 14.1-21.5	18.4 (1.6) 15.7-21.6	17.7 (2.2) 14.0-22.5	F(2,109): 16.119	< .001	-1.48 (< .001)	-0.85 (< .001)	0.36 (ns)
Parents´ highest education, years (SD)	16.1 (2.3)	14.8 (2.8)	15.3 (2.4)	F(2,109): 2.591	.08			
Living with both parents, N (%)	24 (56%)	17 (61%)	21 (51%)	$Chi^2(2)$= .613	.74			
BMI (kg/m^2), mean (SD)	16.6 (1.2)	21.3 (1.8)	22.0 (2.6)	F(2,109): 92.608	< .001	-3.07 (< .001)	-2.67 (< .001)	-0.31 (ns)
BMI percentile corrected for age[b], mean (SD)	7.5 (7.6)	47.3 (19.0)	56.9 (21.2)	F(2,109): 101.948	< .001	-2.75 (< .001)	-3.10 (< .001)	-0.48 (ns)
Comorbid depressive disorder[c,d], N (%)	8 (19)	3 (11)		Fishers exact (2-sided)	.51			
Comorbid OCD, N (%)	3 (7)	0 (0)		Fishers exact (2-sided)	.27			
Comorbid anxiety other than OCD, N (%)	4(9)	5 (18)		Fishers exact (2-sided)	.30			
EDE global score, mean (SD)	2.8 (1.5)	0.6 (0.5)		t(69): 9.119	< .001	1.97		
RecAN duration of treatment (months)[e], (SD)		23.9 (11.8)						
RIAS Intelligence Quotient, mean (SD)	107.7 (10.5)	102.8 (11.5)	107.3 (9.5)	F(2,109): 2.137	.12			

EDI[f] Eating Disorder Risk Composite, mean (SD)	47.7 (10.1)	36.5 (6.4)	36.1 (7.0)	F(2,105): 24.861	< .001	1.32 (< .001)	1.33 (< .001)	0.06 (ns)
EDI Body Dissatisfaction Scale T-score, mean (SD)	49.0 (8.8)	37.9 (8.2)	36.9 (7.7)	F(2,105): 25.254	< .001	1.31 (< .001)	1.46 (< .001)	0.13 (ns)
EDI Interoceptive Deficits Scale T-score, mean (SD)	49.4 (8.1)	35.3 (8.4)	36.0 (8.2)	F(2,105): 34.794	< .001	1.71 (.001)	1.64 (< .001)	-0.08 (ns)
BYI Anxiety Index T-score, mean (SD)	57.1 (9.8)	51.8 (12.7)	47.8 (9.9)	F(2,109): 8.092	.001	0.47 (ns)	0.94 (< .001)	0.35 (ns)
BYI Depression Index T-score, mean (SD)	60.9 (10.8)	49.8 (12.3)	48.5 (9.5)	F(2,109): 16.262	< .001	0.96 (.001)	1.22 (< .001)	0.12 (ns)
ADOS Total	2.77 (3.1)	2.79 (3.2)	1.05 (1.47)	F(2,109: 5.450	.006	-0.06 (ns)	0.71 (.005)	0.70 (.03)
1.b AT THE TIME OF TREATMENT INITIATION								
Age, mean (SD)	16.1 (1.5)	14.8 (1.6)		t(69)=3.357	.001	0.84		
BMI percentile corrected for age, mean (SD)	3.8 (5.4)	4.8 (6.0)		t(69)= - .722	.5			
EDE global score at time of treatment[g], mean (SD)	2.8 (1.5)	2.8 (1.3)		t(54)= - .051	1.0			
Binge-purge subtype AN, N (%)	4 (9%)	4 (14%)		Fishers exact (2-sided)	.7			
Comorbid depressive disorder, N (%)	8 (19%)	4 (14%)		Fishers exact (2-sided)	.75			

FeAN=first-epsiode AN participants; RecAN=recovered AN participants; Controls= control participants; ns=non-significant (p< .05); BMI=Body Mass Index; EDI=Eating Disorder Inventory-3; OCD=obsessive-compulsive disorder; EDE=Eating Disorder Examination; RIAS= Reynolds Intellectual Assessment Scales.; ADOS-Total = Autism Diagnostic Observation Schedule-2, Communication and Social Interaction Total algorithm score

a. Between-group effect sizes presented as Cohen´s d.
b. BMI percentiles corrected for age <0.02 are calculated as =0.02. Participants>20 yr old were given percentile of 20 yr olds.
c. Depressive disorder includes mild depression, moderate depression and severe depression according to ICD-10.
d. We used the term "comorbid" although anxiety and depression are only comorbid to AN in the case of the participants with first-episode AN.

e. We use months in treatment for the recovered as a proxy for duration of AN, knowing that this might not be entirely precise, because AN typically has a gradual onset.
f. EDI-3 answers are missing from four FeAN.
g. EDE data available from time of treatment for recovered participants, N=13 (46%). T-scores are derived from American norms in the absence of Danish norms for adolescents.

The three groups did not differ with respect to parental education, number of participants living with both parents, or intelligence level. However, participants with first-episode AN were younger than the two other groups (Table 1). The participants with first-episode AN and those recovered did not differ concerning their rate of current comorbid psychiatric disorders as assessed with the Schedule for Affective Disorders and Schizophrenia in School-Age Children - Present and Lifetime version (K-SADS-PL) (Table 1).[43] The subgroup of participants recovered from AN, who had other psychiatric disorders (N=8), were all in remission, and these disorders were assessed not to interfere with a generally favorable outcome (MROAS),[39] yet three recovered participants used an SSRI at the time of testing. Clinical characteristics did not differ between the two diagnostic groups when they started treatment (Table 1), apart from the fact that recovered participants were younger at admission (Table 1). We omitted participants with anosmia from analyses of olfactory sensitivity and identification (recovered: N=1, controls: N=2). Anosmia was defined as a score of zero on the Odor Threshold Test, or ≤ 7 correct answers on the Odor Identification Test, as the latter is randomly obtainable.[44]

Measures

We used the Sniffin' Sticks Odor Threshold Test and Odor Identification Test[45] to assess olfactory performance. The Sniffin' Sticks battery is the test most frequently used in studies of individuals with AN.[11] Both tests consist of felt-tip pens with odorants and were administered to both nostrils simultaneously. The Odor Threshold Test contains *n*-buthanol in 16 dilutions of increasing strength. They were presented in a triple forced-choice paradigm in which one contains the target odor (*n*-buthanol) and the other two contain a non-odorant solvent. The final score was calculated as the mean of the last four turning points, i.e. either the highest dilution in which the participant correctly identified the odorant twice in a row, or the lowest dilution in which the participant failed to identify the dilution once. Higher scores thus represent higher sensitivity. The Odor Identification Test consists of 16 different common odors, each with a forced-choice answer with four alternatives. Scores represent the

number of odors correctly identified.

We differed from the recommended procedure of the test in three ways. [45] First, we did not blindfold our participants, but let them face away and covered the color code of the sticks to allow for a more comfortable administration of the threshold test. Second, we only required participants to identify one stick correctly instead of two in a row before moving up the staircase in order to increase tolerability and reduce administration time of the test. Third, we presented the sticks in a pseudo-random order instead of the predetermined sequence to prevent participants from guessing based on the sequence of presentation.

We assessed participants' subjective experience of olfaction with the 'Importance of Olfaction' questionnaire.[33] The questionnaire consists of three subscales with six items each, formulated as personal statements on a Likert Scale, with higher scores representing more importance ascribed to olfaction. The *Association Subscale* assesses emotions, memories, and evaluations triggered by the sense of smell. The *Application Subscale* assesses the degree to which a person uses his or her sense of smell in daily life. The *Consequence Subscale* assesses the conclusions someone draws from their olfactory impressions. The questionnaire includes five items with food-related content, which may potentially bias the results in participants with first-episode AN due to prevalent food aversion.[46] Additionally, it includes two questions pertaining to response bias when presenting for treatment of olfactory loss. They were not considered relevant for the present study and thus were not included in the analyses. The original questionnaire was translated into Danish by one of the authors and back-translated into German by a Danish-speaking German and then approved by the author.

Participants were interviewed using a K-SADS_PL interview and completed the Beck Youth Inventory (BYI)[47] that includes dimensional measures of depression symptoms (BDI-Y) and anxiety (BAI-Y). Preliminary analysis revealed a strong bivariate correlation between the BDI-Y and BAI-Y scores (r^2= .80, $p < .001$ in the total sample). Moreover, the factor structure of the BYI indicate that the two scales tap into the same domain of emotional distress.[48] However, depressive disorders reduce the ability of olfaction,[21] whereas the presence of anxiety enhances olfaction,[22] which is why we analyzed both scales. Participants also completed the Eating Disorder Inventory, 3rd edition (EDI-3),[49] to describe thoughts and emotions related to AN.

We used the Communication and Social Interaction Total algorithm of the Autism Diagnostic Observation Schedule (ADOS-Total), second edition, module 4, Danish version to assess social function.[50] All ADOS observations were performed by the same researcher, who met the standard requirement for research reliability of ADOS administration, while assessing interrater reliability against an expert in a random sample of cases based on video recordings.[42] Finally, we assessed intelligence level with the Reynolds Intellectual Assessment Scales (RIAS).[51]

The assessment procedures lasted approximately 8 hours, distributed over 1-3 visits, preferably scheduled in the afternoons after school hours. All tests, clinical interviews, and questionnaires in the study were administered in a fixed, pseudo-randomized order, taking variety into account, and beginning with the ADOS interview. Tests of olfaction were administered in the middle of the assessment procedures. Participants were offered breaks when needed.

Statistical procedures

Main analyses

Statistical analyses were carried out in IBM SPSS statistics version 22.[52] Odor Threshold Test scores and Odor Identification Test scores were analyzed separately with one-way analyses of variance (ANOVAs) after checking for model assumptions. We used a Bonferroni-adjusted level of significance of 2.5 % ($p < .025$) for the two main analyses of olfaction tests scores to control for type I errors when testing two hypotheses. Post hoc analyses of difference between groups are reported as Cohen´s d (pooled standardized mean difference).

To assess potential impact of factors known to be associated with olfaction we repeated the ANOVAs of the two olfaction test scores four times, each time excluding the participants with the characteristic in question: smoking on a daily basis (N= 15; 3 first-episode AN, 5 recovered, 7 controls),[53] current major depressive disorder (N=11; 8 first-episode AN, 3 recovered),[37] anxiety disorder other than OCD (N=9; 4 first-episode AN, 5 recovered),[22] serotonergic medication (N=3 recovered).[15] If these sensitivity analyses did not change the main results, then the subgroups were kept in the main analysis to maintain statistical power.

We adjusted olfaction test and questionnaire outcome scores by age by weighting cases with a standardized frequency weight[54] based on four age groups (14-16.5 yr, 16.5-17.25 yr, 17.25-18.5 yr,

18.5-22.5 yr) due to the between-group differences in mean age (Table 1), i.e. to prevent potential effects of the significant between-group mean age difference.
Before performing the weighting procedure we inspected scatterplots of each variable with age and observed no outliers. For the additional sensitivity analyses, age weighting was based on three age groups to verify that no age group was smaller than N=3.

Exploratory analyses

To assess group differences in the mean scores of the three subscales of the Importance of Olfaction questionnaire (Association, Application, and Consequence), we conducted a one-way multivariate analysis of variance (MANOVA) after checking for model assumptions. In the case of a significant result, we performed post hoc ANOVAs. The outliers of the age-weighted subscale scores (N=3) were truncated to the next observed age weighted subscale score in that particular group. As a sensitivity analysis, we performed an ANOVA with the Importance of Olfaction total scores excluding all questionnaire items with food-related content. One item from the Association subscale, four items from the Application subscale and no items from the Consequence subscale had food-related content and thus were removed.

We performed two sets of ANCOVAs with appropriate checking for model assumptions; one set of ANCOVAs with age-weighted Odor Threshold Test score, and one with age-weighted Odor Identification Test score as the dependent variable. The purpose of the ANCOVAs was to a) assess whether a potential difference between groups in olfactory sensitivity or identification was associated with severity of depressive or anxiety symptoms, and b) to assess whether olfaction was associated with social functioning in the groups. Each ANCOVA had group as fixed factor and either BDI-Y, BAI-Y, or ADOS-Total score as independent variable besides group. Interaction terms between group and each of the remaining independent variables were checked and included if significant.

For the analysis of potential associations between scores of each of the olfaction tests (Odor Threshold Test and Odor Identification Test) and the clinical variables, we performed multiple regression analyses within the group of participants with first-episode AN. BMI adjusted for age and the EDI-3 Body Dissatisfaction Scale score were independent variables, and each of the olfaction measures were

dependent variables. We employed no correction of the level of significance in the exploratory analyses.

Results

Olfactory sensitivity

The between-group difference on the mean Odor Sensitivity Test scores was significant with a medium effect size (Table 2).

Table 2. Sniffin´Sticks Odor Identification Test and Odor Threshold Test results.

Measure	Participants, Mean (SD)			ANOVA			Pairwise comparisons: Effect sizes d (p)[a]		
	FeAN	RecAN	Controls	F	p	R^2	FeAN vs. RecAN	FeAN vs. Con	RecAN vs. Con
Odor Threshold Test[b]	N=43 9.18 (1.52)	N=27 8.85 (2.13)	N=39 7.45 (2.31)	F(2,106): 8.364	< .001	.14	0.18 (ns)	0.88 (.001)	0.63 (.04)
Odor Threshold Test excluding smokers	N=40 9.33 (1.48)	N=22 8.86 (2.09)	N=32 7.50 (2.39)	F(2,91): 7.864	.001	.15	0.26 (ns)	0.92 (.001)	0.61 (ns)
Odor Threshold Test excluding participants with depression	N=35 8.94 (1.50)	N=24 9.01 (2.07)	N=39 7.37 (2.27)	F(2,95): 7.696	.001	.14	-0.04 (ns)	0.82 (.003)	0.75 (.005)
Odor Threshold Test excluding participants with anxiety[d]	N=39 8.96 (1.44)	N=22 8.95 (1.99)	N=39 7.38 (2.29)	F(2,97): 7.971	.001	.14	0.01 (ns)	0.83 (.001)	0.73 (.02)
Odor Threshold Test excluding participants using SSRI	N=43 9.12 (1.50)	N=24 8.89 (2.20)	N=39 7.37 (2.28)	F(2,103): 8.827	< .001	.15	0.12 (ns)	0.93 (.001)	0.70 (.01)
Odor Identification Test[c]	N=43 12.98 (1.24)	N=27 11.96 (1.64)	N=39 12.65 (1.83)	F(2,106): 3.581	.03	.06	0.70 (.03)	0.21 (ns)	-0.40 (ns)
Odor Identification Test excluding smokers	N=40 12.86 (1.29)	N=22 11.80 (1.64)	N=32 12.62 (1.94)	F(2, 91): 3.177	.05	.07	0.72 (.04)	0.14 (ns)	-0.46 (ns)
Odor Identification Test excluding participants with depression	N=35 12.92 (1.20)	N=24 11.77 (1.62)	N=39 12.66 (1.84)	F(2, 95): 4.007	.02	.08	0.81 (.02)	0.17 (ns)	-0.51 (ns)
Odor Identification Test excluding participants with anxiety[d]	N=39 12.95 (1.14)	N=22 11.87 (1.69)	N=39 12.66 (1.82)	F(2, 97): 3.421	.04	.07	0.75 (.03)	0.19 (ns)	-0.45 (ns)
Odor Identification Test excluding SSRI	N=43 12.85 (1.24)	N=24 11.80 (1.64)	N=39 12.66 (1.83)	F(2, 103): 3.578	.03	.07	0.72 (.03)	0.12 (ns)	-0.49 (ns)

SD= standard deviation; d=Cohen's d; FeAN= participants with first-episode AN; RecAN= participants recovered from AN; Controls= control participants; ns= non-significant.

a. We used Tukey´s or Games-Howell test for post hoc comparisons depending on the homogeneity of variances.
b. Odor Threshold Test scores represent mean of last 4 turning points.
c. Odor Identification Test scores represent mean number of odors correctly identified.
d. Anxiety disorders other than OCD.

Post hoc comparisons revealed that participants with first-episode AN and recovered participants did not differ significantly from each other and had significantly higher mean Odor Sensitivity Test scores than controls.

When excluding participants who smoked, had a diagnosis of depression or anxiety, or were currently treated with SSRI medication, results of the ANOVA were unaltered (Table 2). Post hoc comparison results stayed the same, except when participants who smoked were excluded. In this case only the mean Odor Sensitivity Test score of individuals with first-episode AN was significantly higher than the score of the controls.

Odor identification

Participants in the three groups did not significantly differ in their ability to identify odors within the Odor Identification Test (Table 2). However, when excluding participants with a comorbid diagnosis of depression, the ANOVA revealed a significant between-group difference. Post hoc tests showed that the remaining participants with first-episode AN identified significantly more odors than the remaining recovered participants (Table 2). The ANOVAs without participants who either smoke, had a diagnosis of anxiety, or were currently treated with SSRI medication showed no statistically significant difference between groups.

Exploratory

Subjective Importance of Olfaction

The MANOVA revealed a significant between-group difference in the Importance of Olfaction questionnaire subscale means with a small effect size [F(6, 214): 3.069, p= .01; Wilk´s Lambda= .848; R^2= .079]. Post hoc ANOVAs showed that only the Association subscale was significantly different

between the groups, because participants with first-episode AN indicated a significantly lower importance of olfaction than recovered participants and controls (Table 3).

Table 3. Importance of Olfaction Questionnaire results, age weighted mean.

	Participants, Mean (SD)			ANOVA			Pairwise comparisons: Effect size d[a] (p)[b]		
Measure	**FeAN**	**RecAN**	**Controls**	**F(2,109)**	**p**	**R^2**	**FeAN vs. RecAN**	**FeAN vs. Con**	**RecAN vs. Con**
Questionnaire total score	25.33 (7.86)	29.76 (6.10)	29.67 (7.40)	F(2,109): 4.768	.01	.08	-0.63 (.04)	-0.57 (.02)	0.01 (ns)
Association subscale	8.38 (3.37)	10.29 (2.62)	10.45 (2.96)	F(2,109): 5.759	.004	.10	-0.63 (.03)	-0.65 (.01)	-0.06 (ns)
Application subscale	8.37 (3.35)	9.23 (3.31)	10.05 (3.32)	F(2,109): 2.673	.07	.05	-0.05 (ns)	-0.41 (ns)	-0.50 (ns)
Consequence subscale	8.58 (3.06)	10.23 (2.36)	9.17 (2.88)	F(2,109): 2.859	.06	.05	-0.60 (.05)	-0.20 (ns)	0.40 (ns)
Questionnaire total score excluding 5 food-related items	18.39 (6.51)	21.24 (4.75)	20.37 (5.84)	F(2,109): 2.261	.11	.04	-0.50 (ns)	-0.32 (ns)	0.16 (ns)

SD= standard deviation; FeAN= participants with first-episode AN; RecAN= participants recovered from AN; Controls= control participants; ns= non-significant.

a. d=Cohen's d. b. We used Tukey´s or Games-Howell test for post hoc comparisons depending on the homogeneity of variances.

After exclusion of the food-related questions, the ANOVA showed no significant difference between groups (Table 3).

Associations between olfaction and clinical variables

Adjusting the between-group comparison of mean Odor Threshold Test scores for the severity of depressive (BDI-Y) or anxiety symptoms (BAI-Y) did not change the pattern of results observed in the unadjusted analysis (Table 4).

Table 4. Unadjusted and adjusted olfaction test score means with confidence interval.

		Unadjusted		Adjusted for depression[a]		Adjusted for anxiety[b]	
	N	mean	95% CI	mean	95% CI	mean	95% CI
Olfactory threshold							
FeAN	43	9.18*	8.56-9.78	9.32*	8.68-9.96	9.17*	8.55-9.79
RecAN	27	8.85*	8.09-9.61	8.77*	8.01-9.54	8.85*	8.09-9.61
Controls	39	7.45	6.82-8.08	7.35	6.70-8.00	7.47	6.81-8.13
Odor identification							
FeAN	43	12.98	12.51-13.46	13.02	12.51-13.53	12.96	12.47-13.45
RecAN	27	11.96	11.36-12.55	11.93	11.32-12.54	11.95	11.35-12.55
Controls	39	12.65	12.15-13.14	12.62	12.10-13.13	12.67	12.15-13.19

FeAN=participants with first-episode AN; RecAN=participants recovered from AN; Controls=control participants; *=Statistically different from controls (Bonferroni-adjusted $p < .05$).

a. Depressive symptoms measured by Beck Depression Inventory-Youth Index, evaluated at the value of T-score=53.44.

b. Anxiety symptoms measured by Beck Anxiety Inventory-Youth Index, evaluated at the value of T-score=52.76.

Likewise, adjusting the between-group comparison of mean Odor Identification Test scores for BDI-Y or BAI-Y did not change the pattern of results observed in the unadjusted analysis (Table 4).

In the regression analysis within the group of first-episode AN participants, neither EDI-3 Body Dissatisfaction Scale scores (p= .43) nor BMI-percentile adjusted for age (p= .25) significantly predicted Odor Threshold Test scores. In the second regression analysis, lower EDI-3 Body Dissatisfaction Scale scores, representing less severe body image disturbance, significantly predicted higher Odor Identification Test scores with a small effect size, [β= - .37, p= .02, R^2= .136], whereas BMI-percentile adjusted for age did not (p= .54).

Associations between olfaction and social functioning

The ADOS-Total score was not a significant predictor of olfactory sensitivity [F(1,105)=0.728, p= .40, R^2= .01] nor of odor identification [F(1,105)=2.499, p= .12, R^2= .02]. Further, the pattern of group differences in olfactory performance did not change, when ADOS-Total was added as a predictor.

Discussion

In terms of the primary aims of the present study, individuals with first-episode AN and recovered individuals demonstrated higher olfactory sensitivity than controls and did not differ from one another. Furthermore, the three groups did not differ in their ability to identify odors. However, after excluding participants with a comorbid depressive disorder, the remaining participants with first-episode AN were able to identify odors more accurately than recovered participants. Thus, our finding supports earlier findings of superior olfactory functions in persons with AN, specifically concerning young persons with a short duration of illness.

We observed no associations between the olfactory functions and social functioning. We cannot discern whether this lack of association reflects truly unrelated areas of functioning in individuals with AN, or whether it reflects the limited range of scores in our participants. The impairment of social function in our groups without ASD may be less severe than in other diagnostic groups. Moreover, the ADOS scoring system does not include categories to differentiate between normal and superior social functioning, which may limit the range of scores in this population.

Olfaction depends on the orbitofrontal cortex (OFC), an area also involved in assigning reward value to stimuli.[55,56] Alterations in the activation of the OFC in response to food in individuals with AN are documented,[8] a process involved in aberrant learning of aversion toward food.[57,58] Hence,

superior olfaction and especially superior olfactory sensitivity might enhance this aversive learning process.

Prior studies reported that individuals with AN showed either reduced,[15,19,59] normal,[16,20,60–62] or superior[17,18,21] olfactory sensitivity. Several factors, such as different test used, small and heterogeneous samples, lack of control for medication, duration of AN, or the presence of comorbid disorders may explain this inconsistency as outlined in a recent review.[11] With regard to duration of AN, we recruited individuals with first-episode AN shortly after they presented for treatment for the first time, thus minimizing effects of chronic starvation, which may affect olfaction differentially over time. Fasting for 24 hours increases olfaction in healthy individuals,[63] but long-lasting starvation may decrease cell renewal of the olfactory epithelium possibly resulting in reduced sensitivity.[17,19,21] It has been noted, that the sensitivity scores of the controls were unusually low in a prior study, which in part may explain findings of high sensitivity in the clinical group.[11] In comparison, the mean threshold score of the controls in our study falls between the published mean for 5-15-year-old healthy females and that of 16-36-year-old healthy females. This indicates that our control sample is representative of community controls.[4]

The first-episode AN participants included in the present study did not show an association between higher olfactory sensitivity and less severe AN symptoms (lower body dissatisfaction, and higher BMI), previously demonstrated in adults with AN.[64] However, differences of sample characteristics render direct comparisons difficult. Moreover, the clinical homogeneity of the present sample with first-episode AN may have reduced the variability of symptom severity, thus making it difficult to identify associations. Furthermore, olfactory sensitivity in our participants was not related to self-reported symptoms of depression or anxiety. Finally, excluding participants with depressive or anxiety disorders, participants who smoke, or participants undergoing SSRI treatment, did not change the findings regarding olfactory sensitivity. Thus, differences in olfactory sensitivity between controls and the clinical groups were not affected by factors that had an influence on this function in groups with depression or anxiety. It is plausible that the associations between these disorders and olfactory sensitivity may be differentially modified by the presence of AN. Regarding depression, it appears that AN "overrules" possible effects of depression on olfaction. Regarding anxiety, while AN as well as anxiety are associated with superior olfaction ability, our results suggest there may not be an additive effect, when both disorders are present.

Regarding odor identification, lack of controlling for comorbid depressive disorder may partly explain the divergent findings in prior studies[11] that report either reduced identification[19,60,61] or no

significant alterations compared with controls.[15,20,21,64,65] In the current study, the subgroup of participants with first-episode AN without a depressive disorder displayed more precise odor identification than controls, which is in line with an earlier observation in adolescents with AN without comorbidity.[66] However, the dimensional measure of depression symptoms, BDI-Y, did not significantly influence the between-group differences in odor identification. Possibly, the BDI-Y items may represent more transient aspects of emotional distress that frequently accompany a diagnosis of AN than a manifest diagnosis of a depressive disorder.[67]

The presence of anxiety may improve odor identification in individuals with first-episode AN, because symptom provoking stimuli, such as food, activate brain regions associated with anxiety, e.g. hippocampus and amygdala, in individuals with AN.[68] Indeed, nine of 16 target smells in the Odor Identification Test represent a smell from foods or beverages. A higher level of anxiety is significantly associated with enhanced odor identification in individuals without AN,[22,69] and anxiety is associated with a tendency to attend to threatening information.[70] Superior odor identification in individuals with AN may therefore represent an attentional bias toward feared stimuli related to eating.[16]

Our findings further suggest that less accurate odor identification is associated with higher levels of body dissatisfaction in participants with first-episode AN. This points to a more general impairment of interoceptive awareness,[7] which is common in individuals with AN and reflected in their distorted body image and body dissatisfaction.[71] Altered interoceptive awareness may promote aversive conditioning of the bodily cues of hunger and satiety in AN and thus lead to a top-down cognitive avoidance of food-related stimuli such as smells.[7] We thus hypothesize that altered interoceptive awareness may explain the association between less accurate odor identification and higher levels of body dissatisfaction.

In summary, odor identification may be superior in the initial phases of AN, as confirmed on the group level in our study, but this effect may be counteracted by a top-down cognitive avoidance based on altered interoceptive awareness. Furthermore, a longer duration of illness may impede odor identification, in line with decreasing olfactory sensitivity in adults with a chronic course of the disorder.[19,66] This was confirmed in a sample of adults with AN, in which only participants with the lowest weight, associated with length of illness, displayed reduced odor identification.[19] Thus, avoidance related to altered interoceptive awareness, or factors related to duration of starvation, or both, may counteract the otherwise heightened odor identification in individuals first-episode AN.

Participants with first-episode AN indicated less importance of olfaction in everyday life than controls, whereas participants recovered from AN indicated a similar level of importance of olfaction as the controls. The difference was only statistically significant when food-related items were included and may point to the importance of food-related content. Although highly speculative, we suggest that not ascribing subjective importance to olfaction in first-episode AN may reflect aspects of the above-mentioned top-down avoidance following attentional bias toward feared, food-related stimuli in acutely ill AN individuals, although on the group level they display heightened odor identification.

Due to the cross-sectional design of the present study, it is impossible to know whether the observed higher olfactory sensitivity and more accurate olfactory identification in participants with first-episode AN were present before the onset of AN, as well as how those measures will develop further after this early phase of AN. Although we cannot entirely exclude the possibility that the higher olfactory sensitivity in recovered participants is a cohort effect, our findings suggest that higher olfactory sensitivity in AN may be relatively independent of weight loss and other characteristics of the acute phase, whereas the finding of more accurate odor identification is only present in the initial phase of AN.

Strengths and limitations

The major strength of the current study is the detailed characterization of the clinical groups and the inclusion of participants recovered from AN. Moreover, participants with first-episode AN had a short duration of illness thereby avoiding the potential confounding effects of chronicity, and the recovered participants met strict and multifaceted criteria for recovery. However, there were also some limitations. First, our findings cannot be generalized to males with AN, as sex differences in olfaction have been noted.[5] Second, the differences in administration of the Sniffin' Sticks Test may influence direct comparisons with previous studies that have employed this test. The reliability of odor threshold determination is lower than other olfaction measures and has been questioned for several reasons, including the use of only one target odor.[22] Furthermore, we used the standard *n*-buthanol as target odor for the Sniffin´ Sticks Odor Threshold Test. *N*-buthanol stimulates not only the olfactory system but also the trigeminal system of nasal receptors,[72] and therefore the observed sensitivity may not be an exclusive effect of the olfactory system. Lastly, we did not control for state of satiety in participants when testing olfaction. Future studies may benefit and possibly obtain more consistent results by including state of satiety in participants.

Conclusion and applications

We observed enhanced olfactory sensitivity in participants with first-episode AN and in recovered participants, whereas only participants with first-episode AN and without comorbid depression displayed superior odor identification. Less accurate odor identification was associated with higher levels of body dissatisfaction in participants with first-episode AN, which ascribed less importance to olfaction than did the other two groups. We observed no association between olfaction and social function in these participants.

Olfaction has been proposed as a biomarker for diagnosis and prognosis in a range of disorders.[22] However, given the inconsistency of findings, populations and methodologies in studies of olfaction in AN to date, [11] its use as a marker for diagnosis seems unwarranted. Moreover, the theoretical framework that places olfaction within a generally disturbed processing of sensory perceptions in AN via anxiety and avoidance, needs further investigation.[7,35] If confirmed, olfaction might be a more distal and hence less fear-provoking area to begin habituation and reversal training than i.e. the sense of satiety. To the degree that the heightened olfactory sensitivity in AN is aversive, clinical care programs may take this evidence into account by accommodating food and environments without strong smells, thus making the process of re-nourishment less stressful.

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Supporting information caption

S1 Dataset. The data used for conclusions in the article can be found in the supporting information file S1.

11.4 Declarations of co-authorship

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Title of PhD thesis:
Social function in young persons with anorexia nervosa

This declaration concerns the following article:
Impairment of social function in young females with recent onset anorexia nervosa and recovered individuals

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
2. Planning of the experiments and methodology design, including selection of methods and method development	B
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

Benchmark scale of the PhD student's contribution to the article		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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Title of PhD thesis:
Social function in young persons with anorexia nervosa

This declaration concerns the following article:
Heightened olfactory sensitivity in young females with recent onset anorexia nervosa and recovered individuals

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
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B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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Appendices

Appendix 1 Flow chart, literature search, social function in young persons with AN

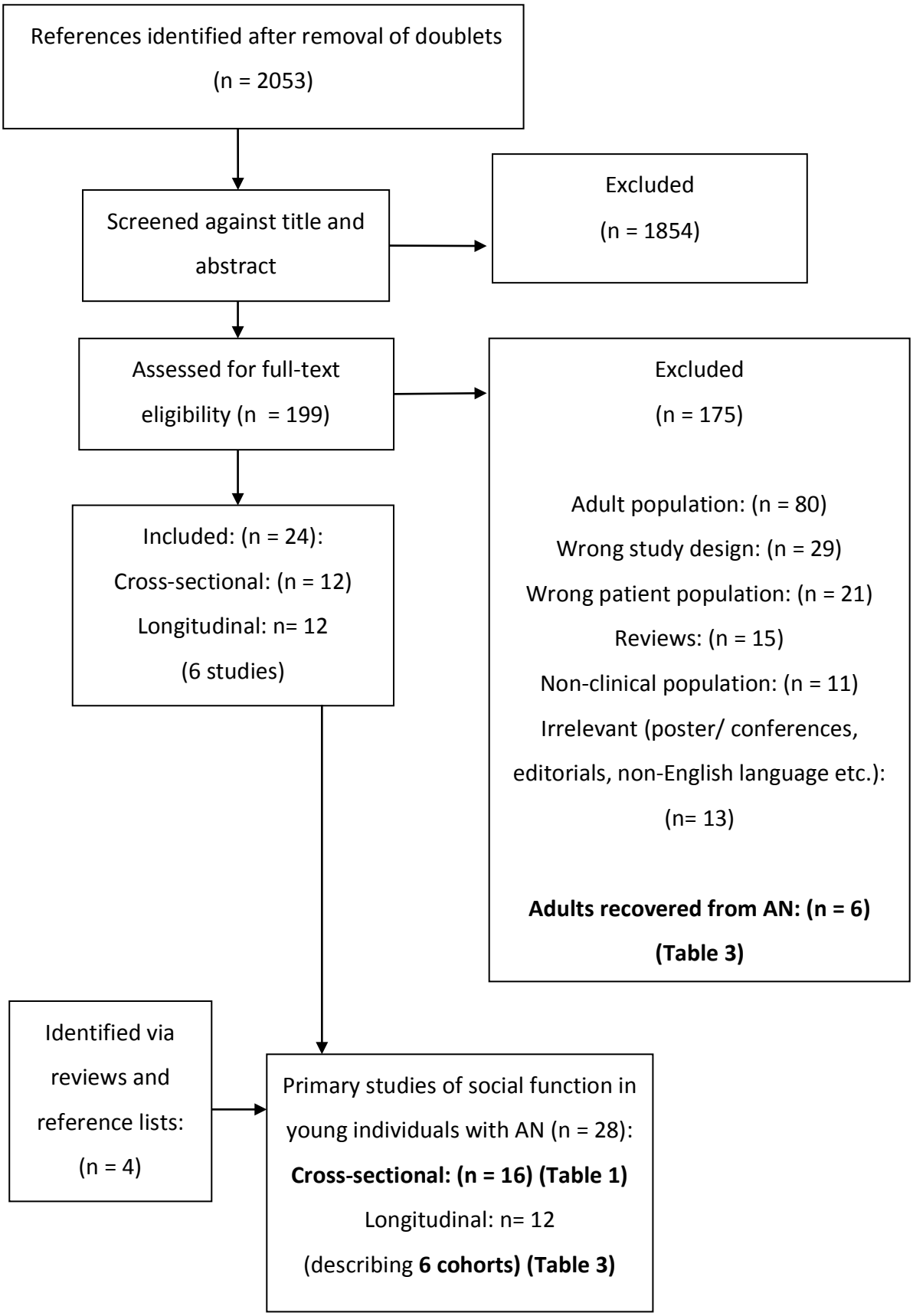
Appendix 2 Details concerning studies included in Table 1

Appendix 2 Details concerning studies included in Table 1

Appendix 4 Details concerning studies included in Table 3

Appendix 5 RdoC domain: Systems for social processes

11.5 Appendix 1 Flow chart: literature search for social function in young persons with AN



11.6 Appendix 2 Details concerning studies included in Table 1

Capolli et al., 1989

Title	Gaze and eye-contact with anorexic adolescents
N (% female)	7 AN (100)
mean age (SD), range	15-18
duration of AN (months)	not reported
instruments (relevant for the present review)	number and duration of individual looking and mutual gazes
confounders adjusted for	none
methodological issues	small sample

Lattimore, Wagner, & Gowers, 2000

Title	Conflict avoidance in anorexia nervosa: An observational study of mothers and daughters
N (% female)	20 (100)
mean age (SD), range	15.7 (1.5), range not reported
duration of AN (months)	not reported
instruments (relevant for the present review)	Observational coding scheme developed for this study
confounders adjusted for	none
methodological issues	unvalidated instrument

Broberg, Hjamlers, & Nevonen, 2001

Title	Eating disorders, attachment and interpersonal difficulties: A comparison between 18- to 24-year-old patients and normal controls
N (% female)	84 mixed ED (17 AN)(100)
mean age (SD), range	21.3 (2.1), 18-24 yr
duration of AN (months)	not reported
instruments (relevant for the present review)	The Relationship Questionnaire (RQ)
confounders adjusted for	none
methodological issues	small sample of AN participants

Zonnevijlle-Bendek et al., 2002

Title	Do adolescent anorexia nervosa patients have deficits in emotional functioning?
N (% female)	30 mixed ED (16 AN) (100)
mean age (SD), range	14.9 (SD n/i), 12-18 yr

duration of AN (months)	not reported
instruments (relevant for the present review)	TAS-20, Emotion Recognition Test (ERT)(free labeling plus forced-choice)
confounders adjusted for	performance on parallel, non-social tasks
methodological issues	small AN sample

Zonnevylle-Bender et al., 2004

Title	Emotional functioning in anorexia nervosa patients: Adolescents compared to adults
N (% female)	28 (100)
mean age (SD), range	15.5 (1.1), up to 18 yr
duration of AN (months)	range 4-12
instruments (relevant for the present review)	TAS-20, Emotion Recognition Test (ERT)(free labelling plus forced-choice)
confounders adjusted for	IQ, performance on parallel, non-social tasks
methodological issues	no healthy control group, no control for age and duration of illness (all adult participants had illness onset before the age of 18)

Ruuska, Koivisto, Rantanen, & Kaltiala-Heino, 2007

Title	Psychosocial functioning needs attention in adolescent eating disorders
N (% female)	34 (100)
mean age (SD), range	16.2 (1.2), 14-19 yr
duration of AN (months)	median 18
instruments (relevant for the present review)	Global Assessment of Functioning (GAF), Morgan-Russell psychosocial subscales (MROAS)
confounders adjusted for	age, duration of illness, BMI, psychological distress
methodological issues	no healthy control group, BN comparison group older and longer illness duration, GAF considered a crude measure of social function

Buchholz et al., 2007

Title	Self-silencing in a clinical sample of female adolescents with eating disorders
N (% female)	149 mixed ED (49 AN) (100)
mean age (SD), range	15.6 (1.2), 13-18 yr
duration of AN (months)	not reported
instruments (relevant for the present review)	The Silencing the Self Scale (STSS) (adolescent adaptation), EDI-2, Multidimensional Anxiety Scale for Children (MASC): subscales Anxious Coping and Social Anxiety

confounders adjusted for	age, BMI
methodological issues	results for AN participants not reported separately, no control group

Pooni et al. 20012

Title	Investigating autism spectrum disorder and autistic traits in early onset eating disorder
N (% female)	22 (86)
mean age (SD), range	13.0 (1.6), 10-16 yr
duration of AN (months)	not reported
instruments (relevant for the present review)	The Developmental, Dimensional, and Diagnostic Interview short version (3Di-sv), Repetitive Behavior Scale-Revised (RBS-R)
confounders adjusted for	
methodological issues	ASD group was younger, comprised more males

Obeid et al., 2013

Title	Self-esteem and social anxiety in an adolescent female eating disorder population: Age and diagnostic effects
N (% female)	344 mixed ED (182 AN)(100)
mean age (SD), range	15.6 (1.4), 12-18 yr
duration of AN (months)	not reported
instruments (relevant for the present review)	Social Anxiety Scale of MASC, Harter Self-Perception Profile for Adolescents (SPPA).
confounders adjusted for	stratified for age and diagnostic groups
methodological issues	no control group

Schulze et al., 2013

Title	Trait anxiety in children and adolescents with anorexia nervosa
N (% female)	23 (100)
mean age (SD), range	14,5 (1,5), 10-18 yr
duration of AN (months)	first admission for AN
instruments (relevant for the present review)	Social Phobia and Anxiety Inventory for Children (SPAI-C), EDI, anamnestic interview with parents
confounders adjusted for	BMI
methodological issues	no control group, but published norms

Lule et al., 2014

Title	Anorexia nervosa and its relation to depression, anxiety, alexithymia and emotional processing deficits
N (% female)	15 (100)
mean age (SD), range	16.2 (1.3), 14-18 yr
duration of AN (months)	not reported
instruments (relevant for the present review)	TAS-20, Facially Expressed Emotion Labelling Test (FEEL)
confounders adjusted for	eating disorder, anxiety and depressive pathology
methodological issues	small sample

Bomba et al., 2014

Title	Autobiographical memory in adolescent girls with anorexia nervosa
N (% female)	60 (100)
mean age (SD), range	15.4 (1.6), 11-18 yr
duration of AN (months)	mean 11.2 (SD 8.8)
instruments (relevant for the present review)	Autobiographical Memory Test (AMT) supplemented by ED-relevant cues, TAS-20
confounders adjusted for	age, BMI, duration and severity of illness, anxiety, depression
methodological issues	

Rhind, Mandy et al., 2014

Title	An exploratory study of evoked facial affect in adolescent females with anorexia nervosa
N (% female)	17 (100)
mean age (SD), range	14.8 (1.7), 13-18 yr
duration of AN (months)	mean 20.7 (SD 15.1)
instruments (relevant for the present review)	Facial Expression Coding System (FACES)
confounders adjusted for	anxiety, depression, IQ
methodological issues	small sample

Rhind, Bonfioli et al., 2014

Title	An examination of autism spectrum traits in adolescents with anorexia nervosa and their parents
N (% female)	150 (91)
mean age (SD), range	16.9 (2.3), 13-21 yr
duration of AN (months)	mean 22.6 (SD 22.8)

instruments (relevant for the present review)	Development and Well-being Assessment (DAWBA) (autism spectrum disorder and eating disorder sections), SDQ, Social Aptitude Scale (SAS)
confounders adjusted for	BMI, illness duration, illness severity, clinical impairment, depression, anxiety
methodological issues	no control group, but published norms. Instruments validated in epidemiological, not clinical studies.

Lang et al. 2015

Title	Exploring emotion recognition in adults and adolescents with anorexia nervosa using a body motion paradigm
N (% female)	97 (36 adolescents)(100)
mean age (SD), range	mean age of adolescents not reported separately, 11-18 yr
duration of AN (months)	not reported
instruments (relevant for the present review)	Point-Light Walkers Task (emotion recognition from movement). Hospital Anxiety and Depression Scale, Autism Quotient-10
confounders adjusted for	age, %IBW, BMI, anxiety, depression, and autistic traits
methodological issues	

Dakanalis et al., 2015

Title	The Social Appearance Anxiety Scale in Italian adolescent populations: Construct validation and group discrimination in community and clinical eating disorders samples
N (% female)	703 mixed ED (212 AN)(90)
mean age (SD), range	not reported, 11-18 yr
duration of AN (months)	not reported
instruments (relevant for the present review)	Social Appearance Anxiety Scale, Social Interaction Anxiety Scale, Social Phobia Scale, Brief Fear of Negative Evaluation Scale
confounders adjusted for	depression, gender, age, BMI, stratified by ED-diagnosis
methodological issues	scale validation study

11.7 Appendix 3 Details concerning studies included in Table 2

Leon, Lucas, Colligan, Ferdinande, & Kemp, 1985

Title	Sexual, body-image, and personality attitudes in anorexia nervosa
N (% female)	31(100)
mean age (SD), range	median 16.6, range 11-20 yr
duration of AN (months)	Prior hospitalisations for AN: 0, 1 or 2
instruments (relevant for the present review)	a social skills composite formed by parts of MMPI and the History and Personality Questionnaires (HPQ)

confounders adjusted for	
methodological issues	social skills composite not validated

The Gothenbourg study (Gillberg, Gillberg, Råstam, Wentz, Ankarsäter et al., 1992-2012)

Authors & Titles	Gillberg, Råstam & Gillberg, 1994	Anorexia nervosa outcome: six-year controlled longitudinal study of 51 cases including a population cohort
	Gillberg, Råstam & Gillberg, 1995	Anorexia nervosa 6 years after onset: Part I. Personality disorders
	Råstam, Gillberg og Gillberg, 1995	Anorexia nervosa 6 years after onset: Part II. Comorbid psychiatric problems
	Nilsson, Gillberg & Gillberg, 1999	Ten-year follow-up of adolescent-onset anorexia nervosa: Personality disorders
	Wentz, Gillberg, Gillberg & Råstam, 2001	Ten-year follow-up of adolescent-onset anorexia nervosa: Psychiatric disorders and overall functioning scales
	Anckarsäter et al., 2012	The sociocommunicative deficit subgroup in anorexia nervosa: Autism spectrum disorders and neurocognition in a community-based, longitudinal study
N (% female)	51 (94)	
mean age (SD), range	initial assessment: 16 yr.	
duration of AN (months)	mean 1.7 yr at initial assessment	
instruments (relevant for the present review)	6 yr FU: Dewey Social Awareness Test, MROAS, clinician´s rating of empathy. 10 yr FU: Autism Spectrum Diagnostic Interview (ASDI). 18 yr FU: ASDI, MROAS, AQ	
confounders adjusted for		
methodological issues	instrument for assessing ASD and empathy disorder not validated	

Herpertz-Dahlmann et al. 2001-2011

Authors & Titles	Herpertz-Dahlmann et al., 2001	Depression and psychosocial adjustment in adolescent anorexia nervosa: A controlled 3-year follow-up study
	Herpertz-Dahlmann et al., 2011	Prospective 10-year follow-up in adolescent anorexia nervosa - Course, outcome, psychiatric comorbidity, and psychosocial adaptation
N (% female)	39 (82)	
mean age (SD), range	discharge: 16.2 (2.0), 10-21	
duration of AN (months)	at admission: 16 (16)	
instruments	Morgan-Russell Outcome Assessment Schedule (MROAS)	
confounders adjusted for	stratified for recovery/not recovery of ED	
methodological issues	MROAS rather crude measure of social function	

Halvorsen, Andersen & Heyerdahl, 2005

Title	Girls with anorexia nervosa as young adults. Self-reported and parent-reported emotional and behavioural problems compared with siblings
N (% female)	48 mixed ED, 25 siblings (100)
mean age (SD), range	initial assessment: 14.9 (1.8), 9-18.
duration of AN (months)	not reported
instruments	Young Adult Self-Report (YASR) & Young Adult Behavior Checklist (YABCL): subscale Adaptive Functioning concerns friends, education, job, family and spouse.
confounders adjusted for	age sex, variation between sibling pairs, source of informant (self compared to parent report)
methodological issues	not reported whether the persisting ED group accounted for the entire difference in adaptive function.

Lázaro et al., 2011

Title	Effectiveness of self-esteem and social skills group therapy in adolescent eating disorder patients attending a day hospital treatment programme
N (% female)	95 (94)
mean age (SD), range	15.3 (1.2), 13-18 yr
duration of AN (months)	14.2 (12.8)
instruments	The Socialization Battery (BAS-3)
confounders adjusted for	age
methodological issues	no control group, treatment study

Schultze-Rüther, Mainz, Fink, Herpertz-Dahlmann, & Konrad, 2012

Title	Theory of mind and the brain in anorexia nervosa: Relation to treatment outcome
N (% female)	19 (100)
mean age (SD), range	15.7 (1.5), 12-18 yr
duration of AN (months)	not reported
instruments	fMRI, geometrical shape films (social attribution), MROAS
confounders adjusted for	sensitivity analyses without medicated participants; reduced gray matter in starved states
methodological issues	

Courty, Godart, Lalanne, & Berthoz, 2015

Title	Alexithymia, a compounding factor for eating and social avoidance symptoms in anorexia nervosa

N (% female)	60 (100)
mean age (SD), range	16.0 (1.6), 13-21 yr
duration of AN (months)	16.6 (6.8)
instruments	Toronto Alexithymia Scale, short version (TAS-20), EDI, SCL-90, LSAS-interview
confounders adjusted for	anxiety, depression, age, AN-subtype
methodological issues	homogenous sample, severe AN

11.8 Appendix 4 Details concerning studies included in Table 3

Bachner-Melman, Zohar, Ebstein & Bachar, 2007

title	The relationship between selflessness levels and the severity of anorexia nervosa symptomatology
N (% females)	42 AN, 78 recAN (100)
mean age (SD), range	AN:23.6 (5.2), rec: 23.9 (3.6)
AN duration (months)	rec: 25.6 (19.8)
instruments	Selflessness Scale
confounders adjusted for	perfectionism, obsessiveness, self-esteem, ED symptoms
methodological issues	
definition of recovery	physical (BMI>18, regular menstruation), no present behavioral symptoms

Connan, Troop, Landau, Campbell, & Treasure, 2007

title	Poor social comparison and the tendency to submissive behavior in anorexia nervosa.
N (% females)	18 AN, 13 recAN (100)
mean age (SD), range	27.4 (4.5), 18-45
AN duration (months)	median 30 (inter-quartile range 15-72)
instruments	Measure of Parental Style (MOPS), Psychological Abuse Scale (PAS), Social Comparison Rating Scale (SCRS), Submissive Behavior Scale (SBS)
confounders adjusted for	
methodological issues	
definition of recovery	Physical (BMI 19-25, regular menstruation) during one yr, no present psychiatric illness.

Bachner-Melman et al., 2009

title	Self-monitoring in anorexia nervosa
N (% females)	17 AN, 106 partially recovered, 71 recAN (100)
mean age (SD), range	recAN: 23.7 (3.4)
AN duration (months)	partially recovered: (34 (27), recAN: 24.5 (16.9)
instruments	Snyder´s Self-Monitoring Scale
confounders adjusted for	ED symptoms

methodological issues	
definition of recovery	physical (3 months) and psychological recovery required (8 weeks)

Oldershaw, Hambrook, Tchanturia, Treasure, & Schmidt, 2010

title	Emotional theory of mind and emotional awareness in recovered anorexia nervosa patients.
N (% females)	40 AN, 24 recAN (96)
mean age (SD), range	recAN: 29.9 (7.7)
AN duration (months)	5.6 (3.8)
instruments	Reading the Mind Tasks (Eyes, Voices, Film), Music task, Level of Emotional Awareness Scale
confounders adjusted for	IQ, BMI, age of onset, AN duration, lowest ever BMI, bulimic behaviors
methodological issues	
definition of recovery	physical and psychological recovery required for 1 yr

Tchanturia et al., 2012

title	Altered social hedonic processing in eating disorders
N (% females)	72 AN, 14 recAN (no info)
mean age (SD), range	recAN: 25.2 (8.7)
AN duration (months)	3.8 (2.6)
instruments	Revised Social Anhedonia Scale (RSAS), TAS-20
confounders adjusted for	BMI, depression, anxiety, ED severity
methodological issues	AN significantly longer illness duration than recAN
definition of recovery	physical (1 years) and psychological recovery required (4 weeks)

Oldershaw et al., 2012

title	Emotional processing following recovery from anorexia nervosa.
N (% females)	40 AN, 24 recAN (96)
mean age (SD), range	AN: 26.0 (8.8), recAN: 28.0 (8.5)
AN duration (months)	rec: 5.5 (5.8)
instrument	Silencing the Self Questionnaire
confounders adjusted for	anxiety, depression and ED symptoms, BMI
methodological issues	
definition of recovery	physical (BMI>19) and psychological recovery (EDE-Q) required for 1 year

Cowdrey, Harmer, Park, & McCabe, 2012

title	Neural responses to emotional faces in women recovered from anorexia nervosa
N (% females)	16 recAN (100)
mean age (SD), range	23.1 (3.6)
AN duration (months)	not reported
instruments	fMRI watching fearful and happy faces
confounders adjusted for	groups comparable on BMI, anxiety and depression.
methodological issues	
definition of recovery	Physical (BMI 19-25, regular menstruation) during 12 months, no present psychotropic medication, no psychological symptoms (EDE-Q, 4 weeks).

Harrison et al., 2010 & 2012

Harrison et al., 2012	Social emotional functioning and cognitive styles in eating disorders
Harrison, Tchanturia, & Treasure, 2010	Attentional bias, emotion recognition, and emotion regulation in anorexia: state or trait?
N (% females)	50 AN, 35 recAN (100)
mean age (SD), range	recAN: 29.0 (10.6), 18-55
AN duration (months)	rec: 5.5 (2.9)
instruments	Pictorial Stroop (social-emotional stimuli), RME-R, Difficulties in Emotion Regulation Scale (DERS)
confounders adjusted for	depression, anxiety
methodological issues	AN significantly longer illness duration than recAN
definition of recovery	physical (1 yr) and psychological recovery required (4 weeks)

Davies, Schmidt, & Tchanturia, 2013

title	Emotional facial expression in women recovered from anorexia nervosa
N (% females)	49 AN, 31 recAN (100)
mean age (SD), range	28.4 (8.7)
AN duration (months)	5.5 (3.5)
instruments	Facial Expression Coding System (FACES) recording of facial expressions, PANAS
confounders adjusted for	age, medication, depression, anxiety
methodological issues	AN significantly longer illness duration than recAN
definition of recovery	physical (1 yr) and psychological recovery required (4 weeks) and no present DSM-IV diagnosis.

Cardi, Di Matteo, Corfield, & Treasure, 2013

title	Social reward and rejection sensitivity in eating disorders: an investigation of

	attentional bias and early experiences.
N (% females)	29 AN, 13 recAN (100)
mean age (SD), range	29.5 (8.4)
AN duration (months)	8.0 (6.2)
instruments	Dot-probe task (accepting and rejecting faces), Parental Bonding Instrument
confounders adjusted for	anxiety, stress
methodological issues	
definition of recovery	physical and psychological recovery required (4 weeks and regular menstruation)

Brochmeier et al. 2013

title	Interpersonal motives in anorexia nervosa: the fear of losing one's autonomy
N (% females)	33 AN, 26 recAN (100)
mean age (SD), range	recAN: 27.5 (5.4), 18-45
AN duration (months)	5.3 (4.2)
instruments	Inventory of Approach and Avoidance Motivation (IAAM), Incongruence Questionnaire (INQ)
confounders adjusted for	BMI, duration of illness
methodological issues	
definition of recovery	physical (6 months) and behavioral recovery required (12 months)

Morris, Bramham, Smith, & Tchanturia, 2014

title	Empathy and social functioning in anorexia nervosa before and after recovery
N (% females)	28 AN, 23 recAN (100)
mean age (SD), range	recAN: 29.5 (9.2)
AN duration (months)	rec: 46 (37)
instrument	Socio-Emotional Questionnaire (SEQ)
confounders adjusted for	BMI, depression, AN duration, age, IQ, ED symptoms
methodological issues	AN significantly longer illness duration than recAN
definition of recovery	physical (1 yr) and psychological recovery required (4 weeks)

Harrison, Mountford, & Tchanturia, 2014

title	Social anhedonia and work and social functioning in the acute and recovered phases of eating disorders
N (% females)	105 AN, 30 recAN (100)
mean age (SD), range	27.8 (9.9)
AN duration (months)	similar between groups
instruments	Work and Social Adjustment Scale (WSAS), RSAS
confounders adjusted for	anxiety and depression

methodological issues	
definition of recovery	physical and psychological recovery required (4 weeks and regular menstruation)

Striegel-Moore, Seeley, & Lewinsohn, 2003

title	Psychosocial adjustment in young adulthood of women who experienced an eating disorder during adolescence
N (% females)	36 (100)
mean age (SD), range	24.2 (0.6), 23-25
AN duration (months)	not reported
instrument	specific questionnaire items
confounders adjusted for	comorbid depression
methodological issues	crude measure of social function, ED not clinically verified. Strength: population-based sample.
definition of recovery	longitudinal: revaluated 6 yrs after initial assessment

Beadle, Paradiso, Salerno, & McCormick, 2013

title	Alexithymia, emotional empathy, and self-regulation in anorexia nervosa
N (% females)	20 (100)
mean age (SD), range	24.4 (5.5)
AN duration (months)	not reported
instruments	TAS-20, The Interpersonal Reactivity Index
confounders adjusted for	time points (starvation + weight recovery), depression, BMI
methodological issues	
definition of recovery	Longitudinal: revaluated shortly after weight restoration

Hartmann, Zeeck, & Barrett, 2010

title	Interpersonal problems in eating disorders
N (% females)	208 mixed ED (113 AN)(94)
mean age (SD), range	24.5 (7.5), 16-56
AN duration (months)	not reported
instruments	Inventory of Interpersonal Problems (IIP-C)
confounders adjusted for	BMI, general distress, severity of binges
methodological issues	no control group, but compared to German normative material
definition of recovery	Longitudinal: revaluated at end of treatment.

11.9 Appendix 5 RdoC domain: Systems for social processes

Source: http://www.nimh.nih.gov/research-priorities/rdoc/development-and-definitions-of-the-rdoc-domains-and-constructs.shtml

Systems for Social Processes: Systems that mediate responses to interpersonal settings of various types, including perception and interpretation of others' actions.

- **Affiliation and Attachment:** Affiliation is engagement in positive social interactions with other individuals. Attachment is selective affiliation as a consequence of the development of a social bond. Affiliation and Attachment are moderated by social information processing (processing of social cues) and social motivation. Affiliation is a behavioral consequence of social motivation and can manifest itself in social approach behaviors. Affiliation and Attachment require detection of and attention to social cues, as well as social learning and memory associated with the formation of relationships. Affiliation and Attachment include both the positive physiological consequences of social interactions and the behavioral and physiological consequences of disruptions to social relationships. Clinical manifestations of disruptions in Affiliation and Attachment include social withdrawal, social indifference and anhedonia, and over-attachment.

- **Social Communication:** A dynamic process that includes both receptive and productive aspects used for exchange of socially relevant information. Social communication is essential for the integration and maintenance of the individual in the social environment. This construct is reciprocal and interactive, and social communication abilities may appear very early in life. Social communication is distinguishable from other cognitive systems (e.g., perception, cognitive control, memory, attention) in that it particularly involves interactions with conspecifics. The underlying neural substrates of social communication evolved to support both automatic/reflexive and volitional control, including the motivation and ability to engage in social communication. Receptive aspects may be implicit or explicit; examples include affect recognition, facial recognition and characterization. Productive aspects include eye contact, expressive reciprocation, and gaze following. Although facial communication was set aside as a separate sub-construct for the purposes of identifying matrix elements, social communication typically utilizes information from several modalities, including facial, vocal, gestural, postural, and olfactory processing. Social Communication was organized into the following sub-constructs:
    - Reception of Facial Communication: The capacity to perceive someone's emotional state non-verbally based on facial expressions.
    - Production of Facial Communication: The capacity to convey one's emotional state non-verbally via facial expression.
    - Reception of Non-Facial Communication: The capacity to perceive social and emotional information based on modalities other than facial expression, including non-verbal gestures, affective prosody, distress calling, cooing, etc.
    - Production of Non-Facial Communication: The capacity to express social and emotional information based on modalities other than facial expression, including non-verbal gestures, affective prosody, distress calling, cooing, etc.

- **Perception and Understanding of Self**: The processes and/or representations involved in being aware of, accessing knowledge about, and/or making judgments about the self. These processes/representations can include current cognitive or emotional internal states, traits, and/or abilities, either in isolation or in relationship to others, as well as the mechanisms that support self-awareness, self-monitoring, and self-knowledge. Perception and Understanding of Self was organized into the following sub-constructs:
    - Agency: The ability to recognize one's self as the agent of one's actions and thoughts, including the recognition of one's own body/body parts.

    - Self-Knowledge: The ability to make judgments about one's current cognitive or emotional internal states, traits, and/or abilities.

- **Perception and Understanding of Others**: The processes and/or representations involved in being aware of, accessing knowledge about, reasoning about, and/or making judgments about other animate entities, including information about cognitive or emotional states, traits or abilities. Perception and Understanding of Others was organized into the following sub-constructs:
    - Animacy Perception: The ability to appropriately perceive that another entity is an agent (i.e., has a face, interacts contingently, and exhibits biological motion).
    - Action Perception: The ability to perceive the purpose of an action being performed by an animate entity.
    - Understanding Mental States: The ability to make judgments and/or attributions about the mental state of other animate entities that allows one to predict or interpret their behaviors. Mental state refers to intentions, beliefs, desires, and emotions.

12 Addendum

Social Function in Young persons with Anorexia Nervosa

Addendum:
Figure 1 and Table 1a & b are not shown in Paper 2 (pp. 75-93), where they should also have been inserted, but are part of the work as presented.

- Figure 1 is a graph showing a profile plot of z-scores from seven cognitive domains split by participant group. The graph is depicted in the dissertation text as Figure 5 (p. 39).
-
- Table 1a & b consists of clinical description of the participant groups at treatment initiation and at testing. The Table is identical to Table 1a & b of Paper 3, (shown at p. 100-101).